KNEE JOINT DISTRACTION: MOVING FORWARD

MYLÈNE P. JANSEN

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Mylène P. Jansen

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KNEE JOINT DISTRACTION: MOVING FORWARD

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Mylène Paulien Jansen
geboren op 10 mei 1992
te Zevenaar

Promotor:	Prof. dr. F.P.J.G. Lafeber
Copromotoren:	Dr. S.C. Mastbergen
	Dr. R.J.H. Custers

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CONTENTS

CHAPTER 1

General introduction

The knee joint

The knee is a synovial joint: the articulating bones forming the joint are covered by a layer of hyaline articular cartilage, and united by a joint capsule that consists of an outer fibrous layer and inner synovial membrane.[1]

Bone

Bone is hard, calcified connective tissue, and is fully innervated and vascularized.[2] It possesses an intrinsic capacity for repair and undergoes constant regeneration and remodeling in response to loading and unloading.[3,4] Its function is not only mechanical, but metabolic as well, storing important minerals and secreting cytokines and growth factors.[5] At the endings of articulating bones, an outer cortical bone plate (or subchondral bone plate) with underneath more porous trabecular bone make up the subchondral bone, which is covered by cartilage.[6]

Cartilage

Articular cartilage is hyaline in nature, with exceptional resilience and tensile strength and an extremely low friction coefficient, responsible for providing a smooth surface for articulation, load distribution and resistance to compressive forces during normal and high impact loading. It consists mainly of extracellular matrix (ECM), produced and maintained by a relatively small number of chondrocytes. ECM is primarily composed of water and macromolecules such as collagen, predominantly collagen type II, which forms an extensive network in which large aggrecan molecules are entrapped, providing cartilage with mechanical integrity. Cartilage is considered to have a limited, low rate, regeneration capacity and is aneural and avascular, depending on diffusion from the surrounding synovial fluid for its nutrition.[7–9]

Synovium

The synovium, or synovial membrane, lines the inner surface of synovial joints. It is made up of a thick fibrous outer layer and a thin inner layer called the intema, which consists of cells called synoviocytes and is in direct contact with the synovial fluid inside the joint. The synovium is responsible for maintaining joint homeostasis through this synovial fluid, which in turn provides lubrication of cartilage surfaces and nutrition of chondrocytes.[10,11]

It is the integrated activity between these 3 tissues (in addition to menisci, ligaments, muscles and tendons stabilizing the joint), all in contact with each other mechanically and biochemically, that determines the condition of a knee joint.

Knee osteoarthritis

Osteoarthritis

Osteoarthritis (OA) is the most common chronic musculoskeletal disorder, affecting more than 300 million people worldwide.[12] Prevalence is expected to rise with an aging population and increasing obesity, as both are related to incidence and prevalence of OA.[13] The knee is a frequent site of OA, involving the entire joint, encompassing bone, cartilage, and synovium.[14] Bone changes include an increase in subchondral bone density, formation of osteophytes, and bone shape alterations.[15] Cartilage volume decrease is perhaps the most well-known characteristic of OA, but the quality of cartilage deteriorates as well, as the collagen type II in the ECM is affected.[16] Both the bone and cartilage alterations influence the joint mechanically and biochemically. Often synovial inflammation, or synovitis, is present, affecting the composition of the synovium and synovial fluid.[17,18] Not all changes occur similarly in all patients: they show heterogeneity, leading to attempts to define different subgroups or phenotypes.[19]

Diagnosis and monitoring

Diagnosis of knee OA starts with the symptoms that bring patients to visit their doctor, including pain, reduced function, and stiffness. A definitive diagnosis is made based on these symptoms, in combination with physical examination, and a radiograph of the knee.[20] Classification and monitoring of disease progression is usually done with plain radiographs as well, often using relatively rough grading scales.[21] However, while radiographs have the advantage of being fast and cheap, they only provide a 2D image and do not show soft tissue such as cartilage. Alternative imaging techniques can be used, such as computed tomography (CT) for a 3D image of the bones or magnetic resonance imaging (MRI) for a 3D image of hard and soft tissue, including synovial tissue and cartilage, enabling measurement of not only cartilage quantity but also quality using specialized scans.[22] While these imaging techniques are applied more and more in research, radiography is still dominant in regular care.

Treatment

Treatment of tibiofemoral knee OA usually starts with conservative, non-surgical options such as weight loss, bracing, use of oral pain medication and anti-inflammatories, and, if that fails, intra-articular injections.[23] Eventually, as the disease progresses towards end-stage knee OA, many patients need a joint replacement, a partial or total knee arthroplasty (UKA/TKA). While TKA and more recently also UKA are applied often and have shown good clinical results, still around 20% of patients express dissatisfaction after TKA surgery.[24] Furthermore, the prosthesis itself has a limited life span, meaning it could eventually need replacement in an expensive and usually less clinically successful revision surgery. The chance for revisions surgery increases significantly when the arthroplasty is performed in relatively young patients,

aged 65 or younger.[25] It is therefore of paramount importance that placement of a knee prosthesis is postponed in these young patients with joint-preserving treatments. In case OA primarily affects only 1 compartment of the joint combined with varus or valgus leg axis deviation, (high) tibial or (low) femoral osteotomy can be applied, which (over)correct the leg axis, relieving the affected compartment.[26,27]

A joint-preserving technique that can be used in uni- and bilateral OA is knee joint distraction (KJD). In joint distraction, the 2 bony ends of a joint are temporarily (6–9 weeks) placed at a certain distance (generally 5 mm), using an external fixation frame.[28] Following successful application of ankle distraction for ankle OA, KJD has been applied in several clinical trials and even in regular care conditions in a limited number of Dutch hospitals, focusing not only on symptom relieve but on cartilage regeneration as well. Although the exact working mechanism of the treatment is not yet clear, more and more details of the underlying processes are being revealed.

Aim and outline thesis

Many previous PhD theses have laid the foundation and brought KJD to where it is at present, from dissertations by Van Valburg in 1997, Marijnissen in 2001, and Intema in 2010 on joint distraction, to those by Wiegant in 2015, Van der Woude in 2016, and Besselink in 2018 specifically on KJD.[29–34] Most of the work in this thesis builds on that foundation, aiming to take the next steps and moving forward with KJD, in 2 directions.

Part I focuses on clinical outcome and patient experience after KJD treatment. In **chapter 2**, an overview of the current literature reporting on the benefit of KJD is given in a systemic manner. **Chapter 3** describes on the first long-term results and clinical success of KJD treatment in an open prospective study. In **chapter 4**, KJD is compared with 2 alternative treatments, HTO and TKA, 2 years after treatment in 2 RCTs. Subsequently, return to sport and work 5 years after treatment is compared between KJD and HTO in **chapter 5**. As successful treatment in these clinical trials led to KJD being applied in regular care, in **chapter 6** clinical outcome in regular care is evaluated and compared with data obtained from clinical trials. Since all patients thus far were treated with a device not specifically intended for KJD, a dedicated device was developed, and its user-friendliness in clinical practice was evaluated in **chapter 7**. The use of cadexomer iodine ointment during KJD is reported on in **chapter 8**, to further improve user-friendliness and patient experience. In **chapter 9**, the 1-year follow-up results of the dedicated device are evaluated in an interim analysis from a currently ongoing prospective study.

Part II focuses on processes and potential working mechanisms occurring inside the joint as a result of KJD treatment. **Chapter 10** provides an overall picture of KJD, from clinical evidence to molecular mechanisms. Before specifically discussing the different joint processes, the

different imaging techniques used are evaluated, reporting on the performance of the radiograph analysis technique KIDA for severe OA in **chapter 11**, and comparing the characteristics of radiographs, MRI and CT in **chapter 12**. Cartilage thickness changes are evaluated with MRI, and they are reported over the long-term after KJD treatment in **chapter 13**, and are compared between KJD and HTO 2 years after treatment in **chapter 14**. Further, cartilage quality represented by collagen structure after both treatments is evaluated using T2-mapping MRI in **chapter 15**. In **chapter 16**, synovial fluid marker changes during and after KJD and their association with clinical outcome are described. Bone changes are evaluated as well, as **chapter 17** reports on osteophyte formation after KJD and HTO treatment. Furthermore, subchondral bone changes after KJD treatment are evaluated with CT, as described in **chapter 18**. Finally, the results of these studies are summarized and discussed in an integrated way within a general perspective in **chapter 19,** the last chapter of this thesis.

References

1. Moore KL, Dalley AF, Agur AMR. Clinically oriented anatomy. 8th ed. Philadelphia: Wolters Kluwer; 2018. p. 138.
2. Marrella A, Lee TY, Lee DH, *et al*. Engineering vascularized and innervated bone biomaterials for improved skeletal tissue regeneration. Materials Today. 2018 May;21(4):362–76.
3. Dimitriou R, Jones E, McGonagle D, *et al*. Bone regeneration: Current concepts and future directions. BMC Medicine. 2011 May 31;9(1):66.
4. McBride SH, Silva MJ. Adaptive and injury response of bone to mechanical loading. Bonekey Osteovision. 2012 Oct 10;1:192.
5. Funck-Brentano T, Cohen-Solal M. Crosstalk between cartilage and bone: When bone cytokines matter. Cytokine and Growth Factor Reviews. 2011 Apr;22(2):91–7.
6. Burr DB. Anatomy and physiology of the mineralized tissues: Role in the pathogenesis of osteoarthrosis. Osteoarthritis and Cartilage. 2004 Jan 1;12(suppl.):20–30.
7. Sophia Fox AJ, Bedi A, Rodeo SA. The basic science of articular cartilage: Structure, composition, and function. Sports Health. 2009 Nov;1(6):461–8.
8. Huber M, Trattnig S, Lintner F. Anatomy, biochemistry, and physiology of articular cartilage. Investigative Radiology. 2000;35(10):573–80.
9. Responte DJ, Natoli RM, Athanasiou KA. Collagens of articular cartilage: Structure, function, and importance in tissue engineering. Critical Reviews in Biomedical Engineering. 2007;35(5):363–411.
10. Redondo ML, Christian DR, Yanke AB. The role of synovium and synovial fluid in joint hemostasis. In: Joint Preservation of the Knee: A Clinical Casebook. Springer International Publishing; 2019. p. 57–67.
11. D. Smith M. The normal synovium. The Open Rheumatology Journal. 2012 Jan 16;5(1):100–6.
12. James SL, Abate D, Abate KH, *et al*. Global, regional, and national incidence, prevalence, and years lived with disability for 354 diseases and injuries for 195 countries and territories, 1990–2017: A systematic analysis for the global burden of disease study 2017. The Lancet. 2018 Nov 10;392(10159):1789–858.
13. Bijlsma JWJ, Knahr K. Strategies for the prevention and management of osteoarthritis of the hip and knee. Best Practice and Research: Clinical Rheumatology. 2007 Feb 1;21(1):59–76.
14. Hunter DJ, Bierma-Zeinstra S. Osteoarthritis. The Lancet. 2019 Apr 27;393(10182):1745–59.
15. Neogi T. Clinical significance of bone changes in osteoarthritis. Therapeutic Advances in Musculoskeletal Disease. 2012;4(4):259–67.
16. Poole AR, Kobayashi M, Yasuda T, *et al*. Type II collagen degradation and its regulation in articular cartilage in osteoarthritis. Annals of the Rheumatic Diseases. 2002 Nov 1;61(suppl. 2):ii78–81.
17. Mathiessen A, Conaghan PG. Synovitis in osteoarthritis: Current understanding with therapeutic implications. Arthritis Research and Therapy. 2017 Feb 2;19(1):1–9.
18. Man GS, Mologhianu G. Osteoarthritis pathogenesis – a complex process that involves the entire joint. Journal of medicine and life. 2014;7(1):37–41.
19. van Spil WE, Bierma-Zeinstra SMA, Deveza LA, *et al*. A consensus-based framework for conducting and reporting osteoarthritis phenotype research. Arthritis Research and Therapy. 2020 Mar 20;22(1):54.
20. Hunter DJ, McDougall JJ, Keefe FJ. The symptoms of osteoarthritis and the genesis of pain. Rheumatic Disease Clinics of North America. 2008 Aug;34(3):623–43.
21. Kellgren JH, Lawrence JS. Radiological assessment of osteo-arthrosis. Annals of the Rheumatic Diseases. 1957 Dec 1;16(4):494–502.
22. Hunter DJ, Guermazi A. Imaging techniques in osteoarthritis. PM&R. 2012 May;4(5 suppl.):S68–74.

23. Crawford DC, Miller LE, Block JE. Conservative management of symptomatic knee osteoarthritis: A flawed strategy? Orthopedic Reviews. 2013 Feb 22;5(1):2.
24. Gunaratne R, Pratt DN, Banda J, *et al*. Patient dissatisfaction following total knee arthroplasty: A systematic review of the literature. Journal of Arthroplasty. 2017 Dec;32(12):3854–60.
25. Bayliss LE, Culliford D, Monk AP, *et al*. The effect of patient age at intervention on risk of implant revision after total replacement of the hip or knee: a population-based cohort study. The Lancet. 2017 Apr 8;389(10077):1424–30.
26. Cao Z, Mai X, Wang J, *et al*. Unicompartmental knee arthroplasty *vs* high tibial osteotomy for knee osteoarthritis: A systematic review and meta-analysis. Journal of Arthroplasty. 2018 Mar;33(3):952–9.
27. Wylie JD, Jones DL, Hartley MK, *et al*. Distal femoral osteotomy for the valgus knee: medial closing wedge versus lateral opening wedge: A systematic review. Arthroscopy. 2016 Oct;32(10):2141–7.
28. Lafeber FP, Intema F, van Roermund PM, *et al*. Unloading joints to treat osteoarthritis, including joint distraction. Current Opinion in Rheumatology. 2006 Sep;18(5):519–25.
29. van Valburg AA. Ilizarov joint distraction in treatment of osteoarthritis. Utrecht University; 1997.
30. Marijnissen ACA. Osteoarthritis and joint distraction: Models, mechanisms and long-term effects. Utrecht University; 2001.
31. Intema F. Loading and unloading in the development and treatment of osteoarthritis. Utrecht University; 2010.
32. Wiegant K. Knee joint distraction: Intrinsic cartilage repair and sustained clinical benefit. Utrecht University; 2015.
33. van der Woude JAD. Unloading the osteoarthritic knee: Osteotomy and joint distraction. Utrecht University; 2016.
34. Besselink NJ. Imaging tissue characteristics in osteoarthritis and rheumatoid arthritis. Utrecht University; 2018.

PART I

Clinical outcome and patient experience

CHAPTER 2

Knee joint distraction as treatment for osteoarthritis results in clinical and structural benefit

A systematic review and meta-analysis of the limited number of studies and patients available

M.P. Jansen
T.A.E.J. Boymans
R.J.H. Custers
R.C.I. van Geenen
R.J. van Heerwaarden
M.R. Huizinga
J.M. Nellensteijn
R. Sollie
S. Spruijt
S.C. Mastbergen

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Abstract

Background: Knee joint distraction (KJD) is a joint-preserving osteoarthritis treatment that may postpone a total knee arthroplasty (TKA) in younger patients. This systematic review and meta-analysis evaluates short- and long-term clinical benefit and tissue structure changes after KJD.

Methods: MEDLINE, EMBASE and Web of Science were searched for eligible clinical studies evaluating at least 1 of the primary parameters: WOMAC, VAS pain, KOOS, EQ-5D, radiographic joint space width or MRI cartilage thickness after KJD. Random effects models were applied on all outcome parameters and outcomes were compared with control groups found in the included studies.

Results: Eleven articles reporting on 7 different KJD cohorts with in total 127 patients and 5 control groups with multiple follow-up moments were included, of which 2 were randomized controlled trials. Significant improvements in all primary parameters were found and benefit lasted up to at least 9 years. Overall, outcomes were comparable with control groups, including high tibial osteotomy, although TKA showed better clinical response.

Conclusions: Current, still limited, evidence shows KJD causes clear benefit in clinical and structural parameters, both short- and long-term. Longer follow-up with more patients is necessary, to validate outcome and to potentially improve patient selection for this intensive treatment. Thus far, for younger knee OA patients, KJD may be an option to consider.

Introduction

Knee osteoarthritis (OA) is a high incident joint disease with total knee arthroplasty (TKA) as final surgical option.[1] While TKA is considered cost-effective, reduces pain and improves function, the prosthesis' limited lifespan brings a greater risk of a future revision when TKA is performed in younger (<65 years) patients.[2] As such, joint-preserving treatment is desirable for younger knee OA patients, to postpone TKA and reduce the chance of costly and less successful revision surgery.[3] When OA is limited to 1 side of the joint because of varus or valgus deviation, high tibial osteotomy (HTO) or distal femur osteotomy (DFO) is an option. These treatments have been applied in regular care for a long time and have been evaluated extensively.[4–7] Unicompartmental knee arthroplasty is an option in unilateral OA as well. A newer joint-preserving treatment for knee OA is knee joint distraction (KJD). Distraction is a surgical treatment where 2 bony ends of a joint are temporarily separated by an external frame, fixed to the bones with bone pins.[8] It has shown progressive and sustained pain reduction, function improvement, and an increased radiographic joint space width (JSW) in patients with ankle OA.[9–11] Following these promising results, multiple studies have investigated distraction of the knee joint. Successful KJD treatment could improve patients' benefit, with reduced health costs for hospitals and society.[3] KJD might fill a gap in the treatment options for young patients with severe knee OA.[12] Before further implementation in regular care is justified based on the limited number of small studies, a meta-analysis is of value to give a more comprehensive overview of the current evidence for KJD as a possible treatment option. The goal of this systematic review and meta-analysis is to evaluate short- and long-term clinical benefit and tissue structure changes after KJD treatment for knee OA.

Methods

The review protocol is based on a protocol of Goh *et al.* for performing a systematic review about knee joint distraction, registered in PROSPERO (CRD42018087032). The PRISMA guidelines for systematic reviews and meta-analyses were followed.

Sources and search terms

On July 8 2019, MEDLINE, EMBASE and Web of Science were searched for relevant articles. Search terms were (osteoarthritis OR arthritis OR cartilage OR osteochondral OR degenerative joint disease) AND distraction AND (knee OR tibiofemoral OR tibiofibular), and were applied on title and abstract and, in Web of Science, Keywords+.

Study selection

All clinical studies where surgical KJD was applied for treatment of knee OA were eligible. One author (MPJ) selected all titles and abstracts that met in- and exclusion criteria.

Inclusion criteria were: 1) the population consisted of knee OA patients; 2) treatment with KJD; 3) reporting the change of at least 1 of WOMAC, VAS pain, KOOS, EQ-5D, radiographic JSW or MRI cartilage thickness between before and after treatment; 4) published or accepted for publication in a peer-reviewed journal or conference abstract of the past 2 years; 5) English or Dutch language.

Exclusion criteria were: 1) animal studies; 2) experimental studies; 3) cadaver studies; 4) reviews; 5) editorials; 6) case reports; 7) letters.

Analysis

A risk of bias analysis, including selective reporting bias, was performed by 1 author (MPJ) in agreement with a second author (SCM). Possible publication bias was assessed as well.

Primary outcome measures were the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC, scale 0–100, 100=best), Visual Analogue Scale of pain (VAS pain, scale 0–100, 0=best), Knee injury and Osteoarthritis Outcome Score (KOOS, scale 0–100, 100=best), EuroQol 5D (EQ-5D, scale 0–1, 1=best), radiographic joint space width (JSW; mm), and MRI cartilage thickness (mm). Other clinical and cartilage-related outcomes found in included articles were analyzed as well. One author (MPJ) extracted data from the articles; investigators were not contacted for confirmation.

Heterogeneity was determined with the I^2-test, where I^2>75% indicates considerable heterogeneity and no meta-analysis was performed for that parameter. Random effects models were used for all outcome measures. For continuous data the mean difference (MD) and 95% confidence interval (95%CI) were calculated with the inverse variance method. For dichotomous data the risk difference and 95%CI were calculated with the Cochran-Mantal-Haenszel method. No sensitivity analyses were performed. All patient groups that were used as a comparator for KJD in included studies are presented as control groups.

Data-analysis was performed according to the Cochrane Handbook for Systematic Reviews of Interventions, using Review Manager 5.3 (The Nordic Cochrane Centre, The Cochrane Collaboration, 2014).

Results

Study selection

The selection process is shown in Figure 1. After duplicate exclusion from the initially found 495 articles, 239 titles and abstracts were screened and, after applying in- and exclusion criteria, 14 complete articles were screened. Of these, 3 were excluded, since they reported on a subgroup from other included articles without reporting extra information on primary outcomes, leaving 11 articles included for analysis.[12,13,22,14–21]

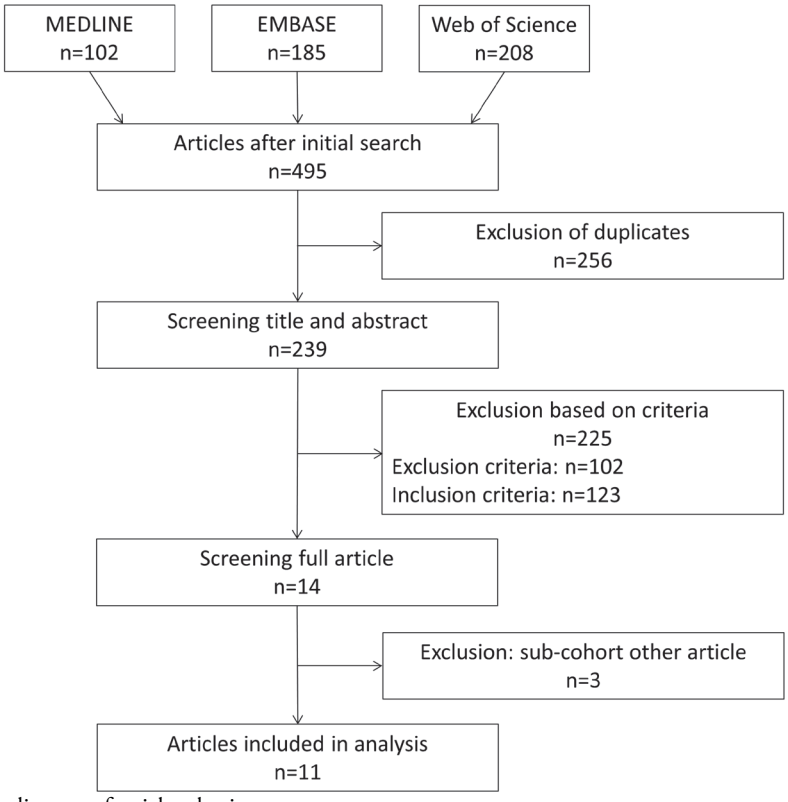


Figure 1: Flow diagram of article selection.

As multiple articles reported on different follow-up moments in the same patient cohorts, the overview of selected studies is separated per cohort of KJD-treated patients and control groups (Table 1).[23]

A total of 7 patient cohorts were treated with KJD, of which 2 in combination with another treatment: 1 cohort of 6 patients was treated with KJD and microfracture (Deie 2007) and 1 cohort of 19 patients treated with KJD, microfracture and debridement (Aly 2011) that also had a control group of 42 patients treated with microfracture and debridement alone. In an open prospective study 20 patients were treated with KJD, without control group, and follow-up was reported after 1 (Intema 2011), 2 (Wiegant 2013), 5 (Van der Woude 2017a),

and 9 (Jansen 2018) years. At 5 years follow-up, this cohort was compared on structural outcome measures with 138 untreated patients from the Osteoarthritis Initiative (OAI), who were matched on patient characteristics with the KJD patients. In a randomized controlled trial (RCT) 20 KJD patients were compared with 40 TKA patients after 1 (Van der Woude 2017b) and 2 (Jansen 2019a) years. In a different RCT 22 KJD patients were compared with 46 HTO patients after 1 (van der Woude 2017c) and 2 (Jansen 2019a) years. In regular care 40 patients were treated with KJD and evaluated after 1 year, without control group, reported in a conference abstract (Jansen 2019b). Lastly, a sub-group of 16 KJD patients and 17 HTO patients from the previously mentioned RCTs were evaluated and compared on an additional outcome measure (MRI cartilage thickness) after 2 years in a conference abstract (Jansen 2019c).

Table 1: Included studies

Study	Level of evidence[23]	Treatment	# patients	Follow-up in years	Reference(s)	Outcome measures
Knee joint distraction						
Case series: Distraction and microfracture	IV	KJD and microfracture	6	Average 3 (1.2–4.3)	Deie *et al.* 2007[13]	VAS pain, JSW
Case series: Distraction, microfracture and debridement	III-2	KJD, microfracture and debridement	19	Average 5 (4.8–6.8)	Aly *et al.* 2011[14]	JSW
Open prospective study	IV	KJD	20	1, 2, 5, 9	Intema *et al.* 2011[15]; Wiegant *et al.* 2013[16]; Van der Woude *et al.* 2017a[17]; Jansen *et al.* 2018[18]	WOMAC, VAS pain, JSW, MRI
RCT: KJD *vs* TKA	II	KJD	20	1, 2	Van der Woude *et al.* 2017b[19]; Jansen *et al.* 2019a[20]	WOMAC, VAS pain, KOOS, EQ-5D, JSW
RCT: KJD *vs* HTO	II	KJD	22	1, 2	Van der Woude *et al.* 2017c[21]; Jansen *et al.* 2019a[20]	WOMAC, VAS pain, KOOS, EQ-5D, JSW
Regular care (abstract)	III-2	KJD	40	1	Jansen *et al.* 2019b[12]	WOMAC
RCT MRI sub-cohort (abstract)	III-1	KJD	16	2	Jansen *et al.* 2019c[22]	MRI

Table 1: Included studies *(continued)*

Study	Level of evidence[23]	Treatment	# patients	Follow-up in years	Reference(s)	Outcome measures
Control groups						
Case series: microfracture and debridement	III-2	Microfracture and debridement	42	Average 4 (3.6–6)	Aly *et al.* 2011[14]	JSW
Osteoarthritis Initiative (OAI)	III-1	None	138	5	Van der Woude *et al.* 2017a[17]	JSW, MRI
RCT: KJD *vs* TKA	II	TKA	40	1, 2	Van der Woude *et al.* 2017b[19]; Jansen *et al.* 2019a[20]	WOMAC, VAS pain, KOOS, EQ-5D, JSW
RCT: KJD *vs* HTO	II	HTO	46	1, 2	Van der Woude *et al.* 2017c[21]; Jansen *et al.* 2019a[20]	WOMAC, VAS pain, KOOS, EQ-5D, JSW
RCT MRI sub-cohort (abstract)	III-1	HTO	17	2	Jansen *et al.* 2019c[22]	MRI

EQ-5D: EuroQol 5D; HTO: high tibial osteotomy JSW: joint space width; KJD: knee joint distraction; KOOS: Knee injury and Osteoarthritis Outcome Score; RCT: randomized controlled trial; TKA: total knee arthroplasty; VAS: Visual Analogue Scale; WOMAC: Western Ontario and McMaster Universities Osteoarthritis Index.

The risk of bias for the included articles is shown in Figure 2. As blinding of patients and personnel was not possible in any study and blinding of outcome measures only for structural parameters, none of the included articles had a completely low risk of bias. Only the RCTs (Jansen 2019a, Van der Woude 2017b/c) had a low selection bias and only Jansen 2018 had a high bias for incomplete outcome data because of loss of patients during the long follow-up time. Aly 2011 had a high reporting bias because no precision/uncertainty of outcome measures is reported. Aly 2011 and Deie 2007 had an unclear risk of other bias because no clear study design was used. All other studies have an unclear risk of other bias because they all come from the same research group. Lastly, Jansen 2019b and Jansen 2019c had a lot of unclear bias since they are conference abstracts and as such did not report all information required to judge. No indication for publication bias was found.

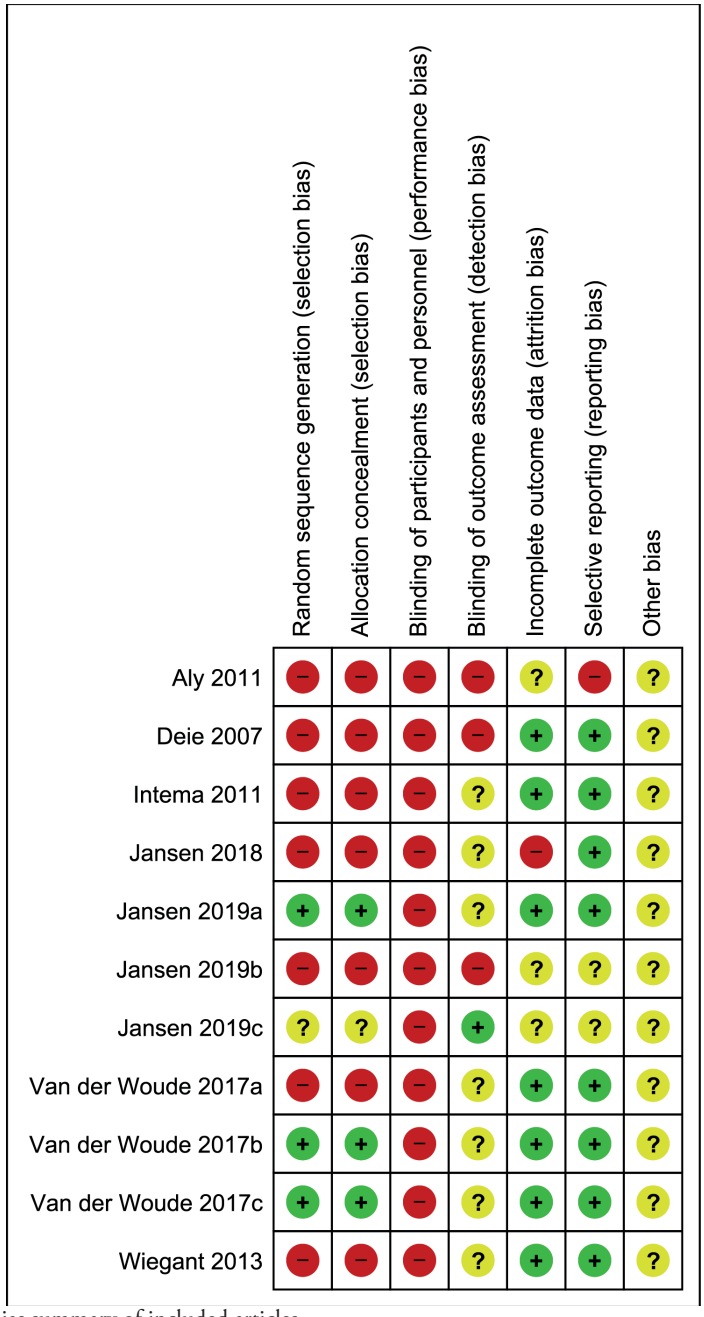


Figure 2: Risk of bias summary of included articles.

The pre-treatment characteristics of the 7 included KJD cohorts are summarized in Table 2, showing only minor differences between studies.

Table 2: Patient characteristics before treatment for patients treated with knee joint distraction in included studies

1st author	Age (year)	Female:male ratio	BMI (kg/m²)	Kellgren-Lawrence grade 1:2:3:4	Distraction duration (weeks)
Deie 2011[13]	51.7 (SD 7.8)	4:2	26.9 (SD 5.0)	0:0:1:5	9.3 (SD 2.1)
Aly 2011[14]	Range 39–65	15:4			4
Van der Woude 2017a[17]	48.5 (SEM 1.3)	11:9	29.6 (SEM 0.8)	3:4:11:2	8
Van der Woude 2017b[19]	54.9 (SEM 1.8)	11:9	27.4 (SEM 0.9)	0:1:8:11	6
Van der Woude 2017c[21]	51.2 (SEM 1.1)	6:16	27.5 (SEM 0.7)	6:4:11:1	6.1 (range 5.6–7.1)
Jansen 2019b[12]	54.3 (SD 6.8)	17:23	27.7 (SD 3.9)	0:7:23:10	6.5 (SD 0.6)
Jansen 2019c[22]				Median 3 (IQR 1)	

Van der Woude 2017a is the open prospective study (also reported on by Intema 2011, Wiegant 2013, Jansen 2018); Van der Woude 2017b is the randomized controlled trial knee joint distraction *versus* total knee arthroplasty (also reported on by Jansen 2019a); Van der Woude 2017c is the randomized controlled trial knee joint distraction *versus* high tibial osteotomy (also reported on by Jansen 2019a). BMI: body mass index; IQR: interquartile range; SD: standard deviation; SEM: standard error of the mean.

Outcome after knee joint distraction

Primary outcome measures

The results of the WOMAC, EQ-5D, and minimum JSW after KJD are summarized in Figures 3–5 respectively. The outcomes for the VAS pain, KOOS, mean JSW, and MRI cartilage thickness can be found in the supplementary data (Figures S1-S4). Patient cohorts treated with a combination of KJD and another therapy are not included in the figures. Neither are results from conference abstracts, as they did not report exact numbers.

The WOMAC and VAS pain are evaluated in 3 cohorts after 1 year (patients n=62) and 2 years (n=59) and in 1 cohort after 5 years (n=20) and 9 years (n=8). The total WOMAC (Figure 3), VAS pain (Figure S1), and all WOMAC subscales were significantly increased compared to pre-treatment at all time points, with an MD varying between 21.2 (5 years, p=0.001) and 29.9 (9 years, p<0.001) for the WOMAC and between 27.6 (5 years, p<0.001) and 46.6 (9 years; p<0.001) for the VAS.

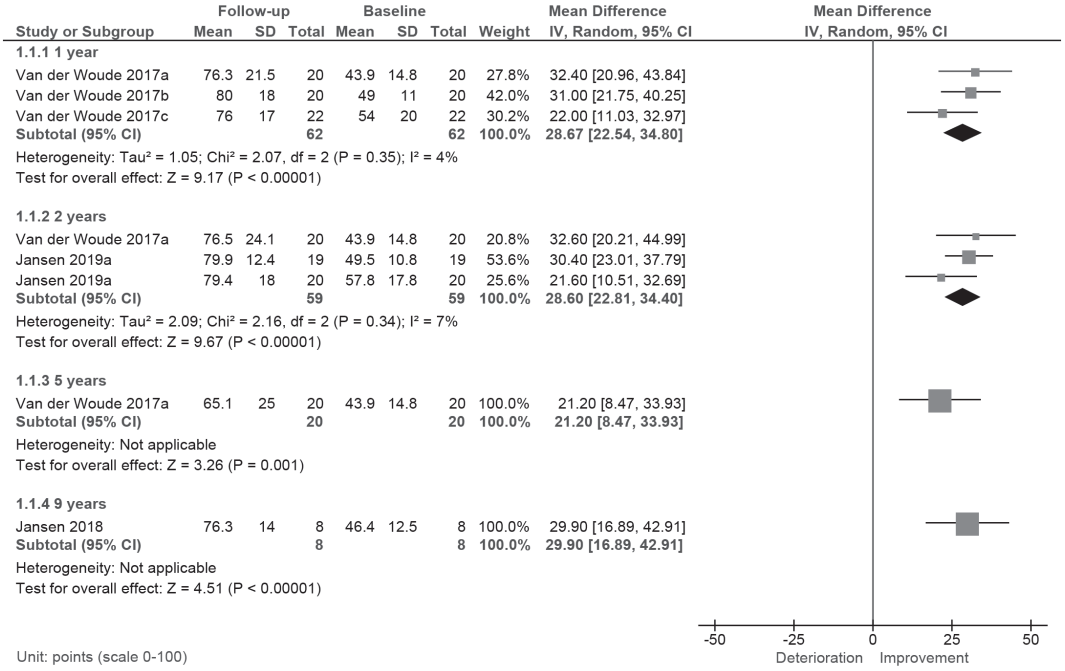


Figure 3: Change in total Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) score 1, 2, 5 and 9 years after treatment with knee joint distraction. References can be used multiple times because of division in patient cohort and years of follow-up. CI: confidence interval; SD: standard deviation.

The KOOS (Figure S2) and EQ-5D (Figure 4) were reported in 2 cohorts after 1 (n=42) and 2 (n=39) years, at both moments showing significant increases compared to pre-treatment, as did all KOOS subscales. The KOOS had an MD of 23.2 (p<0.001) and 24.9 (p<0.001) and EQ-5D of 0.15 (p<0.001) and 0.14 (p<0.001) after 1 and 2 years, respectively.

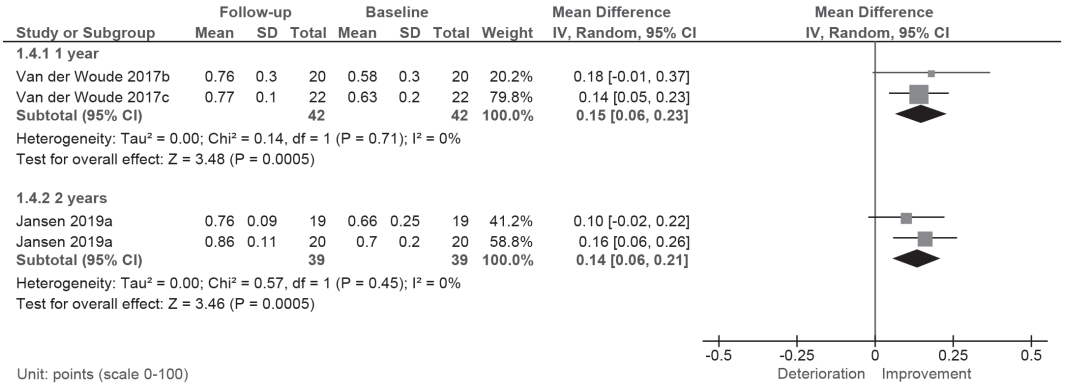


Figure 4: Change in total EuroQol 5D (EQ-5D) score 1 and 2 years after treatment with knee joint distraction. References can be used multiple times because of division in patient cohort and years of follow-up. CI: confidence interval; SD: standard deviation.

The minimum (Figure 5) and mean (Figure S3) JSW of the most affected compartment (MAC) are reported in 3 cohorts, after 1 (n=59), 2 (n=59), 5 (n=20) and 7 (n=8) years. Both JSW measures were statistically significantly increased after 1 and 2 years (MD between 0.68–0.87; all p<0.01), but after 5 and 7 years the JSW increase was no longer statistically significant (MD between 0.30 – 1.00; all p>0.2).

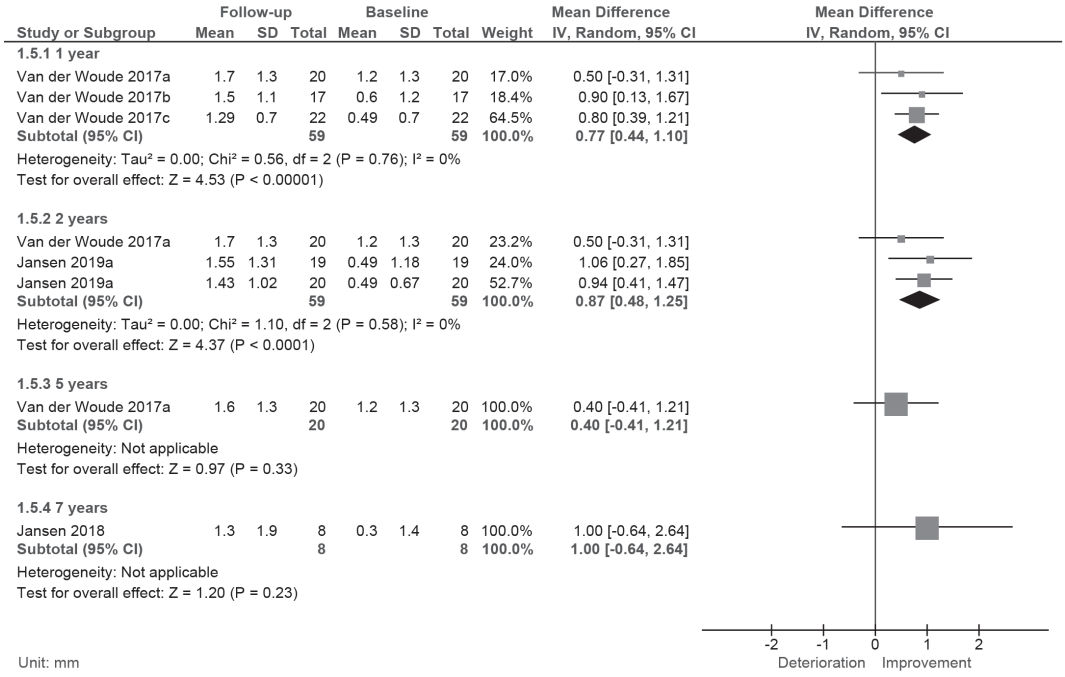


Figure 5: Change in minimum joint space width (JSW) 1, 2, 5 and 7 years after treatment with knee joint distraction. References can be used multiple times because of division in patient cohort and years of follow-up. CI: confidence interval; SD: standard deviation.

The MRI cartilage thickness is reported in 1 cohort after 1, 2 and 5 years (all n=20; Figure S4). After 1 (MD=0.70; p<0.001) and 2 years (MD=0.50; p=0.002) there was a statistically significant increase compared to pre-treatment, but after 5 years the increase was no longer significant (MD=0.20; p=0.21).

For patients treated in regular care (n=41) an increase in total WOMAC and subscales is shown, all with >20 points and p<0.001. The MRI subgroup of RCT patients (n=16) show a cartilage thickness increase of around 0.25mm with p=0.009.

Patients treated with KJD and microfracture (n=6) showed a significant increase in VAS pain (MD=56.7; 95%CI 26.3–87.1; p<0.001) and minimum JSW (MD=1.09; 95%CI 0.19–1.99; p=0.02) after an average of 3 years. Patients treated with KJD, microfracture and debridement (n=19) showed a significant increase in mean JSW from 2.5 to 4.3 mm with p<0.001 after an average of 5 years.

Other outcome measures

Detailed results of additional outcome measures after KJD can be found in Table 3.

In 2 cohorts after 1 (n=42) and 2 (n=39) years, the ICOAP (Intermittent and Constant Osteoarthritis Pain; scale 0–100, 0=best) and SF-36 (Short-Form 36; scale 0–100, 100=best) are reported. The ICOAP on 1 and 2 years and its subscales were significantly increased compared to pre-treatment, as was the SF-36 PCS (physical component scale). The MCS (mental component scale) was not different from pre-treatment values at 1 and 2 years.

Knee flexion (degrees) was measured before and 1 year after KJD in 3 cohorts (n=62) and 2 years after KJD in 2 cohorts (n=40). After both 1 and 2 years there was no significant difference from baseline.

The percentage subchondral bone without cartilage (denuded bone) is reported in 1 cohort (n=20) and was significantly lower (better) than baseline at 1 and 2 years but not at 5 years. The MRI RCT sub-cohort (n=16) graphically shows a significant decrease of this percentage of around 5.

After KJD and microfracture (n=6) a significant increase in knee flexion and the Japanese Orthopaedic Association (JOA) score was reported. After KJD, microfracture and debridement (n=19) a significant increase in active knee flexion, pain, walking capacity, stair climbing and tibiofemoral angle was reported, but no difference in passive flexion.

Table 3: Changes in non-primary outcome parameters after knee joint distraction

Knee joint distraction									
	Δ1 year			**Δ2 years**			**Δ5 years**		
	# cohorts (patients)	**Change**	***P*-value**	**# cohorts (patients)**	**Change**	***P*-value**	**# cohorts (patients)**	**Change**	***P*-value**
ICOAP	2 (42)	-26.7 (-36.4 to -17.0)	**<0.001**	2 (39)	-29.4 (-36.6 to -22.2)	**<0.001**			
SF-36 PCS	2 (42)	7.8 (1.9 to 13.7)	**0.009**	2 (39)	6.1 (2.9 to 9.4)	**<0.001**			
SF-36 MCS	2 (42)	-1.5 (-5.0 to 2.0)	0.41	2 (39)	0.5 (-2.8 to 3.8)	0.76			
Knee flexion	3 (62)	2.4 (-1.0 to 5.7)	0.16	2 (40)	1.4 (-2.0 to 4.9)	0.42			
MRI % denuded bone	1 (20)	-17.3 (-26.5 to -8.1)	**<0.001**	1 (20)	-13.9 (-23.3 to -4.5)	**0.004**	1 (20)	-5.7 (-15.6 to -5.2)	0.30
				1 (16)	-5	**0.010**			

Table 3: Changes in non-primary outcome parameters after knee joint distraction *(continued)*

Knee joint distraction + microfracture			
	Δ~3 years		
	# cohorts (patients)	**Change**	***P*-value**
Knee flexion	1 (6)	14.8 (2.7 to 26.9)	**0.04**
JOA score	1 (6)	28.7 (23.8 to 33.5)	**<0.001**
Knee joint distraction, microfracture + debridement			
	Δ~5 years		
	# cohorts (patients)	**Change**	***P*-value**
Pain (0–4)	1 (19)	Median 2 (IQR 1) to 0 (1)	**<0.004**
Walking capacity	1 (19)	Range 10–15 to 32–51	**<0.001**
Difficulty stair climbing (y/n)	1 (19)	100% to 36% yes	**<0.002**
Knee flexion	1 (19)	Range 75–95 to 110–135 degrees	**<0.029**
Passive flexion	1 (19)	Range 85–120 to 150–170 degrees	<0.193
Tibiofem-oral angle	1 (19)	Range 173–189 to 171–174 degrees	**<0.001**

ICOAP: Intermittent and Constant Osteoarthritis Pain; IQR: interquartile range; JOA: Japanese Orthopaedic Association; MCS: mental component scale; PCS: physical component scale; SF-36: Short-Form 36.

Complications

Complications were reported in 5 studies with 87 patients, with 57 patients developing 1 or more pin tract skin infections, resulting in a risk of pin tract infections of 63% (95%CI 45–81). Only 3 studies (n=62) reported treatment of complications. The majority of infections could be treated with oral antibiotics, resulting in a 57% (95%CI 33–82) risk of an infection requiring oral antibiotics and a 10% (95%CI 1–18) risk of an infection (including osteomyelitis, n=1) requiring intravenous antibiotics. Also, 1 patient experienced postoperative foot drop, 3 patients a pulmonary embolism and 1 patient deep vein thrombosis, all successfully treated. One patient required knee manipulation under anesthesia 17 days after frame removal, 1 patient had a broken bone pin and 1 patient experienced distraction frame failure, requiring re-fixation.

Comparison with control groups

Primary outcome measures

The comparisons with control groups for the VAS pain, KOOS, mean JSW, and MRI cartilage thickness, as well as corresponding figures, can be found in the supplementary data; results were generally similar to those for the WOMAC, EQ-5D, and minimum JSW as described below.

The WOMAC and EQ-5D are compared between KJD and TKA and KJD and HTO in 2 different RCTs, 1 and 2 years after treatment. The change in total WOMAC (Figure S5) was better for the control groups, with an MD varying between -12.0 (compared to TKA at 2 years) and -7.6 (HTO, 2 years), which was statistically significant for the 2-year difference between KJD and TKA (p=0.011; rest p>0.10). The EQ-5D change (Figure S6) was somewhat better for TKA than KJD after 1 (MD=-0.17; p=0.047) and 2 (MD=-0.17; p=0.051) years, with no significant difference between KJD and HTO at 1 (MD=-0.01; p=0.898) and 2 (MD=0.05; p=0.559) years.

The change in minimum (Figure S7) JSW of the MAC is compared between KJD and HTO after 1 and 2 years, showing a significantly better improvement for KJD after 1 year (MD=0.40; p=0.041) but no statistical difference after 2 years (MD=0.32; p=0.230). Compared to the OAI, the minimum JSW showed significantly better results 5 years after KJD (MD=1.10; p<0.001).

Other outcome measures

Other outcome measures compared between KJD and control groups were the SF-36, ICOAP, active and passive knee flexion, pain, walking capacity, stair climbing, tibiofemoral angle and percentage denuded bone. Generally, there were no statistically significant differences in these measures between groups. Parameters that were statistically significantly different can be found in the supplementary data.

Complications

Only in the 2 RCTs the complications of the control groups, patients treated with TKA and with HTO, were described. Of 36 TKA patients, 5 required knee manipulation under anesthesia because of postoperative stiffness and 1 had a myocardial infarct 6 days post-surgery. Of 45 HTO patients, 2 experienced wound infection, 1 treated with oral and 1 with intravenous antibiotics. Furthermore, 1 patient received intravenous antibiotics for erysipelas and 1 patient had a partial medial meniscectomy <6 months after HTO.

Discussion

Overall, this review shows that KJD induces cartilaginous tissue regeneration and clinical improvement on short and intermediate-long term. The effect sizes are large, so the small patient number is sufficient to demonstrate effects. The various clinical outcome measures showed similar results, as did the structural outcomes. The total number of patients is still limited, especially for long-term data, available in only 1 patient cohort. It is shown that prolonged treatment effect results in 75% of patients after 5 years and half of patients after 9 years still not undergoing TKA.[18] This implicates a clear reduction in survival over the long term. Longer follow-up is necessary to evaluate whether successfully postponing this first TKA over a sufficient period of time can indeed prevent a revision TKA as intended and reduce healthcare costs.[3]

KJD provides cartilaginous tissue repair demonstrated by radiographs and MRI, results that are supported by biochemical marker studies that showed a net increase in systemic collagen type II markers and by large animal *in vivo* studies.[20,24] First-year post-treatment structural benefit, male sex and more severe OA before treatment seem predictive for long-term benefit (survival).[18,25] Also for ankle distraction male sex favored clinical outcome.[26] In contrast, young males perform less well after TKA compared to older females.[2] Young active males with severe damage might provide a more specific indication for KJD, although future cohorts and registries should confirm this.

Despite promising outcomes, KJD should not be perceived as an easy treatment for patients. The knee is immobilized for 6 weeks, and there is a high risk of pin tract skin infections. It is of importance that methods are found to decrease this risk as these can result in osteomyelitis, lead to significant use of oral antibiotics, and have a great impact on patients burden. However, these infections do not seem to cause problems for future TKA. Wiegant *et al.* showed that TKA years after KJD did not result in extra complications whereas clinical benefit was not different from matched TKA patients without prior KJD.[27] Future studies to reduce pin tract infection rates are needed, and preliminary results seem to make this feasible.[28] Apart from pin tract infections there were not many complications, but the few that did occur were relatively serious. While the number of complications after KJD besides pin tract infections was not that different than those in the control groups HTO and TKA, it is of importance to keep monitoring complications after KJD in larger studies and when introduced in regular care.

The included studies used different distraction periods (4–12 weeks). What effects this difference has and what period is ideal, is not known with certainty. No statistically significant difference between 6 and 8 weeks of distraction was observed, although at 6 weeks the benefit was slightly less.[29] This resulted in a 6-week distraction chosen for regular care.[12]

Despite multiple studies showing cartilage regeneration after KJD, the mechanism enabling the regenerative process is not yet clear. Systemic biomarker analysis showed that KJD causes a decrease in collagen type II degeneration marker CTXII and an increase in collagen type II synthesis marker PIIANP.[16,20] Synovial fluid biomarkers showed changes in degenerative and regenerative pathways, and cartilage quality measurements (dGEMRIC) showed no changes over 2 years post-treatment, while cartilage volume increased and untreated patients might have shown a cartilage quality decrease.[30,31] These results suggest that joint unloading by KJD stimulates intrinsic intra-articular conditions that promote cartilaginous tissue regeneration with an optimum between 1 and 2 years.

Patients treated with KJD show clearly better results than patients without KJD, while results were comparable between KJD and HTO. TKA patients often showed more clinical improvement but lost their native knee. Adding KJD to microfracture and debridement significantly improved results as well. Apart from pin tract infections, complications were not different in severity and number than those in other treatments. Knee contracture after 6-week fixation seemed no significant risk (on the contrary, flexion was regained quicker than after TKA).[19]

Our study had several limitations. First, the number of patients was limited. Although the effect sizes were generally large, a larger number of patients would allow for stronger conclusions, especially for long-term results. Also, the treatment protocol (distraction duration) differed between studies. Furthermore, only 2 studies performed patient randomization, and none of the studies had a completely low risk of bias. Also, most studies were conducted by 1 research group, although in multi-center approach. Nevertheless, there were no indications for publication bias, and patient characteristics were generally very similar between the different studies. All studies seem to have included younger patients with severe knee OA, which is the target group for KJD treatment in regular care, increasing the likelihood that results found in this review may be expected in regular care as well.

In conclusion, this review analyzed data of available KJD studies for an extensive meta-analysis with multiple outcome measures, cohorts, and follow-up periods. Despite clear effects, it remains important that more patients are studied with longer follow-up, preferably in dedicated medical centers. This may also support treatment indication and patient selection. Better understanding of the underlying mechanisms of tissue structure repair and clinical benefit due to KJD might add to the above. Irrespectively, KJD provides for an additional option in joint-preserving treatments for osteoarthritis and a viable alternative to joint replacement, especially in younger patients.

References

1. Bijlsma JW, Berenbaum F, Lafeber FP. Osteoarthritis: an update with relevance for clinical practice. The Lancet. 2011 Jun 18;377(9783):2115–26.
2. Bayliss LE, Culliford D, Monk AP, *et al*. The effect of patient age at intervention on risk of implant revision after total replacement of the hip or knee: a population-based cohort study. The Lancet. 2017 Apr 8;389(10077):1424–30.
3. van der Woude JAD, Nair SC, Custers RJH, *et al*. Knee joint distraction compared to total knee arthroplasty for treatment of end stage osteoarthritis: Simulating long-term outcomes and cost-effectiveness. PLOS ONE. 2016 May 12;11(5):e0155524.
4. Cao Z, Mai X, Wang J, *et al*. Unicompartmental knee arthroplasty *vs* high tibial osteotomy for knee osteoarthritis: A systematic review and meta-analysis. Journal of Arthroplasty. 2018 Mar;33(3):952–9.
5. Lee O-S, Ahn S, Ahn JH, *et al*. Effectiveness of concurrent procedures during high tibial osteotomy for medial compartment osteoarthritis: A systematic review and meta-analysis. Archives of Orthopaedic and Trauma Surgery. 2018 Feb 15;138(2):227–36.
6. Wylie JD, Jones DL, Hartley MK, *et al*. Distal femoral osteotomy for the valgus knee: medial closing wedge versus lateral opening wedge: A systematic review. Arthroscopy. 2016 Oct 1;32(10):2141–7.
7. Brouwer RW, Huizinga MR, Duivenvoorden T, *et al*. Osteotomy for treating knee osteoarthritis. Cochrane Database of Systematic Reviews. 2014 Dec 13;2014(12).
8. Lafeber FP, Intema F, van Roermund PM, *et al*. Unloading joints to treat osteoarthritis, including joint distraction. Current Opinion in Rheumatology. 2006 Sep;18(5):519–25.
9. Bernstein M, Reidler J, Fragomen A, *et al*. Ankle distraction arthroplasty. Journal of the American Academy of Orthopaedic Surgeons. 2017 Feb;25(2):89–99.
10. Marijnissen ACA, van Roermund PM, van Melkebeek J, *et al*. Clinical benefit of joint distraction in the treatment of severe osteoarthritis of the ankle: Proof of concept in an open prospective study and in a randomized controlled study. Arthritis and Rheumatism. 2002 Nov;46(11):2893–902.
11. Ploegmakers JJW, van Roermund PM, van Melkebeek J, *et al*. Prolonged clinical benefit from joint distraction in the treatment of ankle osteoarthritis. Osteoarthritis and Cartilage. 2005 Jul;13(7):582–8.
12. Jansen M, Mastbergen SC, van Empelen MD, *et al*. Knee joint distraction as standard of care treatment for knee osteoarthritis: A comparison with clinical trial patients. Osteoarthritis and Cartilage. 2019 Apr;27(1):S515–6.
13. Deie M, Ochi M, Adachi N, *et al*. A new articulated distraction arthroplasty device for treatment of the osteoarthritic knee joint: a preliminary report. Arthroscopy. 2007;23(8):833–8.
14. Aly TA, Hafez K, Amin O. Arthrodiatasis for management of knee osteoarthritis. Orthopedics. 2011;34(8):e338–43.
15. Intema F, van Roermund PM, Marijnissen ACA, *et al*. Tissue structure modification in knee osteoarthritis by use of joint distraction: An open 1-year pilot study. Annals of the Rheumatic Diseases. 2011 Aug 1;70(8):1441–6.
16. Wiegant K, van Roermund PM, Intema F, *et al*. Sustained clinical and structural benefit after joint distraction in the treatment of severe knee osteoarthritis. Osteoarthritis and Cartilage. 2013 Nov;21(11):1660–7.
17. van der Woude JAD, Wiegant K, van Roermund PM, *et al*. Five-year follow-up of knee joint distraction: Clinical benefit and cartilaginous tissue repair in an open uncontrolled prospective study. Cartilage. 2017;8(3):263–71.
18. Jansen MP, van der Weiden GS, van Roermund PM, *et al*. Initial tissue repair predicts long-term clinical success of knee joint distraction as treatment for knee osteoarthritis. Osteoarthritis and Cartilage. 2018;26(12):1604–8.

19. van der Woude JAD, Wiegant K, van Heerwaarden RJ, *et al*. Knee joint distraction compared with total knee arthroplasty: A randomised controlled trial. Bone and Joint Journal. 2017;99-B(1):51–8.
20. Jansen MP, Besselink NJ, van Heerwaarden RJ, *et al*. Knee joint distraction compared with high tibial osteotomy and total knee arthroplasty: Two-year clinical, radiographic, and biochemical marker outcomes of two randomized controlled trials. Cartilage. 2019 Feb 13;194760351982843.
21. van der Woude JAD, Wiegant K, van Heerwaarden RJ, *et al*. Knee joint distraction compared with high tibial osteotomy: A randomized controlled trial. Knee Surgery, Sports Traumatology, Arthroscopy. 2017;25(3):876–86.
22. Jansen MP, Maschek S, van Heerwaarden RJ, *et al*. Knee joint distraction is more efficient in rebuilding cartilage thickness in the more affected compartment than high tibial osteotomy in patients with knee osteoarthritis. Osteoarthritis and Cartilage. 2019 Apr;27(1):S330–1.
23. McNair P, Lewis G. Levels of evidence in medicine. International Journal of Sports Physical Therapy. 2012 Oct;7(5):474–81.
24. Wiegant K, Intema F, Roermund PM, *et al*. Evidence of cartilage repair by joint distraction in a canine model of osteoarthritis. Arthritis and Rheumatology. 2015 Feb 28;67(2):465–74.
25. van der Woude JAD, Welsing PM, van Roermund PM, *et al*. Prediction of cartilaginous tissue repair after knee joint distraction. The Knee. 2016 Oct;23(5):792–5.
26. Marijnissen ACA, Hoekstra MCL, Pré BCD, *et al*. Patient characteristics as predictors of clinical outcome of distraction in treatment of severe ankle osteoarthritis. Journal of Orthopaedic Research. 2014 Jan;32(1):96–101.
27. Wiegant K, van Roermund PM, van Heerwaarden RJ, *et al*. Total knee prosthesis after knee joint distraction treatment. Journal of Surgery and Surgical Research. 2015 Nov 5;1(3):066–71.
28. Jansen MP, van Egmond N, Kester EC, *et al*. Iodosorbzalf ter preventie van pengatinfecties bij kniedistractie. NOV-Jaarcongres. 2020.
29. van der Woude JAD, van Heerwaarden RJ, Spruijt S, *et al*. Six weeks of continuous joint distraction appears sufficient for clinical benefit and cartilaginous tissue repair in the treatment of knee osteoarthritis. Knee. 2016 Oct 1;23(5):785–91.
30. Watt FE, Hamid B, Garriga C, *et al*. Analysis of proteins in the synovial fluid during joint distraction: unravelling mechano-sensitive pathways that drive intrinsic cartilage repair? Osteoarthritis and Cartilage. 2018 Apr;26:S17–8.
31. Besselink NJ, Vincken KL, Bartels LW, *et al*. Cartilage quality (dGEMRIC Index) following knee joint distraction or high tibial osteotomy. Cartilage. 2018;1947603518777578.

SUPPLEMENTARY DATA

Supplementary results

Comparison with control groups

Primary outcome measures

The change in VAS pain (Figure S8) was better for both TKA and HTO compared to KJD at both time points (all $p<0.02$), with the MD varying between -16.6 (HTO, 2 years) and -19.5 (TKA, 2 years). The original 2-year article (Jansen 2019a) corrects the comparisons for baseline values, which results in no statistically significant difference in 2-year VAS pain change between KJD and HTO ($p=0.120$). The 1-year comparison between KJD and HTO (Van der Woude 2017b) was also reported not to be statistically significantly different (no p-value given).

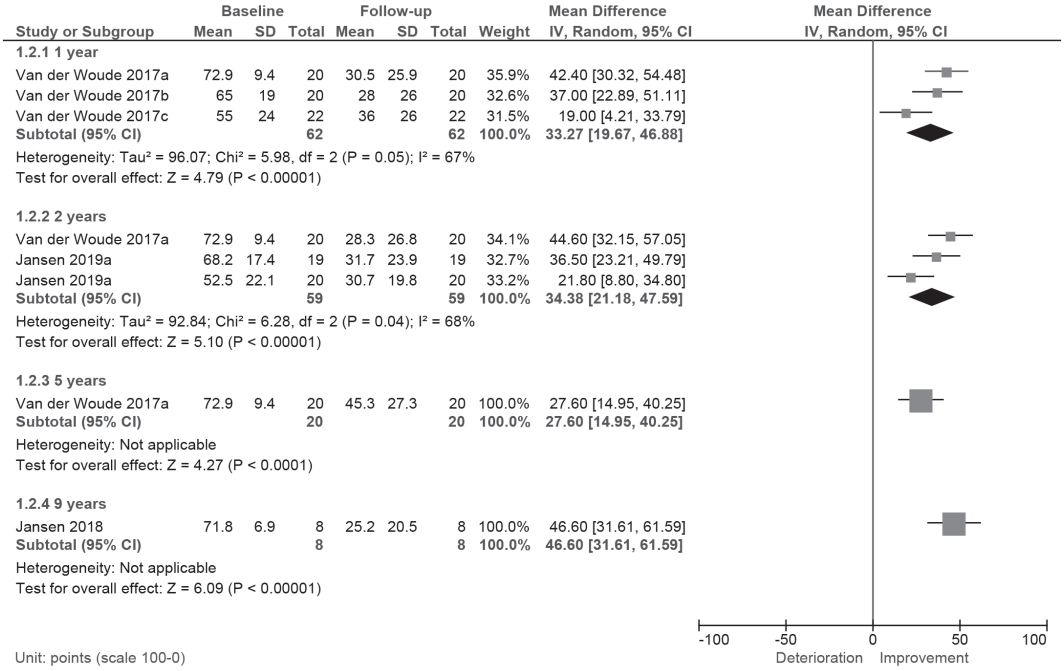
The change in total KOOS (Figure S9) after 2 years was significantly better for TKA than KJD (MD=-14.6; $p=0.001$) while there was no significant 1-year difference between TKA and KJD and no significant 1- and 2-year difference between HTO and KJD, with MDs between -8.0 (HTO, 1 year) and -10.0 (TKA, 1 year) and all $p>0.05$.

The mean JSW of the MAC (Figure S10) is compared between KJD and HTO after 1 and 2 years. There was no significant difference after either 1 (MD=0.40; $p=0.099$) or 2 (MD=-0.05; $p=0.853$) years. Compared to the OAI, the mean JSW showed significantly better results 5 years after KJD (MD=1.06; $p<0.001$). Treatment with KJD, microfracture and debridement showed a greater increase in mean JSW after 4–7 years than microfracture and debridement alone (MD=2.10; $p<0.001$).

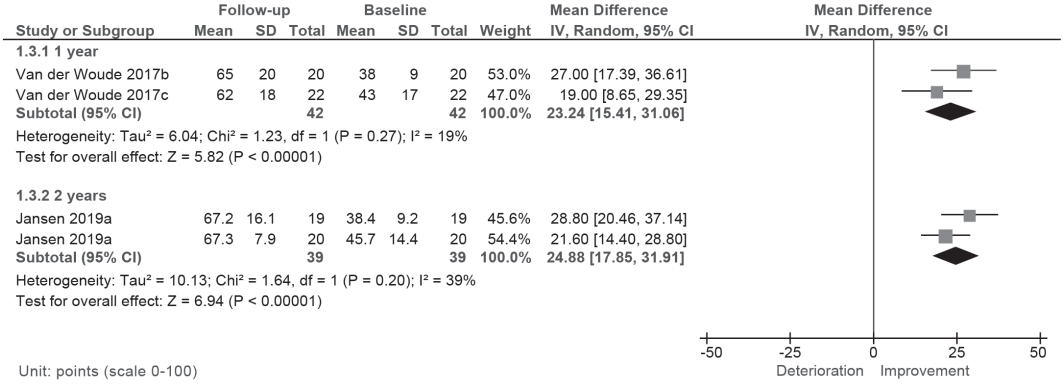
The mean MAC cartilage thickness (Figure S11) shows a significantly better result over 5 years for KJD patients than the OAI (MD=0.48; $p<0.001$). For HTO patients from the MRI RCT sub-cohort, a cartilage thickness decrease of around 0.2mm is reported ($p<0.05$), and the thickness increase observed in KJD patients is significantly better than HTO ($p<0.01$).

Other outcome measures

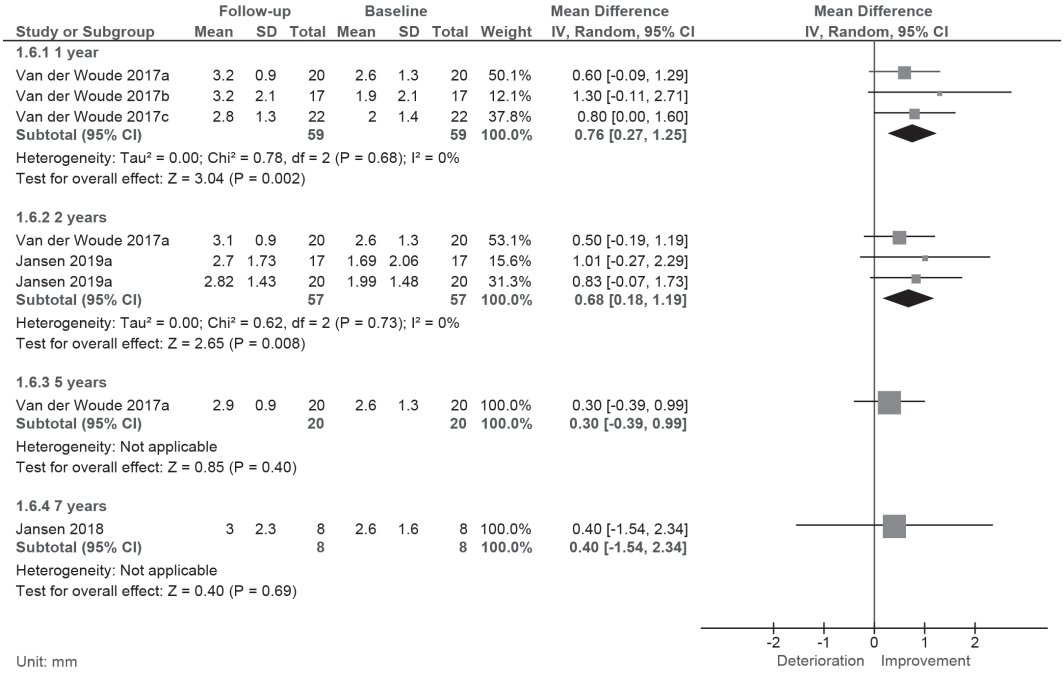
The 2-year SF-36 PCS change was better for TKA than KJD (MD=-12.6; 95%CI -18.9– -6.3; $p<0.001$), while the 1-year change in knee flexion was better for KJD than TKA (MD=7.0; 95%CI 1.0–13.0; $p=0.027$). The SF-36 PCS change was significantly better for HTO over 1 (MD=-5.0; 95%CI -9.3 to -0.8; $p=0.031$) and 2 (MD=-5.4; 95%CI -10.1 to -0.7; $p=0.034$) years, while the 1-year change in knee flexion was better for KJD than HTO (MD=6.0; 95%CI 0.5–11.5; $p=0.042$). Adding KJD to microfracture and debridement improved stair climbing ($p<0.000$). De decrease (improvement) in denuded bone was significantly more for KJD than HTO ($p<0.01$).



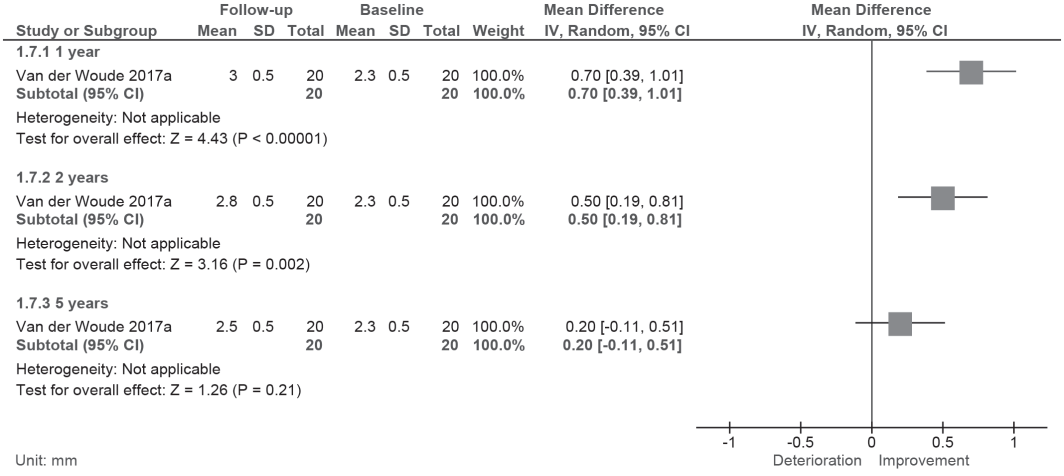
Supplementary Figure S1: Change in visual analogue score (VAS) of pain 1, 2, 5 and 9 years after treatment with knee joint distraction. References can be used multiple times because of division in patient cohort and years of follow-up. CI: confidence interval; SD: standard deviation.



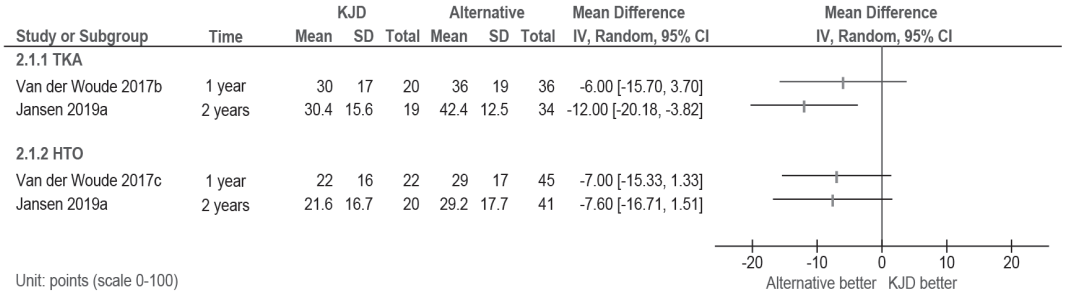
Supplementary Figure S2: Change in total Knee injury and Osteoarthritis Outcome Score (KOOS) 1 and 2 years after treatment with knee joint distraction. References can be used multiple times because of division in patient cohort and years of follow-up. CI: confidence interval; SD: standard deviation.



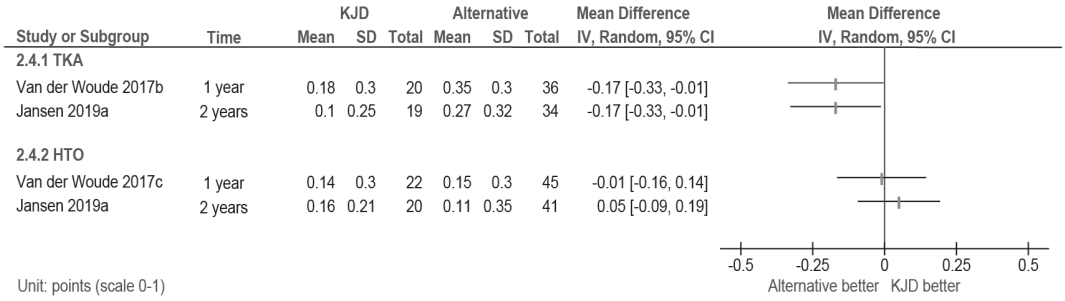
Supplementary Figure S3: Change in mean joint space width (JSW) 1, 2, 5 and 7 years after treatment with knee joint distraction. References can be used multiple times because of division in patient cohort and years of follow-up. CI: confidence interval; SD: standard deviation.



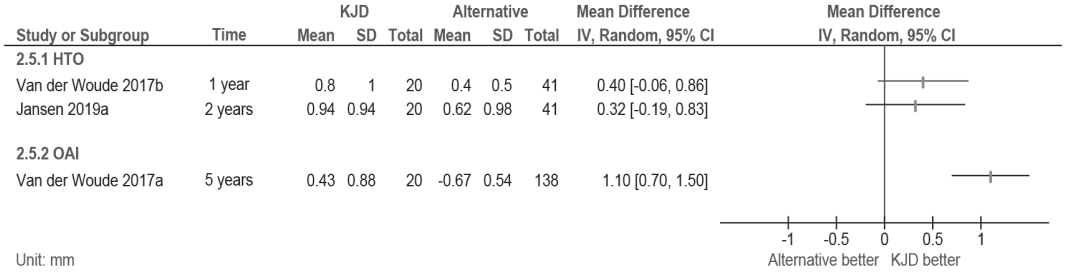
Supplementary Figure S4: Change in MRI cartilage thickness in the most affected compartment 1, 2 and 5 years after treatment with knee joint distraction. References can be used multiple times because of division in patient cohort and years of follow-up. CI: confidence interval; SD: standard deviation.



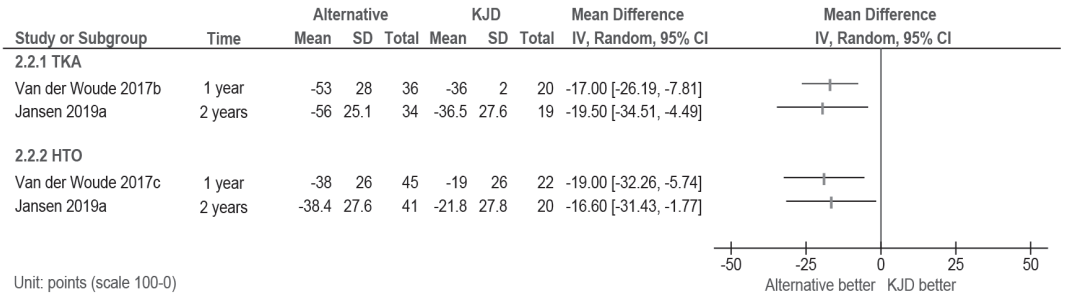
Supplementary Figure S5: Change in total Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) score compared between knee joint distraction (KJD) and total knee arthroplasty (TKA) and between KJD and high tibial osteotomy (HTO), both 1 and 2 years after treatment. References can be used multiple times because of division in patient cohort. CI: confidence interval; SD: standard deviation.



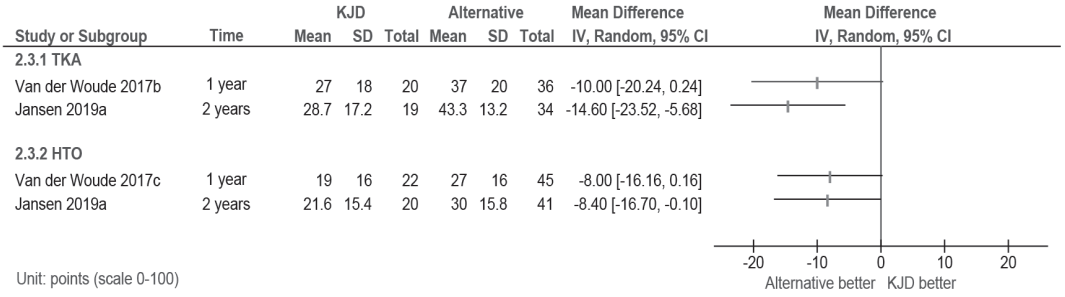
Supplementary Figure S6: Change in EuroQol 5D (EQ-5D) score compared between knee joint distraction (KJD) and total knee arthroplasty (TKA) and between KJD and high tibial osteotomy (HTO), both 1 and 2 years after treatment. References can be used multiple times because of division in patient cohort. CI: confidence interval; SD: standard deviation.



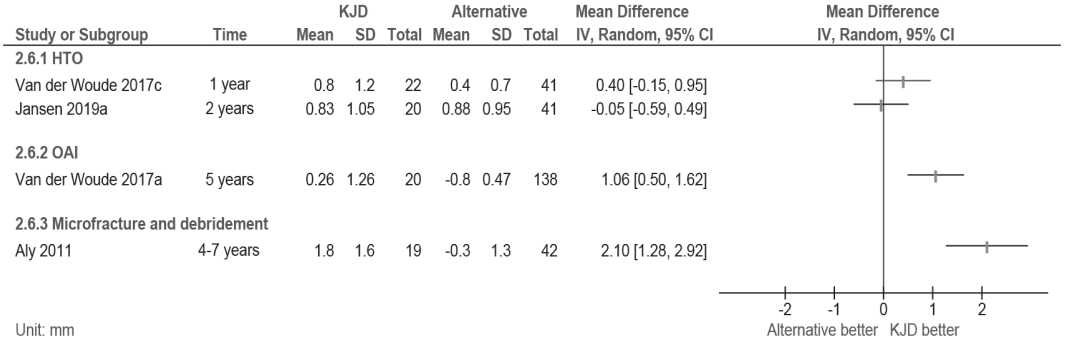
Supplementary Figure S7: Change in minimum joint space width (JSW), compared between knee joint distraction (KJD) and high tibial osteotomy (HTO) at 1 and 2 years after treatment, and between KJD and the untreated osteoarthritis initiative (OAI) cohort at 5 years after baseline. CI: confidence interval; SD: standard deviation.



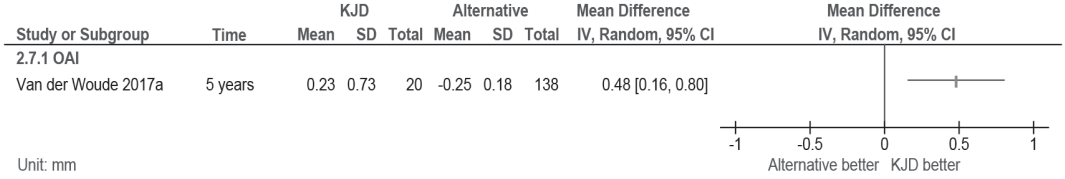
Supplementary Figure S8: Change in visual analogue score (VAS) of pain compared between knee joint distraction (KJD) and total knee arthroplasty (TKA) and between KJD and high tibial osteotomy (HTO), both 1 and 2 years after treatment. References can be used multiple times because of division in patient cohort. CI: confidence interval; SD: standard deviation.



Supplementary Figure S9: Change in total Knee injury and Osteoarthritis Outcome Score (KOOS) compared between knee joint distraction (KJD) and total knee arthroplasty (TKA) and between KJD and high tibial osteotomy (HTO), both 1 and 2 years after treatment. References can be used multiple times because of division in patient cohort. CI: confidence interval; SD: standard deviation.



Supplementary Figure S10: Change in mean joint space width (JSW), compared between knee joint distraction (KJD) and high tibial osteotomy (HTO) at 1 and 2 years after treatment, between KJD and the untreated osteoarthritis initiative (OAI) cohort at 5 years after baseline, and between patients treated with KJD, microfracture and debridement and patients treated with microfracture and debridement alone after 4–7 years. For Aly 2011, *p*-values were used to calculate standard deviations (SD); for KJD the reported *p*-value of $p<0.000$ was assumed to be $p=0.0001$. CI: confidence interval; SD: standard deviation.



Supplementary Figure S11: Change in MRI cartilage thickness in the most affected compartment, compared between patients treated with knee joint distraction (KJD) and the untreated osteoarthritis initiative (OAI) cohort at 5 years after baseline. CI: confidence interval; SD: standard deviation.

CHAPTER 3

Initial tissue repair predicts long-term clinical success of knee joint distraction as treatment for knee osteoarthritis

M.P. Jansen
G.S. van der Weiden
P.M. van Roermund
R.J.H. Custers
S.C. Mastbergen
F.P.J.G. Lafeber

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Abstract

Background: Knee joint distraction (KJD), a joint-preserving surgery for severe osteoarthritis (OA), provides clinical and structural improvement and postpones the need for total knee arthroplasty (TKA). This study evaluates 9-year treatment outcome and identifies characteristics predicting long-term treatment success.

Methods: Patients with severe tibiofemoral OA (n=20; age <60 years) indicated for TKA were treated with KJD. Questionnaires, radiographs, and MRI were used for evaluation. Survival after treatment was analyzed, where 'failure' was defined by TKA over time.

Results: Nine-year survival was 48%, and 72% for men (compared to 14% for women; p=0.035) and 73% for those with a first-year minimum joint space width (JSW) increase of >0.5mm (compared to 0% for <0.05mm; p=0.002). Survivors still reported clinical improvement compared to baseline (ΔWOMAC +29.9 points (95%CI 16.9–42.9; p=0.001), ΔVAS -46.8mm (-31.6 to -61.9; p<0.001)). Surprisingly, patients getting TKA years after KJD still reported clinical improvement although less pronounced (ΔWOMAC +20.5points (-1.8 to 42.8; p=0.067), ΔVAS -25.4mm (-3.2 to -47.7; p=0.030)). Survivors showed long-lasting minimum JSW increase (baseline 0.3mm (IQR 1.9), follow-up 1.3mm (2.5); p=0.017) while 'failures' did not (baseline 0.4mm (1.8), follow-up 0.2mm (1.5); p=0.161). First-year minimum JSW on radiographs and cartilage thickness increase on MRI predict 9-year survival (HR 0.05 and 0.12, respectively; both p<0.026). Male sex was associated with survival (HR 0.24; p=0.050).

Conclusion: KJD shows long-lasting clinical and structural improvement. In addition to a greater survival rate for males (>two out of three), the initial cartilage repair activity appears to be important for long-term clinical success.

Introduction

Few possibilities are available for treatment of end-stage (conservative treatment resistant, persistently painful with clear radiographic joint damage) knee osteoarthritis (OA). Although total knee arthroplasty (TKA) has been shown to be effective in reducing pain and regaining function, it comes with an increased risk of future revision surgery, specifically when placed at a relatively young age (<65 years).[1,2] Therefore, joint-preserving surgery such as knee joint distraction (KJD) would be preferable in this younger patient group.

In distraction treatment, an external fixation frame is used to gradually separate 2 bony ends of a joint for a few millimeters for a number of weeks.[3,4] KJD has been shown to result in improvement of patient-reported clinical outcomes and improved tissue structure parameters based on digitally analyzed standardized radiographs and magnetic resonance images (MRI), for up to 5 years.[5–10] However, long-term survival of KJD as a joint-preserving treatment has not yet been evaluated.

In this study, the 20 patients treated with KJD in an open prospective study were followed to observe long-term clinical and structural changes, as previously reported for up to 5 years of follow-up.[5–7] Additionally, long-term survival of the native knee joint was evaluated and the effect of patient characteristics as well as disease-specific clinical and structural parameters on long-term survival was assessed.

Methods

Patient selection

Between 2006 and 2008, 20 patients with knee OA were included in an open uncontrolled prospective study at the department of orthopedics of the University Medical Center Utrecht (UMCU). Inclusion criteria were age <60 years, Visual Analogue Scale (VAS) of pain ≥60 mm, radiographic signs of joint damage and primarily tibiofemoral OA. The included patients were indicated for TKA surgery, but their relatively young age was reason to propose KJD as an alternative. Exclusion criteria were severe symptoms in both knees, a history of inflammatory or septic arthritis and severe knee malalignment requiring surgical correction (>10°). The study was approved by the medical ethical review committee of the University Medical Center Utrecht (No 04/086) and all patients gave written informed consent.

Distraction method

The distraction method was applied as previously described by Intema *et al*.[5] An external fixation frame was placed to bridge the knee joint. The frame consisted of 2 dynamic monotubes, both fixed to 2 bone-pins on each end, elongated in stages until at least 5 mm distraction was reached

(confirmed by radiography). Full weight-bearing of the distracted joint was encouraged with the use of crutches if needed with springs in the device to ascertain sufficient synovial fluid dynamics. Patients got anticoagulants (subcutaneous low molecular weight heparin) during treatment time and antibiotics (flucloxacillin) in case of pin-tract skin infections. After 2 months (average 60 days, range 54–64 days) the pins and monotubes were removed under anesthesia and patients were discharged without imposed functional restrictions.

Follow-up

Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) questionnaires and visual analogue scores (VAS) of pain were assessed at baseline and yearly thereafter. Structural outcome was assessed at baseline, 1, 2, 5, and 7 years' follow-up using radiographs. MRI was performed pre- and 1-year post-treatment.

Treatment 'failure' was defined as undergoing TKA in the subsequent years after KJD (these patients were not further followed), whereas survivors still had their native knee without additional surgery at 9 years.

Clinical outcome

The WOMAC questionnaire (version 3.0, normalized to a 100-point scale for total and subscales; "100" being the best score) was used as primary outcome parameter. The secondary clinical outcome parameter was the VAS pain score (0–100 mm; "0" meaning no pain).

Structural outcome

Radiographic analysis

Standardized weight-bearing, semi-flexed, posterior-anterior radiographs were made and evaluated by use of knee images digital analysis (KIDA) software.[11] Analyses were performed by 1 experienced observer, blinded to acquisition order and patient characteristics. The minimum and mean joint space width (JSW) of the most affected compartment (MAC) are presented. Subchondral bone density was measured in the MAC of the tibia and femur averaged and expressed in mm aluminum equivalents (Al eq), using an aluminum step wedge as reference.

Quantitative MRI analysis

MRI scans were performed with the Eckstein protocol.[6,12] The mean cartilage thickness over the subchondral bone area and the percentage of denuded subchondral bone area were calculated at baseline and 1-year follow-up for the MAC.[7]

Statistical analysis

Baseline characteristics and initial clinical and structural improvement (first year post-treatment) were compared in survivors and patients that underwent TKA during follow-up. For the baseline characteristics, normally distributed data are described with the mean and SD while not normally distributed and categorical data are described with the median and interquartile range (IQR). For comparing the characteristics between groups, independent *t*-tests were used for normally distributed data, Mann-Whitney *U* Tests were used when baseline data were not normally distributed in either or both groups, and the chi-square test was used for categorical variables.

Survival analysis was performed using the Kaplan-Meier estimator, where event occurrence was defined by patients undergoing TKA. Patients were censored when withdrawing consent for further follow-up or after the maximum follow-up period of 9 years. Survival was compared for all baseline characteristics and initial clinical and structural change using the log-rank test, for which continuous data was divided into groups based on the distribution of the variable. For JSW measures, the smallest detectable difference was used as cut-off.[11]

To evaluate whether clinical and structural follow-up values significantly differed from baseline values, 2-sided paired *t*-tests were used. In case of not normally distributed baseline or follow-up data, the Wilcoxon Signed-Rank Test was used instead. The tests were performed separately for survivors and those who got TKA over time. Since failures have no follow-up results after receiving TKA, last-measured outcomes were used for comparison with baseline values. Nine-year clinical and structural outcomes for survivors were compared with last-reported outcomes for patients receiving TKA using independent *t*-tests. Mean changes and 95% confidence interval (95%CI) are given for clinical outcome parameters, mean and standard deviation (SD) before and after treatment are given for structural parameters, and median and interquartile range (IQR) before and after treatment for not normally distributed data.

Long-term survival of KJD was predicted using Cox regression analyses, where the influence of different covariates on survival time was analyzed. Covariates were all baseline characteristics and initial clinical and structural improvement separately. Initial improvement as potential predictors were corrected for baseline values by adding them as covariates. Survival prediction effects are estimated with a hazard ratio (HR) with 95%CI.

P-values <0.05 were considered statistically significant. For all statistical tests, IBM SPSS Statistics version 20.0.0 was used.

Results

Patients

During 9 years of follow-up, 3 patients withdrew their consent for further follow-up. Nine patients underwent TKA after on average 6.4 years (range 3.8–9.0 years), leaving 8 survivors

and an overall survival of 48% (Figure 1). Baseline characteristics and 1-year improvement for both groups are summarized and compared in Table 1. A statistically significant difference in sex was found between survivors and failures (survivors 88% male; failures 33% male; p=0.024). Survivors showed a significantly larger initial increase in minimum JSW (survivors 1.5 (SD 0.7) mm; failures 0.4 (0.6) mm; p=0.002) and a significantly greater decrease in bone density (survivors -6.5 (3.5) mm Al eq; failures -2.7 (3.7) mm Al eq; p=0.046) than patients whose treatment failed. No statistically significant differences in other initial clinical or structural improvements were found between the 2 groups.

Table 1: Baseline characteristics and clinical and structural improvement in first year after treatment of survivors and patients whose treatment failed 9 years after treatment

	Survivors (n=8)	**Failures (n=9)**	***P*-value**
Baseline			
Age (years), median (IQR)	51.0 (3.3)	50.0 (9.0)	0.961#
Male sex, n (%)	7 (87.5)	3 (33.3)	**0.024***
BMI (kg/m^2)	27.7 (2.0)	30.1 (4.3)	0.161
Kellgren-Lawrence grade, median (IQR)	3.0 (0.0)	3.0 (0.5)	0.567*
- Grade 0, n (%)	0 (0)	0 (0)	
- Grade 1, n (%)	0 (0)	1 (11)	
- Grade 2, n (%)	1 (13)	1 (11)	
- Grade 3, n (%)	7 (88)	6 (67)	
- Grade 4, n (%)	0 (0)	1 (11)	
WOMAC total (0–100)	46.4 (12.5)	45.4 (16.3)	0.884
VAS pain (100–0)	71.8 (6.9)	74.3 (9.3)	0.532
Mean MAC JSW (mm)	2.6 (1.6)	2.3 (1.0)	0.622
Minimum JSW (mm), median (IQR)	0.4 (1.9)	0.2 (1.5)	0.664#
Bone density (mm Al eq)	43.6 (6.5)	40.4 (2.9)	0.231
Mean cartilage thickness (mm)	2.2 (0.7)	2.2 (0.4)	0.891
Denuded bone area (%)	30.0 (20.1)	21.5 (17.4)	0.367
Initial (First-year) changes			
Δ WOMAC total (0–100)	32.3 (19.5)	39.9 (24.1)	0.489
Δ VAS pain (100–0)	-48.0 (30.9)	-45.4 (29.1)	0.863
Δ Mean MAC JSW (mm)	1.4 (1.0)	0.6 (1.1)	0.157
Δ Minimum JSW (mm)	1.5 (0.7)	0.4 (0.6)	0.002
Δ Bone density (mm Al eq)	-6.5 (3.5)	-2.7 (3.7)	**0.046**
Δ MRI mean cartilage thickness (mm)	0.9 (0.6)	0.4 (0.7)	0.068#
Δ MRI Denuded bone area (%)	-25.9 (20.2)	-15.5 (15.8)	0.254

Mean and standard deviation are given unless otherwise indicated. Significant p-values (<0.05) are in bold and calculated using independent t-tests, except values indicated with *, for which chi-square tests were used, or values indicated with #, for which Mann-Whitney U Tests were used. Al eq: aluminum equivalent; BMI: body mass index; IQR: interquartile range; JSW: joint space width; MAC: most affected compartment; VAS: Visual Analogue Scale; WOMAC: Western Ontario and McMaster Universities Osteoarthritis Index.

Survival

Survival after 9 years was 8 out of 17 patients (48%), as seen in Figure 1A. Survival analyses supported the differences found in survival percentage 9 years after treatment for sex (14% survival in women; 72% survival in men; p=0.035; Figure 1B) and for initial increase in minimum JSW (0% survival in patients with <0.5mm increase; 73% survival in patients with >0.5mm increase; p=0.002; Figure 1C).

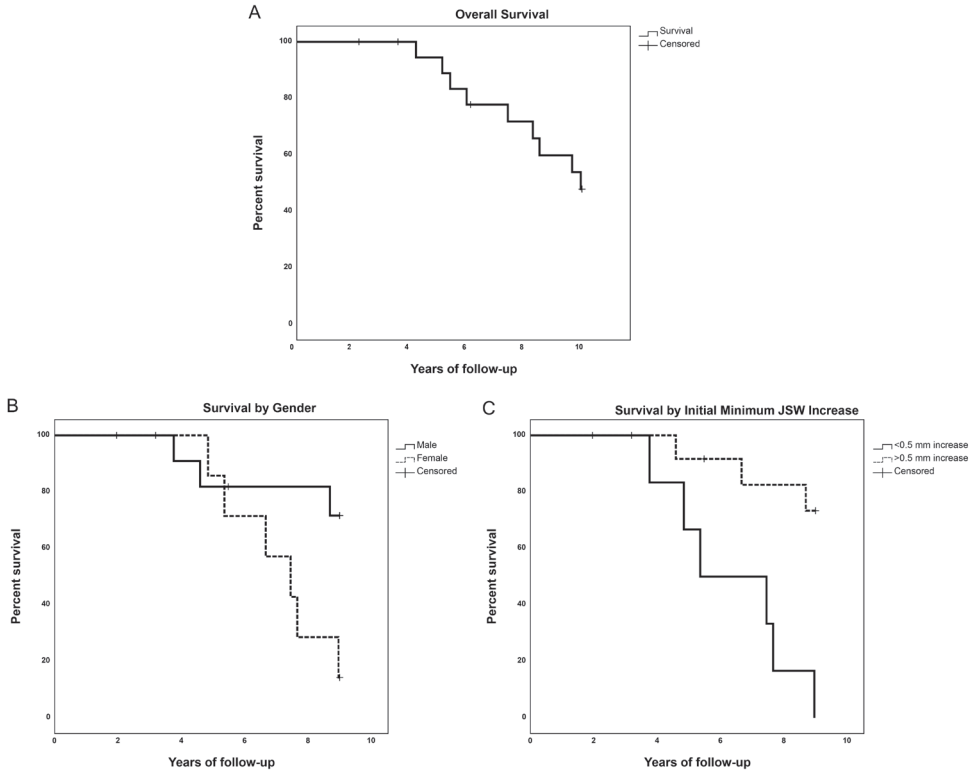

Figure 1: (A) Survival curve of 20 patients with end-stage knee osteoarthritis treated with joint distraction. (B) Survival curve by sex, men (n=11) *versus* women (n=9). (C) Survival curve by increase in minimal joint space width (JSW) 1 year after treatment, less than 0.5 mm increase (n=7) *versus* more than 0.5 mm increase (n=13).

Clinical outcome

Survivors reported a statistically significant average 9-year increase in total WOMAC scores of 29.9 points (95%CI 16.9–42.9; p=0.001; Figure 2A) compared to baseline. Surprisingly, also patients who underwent TKA in the years after KJD reported an average increase in total WOMAC scores of 20.5 points on last-reported scores compared to baseline (-1.8 to 42.8; p=0.067; Figure 2A). Moreover, last-reported total WOMAC scores were not statistically significantly different between survivors and patients who received TKA after KJD (76.3 (60.3–92.4) and 65.8 (48.7–82.9); p=0.317).

Survivors reported improvement in pain, stiffness, and function 9 years after treatment compared to baseline (32 points (95%CI 20.1–45.1; p<0.001), 22.4 points (3.6–41.2; p=0.026), and 31.0 points (17.1–44.8; p=0.001), respectively). In patients who obtained TKA in the years after KJD, increases for pain, stiffness, and function were observed at last reported scores compared to baseline, 16.7 points (-7.0 to 40.3; p=0.143), 18.7 points (-2.7 to 40.2; p=0.079), and 21.0 points (-2.3 to 44.3; p=0.072), respectively.

Both survivors and those that underwent TKA reported a statistically significant average improvement in VAS pain scores compared to baseline (-46.8mm (95%CI -31.6 to -61.9; p<0.001 and -25.4mm (-3.2 to -47.7; p=0.030; Figure 2B). Last-reported VAS pain scores were better in survivors (25.0 (10.9–39.1) and 48.9 (28.4–69.4); p=0.046).

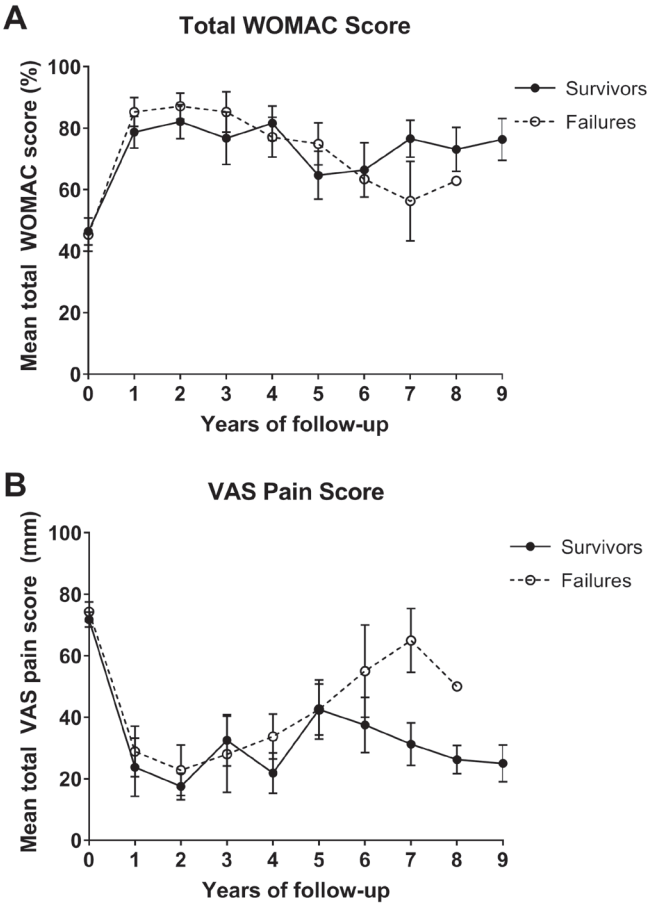

Figure 2: (A) Total Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC; 100 best) scores of survivors 9 years after treatment *versus* patients whose treatment failed within 9 years. (B) Visual Analogue Scale (VAS; 0 best) pain score of survivors 9 years after treatment *versus* patients whose treatment failed within 9 years. Mean values and standard errors are shown.

Structural outcome

In patients who survived for at least 9 years, the minimum JSW was still statistically significantly increased at 7 years when compared to baseline (1.3 mm (IQR 2.5) and 0.3 (1.9), respectively; p=0.017; Figure 3A). The mean JSW of the MAC in these patients was 3.0 (SD 2.3) mm at 7 years and 2.6 (1.6) mm at baseline (p=0.505; Figure 3B). The bone density at 7 years was 40.4 (SD 3.5) mm Al eq compared to 43.6 (6.5) mm Al eq at baseline (p=0.173; Figure 3C).

In patients who received TKA in the years after KJD, no statistically significant differences in structural parameters were found between the last measurement and baseline. The minimum JSW was 0.4 (IQR 1.8) mm at last measurement compared to 0.2 (1.5) mm at baseline (p=0.161; Figure 3A dotted line). The mean JSW of the MAC was 2.5 (SD 1.8) mm at last measurement and 2.7 (1.2) mm at baseline (p=0.712; Figure 3B). The same was found for the bone density in patients who failed treatment, which was 41.3 (SD 4.9) mm Al eq at last measurement and 40.4 (2.9) mm Al eq at baseline (p=0.447; Figure 3C).

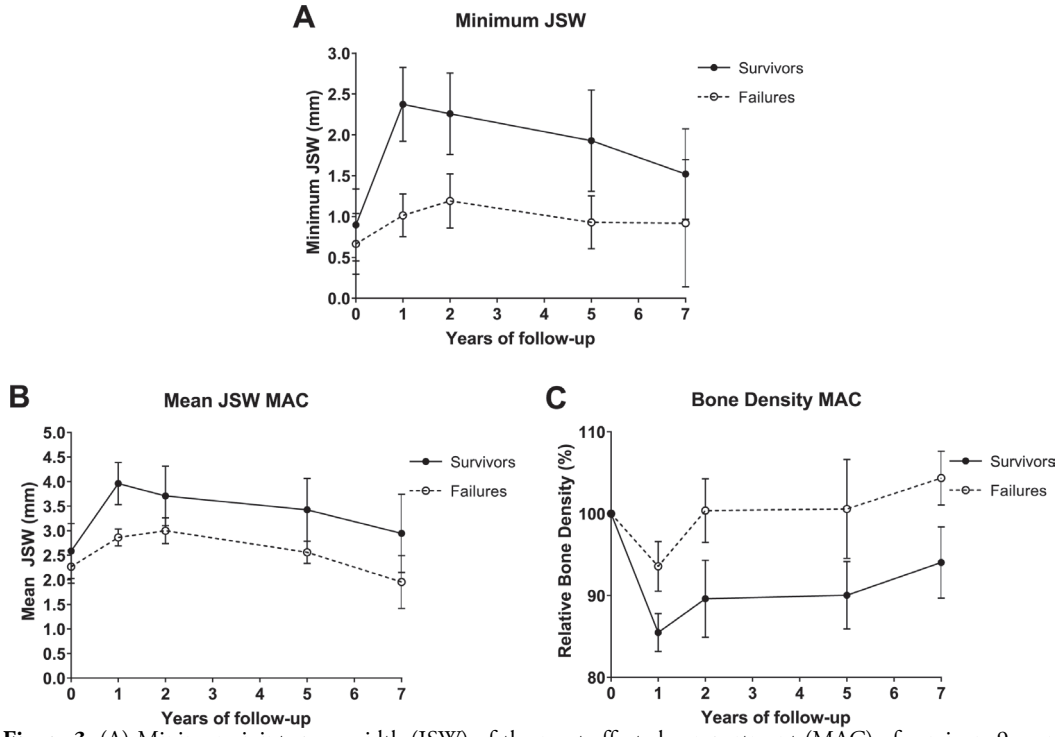

Figure 3: (A) Minimum joint space width (JSW) of the most affected compartment (MAC) of survivors 9 years after treatment *versus* patients whose treatment failed within 9 years. (B) Mean JSW of the MAC of survivors 9 years after treatment *versus* patients whose treatment failed within 9 years. (C) Mean bone density of the MAC of survivors 9 years after treatment *versus* patients whose treatment failed within 9 years, shown relative to baseline as survivors have a higher baseline bone density. Mean values and standard errors are shown.

Prediction of nine-year clinical survival

A larger initial increase in minimum JSW was found to be a positive predicting factor for survival of the native knee joint both uncorrected (HR 0.28 (95%CI 0.11–0.72); p=0.008) and corrected for baseline (0.05 (0.01–0.58); p=0.016). A larger increase in mean cartilage thickness showed a higher incidence of survival when corrected for baseline as well (0.21 (0.02–0.76); p=0.025). Male sex was positively associated with survival (0.24 (0.06–1.00); p=0.050). For all data see Table 2.

Table 2: Crude and adjusted Cox regression analyses displaying the influence of baseline and 1-year change characteristics on undergoing total knee arthroplasty

	Crude hazard ratio		Adjusted hazard ratio	
	HR	***P*-value**	**HR**	***P*-value**
Baseline				
Age	1.04 (0.90–1.20)	0.586		
Male sex	0.24 (0.06–1.00)	0.050		
BMI	1.12 (0.91–1.34)	0.286		
Kellgren-Lawrence grade	1.08 (0.34–3.43)	0.894		
WOMAC total	1.00 (0.95–1.05)	0.976		
VAS pain	1.03 (0.94–1.12)	0.568		
Mean MAC JSW	0.82 (0.49–1.35)	0.424		
Minimum JSW	0.82 (0.43–1.56)	0.550		
Bone density	0.92 (0.79–1.08)	0.322		
Mean cartilage thickness	0.78 (0.26–2.34)	0.663		
Denuded bone area %	0.99 (0.96–1.03)	0.666		
Initial (First-year) changes				
ΔWOMAC total	1.02 (0.98–1.05)	0.356	1.03 (0.98–1.07)	0.288
ΔVAS pain	1.01 (0.98–1.03)	0.692	1.01 (0.99–1.04)	0.408
ΔMean MAC JSW	0.71 (0.36–1.40)	0.321	0.31 (0.09–1.04)	0.058
ΔMinimum JSW	0.28 (0.11–0.72)	**0.008**	0.05 (0.01–0.58)	**0.016**
ΔBone density	1.13 (0.96–1.33)	0.143	1.12 (0.90–1.38)	0.312
ΔMean cartilage thickness	0.31 (0.06–1.62)	0.164	0.12 (0.02–0.76)	**0.025**
ΔDenuded bone area %	1.01 (0.98–1.06)	0.476	1.03 (0.96–1.11)	0.414

Hazard ratio (HR) and 95% confidence interval are given. Significant p-values (<0.05) are in bold. BMI: body mass index; JSW: joint space width; MAC: most affected compartment; VAS: Visual Analogue Scale; WOMAC: Western Ontario and McMaster Universities Osteoarthritis Index.

Discussion

Nine years after KJD treatment, nearly half of the patients still had no joint prosthesis, even though they were originally indicated for TKA. Survivors reported still significantly increased clinical scores 9 years post-KJD. Moreover, the minimum JSW as a measure for cartilage thickness was still increased compared to pre-treatment values 7 years post-treatment in these patients. Interestingly, patients who underwent TKA in the years after KJD reported increased clinical scores at last follow-up as well; compared to survivors' 9-year parameters, there was

no statistically significant difference in WOMAC scores. Considering a minimally clinical important difference of 15–20 points for the total WOMAC and 25–30 mm for VAS pain, numbers that have been reported as clinically relevant differences in other studies[13,14], there was no clinical difference between survivors or failures either.

As clinical scores are still improved compared to baseline at the moment of choosing TKA after KJD, it could be questioned whether TKA is a valid end-point for survival. Additional reasons may have lead these patients to choose for a subsequent TKA. The average time to TKA for failures was 6.4 years, and the potentially temporary decrease in clinical benefit seen around 5 years post-treatment (Figure 2) might be causative to choose a subsequent TKA. Anecdotally knee OA patients treated with distraction are willing to undergo a second KJD years after the first KJD which has for ankle distraction been proven to be successful again.

The minimum and mean JSW of the MAC at baseline were not different for survivors and patients who underwent TKA, where survivors showed a larger JSW increase in the first year. The gradual decrease that was subsequently observed seemed parallel for the 2 groups, suggesting that the initial JSW gain is crucial as it is this increase that is largely maintained during the remainder of follow-up. Despite the smaller initial JSW increase in patients who underwent TKA after KJD, their JSW was on average not decreased compared to baseline at the last measurement before TKA. This should be considered in the context of a general decrease in JSW over time as natural course of joint degeneration in case the disease remains untreated.[7]

Regression analysis showed several factors predicting 9-year survival of KJD treatment. In the present study, for the first time it is shown that structural improvement in the first year after distraction predicts long-term clinical survival. Chance for survival is better after a higher initial minimum JSW increase and increase in mean cartilage thickness on MRI when corrected for baseline values.

Also men had a better chance for survival, as described previously for hip and ankle distraction as well.[15,16] It was observed that male patients generally had a larger initial increase in minimum JSW (>0.5 mm increase: 9 males, 2 females; <0.5 mm increase: 1 male, 5 females), but performing a Cox regression analysis with both sex and 1-year change in minimum JSW as covariates showed this barely affected the HR (0.29 uncorrected for baseline), indicating that the minimum JSW increase has a strong association with survival even when corrected for sex.

Pin-tract infections during treatment, which occurred in 17 of the 20 patients, were not predictive of survival (p=0.578). The previously reported decrease in knee flexion angle at 3 and 6 months also was not predictive (p=0.776 and p=0.698, respectively).[7]

A clear limitation of the present study is the small number of patients. However, this is thus

far the only cohort of KJD patients followed for such a long period of time. While the small number of patients could have resulted in larger confidence intervals, the intervals of parameters significantly associated with survival do not cross 1. As the data does not allow the usage of multivariable modeling, Cox regression analyses had to be performed separately for every parameter. This may have increased the rate of type I errors as a result of multiple testing. A best-worst case Kaplan-Meier and Cox regression analysis was performed, where the 3 patients lost to follow-up were either defined as failures at the moment of drop-out or as survivors for at least 9 years. These results did not change the outcome of this study significantly (see supplementary data).

In conclusion, joint distraction for knee OA patients considered for TKA shows long-lasting clinical and structural improvement and an overall survival of the native knee 9 years after treatment in half of the treated patients and over 2/3 in males and those with the better initial structural response after KJD.

References

1. Lützner J, Kasten P, Günther K-P, *et al*. Surgical options for patients with osteoarthritis of the knee. Nature Reviews Rheumatology. 2009 Jun;5(6):309–16.
2. Kurtz SM, Lau E, Ong K, *et al*. Future young patient demand for primary and revision joint replacement: National projections from 2010 to 2030. Clinical Orthopaedics and Related Research. 2009;467(10):2606–12.
3. Lafeber FP, Intema F, van Roermund PM, *et al*. Unloading joints to treat osteoarthritis, including joint distraction. Current Opinion in Rheumatology. 2006 Sep;18(5):519–25.
4. Wiegant K, van Heerwaarden RJ, van Roermund PM, *et al*. Intrinsic joint tissue repair by joint distraction. OA Arthritis. 2013 Feb;1(1).
5. Intema F, van Roermund PM, Marijnissen ACA, *et al*. Tissue structure modification in knee osteoarthritis by use of joint distraction: An open 1-year pilot study. Annals of the Rheumatic Diseases. 2011 Aug 1;70(8):1441–6.
6. Wiegant K, van Roermund PM, Intema F, *et al*. Sustained clinical and structural benefit after joint distraction in the treatment of severe knee osteoarthritis. Osteoarthritis and Cartilage. 2013 Nov;21(11):1660–7.
7. van der Woude JAD, Wiegant K, van Roermund PM, *et al*. Five-year follow-up of knee joint distraction: Clinical benefit and cartilaginous tissue repair in an open uncontrolled prospective study. Cartilage. 2017;8(3):263–71.
8. van der Woude JAD, Wiegant K, van Heerwaarden RJ, *et al*. Knee joint distraction compared with high tibial osteotomy: A randomized controlled trial. Knee Surgery, Sports Traumatology, Arthroscopy. 2017;25(3):876–86.
9. van der Woude JAD, Wiegant K, van Heerwaarden RJ, *et al*. Knee joint distraction compared with total knee arthroplasty: A randomised controlled trial. Bone and Joint Journal. 2017;99-B(1):51–8.
10. Deie M, Ochi M, Adachi N, *et al*. A new articulated distraction arthroplasty device for treatment of the osteoarthritic knee joint: a preliminary report. Arthroscopy. 2007;23(8):833–8.
11. Marijnissen ACA, Vincken KL, Vos PAJM, *et al*. Knee Images Digital Analysis (KIDA): A novel method to quantify individual radiographic features of knee osteoarthritis in detail. Osteoarthritis and Cartilage. 2008 Feb 1;16(2):234–43.
12. Eckstein F, Ateshian G, Burgkart R, *et al*. Proposal for a nomenclature for magnetic resonance imaging based measures of articular cartilage in osteoarthritis. Osteoarthritis and Cartilage. 2006 Oct 1;14(10):974–83.
13. Escobar A, García Pérez L, Herrera-Espiñeira C, *et al*. Total knee replacement; minimal clinically important differences and responders. Osteoarthritis and Cartilage. 2013 Dec 1;21(12):2006–12.
14. Katz NP, Paillard FC, Ekman E. Determining the clinical importance of treatment benefits for interventions for painful orthopedic conditions. Journal of Orthopaedic Surgery and Research. 2015 Feb 3;10(1):24.
15. Marijnissen ACA, Hoekstra MCL, Pré BCD, *et al*. Patient characteristics as predictors of clinical outcome of distraction in treatment of severe ankle osteoarthritis. Journal of Orthopaedic Research. 2014 Jan;32(1):96–101.
16. Gomez JA, Matsumoto H, Roye DP, *et al*. Articulated hip distraction: A treatment option for femoral head avascular necrosis in adolescence. Journal of Pediatric Orthopaedics. 2009 Mar;29(2):163–9.

CHAPTER 4

Knee joint distraction compared with high tibial osteotomy and total knee arthroplasty

Two-year clinical, radiographic, and biochemical marker outcomes of two randomized controlled trials

M.P. Jansen
N.J. Besselink
R.J. van Heerwaarden
R.J.H. Custers
P.J. Emans
S. Spruijt
S.C. Mastbergen
F.P.J.G. Lafeber

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Abstract

Background: Both, knee joint distraction (KJD) and high tibial osteotomy (HTO) are joint-preserving surgeries that postpone total knee arthroplasty (TKA) in younger osteoarthritis (OA) patients. Here we evaluate the 2-year follow-up of KJD *versus* TKA and KJD *versus* HTO in 2 non-inferiority studies.

Methods: Knee OA patients indicated for TKA were randomized to KJD (n=20; KJD_{TKA}) or TKA (n=40). Medial compartmental knee OA patients considered for HTO were randomized to KJD (n=23; KJD_{HTO}) or HTO (n=46). Patient-reported outcome measures were assessed over 2 years of follow-up. The radiographic joint space width (JSW) was measured yearly. In the KJD groups, serum-PIIANP and urinary-CTXII levels were measured as collagen type II synthesis and breakdown markers. It was hypothesized that there was no clinically important difference in the primary outcome, the total WOMAC, when comparing KJD with HTO and with TKA.

Results: Both trials were completed, with 114 patients (19 KJD_{TKA}; 34 TKA; 20 KJD_{HTO}; 41 HTO) available for 2-year analyses. The total WOMAC score and radiographic minimum JSW at 2 years were still increased for all groups (KJD_{TKA} 38.9 points (95%CI 28.8–48.9); TKA 42.1 (34.5–49.7); KJD_{HTO} 26.8 (17.1–36.6); HTO 34.4 (28.0–40.7); all $p<0.05$) and (KJD_{TKA} 0.9 mm (0.2–1.6); KJD_{HTO} 0.9 (0.5–1.4); HTO 0.6 (0.3–0.9); all $p<0.05$). The net collagen type II synthesis 2 years after KJD was increased ($p<0.05$). Half of KJD patients experienced pin tract infections, successfully treated with oral antibiotics.

Conclusion: Sustained improvement of clinical benefit and (hyaline) cartilage thickness increase after KJD is demonstrated. KJD was clinically non-inferior to HTO and TKA in the primary outcome.

Introduction

In patients with severe knee osteoarthritis (OA), total knee arthroplasty (TKA) is generally performed effectively to reduce pain and function impairment. However, younger patients have a higher risk of failure and future revision surgery later in life.[1] With up to 40% of TKAs performed under the age of 65, joint-preserving surgery is of major importance to postpone a first prosthesis, decreasing the risk for revision surgery.[1,2]

High tibial osteotomy (HTO) is a well-established surgical treatment for patients with medial unicompartmental OA in varus malalignment and shows good long-term survival with significant improvement of patient-reported outcome measures.[3,4] Also, cartilage tissue repair activity has been suggested following HTO.[5–7]

Knee joint distraction (KJD) is a more recently introduced joint-preserving surgery used for bi-compartmental tibiofemoral knee osteoarthritis or unilateral OA with limited malalignment. Long-term significant clinical benefit as well as profound cartilage tissue repair have been reported in an open prospective long-term follow-up study.[8–10]

In 2 independent randomized controlled trials (RCTs), KJD has been compared with TKA and KJD has been compared with HTO.[11] At 1-year follow-up KJD was non-inferior to both other treatments with respect to patient-reported outcome measures.[12,13] Cartilage repair activity appeared more pronounced in case of KJD as compared to HTO and was present in case of KJD when compared to TKA, being obviously absent in case of TKA.[12,13] The present study presents the 2-year follow-up results of these 2 independent trials at the level of patient-reported outcomes, radiographic (joint space width), and systemic biochemical (collagen type II) marker changes. It was hypothesized that there is no clinically important difference in efficacy when comparing KJD with HTO and KJD with TKA, 2 years post treatment. The primary outcome was the total Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) score.

Methods

Patients

Knee OA patients were included in a randomized controlled trial comparing TKA with KJD, conducted in 2 centers (Maartenskliniek Woerden and Maastricht University Medical Center) between 2011 and 2014. Patients considered for TKA were randomized (2:1) to either TKA (n=40) or to KJD (n=20; KJD_{TKA}) treatment in blocks of 6 at each institute, using standard randomization software. The 2:1 randomization ratio was an obligation of the medical ethics committee. The sample size was on a non-inferiority hypothesis in the primary outcome measure, the WOMAC score, for which a difference of more than 15 points (standard deviation

(SD) 16.7) was deemed clinically relevant.[14] A 5% type I error and power of 80% were used, with a 15% margin allowed for loss to follow-up. The trial was granted ethical approval (No 10/359/E) and was registered in the Netherlands National Trial Register (NTR2809).

In a separate RCT conducted between 2011 and 2013 at 2 centers (Maartenskliniek Woerden and University Medical Center Utrecht), patients with medial compartmental knee OA considered for HTO and less than 10° varus were randomized 2:1 to either HTO (n=46) or to KJD (n=23; KJD_{HTO}) treatment. Randomization was done in the same way as the TKA trial. The original sample size calculation was based on the change in percentage of denuded bone area as evaluated by quantitative MRI. The group sizes calculated however were sufficiently large to evaluate clinical outcome based on WOMAC score (15 points difference, with a 5% type I error and a power of 80%), all based on non-inferiority as described above. MRI data are not available yet and because of the combination of both independent trials in 1 manuscript, it was chosen to use WOMAC as primary outcome for both studies. The trial was granted ethical approval (No 11/072) and was registered in the Netherlands National Trial Register (NTR2900).

Table 1: In- and exclusion criteria of the 2 randomized controlled trials

	Both KJD *vs* TKA and KJD *vs* HTO	**KJD *vs* TKA only**	**KJD *vs* HTO only**
Inclusion criteria	• Age <65 years • Radiological joint damage: Kellgren & Lawrence score above 2 (as indicated by orthopedic specialist) • Intact knee ligaments • Normal range-of-motion (min. of 120° flexion) • Normal stability • Body Mass Index <35.	• Patients considered for TKA according to regular clinical practice	• Patients with medial tibiofemoral compartmental OA considered for HTO according to regular clinical practice
Exclusion criteria	• Psychological inabilities or difficult to instruct • Not able to undergo MRI examination (standard protocol) • Inflammatory or rheumatoid arthritis present or in history • Post-traumatic fibrosis due to fracture of the tibial plateau • Bone-to-bone contact in the joint (absence of any joint space on radiograph); • Surgical treatment of the involved knee <6 months ago • Primary patellofemoral OA	• An infectious susceptible prosthesis (joint replacement) in situ	• Mechanic varus axis-deviation of more than 10 degrees • Contralateral knee OA that needs treatment

HTO: high tibial osteotomy; KJD: knee joint distraction; TKA: total knee arthroplasty.

The similarities and differences in selection criteria of both trials are listed in Table 1. In both trials, insuperable, patients and physicians were aware of treatment assignment after allocation. The statistical methods of the patient selection and randomization process have been described elaborately before.[11]

Both trials were performed in accordance with the ethical principles from the Declaration of Helsinki and all patients gave written informed consent.[11]

Treatments

TKA was performed using the Genesis II posterior stabilized system (Smith & Nephew, Warsaw, Indiana) with fixation using GentaPalacos cement (Heraeus, Hanau, Germany). For HTO treatment, bi-plane medial-based opening-wedge osteotomy was performed. TomoFix medial high tibial plates and screws (DePuy Synthes, Switzerland) or Synthes locking compression plate system (DePuy Synthes, Switzerland) were used for fixation. The method of Miniaci[15] was used to preoperatively define the size of the opening. After both TKA and HTO, routine rehabilitation and thrombo-embolism prophylaxis was provided after surgery. Distraction surgery was performed with a proof-of-concept device consisting of 2 dynamic monotubes (Triax, Stryker, 45 kg spring with 3 mm displacement) bridging the knee joint medially and laterally. Each monotube was fixed to 2 bone-pins on each end (tibia and femur). The tubes were distracted by 2 mm during surgery and by 1 mm every day post-surgery, until a total distraction of 5 mm was reached, confirmed on radiographs. Afterwards patients were discharged, with heparin prescribed for 9 weeks, and allowed full weight-bearing of the distracted knee, supported by crutches if needed. At 3 to 4 weeks after surgery, radiographic evaluation of distraction and clinical evaluation of pin tracts was performed in the outpatient clinic. After 6 to 7 weeks the frame and pins were surgically removed.

Patient-reported outcome measures

Primary outcome was the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC, version 3.1) to score clinical improvement. As secondary measures, we used the validated Dutch Knee injury and Osteoarthritis Outcome Score (KOOS) (normalized to a 100-point scale; 100 being the best condition); the Intermittent and Constant Osteoarthritis Pain score (ICOAP) for the knee was assessed (0–100, 0 reflecting no pain); a Visual Analogue Scale for pain (VAS pain; 0–100 mm, 0 reflecting no pain); the EuroQol (EQ)-5D-3L for quality of life (transformed to an EQ-5D index score; 0–1, 1 being the best); and the Short Form 36 (SF-36) for general health (transformed to the physical (PCS) and mental (MCS) component summary score; 0–100, 100 being the best). All clinical outcome parameters were assessed at baseline (0), and after 3, 6, 12, 18, and 24 months except for the SF-36, which was not assessed at 3 months (no change within this time period for the SF-36 anticipated).

Radiographic evaluation

As tertiary measure, the change in joint space width (JSW) was evaluated. Standardized weight-bearing, semi-flexed posterior-anterior radiographs were obtained at baseline (0), 12, and 24 months post-treatment to assess structural outcome for the KJD_{TKA}, KJD_{HTO}, and HTO groups. An aluminum step wedge was used as a reference standard for linear measures and density. The images were evaluated using knee images digital analysis (KIDA) software[16] to analyze the minimum and mean JSW of the most affected compartment (MAC) of the knee. All image analyses were performed by a single, experienced observer, blinded to patient characteristics, and the intra-observer variation of this measurement method was shown to be good (ICC 0.73–0.99).[16]

Systemic biochemical marker analyses

In a smaller, open prospective study on KJD, a beneficial change in systemic cartilage biomarkers (serum/urine collagen type II biomarkers) was observed between 6 and 12 months of follow-up.[8] Therefore, in the present study, systemic collagen type II biomarkers were measured again in this combined for both studies, larger group of KJD patients. Serum and urine samples were collected from all KJD patients at baseline (0), 3, 6, 12, 18, and 24 months and stored at –80°C. Cartilage collagen type II synthesis and breakdown were determined by serum N-propeptide of type IIA procollagen (PIIANP; Linco, EZPIIANP-53K) and urinary C-telopeptide of type II collagen (CTXII; Cartilaps; corrected for urine creatinine), respectively. Longitudinal samples of each patient were analyzed in the same micro-titter plate to prevent influence of variability between kits.

Statistical analyses

Two-sided paired *t*-tests were used to evaluate changes between 2 years follow-up and baseline scores, for each group separately. Differences in changes between groups were evaluated using linear regression, corrected for baseline. For all graphs, the mean and standard error of the mean (SEM) are given. For the changes over 2 years' time, the mean and 95% confidence interval (95%CI) are given as well.

Biochemical marker measurements outside the 95%CI of each group (KJD_{TKA} or KJD_{HTO}) were defined as outliers and removed. Outlier exclusion was validated by a sensitivity analysis. Since there were no differences in relative biochemical marker response between the 2 KJD groups anticipated, the groups were combined to increase statistical power. For both biomarkers, combined normalized Z-scores were calculated, and the net collagen type II synthesis was expressed as a Z-index ($Z_{index} = Z_{PIIANP} - Z_{CTXII}$).

P-values <0.05 were considered statistically significant. SPSS v.22 software (IBM, Armonk, New York) was used to perform statistical analyses.

Results

Over the 2 years of follow-up, in the KJD_{TKA} group, 1 patient was lost to follow-up after undergoing TKA surgery because of unsatisfactory clinical benefit (after 9 months). In the TKA group, 4 patients withdrew consent before surgery and 2 patients were lost to follow-up due to comorbidities discovered after treatment.

In the KJD_{HTO} group, 1 patient was excluded before surgery due to inoperability and 2 patients were lost to follow-up after undergoing a TKA and HTO because of unsatisfactory treatment benefit (both after 12 months). In the HTO group, 1 patient was excluded before treatment due to anxiety and 4 patients were lost to follow-up because of comorbidities interfering with follow-up but unrelated to the procedure.

Of the remaining 114 patients (out of the original 129), the baseline characteristics are presented in Table 2.

Table 2: Baseline characteristics of patients from the 2 randomized controlled trials

	KJD *vs* TKA		**KJD *vs* HTO**	
	KJD_{TKA} (n=19)	**TKA (n=34)**	**KJD_{HTO} (n=20)**	**HTO (n=41)**
Male sex, n (%)	8 (42)	12 (35)	15 (75)	24 (58)
BMI (kg/m^2)	27.1 (3.8)	28.4 (6.0)	27.4 (3.3)	27.1 (3.3)
Age (years)	55.7 (7.4)	55.4 (6.0)	51.2 (5.8)	49.3 (6.3)
Leg axis (degrees)	2.1 (7.0)	2.8 (6.2)	5.9 (2.7)	6.1 (2.2)
Kellgren-Lawrence grade, (median, IQR)	4 (1.0)	3 (0.0)	3 (1.8)	3 (1.0)
- Grade 0, n (%)	0 (0)	0 (0)	0 (0)	1 (2)
- Grade 1, n (%)	0 (0)	0 (0)	5 (25)	4 (10)
- Grade 2, n (%)	1 (5)	7 (21)	4 (20)	11 (27)
- Grade 3, n (%)	8 (42)	21 (62)	10 (50)	21 (51)
- Grade 4, n (%)	10 (53)	6 (18)	1 (5)	4 (10)
Flexion (degrees)	121 (10.5)	123 (7.7)	130 (7.2)	132 (8.5)
Total WOMAC (0–100)	39.2 (15.6)	44.7 (20.6)	52.5 (20.5)	46.5 (19.6)
Total KOOS (0–100)	38.4 (9.2)	35.8 (11.6)	45.7 (14.4)	40.6 (12.8)
VAS pain (100–0)	63.8 (19.0)	71.9 (15.7)	52.3 (22.1)	64.7 (17.9)
EQ-5D (0–1)	0.66 (0.25)	0.61 (0.24)	0.70 (0.20)	0.72 (0.18)
ICOAP Combined (100–0)	57.7 (12.0)	64.9 (17.2)	54.2 (16.3)	58.5 (15.1)
SF-36 PCS (0–100)	33.6 (9.0)	31.3 (7.2)	37.7 (6.7)	35.8 (8.1)
SF-36 MCS (0–100)	54.5 (8.4)	54.0 (9.8)	55.0 (8.2)	55.1 (8.5)
Minimum JSW (mm)	0.65 (1.3)	-	0.49 (0.7)	0.54 (1.0)
Mean JSW (mm)	1.93 (2.0)	-	1.99 (1.5)	1.89 (1.2)

Mean and standard deviation are given unless otherwise indicated. BMI: body mass index; EQ-5D: EuroQol-5D; HTO: high tibial osteotomy; ICOAP: Intermittent and Constant Osteoarthritis Pain score; IQR: interquartile range; JSW: joint space width; KJD_{HTO}: KJD patients from the KJD *versus* HTO trial; KJD_{TKA}: knee joint distraction patients from the KJD *versus* TKA trial; KOOS: Knee injury and Osteoarthritis Outcome Score; MSC: mental component scale; PCS: physical component scale; SF-36: Short Form 36; TKA: total knee arthroplasty; VAS: Visual Analogue Scale; WOMAC: Western Ontario and McMaster Universities Osteoarthritis Index.

Patient-reported outcome measures

As primary outcome, a clear and clinically significant improvement in total WOMAC score (Figure 1) was present 2 years after treatment for all 4 groups (KJD_{TKA} Δ39; TKA Δ42; KJD_{HTO} Δ27; HTO Δ34; all p<0.001).

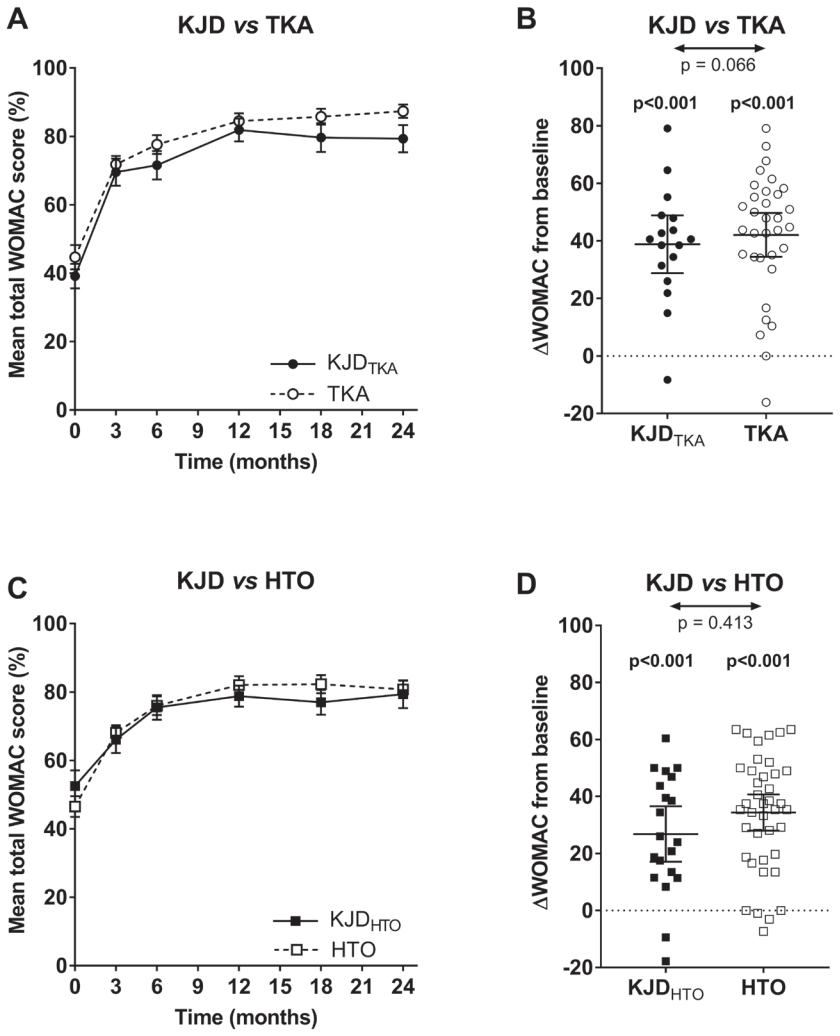


Figure 1: Total Western Ontario and McMaster Universities Osteoarthritis index (WOMAC). (A)WOMAC score over 2 years for the subgroups indicated for total knee arthroplasty (TKA) and treated with knee joint distraction (KJD_{TKA}) or TKA, represented as mean ± standard error of the mean (SEM). (B) Two-year change in WOMAC score for individual TKA-indicated patients (markers) and the subgroups (mean ± SEM, dashes). (C) Total WOMAC score over 2 years for the subgroups indicated for high tibial osteotomy (HTO) and treated with KJD (KJD_{HTO}) or HTO, represented as mean ± SEM. (D) Two-year change in WOMAC score for individual HTO-indicated patients (markers) and the subgroups (mean ± SEM, dashes). The p-values above subgroups indicate significant 2-year changes while the p-values between subgroups indicate the differences between each 2 groups.

As for secondary outcomes, the total KOOS (Figure 2) was significantly improved at 2 years for all 4 groups as well (KJD_{TKA} Δ29; TKA Δ43; KJD_{HTO} Δ22; HTO Δ30; all p<0.001). All 3 subscales of the WOMAC and 5 subscales of the KOOS as well as the VAS pain score, the EQ-5D, the SF-36 PCS, and the ICOAP showed similar positive trends, while only the SF-36 MCS showed almost no change compared to baseline (Table 3).

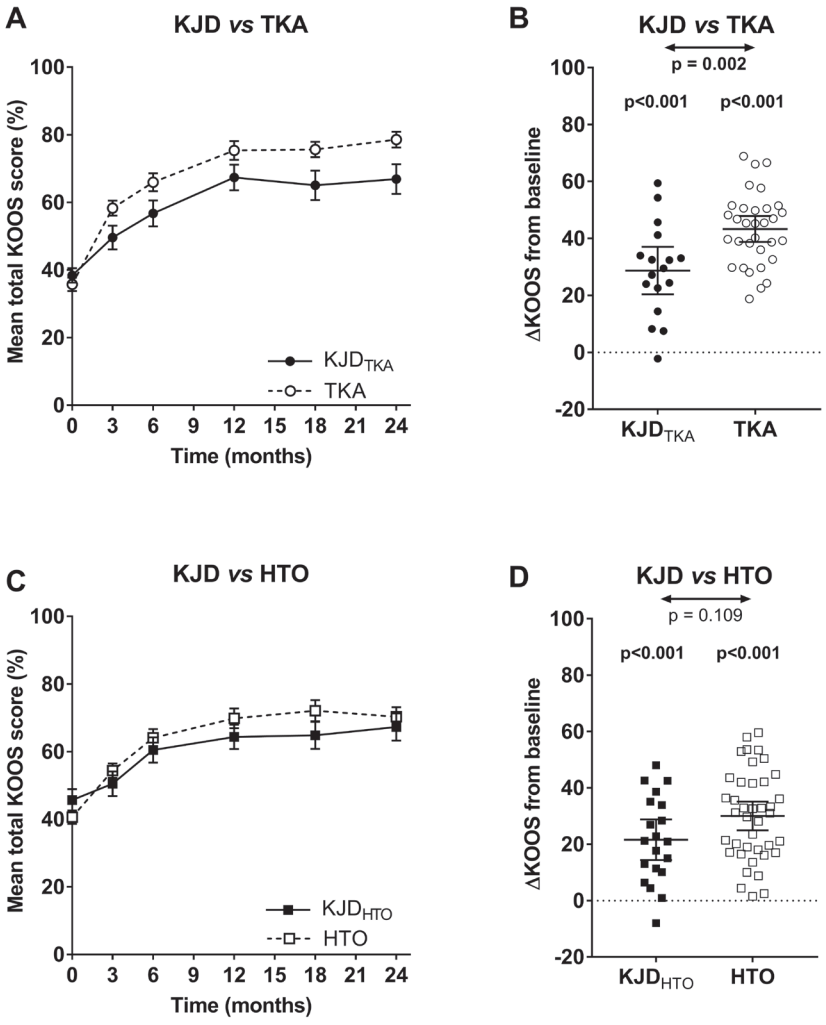


Figure 2: Total Knee injury and Osteoarthritis Outcome Score (KOOS). (A) KOOS score over 2 years for the subgroups indicated for total knee arthroplasty (TKA) and treated with knee joint distraction (KJD_{TKA}) or TKA, represented as mean ± standard error of the mean (SEM). (B) Two-year change in KOOS score for individual TKA-indicated patients (markers) and the subgroups (mean ± SEM, dashes). (C) Total KOOS score over 2 years for the subgroups indicated for high tibial osteotomy (HTO) and treated with KJD (KJD_{HTO}) or HTO, represented as mean ± SEM. (D) Two-year change in KOOS score for individual HTO-indicated patients (markers) and the subgroups (mean ± SEM, dashes). The p-values above subgroups indicate significant 2-year changes while the p-values between subgroups indicate the differences between each 2 groups.

KJD versus TKA

The TKA group showed statistically significantly greater improvements than the KJD_{TKA} group for most of the clinical parameters (Table 3), including the total KOOS and most of its subscales (all $p<0.035$), the VAS pain ($p=0.016$), the EQ-5D ($p=0.023$), and the SF-36 PCS ($p<0.001$). There was no significant difference for the total WOMAC ($p=0.066$), WOMAC stiffness ($p=0.098$), KOOS stiffness ($p=0.212$), the ICOAP ($p=0.089$), and ICOAP subscales (both $p>0.167$). As the change in WOMAC over 2 years was on average considerably more than 15 points and with that clinically significant, this change in WOMAC was not clinically relevantly different between both treatments (Δ38.9 (95%CI 28.8–48.9) points *versus* Δ42.1 (34.5–49.7)). The total WOMAC score at 2 years was 79.3 (70.9–87.8) for the KJD_{TKA} group and 87.4 (83.4–91.4) for the TKA group, indicating no clinically significant difference cross-sectionally at 2 years in the primary outcome.

Table 3: Two-year changes in clinical and structural parameters

		KJD *vs* TKA			**KJD *vs* HTO**		
		KJD_{TKA} (n=19)	**TKA (n=34)**	***P*-value**	**KJD_{HTO} (n=20)**	**HTO (n=41)**	***P*-value**
WOMAC (0–100)	Total	38.9 * (28.8 to 48.9)	42.1 * (34.5 to 49.7)	0.066	26.8 * (17.1 to 36.6)	34.4 * (28.0 to 40.7)	0.413
	Stiffness	25.8 * (14.2 to 37.4)	32.7 * (25.0 to 40.4)	0.098	16.2 * (5.2 to 27.3)	24.5 * (18.0 to 31.0)	0.337
	Pain	28.4 * (18.5 to 38.4)	43.6 * (37.0 to 50.1)	**0.008**	23.6 * (15.5 to 31.8)	31.8 * (25.4 to 38.3)	0.408
	Function	26.3 * (17.0 to 35.6)	40.9 * (35.7 to 46.2)	**0.016**	21.5 * (13.6 to 29.5)	28.9 * (23.0 to 34.7)	0.318
KOOS (0–100)	Total	28.7 * (20.4 to 37.1)	43.3 * (38.7 to 47.9)	**0.002**	21.6 * (14.4 to 28.8)	30.0 * (25.0 to 35.1)	0.109
	Symptom	28.3 * (20.5 to 36.0)	33.6 * (27.5 to 39.6)	0.212	16.7 * (10.2 to 23.3)	22.6 * (17.7 to 27.5)	0.276
	Pain	29.8 * (20.3 to 39.3)	47.9 * (42.3 to 53.5)	**0.001**	25.7 * (17.6 to 33.8)	32.5 * (27.0 to 38.1)	0.347
	Function	31.0 * (23.0 to 38.9)	42.5 * (38.2 to 46.9)	**0.034**	21.6 * (13.6 to 29.6)	28.9 * (23.1 to 34.8)	0.317
	Sport	28.3 * (14.6 to 42.0)	49.2 * (41.0 to 57.5)	**0.007**	25.7 * (15.1 to 36.3)	33.8 * (25.3 to 42.3)	0.314
	QOL	26.3 * (13.7 to 38.8)*	44.5 * (36.4 to 52.6)	**0.015**	17.7 * (10.1 to 25.2)	32.2 * (25.4 to 39.0)	**0.013**
VAS (100–0)	Pain	-31.9 * (-48.5 to -15.4)	-55.9 * (-64.3 to -47.6)	**0.016**	-21.4 * (-33.3 to -9.8)	-38.5 * (-46.2 to -30.7)	0.120
EQ-5D (0–1)	Index	0.10 (-0.02 to 0.22)	0.27 * (0.16 to 0.38)	**0.023**	0.16 * (0.06 to 0.26)	0.11 * (0.04 to 0.19)	0.564

Table 3: Two-year changes in clinical and structural parameters (*continued*)

		KJD *vs* TKA			KJD *vs* HTO		
		KJD_{TKA} (n=19)	**TKA (n=34)**	***P*-value**	**KJD_{HTO} (n=20)**	**HTO (n=41)**	***P*-value**
ICOAP (100–0)	Constant	-28.0 * (-35.7 to -20.3)	-39.2 * (-47.3 to -31.1)	0.089	-19.8 * (-28.8 to -10.7)	-22.9 * (-30.7 to -15.1)	0.770
	Intermittent	-26.0 * (-33.8 to -18.2)	-35.5 * (-42.4 to -28.7)	0.284	-17.1 * (-26.6 to -9.8)	-22.3 * (-28.9 to -15.7)	0.669
	Combined	-26.9 * (-34.5 to -19.4)	-37.2 * (-44.2 to -30.2)	0.168	-18.3 * (-27.3 to -9.2)	-22.6 * (-28.9 to 16.2)	0.673
SF-36 (0–100)	PCS	5.3 (-0.5 to 11.1)	17.9 * (14.6 to 21.2)	**<0.001**	6.5 * (2.6 to 10.4)	11.9 * (8.9 to 14.9)	0.051
	MCS	0.4 (-6.0 to 6.7)	-0.6 (-6.6 to 5.3)	0.728	1.0 (-2.9 to 4.9)	-1.1 (-4.5 to 2.3)	0.468
Flexion (°)	Knee	-	-	-	1.4 (-2.3 to 5.0)	-2.0 (-5.0 to 1.0)	0.254
JSW (mm)	Minimum	0.90 * (0.22 to 1.57)	-	-	0.94 * (0.50 to 1.37)	0.62 * (0.31 to 0.92)	0.233
	Mean	0.99 * (0.32 to 1.65)	-	-	0.83 * (0.34 to 1.32)	0.88 * (0.58 to 1.18)	0.884

Western Ontario and McMaster Universities Osteoarthritis index (WOMAC), Knee injury and Osteoarthritis Outcome Score (KOOS), Visual Analogue Scale (VAS), EuroQol (EQ)-5D, intermittent and constant osteoarthritis pain score (ICOAP), and Short Form (SF)-36 clinical scores and sub scores (PCS: Physical Component Score and MCS: Mental Component Score), maximum knee flexion and mean and minimum joint space width (JSW), for each of the 4 patient groups (total knee arthroplasty (TKA), knee joint distraction (KJD) patients indicated for TKA (KJD_{TKA}), high tibial osteotomy (HTO) and KJD patients indicated for HTO (KJD_{HTO}). Mean and 95% confidence intervals are given and ranges from worst to best are indicated for the clinical parameters. Statistically significant change ($p<0.05$) compared to baseline is indicated with *, calculated with paired *t*-tests. Changes between patient groups from each separate trial (KJD/TKA and KJD/HTO) are compared and corrected for baseline values using linear regression, bold *p*-values indicate statistical significance. Flexion parameters were not measured at 2 years in the KJD_{TKA} and TKA groups.

KJD versus HTO

The HTO and KJD_{HTO} groups showed no statistically significant differences in change from baseline (Table 3), except for the KOOS quality of life subscale, where HTO showed a greater improvement (p=0.013). The improvements over 2 years follow-up in total WOMAC score as primary outcome was clinically relevant for both treatment arms, exceeding the 15 points, whereas the change over 2 years was not clinically relevantly different between both treatments (Δ26.8 (95%CI 17.1–36.6) points *versus* Δ34.4 (28.0–40.7) points. With a total WOMAC score of 79.4 (70.9–87.8) for the KJD_{HTO} group and 80.8 (75.7–85.9) for the HTO group at 2 years, the cross-sectional difference at 2 years in the primary outcome was not clinically relevant either.

Radiographic evaluation

KJD versus TKA

In the KJD_{TKA} group, the minimum JSW increased significantly from 0.49 (SEM 0.27) mm at baseline to 1.55 (0.30) mm at 2 years (p=0.002) while the mean JSW of the MAC increased from 1.69 (0.50) mm to 2.70 (0.42) mm at 2 years (p=0.009), as shown in Figure 3. In the TKA group the JSW was not measured, since patients no longer had their native knee.

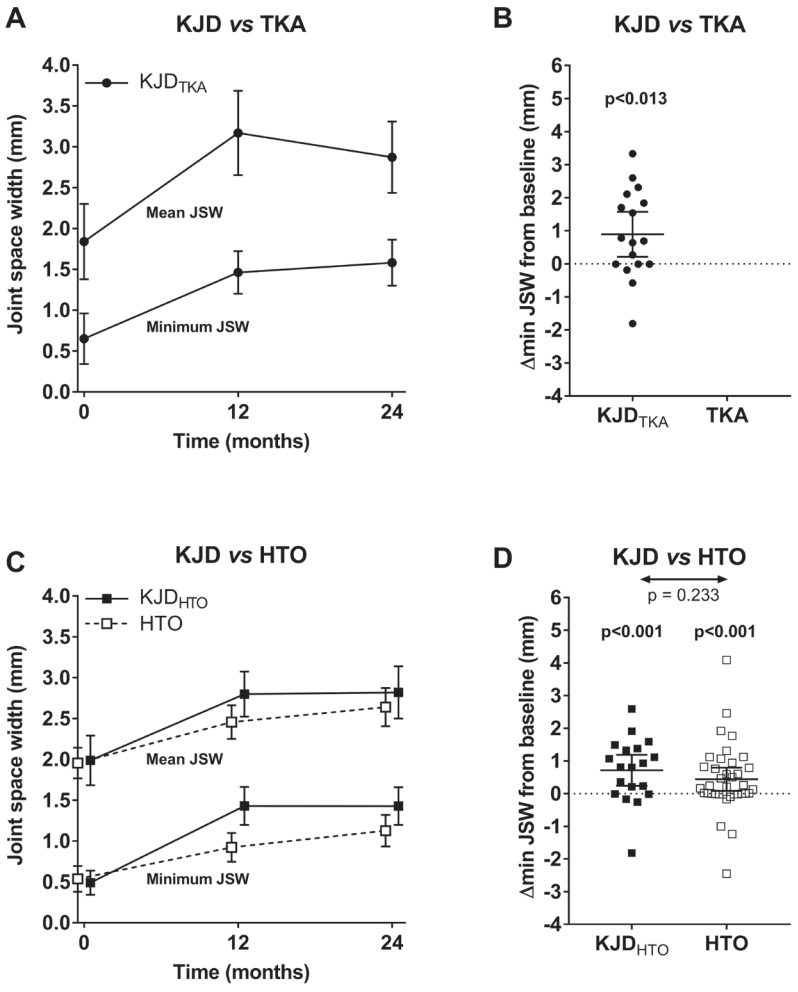


Figure 3: Joint space width (JSW). (A) Mean and minimum JSW over 2 years for the subgroup indicated for total knee arthroplasty (TKA) and treated with knee joint distraction (KJD_{TKA}), represented as mean ± standard error of the mean (SEM). (B) Two-year change in minimum JSW for individual TKA-indicated patients (markers) and the subgroup (mean ± SEM, dashes). (C) Mean and minimum JSW over 2 years for the subgroups indicated for high tibial osteotomy (HTO) and treated with KJD (KJD_{HTO}) or HTO, represented as mean ± SEM. (D) Two-year change in minimum JSW for individual HTO-indicated patients (markers) and the subgroups (mean ± SEM, dashes). The p-values above subgroups indicate significant 2-year changes while the p-values between subgroups indicate the differences between each 2 groups.

KJD versus HTO

In the KJD_{HTO} group the minimum JSW increased from 0.49 (SEM 0.15) mm to 1.43 (0.23) mm (p<0.001) and the mean JSW increased from 1.99 (0.33) mm to 2.82 (0.32) mm (p=0.002). In the HTO group, the minimum and mean JSW increased from 0.57 (SEM 0.16) mm to 1.19 (0.21) mm (p<0.001) and from 1.91 (0.20) mm to 2.80 (0.23) mm (p<0.001), respectively. For the 2-year increase in both mean and minimum JSW, there was no statistically significant difference between the KJD_{HTO} and HTO groups (both p>0.232; Table 3).

Biochemical marker analyses

In the KJD patients, normalized biochemical marker Z-scores showed a significant initial increase in collagen type II degradation marker CTXII, at 3 (p<0.001) and 12 (p=0.020) months, and a longer-term increase in collagen type II synthesis marker PIIANP at 12 (p=0.008) and 24 (p<0.001) months. The Z-index, indicating normalized net collagen type II synthesis, was statistically significantly decreased at 3 months (Δ-0.43 (SEM 0.20); p=0.035) and statistically significantly increased at 24 months (Δ0.59 (0.18); p=0.003) with respect to baseline, as shown in Figure 4. In these analyses, 16 of 452 measurements were excluded as outliers (15 points above 95%CI, 1 point below 95%CI). The sensitivity analysis including these outliers resulted in a loss of statistical significance only at 3 months (p=0.231), the 24 months normalized increase of synthesis over breakdown remained statistically significant (p=0.002). Performing the same analyses in the 2 KJD patient groups separately showed a similar pattern for both groups, although the differences from baseline were not statistically significant.

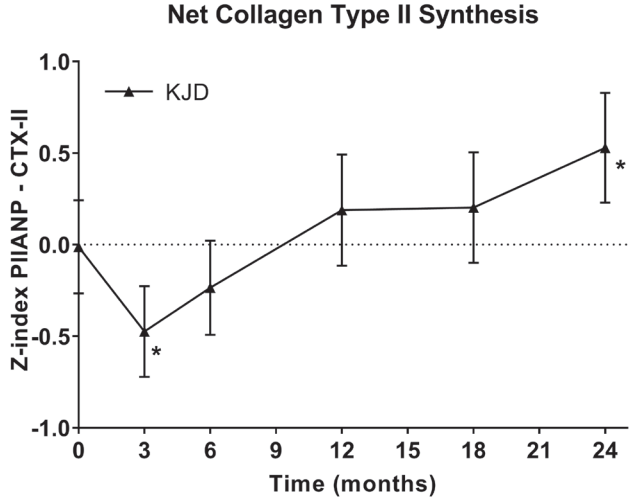


Figure 4: Collagen type II. Normalized biomarker Z-index over 2 years for all knee joint distraction (KJD) patients combined, expressing net collagen type II synthesis ($Z_{index} = Z_{PIIANP} - Z_{CTXII}$). Mean values ± standard error of the mean are shown. Statistically significant changes (p<0.05) compared to baseline are indicated with *.

Adverse events

Although a clear clinical benefit was observed for all 3 treatments, these treatments also come with a chance of adverse events. An overview of the adverse events after all treatments is given in Table 4. Of the knee joint distraction patients, about half of the patients had 1 or multiple pin tract infections, of which most (86%) were successfully treated with oral antibiotics. In the TKA group, 5 patients (14%) required knee manipulation under anesthesia because of postoperative stiffness while in the HTO group 2 patients (4%) experienced postoperative wound infection.

Table 4: Overview of adverse events

Knee joint distraction (KJD_{TKA}/KJD_{HTO})	
Pin tract infection	22 (10/12)
- Antibiotics oral	19 (10/9)
- Antibiotics intravenous	3 (0/3)
- with surgical irrigation and debridement	2 (0/2)
Osteomyelitis (3 weeks after frame removal)	
- Antibiotics intravenous with surgical irrigation and debridement	1 (0/1)
Possible infections diagnosed post-treatment	
- Antibiotics intravenous	2 (2/0)
Postoperative foot drop (ankle-foot orthosis)	1 (1/0)
Monotube failure (re-fixation)	1 (0/1)
Breaking of bone pin during fixation	1 (0/1)
Manipulation knee under anesthesia (17 days after frame removal)	1 (0/1)
Total knee arthroplasty	
Manipulation knee under anesthesia	5
Myocardial infarction (6 days postoperatively, percutaneous coronary intervention and pacemaker implantation)	1
High tibial osteotomy	
Wound infection	2
- Antibiotics oral	1
- Antibiotics intravenous	1
Erysipelas	1
- Antibiotics intravenous	1
Partial medial meniscectomy (affected knee, <6 months)	1

Number of patients is given. KJD_{HTO}: KJD patients from the clinical trial comparing KJD with high tibial osteotomy; KJD_{TKA}: knee joint distraction (KJD) patients from the clinical trial comparing KJD with total knee arthroplasty.

Discussion

Data from both independent randomized controlled trials demonstrated sustained patient-reported clinical benefit up to 2 years for all KJD, TKA, and HTO subgroups. This benefit was clinically relevant for all groups, based on exceeding an increase of 15 points of the total WOMAC scale.[14] KJD and HTO also demonstrated a sustained 2-year increase in radiographic

JSW. For both JSW improvement and clinical benefit, KJD was shown to be non-inferior to HTO. TKA showed better clinical efficacy at 2 years than KJD for the primary and most additional outcome measures, but at the expense of the native knee joint. Difference in clinical efficacy between the treatment arms in both trials was not clinically relevant and far below the 15 points on the WOMAC scale.

Despite the primary outcome not being clinically significantly different between KJD and TKA, the TKA group did show a general better response in most other clinical outcome parameters than the KJD_{TKA} group. While KJD could be considered an alternative to HTO, KJD is not meant to replace TKA, but to postpone a primary TKA and with that potentially prevent complex and costly revision surgery later in life. In patients where TKA has been performed after KJD, there were no complications, and similar beneficial outcomes were reported as TKA recipients that did not have prior KJD treatment.[17] A health technology assessment has demonstrated that a treatment strategy starting with KJD for severe conservative treatment resistant knee OA has a large potential for being a cost-effective intervention, especially for the relatively young patient.[18]

It should be noted that JSW measurements on radiographs depict the distance between bone ends, not actual cartilage thickness. Although in all cases weight-bearing radiographs were made, in case of HTO, opening of the joint space due to the correction[19] might have resulted in an overestimation of the observed JSW at the medial compartment not representing actual cartilage thickness.

Looking at the change in clinical outcome for all groups, almost all parameters are significantly increased (clinical, structural, and biochemical benefit) from baseline values. Data imputation of missing clinical data (including of those lost to follow-up) did not change significance of results or conclusions.

In addition to adverse effects as reported for these surgical treatments, KJD distraction resulted in pin tract infections in half of the patients. However, this is not different from pin tract infections in case of other treatments using external fixation devices.[20,21] While the amount of patients experiencing pin tract infections was lower than in previous KJD studies, as a result of an improved wound care protocol, it still determines a major burden for patients during treatment. Although all infections were successfully treated with antibiotics (mostly orally), there remains a risk for later prosthetic surgery. However, it has been reported that TKA performed within 5 years after KJD, did not result in any peri-surgical complications or prosthetic joint infections, with similar clinical benefit in those that had received KJD before TKA as compared to those that had not received a KJD before TKA.[17]

While these are data from the first 2 independent RCTs comparing 2-year follow-up of KJD

with TKA and with HTO, a prospective uncontrolled study has evaluated outcomes of 20 patients indicated for TKA that were treated with KJD.[8–10] The 2-year clinical results were comparable with the 2 years follow-up data from this study and in particular with the KJD_{TKA} group, which is expected since the 20 patients in the uncontrolled study were indicated for a TKA as well. Given the similar pattern in the first 2 years of the prospective study, the continued clinical benefit that was found up to 5 years[10] and even 9 years[22] after treatment should become evident in the follow-up of the current RCTs as well.

Despite the fact that TKA shows better clinical benefit, 12 patients (age range 52–86 years) with varied clinical history attended a 'patient partners' meeting and were informed on the difference in clinical outcome between KJD and TKA. They were asked if, with KJD not giving as much pain reduction as TKA, they would still consider KJD over a tried and tested TKA procedure. Patients said that retaining their own knee was of utmost importance and they would choose KJD over TKA (prof Pandit H, orthopedic surgeon, University of Leeds, personal communication March 2018).

The clinical and structural benefit at 2 years corresponds with a significantly increased net collagen type II synthesis, which suggests formation of (hyaline) cartilage. The increase in collagen type II synthesis at 2 years is caused by significantly increased levels of PIIANP, while the synthesis decrease seen at 3 months is the result of a significant initial increase in CTXII. It is important to keep in mind that while CTXII is a cartilage breakdown marker, it is also a marker for (subchondral) bone turnover. Subchondral bone density decrease and bone normalization have been shown after distraction of the knee and the ankle, and the initial increase in CTXII could be a result of this bone remodeling process as well, alone or in combination with cartilage breakdown.[9,23] The repair of hyaline cartilage upon KJD is supported by canine *in vivo* studies demonstrating beneficial changes in proteoglycan and collagen turnover.[24] Moreover, beneficial changes regarding proteoglycan content in these canine studies is supported by recent dGEMRIC evaluation in clinical KJD studies.[25]

A clear limitation of this study is the limited amount of patients in both trials, which were powered only for a non-inferiority study between the 2 patients groups. However, this is thus far the largest group of KJD patients followed over time and the results presented here clearly warrant further research with a bigger amount of patients.

In conclusion, evidence up to 2 years suggests KJD can be considered a valid alternative to HTO in knee OA patients with (<10°) varus malalignment and a method to postpone primary total knee arthroplasty, potentially preventing revision surgery later in life.

While future follow-up of these patients will provide additional insight into long term follow-up, the results presented in this study indicate KJD is a clinically useful joint-preserving strategy for relatively young patients with knee OA.

References

1. Kurtz SM, Lau E, Ong K, *et al*. Future young patient demand for primary and revision joint replacement: National projections from 2010 to 2030. Clinical Orthopaedics and Related Research. 2009;467(10):2606–12.
2. Mastbergen SC, Saris DBF, Lafeber FPJG. Functional articular cartilage repair: Here, near, or is the best approach not yet clear? Nature Reviews Rheumatology. 2013 May;9(5):277–90.
3. Efe T, Ahmed G, Heyse TJ, *et al*. Closing-wedge high tibial osteotomy: Survival and risk factor analysis at long-term follow up. BMC Musculoskeletal Disorders. 2011;12.
4. Niinimäki TT, Eskelinen A, Mann BS, *et al*. Survivorship of high tibial osteotomy in the treatment of osteoarthritis of the knee: Finnish registry-based study of 3195 knees. Journal of Bone and Joint Surgery British Volume. 2012 Nov;94(11):1517–21.
5. Jung WH, Takeuchi R, Chun CW, *et al*. Comparison of results of medial opening-wedge high tibial osteotomy with and without subchondral drilling. Arthroscopy – Journal of Arthroscopic and Related Surgery. 2015 Apr 1;31(4):673–9.
6. Jung WH, Takeuchi R, Chun CW, *et al*. Second-look arthroscopic assessment of cartilage regeneration after medial opening-wedge high tibial osteotomy. Arthroscopy – Journal of Arthroscopic and Related Surgery. 2014 Jan;30(1):72–9.
7. Spahn G, Klinger HM, Harth P, *et al*. Cartilage regeneration after high tibial osteotomyresults of an arthroscopic study. Zeitschrift fur Orthopadie und Unfallchirurgie. 2012;
8. Intema F, van Roermund PM, Marijnissen ACA, *et al*. Tissue structure modification in knee osteoarthritis by use of joint distraction: An open 1-year pilot study. Annals of the Rheumatic Diseases. 2011 Aug 1;70(8):1441–6.
9. Wiegant K, van Roermund PM, Intema F, *et al*. Sustained clinical and structural benefit after joint distraction in the treatment of severe knee osteoarthritis. Osteoarthritis and Cartilage. 2013 Nov;21(11):1660–7.
10. van der Woude JAD, Wiegant K, van Roermund PM, *et al*. Five-year follow-up of knee joint distraction: Clinical benefit and cartilaginous tissue repair in an open uncontrolled prospective study. Cartilage. 2017;8(3):263–71.
11. Wiegant K, van Heerwaarden R, van der Woude JAD, *et al*. Knee Joint distraction as an alternative surgical treatment for osteoarthritis: Rationale and design of two randomized controlled trials (*vs* high tibial osteotomy and total knee prosthesis). International Journal of Orthopaedics. 2015 Aug 23;2(4):353–60.
12. van der Woude JAD, Wiegant K, van Heerwaarden RJ, *et al*. Knee joint distraction compared with high tibial osteotomy: A randomized controlled trial. Knee Surgery, Sports Traumatology, Arthroscopy. 2017;25(3):876–86.
13. van der Woude JAD, Wiegant K, van Heerwaarden RJ, *et al*. Knee joint distraction compared with total knee arthroplasty: A randomised controlled trial. Bone and Joint Journal. 2017;99-B(1):51–8.
14. Escobar A, Quintana JM, Bilbao A, *et al*. Responsiveness and clinically important differences for the WOMAC and SF-36 after total knee replacement. Osteoarthritis and Cartilage. 2007 Mar;15(3):273–80.
15. Martineau PA, Fening SD, Miniaci A. Anterior opening wedge high tibial osteotomy: the effect of increasing posterior tibial slope on ligament strain. Canadian journal of surgery Journal canadien de chirurgie. 2010 Aug;53(4):261–7.
16. Marijnissen ACA, Vincken KL, Vos PAJM, *et al*. Knee Images Digital Analysis (KIDA): A novel method to quantify individual radiographic features of knee osteoarthritis in detail. Osteoarthritis and Cartilage. 2008 Feb 1;16(2):234–43.
17. Wiegant K, van Roermund PM, van Heerwaarden RJ, *et al*. Total knee prosthesis after knee joint distraction

treatment. Journal of Surgery and Surgical Research. 2015 Nov 5;1(3):066–71.

18. van der Woude JAD, Nair SC, Custers RJH, *et al*. Knee Joint distraction compared to total knee arthroplasty for treatment of end stage osteoarthritis: Simulating long-term outcomes and cost-effectiveness. PLOS ONE. 2016 May 12;11(5):e0155524.
19. Chiba K, Yonekura A, Miyamoto T, *et al*. Tibial condylar valgus osteotomy (TCVO) for osteoarthritis of the knee: 5-year clinical and radiological results. Archives of Orthopaedic and Trauma Surgery. 2017 Mar 1;137(3):303–10.
20. Lethaby A, Temple J, Santy-Tomlinson J. Pin site care for preventing infections associated with external bone fixators and pins. Cochrane Database of Systematic Reviews. 2013 Dec 3;2013(12).
21. Kazmers NH, Fragomen AT, Rozbruch SR. Prevention of pin site infection in external fixation: a review of the literature. Strategies in Trauma and Limb Reconstruction. 2016;11(2):75–85.
22. Jansen MP, van der Weiden GS, van Roermund PM, *et al*. Initial tissue repair predicts long-term clinical success of knee joint distraction as treatment for knee osteoarthritis. Osteoarthritis and Cartilage. 2018;26(12):1604–8.
23. Intema F, Thomas TP, Anderson DD, *et al*. Subchondral bone remodeling is related to clinical improvement after joint distraction in the treatment of ankle osteoarthritis. Osteoarthritis and Cartilage. 2011 Jun 1;19(6):668–75.
24. Wiegant K, Intema F, van Roermund PM, *et al*. Evidence of cartilage repair by joint distraction in a canine model of osteoarthritis. Arthritis and Rheumatology. 2015 Feb 28;67(2):465–74.
25. Besselink NJ, Vincken KL, Bartels LW, *et al*. Cartilage quality (dGEMRIC index) following knee joint distraction or high tibial osteotomy. Cartilage. 2018;1947603518777578.

SUPPLEMENTARY DATA

Letter to the editor

M.P. Jansen
F.P.J.G. Lafeber

Published in Cartilage, October 2020 [Epub ahead of print]

To the Editor,

Recently, The National Healthcare Institute of the Netherlands reviewed several publications on joint distraction to decide on reimbursement of this treatment in the Netherlands. During their survey, The National Healthcare Institute also reviewed the publication of Jansen *et al.* published in Cartilage.

On reviewing the publication, they found an inconsistency between described data and data presented in tables. Based on that they contacted us as main authors and inquired the correct data. As such, an immediate thorough recheck on all source data files was performed. It was discovered that there was indeed an inconsistency present for some of the parameters.

We feel that despite the minor difference between the published data and the correct data, and despite the fact that the general conclusion and discussion of the publication do not change, this needs to be amended. As such, we will outline the textual changes by presenting the updated text by paragraph, with changes shown in italics, and present updated versions of Table 2, Table 3, and Figure 1.

Abstract

At 2 years, the total WOMAC score (KJD_{TKA} +30.4 (95%CI 23.0–37.9) points; TKA +42.4 (38.1–46.8); KJD_{HTO} +21.6 (13.8–29.4); HTO +29.2 (23.6–34.8); all $p<0.05$) and radiographic minimum JSW (KJD_{TKA} +0.9 (9.2–1.6) mm; KJD_{HTO} +0.9 (0.5–1.4); HTO +0.6 (0.3–0.9); all $p<0.05$) were still increased for all groups.

Results

Patient-reported outcome measures

As primary outcome, a clear and clinically significant improvement in total WOMAC score (Figure 1) was present 2 years after treatment for all 4 groups (KJD_{TKA} Δ30; TKA Δ42; KJD_{HTO} Δ22; HTO Δ29; all $p<0.001$).

KJD versus TKA

The TKA group showed statistically significantly greater improvements than the KJD_{TKA} group for most of the clinical parameters (Table 3), including the total WOMAC and total KOOS and most of their subscales (all $p<0.035$), the VAS pain ($p=0.014$), the EQ-5D ($p=0.023$), and the SF-36 PCS ($p<0.001$). There was no significant difference for WOMAC stiffness ($p=0.277$), KOOS stiffness ($p=0.212$), the ICOAP ($p=0.216$), and ICOAP subscales (both $p>0.108$). As the change in WOMAC over 2 years was on average considerably more than

15 points and with that clinically significant, this change in WOMAC was not clinically relevantly different between both treatments: Δ30.4 (95%CI 23.0–37.9) points *versus* Δ42.4 (38.1–46.8). The total WOMAC score at 2 years was 81.0 (73.3–88.7) for the KJD_{TKA} group and 88.1 (84.2–91.9) for the TKA group, indicating no clinically significant difference cross-sectionally at 2 years in the primary outcome.

KJD versus HTO
The improvements over 2 years follow-up in total WOMAC score as primary outcome was clinically relevant for both treatment arms, exceeding the 15 points, whereas the change over 2 years was not clinically relevantly different between both treatments: Δ21.6 (95%CI 13.8–29.4) points *versus* Δ29.2 (23.6–34.8) points.

Radiographic evaluation

KJD versus TKA
In the KJD_{TKA} group, the minimum JSW increased significantly from 0.69 (SEM 0.33) mm at baseline to 1.58 (0.28) at 2 years (p=0.013) while the mean JSW of the MAC increased from 1.89 (0.51) to 2.87 (0.44) at 2 years (p=0.006), as shown in Figure 3.

(Note: The minimum and mean JSW changes are correct in the table and figure, but the numbers in the text are not correct for the KJD_{TKA} group.)

Tables and figure

Amended versions of Table 2, Table 3, and Figure 1 are included. In both tables, changes were made to the WOMAC, VAS pain, and ICOAP parameters, as indicated in italics. In Figure 1, the most important changes are seen in 1B and 1D, including a change in p-values for differences between groups, which in the case of KJD *versus* TKA is now significant.

On behalf of all authors,

Sincerely,

Mylène Jansen and Floris Lafeber

Amended Table 2: Baseline characteristics of patients from the 2 randomized controlled trials

	KJD *vs* TKA		KJD *vs* HTO	
	KJD_{TKA} (n=19)	**TKA (n=34)**	**KJD_{HTO} (n=20)**	**HTO (n=41)**
Male sex, n (%)	8 (42)	12 (35)	15 (75)	24 (58)
BMI (kg/m²)	27.1 (3.8)	28.4 (6.0)	27.4 (3.3)	27.1 (3.3)
Age (years)	55.7 (7.4)	55.4 (6.0)	51.2 (5.8)	49.3 (6.3)
Axis (degrees)	2.1 (7.0)	2.8 (6.2)	5.9 (2.7)	6.1 (2.2)
Kellgren-Lawrence grade, (median, IQR)	4 (1.0)	3 (0.0)	3 (1.8)	3 (1.0)
- Grade 0, n (%)	0 (0)	0 (0)	0 (0)	1 (2)
- Grade 1, n (%)	0 (0)	0 (0)	5 (25)	4 (10)
- Grade 2, n (%)	1 (5)	7 (21)	4 (20)	11 (27)
- Grade 3, n (%)	8 (42)	21 (62)	10 (50)	21 (51)
- Grade 4, n (%)	10 (53)	6 (18)	1 (5)	4 (10)
Flexion (degrees)	121 (10.5)	123 (7.7)	130 (7.2)	132 (8.5)
Total WOMAC (0–100)	*49.5 (10.8)*	*46.0 (12.4)*	*57.8 (17.8)*	*51.9 (17.0)*
Total KOOS (0–100)	38.4 (9.2)	35.8 (11.6)	45.7 (14.4)	40.6 (12.8)
VAS pain (100–0)	*68.2 (17.4)*	*72.6 (16.4)*	*52.5 (22.1)*	*64.4 (18.1)*
EQ-5D (0–1)	0.66 (0.25)	0.61 (0.24)	0.70 (0.20)	0.72 (0.18)
ICOAP Combined (100–0)	*46.4 (16.1)*	*56.8 (18.2)*	*46.2 (18.4)*	*50.0 (18.6)*
SF-36 PCS (0–100)	33.6 (9.0)	31.3 (7.2)	37.7 (6.7)	35.8 (8.1)
SF-36 MCS (0–100)	54.5 (8.4)	54.0 (9.8)	55.0 (8.2)	55.1 (8.5)
Minimum JSW, mm	0.65 (1.3)	-	0.49 (0.7)	0.54 (1.0)
Mean JSW, mm	1.93 (2.0)	-	1.99 (1.5)	1.89 (1.2)

Mean and standard deviation are given unless otherwise indicated. BMI: body mass index; EQ-5D: EuroQol-5D; HTO: high tibial osteotomy; ICOAP: Intermittent and Constant Osteoarthritis Pain score; IQR: interquartile range; JSW: joint space width; KJD_{HTO}: KJD patients from the KJD *versus* HTO trial; KJD_{TKA}: knee joint distraction patients from the KJD *versus* TKA trial; KOOS: Knee injury and Osteoarthritis Outcome Score; MSC: mental component scale; PCS: physical component scale; SF-36: Short Form 36; TKA: total knee arthroplasty; VAS: Visual Analogue Scale; WOMAC: Western Ontario and McMaster Universities Osteoarthritis Index.

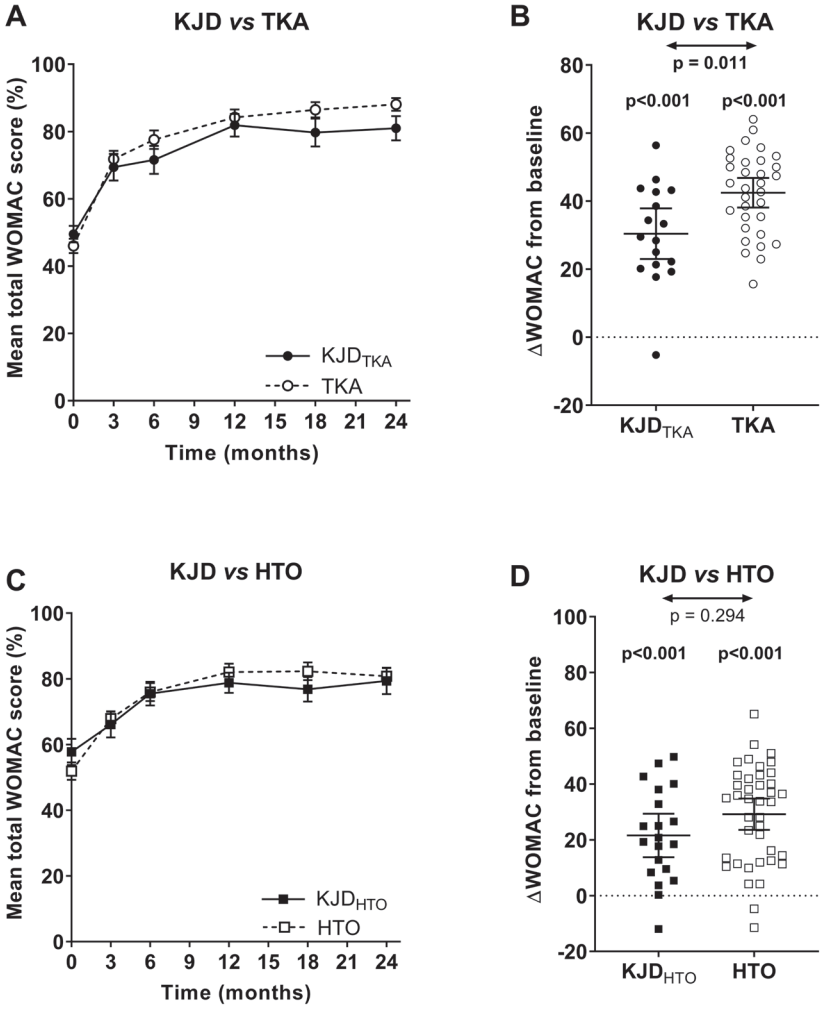
Amended Table 3: Two-year changes in clinical and structural parameters

		KJD *vs* TKA			KJD *vs* HTO		
		KJD_{TKA} (n=19)	**TKA (n=34)**	***P*-value**	**KJD_{HTO} (n=20)**	**HTO (n=41)**	***P*-value**
WOMAC (0–100)	*Total*	*30.4 * (23.0 to 37.9)*	*42.4 * (38.1 to 46.8)*	***0.011***	*21.6 * (13.8 to 29.4)*	*29.2 * (23.6 to 34.8)*	*0.294*
	Stiffness	*30.9 * (22.3 to 39.4)*	*34.4 * (27.2 to 41.6)*	*0.277*	*16.3 * (5.2 to 27.3)*	*24.8 * (18.2 to 31.4)*	*0.314*
	Pain	*28.5 * (18.5 to 38.4)*	*45.4 * (39.6 to 51.2)*	***0.003***	*23.7 * (15.5 to 31.9)*	*31.9 * (25.4 to 38.3)*	*0.416*
	Function	*31.0 * (23.0 to 38.9)*	*42.5 * (38.2 to 46.9)*	***0.033***	*21.6 * (13.7 to 29.6)*	*28.9 * (23.1 to 34.7)*	*0.319*

Amended Table 3: Two-year changes in clinical and structural parameters (*continued*)

		KJD *vs* TKA			KJD *vs* HTO		
		KJD_{TKA} (n=19)	**TKA (n=34)**	***P*-value**	**KJD_{HTO} (n=20)**	**HTO (n=41)**	***P*-value**
KOOS (0–100)	Total	28.7 * (20.4 to 37.1)	43.3 * (38.7 to 47.9)	**0.002**	21.6 * (14.4 to 28.8)	30.0 * (25.0 to 35.1)	0.109
	Symptom	28.3 * (20.5 to 36.0)	33.6 * (27.5 to 39.6)	0.212	16.7 * (10.2 to 23.3)	22.6 * (17.7 to 27.5)	0.276
	Pain	29.8 * (20.3 to 39.3)	47.9 * (42.3 to 53.5)	**0.001**	25.7 * (17.6 to 33.8)	32.5 * (27.0 to 38.1)	0.347
	Function	31.0 * (23.0 to 38.9)	42.5 * (38.2 to 46.9)	**0.034**	21.6 * (13.6 to 29.6)	28.9 * (23.1 to 34.8)	0.317
	Sport	28.3 * (14.6 to 42.0)	49.2 * (41.0 to 57.5)	**0.007**	25.7 * (15.1 to 36.3)	33.8 * (25.3 to 42.3)	0.314
	QOL	26.3 * (13.7 to 38.8)*	44.5 * (36.4 to 52.6)	**0.015**	17.7 * (10.1 to 25.2)	32.2 * (25.4 to 39.0)	**0.013**
VAS (100–0)	*Pain*	*-36.5 * (-49.8 to -23.2)*	*-56.0 * (-64.8 to -47.3)*	***0.014***	*-21.8 * (-34.8 to -8.8)*	*-38.4 * (-47.1 to -29.8)*	*0.269*
EQ-5D (0–1)	Index	0.10 (-0.02 to 0.22)	0.27 * (0.16 to 0.38)	**0.023**	0.16 * (0.06 to 0.26)	0.11 * (0.04 to 0.19)	0.564
ICOAP (100–0)	*Constant*	*-33.0 * (-43.5 to -22.5)*	*-48.8 * (-58.0 to -39.6)*	*0.109*	*-29.3 * (-39.6 to -19.0)*	*-29.8 * (-38.5 to -21.0)*	*0.913*
	Inter -mittent	*-32.6 * (-44.0 to -21.3)*	*-44.9 * (-52.4 to -37.5)*	*0.355*	*-25.3 * (-35.0 to -15.7)*	*-31.9 * (-39.7 to -24.0)*	*0.559*
	Combined	*-32.8 * (-43.6 to -22.0)*	*-45.6 * (-54.4 to -38.7)*	*0.216*	*-26.7 * (-36.3 to -17.1)*	*-30.4 * (-37.7 to 23.1)*	*0.692*
SF-36 (0–100)	PCS	5.3 (-0.5 to 11.1)	17.9 * (14.6 to 21.2)	**<0.001**	6.5 * (2.6 to 10.4)	11.9 * (8.9 to 14.9)	0.051
	MCS	0.4 (-6.0 to 6.7)	-0.6 (-6.6 to 5.3)	0.728	1.0 (-2.9 to 4.9)	-1.1 (-4.5 to 2.3)	0.468
Flexion (deg)	Knee	-	-	-	1.4 (-2.3 to 5.0)	-2.0 (-5.0 to 1.0)	0.254
JSW (mm)	Minimum	0.90* (0.22 to 1.57)	-	-	0.94* (0.50 to 1.37)	0.62* (0.31 to 0.92)	0.233
	Mean	0.99* (0.32 to 1.65)	-	-	0.83* (0.34 to 1.32)	0.88* (0.58 to 1.18)	0.884

Western Ontario and McMaster Universities Osteoarthritis index (WOMAC), Knee injury and Osteoarthritis Outcome Score (KOOS), Visual Analogue Scale (VAS), EuroQol (EQ)-5D, intermittent and constant osteoarthritis pain score (ICOAP), and Short Form (SF)-36 clinical scores and sub scores (PCS: Physical Component Score and MCS: Mental Component Score), maximum knee flexion and mean and minimum joint space width (JSW), for each of the 4 patient groups (total knee arthroplasty (TKA), knee joint distraction (KJD) patients indicated for TKA (KJD_{TKA}), high tibial osteotomy (HTO) and KJD patients indicated for HTO (KJD_{HTO}). Mean and 95% confidence intervals are given and ranges from worst to best are indicated for the clinical parameters. Statistically significant change ($p<0.05$) compared to baseline is indicated with *, calculated with paired *t*-tests. Changes between patient groups from each separate trial (KJD/TKA and KJD/HTO) are compared and corrected for baseline values using linear regression, bold *p*-values indicate statistical significance. Flexion parameters were not measured at 2 years in the KJD_{TKA} and TKA groups.



Amended Figure 1: Total Western Ontario and McMaster Universities Osteoarthritis index (WOMAC). (A) WOMAC score over 2 years for the subgroups indicated for total knee arthroplasty (TKA) and treated with knee joint distraction (KJD_{TKA}) or TKA, represented as mean ± standard error of the mean (SEM). (B) Two-year change in WOMAC score for individual TKA-indicated patients (markers) and the subgroups (mean ± SEM, dashes). (C) Total WOMAC score over 2 years for the subgroups indicated for high tibial osteotomy (HTO) and treated with KJD (KJD_{HTO}) or HTO, represented as mean ± SEM. (D) Two-year change in WOMAC score for individual HTO-indicated patients (markers) and the subgroups (mean ± SEM, dashes). The *p*-values above subgroups indicate significant 2-year changes while the *p*-values between subgroups indicate the differences between each 2 groups.

CHAPTER 5

Return to sport and work after randomization for knee distraction *versus* high tibial osteotomy
Is there a difference?

A. Hoorntje
P.F.M. Kuijer
K.L.M. Koenraadt
S. Waterval-Witjes
G.M.M.J. Kerkhoffs
S.C. Mastbergen
A.C.A. Marijnissen
M.P. Jansen
R.C.I. van Geenen

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Abstract

Background: Knee joint distraction (KJD) is a novel technique for relatively young knee osteoarthritis patients. With KJD, an external distraction device creates temporary total absence of contact between cartilage surfaces, which results in pain relief and possibly limits the progression of knee osteoarthritis. Recently, KJD showed similar clinical outcomes compared to high tibial osteotomy (HTO). Yet, no comparative data exist regarding return to sport (RTS) and return to work (RTW) after KJD. Therefore, our aim was to compare RTS and RTW between KJD and HTO.

Methods: We performed a cross-sectional follow-up study in patients <65 years who previously participated in a Randomized Controlled Trial comparing KJD and HTO. Out of 62 eligible patients, 55 patients responded and 51 completed the questionnaire (16 KJDs and 35 HTOs) at 5 years follow-up. The primary outcome measures were the percentages of RTS and RTW. Secondary outcome measures included time to RTS/RTW, and pre- and postoperative Tegner (higher is more active), and WORQ scores (higher is better work ability).

Results: Patients' baseline characteristics did not differ. One year after KJD, 79% returned to sport *versus* 80% after HTO (n.s.). RTS <6 months was 73% and 75% respectively (n.s.). RTW 1 year after KJD was 94% *versus* 97% after HTO (n.s.), and 91% *versus* 87% <6 months (n.s.). The median Tegner score decreased from 5.0 to 3.5 after KJD, and from 5.0 to 3.0 after HTO (n.s.). The mean WORQ score improvement was higher after HTO (16 (SD 16)) than after KJD (6 (13); p=0.04). Thus, no differences were found for sport- and work participation between KJD and HTO in our small, though first ever, cohort.

Conclusion: Overall, these findings may support further investigation into KJD as a possible joint-preserving option for challenging 'young' knee osteoarthritis patients.

Introduction

Demand for knee arthroplasty (KA) is rising worldwide, especially in younger patients. If this trend continues, by 2035 up to 50% of KAs will be performed in patients younger than 65 years of age.[1–3] Younger knee osteoarthritis (OA) patients are generally more active, are often still working and therefore frequently have high demands and expectations from their surgery.[4,5] Also, KA patients 50–65 years of age have a significantly increased risk of revision surgery, compared to older populations (>65 years), with 1 study reporting a lifetime revision risk of 1 in 3 in patients aged 50–55 years.[6,7] Also, higher rates of dissatisfaction have been reported in younger patients[8], and up to 50% of younger patients reported residual symptoms and limitations after contemporary total KA.[9] Hence, performing KA in this younger active population is unappealing to many surgeons, and as a treatment not a guarantee for satisfaction and return to desired activities for patients. Consequently, KA is often postponed in younger patients with severe functional limitations, who now find themselves trapped inside the so-called 'treatment gap'.[10,11]

To address this gap, the global interest for joint-sparing alternatives has significantly increased. Cartilage regeneration techniques are progressively studied, but still lack the scientific basis to justify broad implementation of these techniques in clinical practice.[12–14] However, osteochondral allograft transplantation techniques can successfully restore joint function in young (up to 55 years of age) and active patients with large focal or multifocal articular cartilage lesions.[15–17]

High tibial osteotomy (HTO) has also been increasingly advocated to treat this younger patient population[18,19] and thus expected to rise in the coming years. The pooled 10-year HTO survivorship, using KA as an endpoint, was 92% for opening-wedge HTO and 85% for closing wedge HTO.[20] Also, rates of return to sport (RTS) of 82–85% and return to work (RTW) of 85–95% have been reported after HTO.[21–23]

Knee joint distraction (KJD) is a less well-known but promising alternative joint-sparing treatment option in relatively young osteoarthritis patients with severe complaints. With KJD, an external distraction device creates a temporary load reduction between focal areas of cartilage surfaces in the knee.[24] Intema *et al.* showed that KJD treatment resulted in radiographic improvement of joint space width (JSW) and increased cartilage thickness on MRI, indicative of tissue structure modification that may have beneficial effects on patients' knee pain and symptoms.[25] A preserved treatment effect up to 5 years has been described, with increased minimum JSW at 5 years post-treatment compared to pre-treatment.[26] In addition, a randomized controlled trial (RCT) comparing KJD with HTO, for patients with medial compartment OA who were eligible for HTO, reported similar improvements for both groups in patient-reported clinical outcomes including the KOOS, WOMAC, VAS pain scores and

EQ-5D.[27,28] The most important difference regarding morbidity was the high incidence of pin tract infections in the KJD group (59%) compared to 5% of wound infections in the HTO group.[27] While the authors discussed the possibility of undertaking knee-demanding activities after KJD, including recreational sports, they did not report actual RTS and RTW rates. Therefore, our aim was to compare RTS and RTW rates, including time to RTS and RTW, between these KJD and HTO patients who participated in the RCT.

We hypothesized that KJD may lead to similar outcomes regarding participation in sport and work, and similar self-reported physical activity and work ability, compared to HTO.

Methods

Study design and patient selection

We performed a survey among patients that were included in an RCT between 2011 and 2013, comparing KJD and HTO.[27] All patients of the RCT were eligible for inclusion in the present study, since they were <65 years of age at inclusion and thus of working age. The inclusion criteria for the original RCT comparing KJD and HTO were: medial tibiofemoral OA considered for HTO, normal range of motion (≥120° of knee flexion), BMI<35 kg/m^2 and normal stability. An overview of the inclusion- and exclusion criteria of the RCT can be found in the supplementary data (Supplementary Table S1). Of the included sample of 69 patients (23 KJDs and 46 HTOs), 2 KJD patients were excluded due to inoperability, 1 HTO patient was diagnosed with multiple sclerosis and could not complete follow-up, and 4 patients (2 KJD, 2 HTO) declared that they did not want to participate in follow-up studies (Figure 1). An online questionnaire was developed using an electronic data management system (Castor EDC, www.castoredc.com). The remaining patients received an invitation by email between September and October 2017, followed by a maximum of 2 e-mail reminders. Institutional Review Board approval was obtained from the local medical ethical review board (reference number 17-538/C) prior to initiation of this study. The study was performed in accordance with the ethical principles from the Declaration of Helsinki and all patients gave written informed consent.

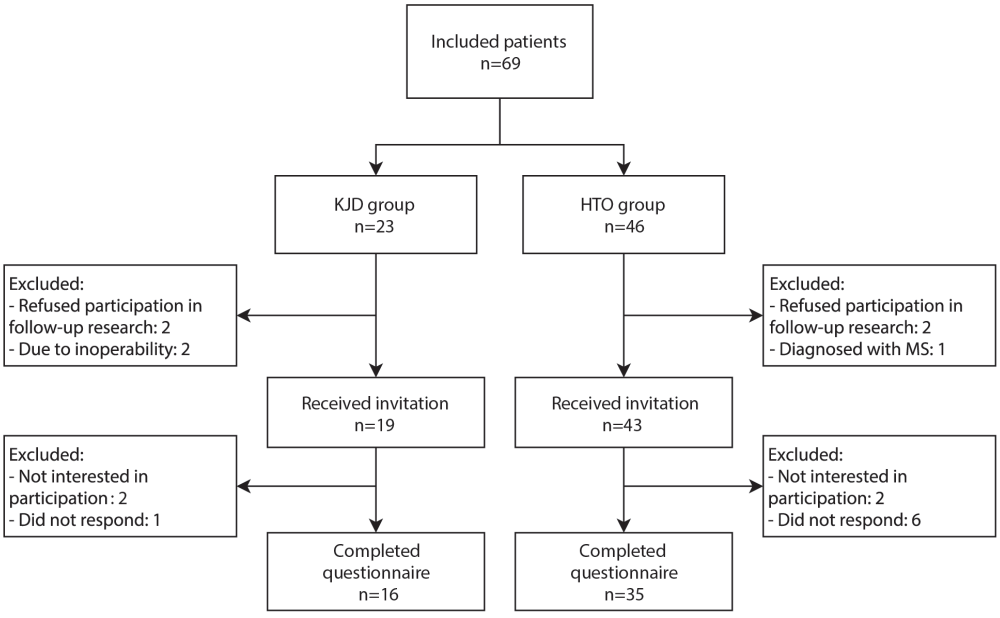

Figure 1: Inclusion flowchart. HTO: high tibial osteotomy; KJD: knee joint distraction; MS: multiple sclerosis.

Surgical techniques and postoperative rehabilitation

A detailed description of surgical techniques can be found in previous publications.[24,27,28] All HTO patients underwent a bi-planar, medial opening-wedge osteotomy[29] by 1 of 3 experienced surgeons. Preoperatively, the desired correction was determined on full leg standing radiographs using the Miniaci method.[30] For fixation, the TomoFix plate and screws (DePuy Synthes, Switzerland) or Synthes locking compression plate (LCP) (DePuy Synthes, Switzerland) were used (Figure 2a). Postoperatively, patients were allowed partial weight-bearing (up to 20 kg) for 6 weeks, followed by gradual full weight-bearing. Plate removal was routinely performed in all patients within 2 years.

For KJD, an external distraction device was used: 2 dynamic monotubes (Triax, Stryker, 45 kg spring with 2.5 mm displacement) were fixated to 8 bone pins (Figure 2b). The tubes were distracted 2 mm intra-operatively, followed by 1 mm of distraction per day up to a total of 5 mm of joint distraction. Weight-bearing radiographs were taken on day 4 to check the amount of distraction. When adequate distraction was obtained, patients were discharged and allowed full weight-bearing with crutches. Radiographic evaluation and pin tract inspection were performed after 3 weeks. The frame and pins were surgically removed after 6 weeks, followed by gradual increase to full weight-bearing in 6 weeks. Both HTO and KJD patients were prescribed subcutaneous low molecular weight heparin, for 6 and 9 weeks respectively. All patients were referred to regular outpatient physical therapy.

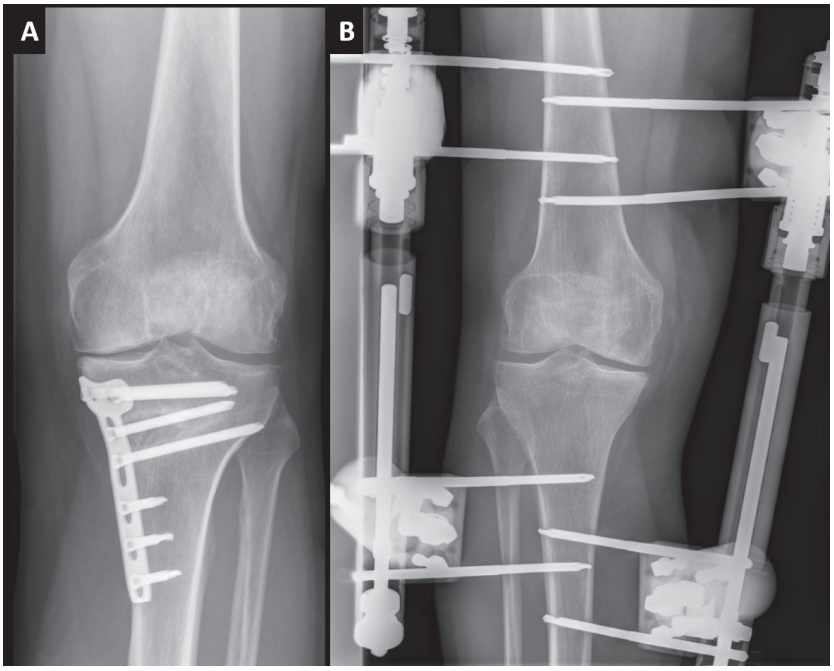

Figure 2: Examples of postoperative radiographs, (A) left knee treated with high tibial osteotomy, (B) right knee treated with knee joint distraction.

Sport and work outcome measures

Our primary outcome measures were the RTS and RTW rates after HTO and KJD at 6 and 12 months. Secondary outcome measures included time to RTS and RTW, the frequency, duration and type of performed sports, experienced difficulty performing work-related knee demanding activities and physical requirements of the jobs performed. Patients were asked to retrospectively report sports participation at 4 time points (presymptomatically, 1 year preoperatively, 1 year postoperatively and at final follow-up). RTS was defined as: a patient participating in 1 or more sports preoperatively (presymptomatically or 1 year preoperatively), who resumed participation in or more sports postoperatively (1 year postoperatively or final follow-up). Also, sports ability at follow-up, compared to the patient's best sports ability in their lifetime, was asked ("much worse", "worse", "unchanged", "improved", "much improved"). To assess the level of impact, sports activities were rated as low-, intermediate- or high-impact according to the classification by Vail *et al.*[31] Finally, the validated Tegner activity scale (0–10; higher is more physically active) and Lysholm score (0–100; higher is better function) were collected.[32] To assess experienced difficulty with work-related knee demanding activities, the 13-items validated WORQ questionnaire was used.[33] Patients grade the difficulty they experience when performing different activities on a 5-point Likert scale, with 4 indicating 'no difficulty' and 0 indicating 'extreme difficulty/unable to perform'. Patients were asked to retrospectively grade the difficulty at 3 time points: presymptomatically, 3 months preoperatively and 1

year postoperatively. The sum of the item scores can be converted to a 0–100 score, where 0 represents the worst and 100 the best possible score.[33] A score of 71 or more is classified as being satisfied with their work ability with respect to the knee, while a score of 50 or less is considered as being unsatisfied. In addition, job titles were classified as light, medium or heavy workload by 2 occupational experts, who independently scored all jobs based on work-related physical demands of the knee.[34,35] A more detailed description of the questionnaire can be found in a previous publication.[36]

Statistical analysis

A sample size calculation was performed for the primary RCT.[24] For the present study, a convenience sample was used, aiming for a response rate >80%. Demographic data, pre- and postoperative sport- and work participation were analyzed using descriptive statistics. Also, descriptive statistics were used to analyze time to RTS and RTW, frequency and duration of sports participation. RTS rate was calculated by selecting all patients that participated in 1 or more sports either presymptomatically, preoperatively or both, and calculating which percentage of these patients could RTS at 6 months and 1 year postoperatively. Given the 6-week delay in return to normal activities due to the distraction device, differences between KJD and HTO in RTS and RTW rates were analyzed at 2, 4 and 6 months, and at 1 year follow-up, using the chi-square test. To test for differences in sports participation (level, frequency, hours/week) and work participation (hours/week, workload) between groups, the Fisher's exact test was used. The Wilcoxon Signed-Rank test was used to compare presymptomatic and postoperative Tegner scores within groups. To test for differences between the KJD and HTO group, the Mann-Whitney *U* test was used for the ΔTegner score (postoperative minus presymptomatic score) and the unpaired *t*-test was used for the postoperative Lysholm score. The change in mean total WORQ scores from preoperative to final follow-up was compared using the unpaired *t*-test; mean and standard deviations (SD) are given. Next, the scores of all WORQ items at the 3 time points were dichotomized to determine how many patients experienced severe difficulty with a work-related knee-demanding activity. "Severe difficulty" and "extreme difficulty/unable to perform" were classified as "severe difficulty". "Moderate difficulty," "mild difficulty" and "no difficulty" were classified as "no severe difficulty". A *p*-value of $p<0.05$ was considered significant. All statistical analyses were performed with SPSS for Windows (Version 24.0. Armonk, NY: IBM Corp.).

Results

Out of 62 eligible patients, 55 patients responded (89%) and 51 patients completed the questionnaire (82%). Two KJD patients and 2 HTO patients declared that they were not interested in participation. Baseline characteristics of the respondents are presented in Table 1.

Table 1: Baseline characteristics of both groups

	KJD (n=16)	HTO (n=35)	*P*-value
Mean follow-up (years)	5.1 (0.7)	5.0 (0.6)	n.s.
Age (years)	50.5 (4.8)	49.6 (6.9)	n.s.
Female sex, n (%)	3 (19)	15 (43)	n.s.
BMI (kg/m^2)	27.1 (3.2)	27.2 (3.4)	n.s.
Right leg, n (%)	10 (63)	18 (51)	n.s.
Kellgren-Lawrence grade, n (%)			n.s.
- Grade 0	0 (0)	1 (3)	
- Grade 1	4 (25)	5 (14)	
- Grade 2	3 (19)	10 (29)	
- Grade 3	8 (50)	16 (46)	
- Grade 4	1 (6)	3 (9)	
Tibiofemoral axis (degrees)	6.1 (2.1)	6.2 (2.4)	n.s.
Previous surgery yes, n (%)			
- ACL reconstruction	2 (13)	2 (6)	
- Fixation OD lesion	0 (0)	1 (3)	
- Knee arthroscopy	11 (69)	26 (74)	
- Lateral release + tibial tuberosity transposition	0 (0)	1 (3)	
- Open medial meniscectomy	0 (0)	2 (6)	

Mean and standard deviation or n (%) are given. ACL: anterior cruciate ligament; BMI: body mass index; HTO: high tibial osteotomy; KJD: knee joint distraction; n.s.: not significant; OD: osteochondritis dissecans.

Sport-related outcomes

Out of 51 respondents, 44 patients had participated in 1 or more sports at some time point preoperatively (Table 2). In the KJD group, 11 out of 14 patients (79%) returned to 1 or more sports, compared to 24 out of 30 patients (80%) in the HTO group (Figure 3; n.s.). For the KJD and HTO group, the number of patients that returned to sport within 4 months was 18% and 33% respectively (n.s.), and within 6 months 73% and 75% respectively (n.s.).

No significant differences were found between both groups for sports frequency (times and hours per week) at any of the reported time points (Table 3). A shift from participation in high- and intermediate-impact sports to participation in intermediate- and low-impact sports was reported in both groups (Table 3; Supplementary Table S2).

Table 2: Sport participation in 1 or more sports at each time point

	KJD (n=14)	HTO (n=30)	*P*-value
Presymptomatic	14 (100)	30 (100)	1.00
- Recreational	3 (21)	10 (33)	
- Competitive/professional	11 (79)	20 (67)	
One year preoperative	12 (86)	26 (87)	1.00
- Recreational	10 (83)	21 (81)	
- Competitive/professional	2 (17)	5 (19)	
One year postoperative	9 (64)	20 (67)	0.91
- Recreational	9 (100)	17 (85)	
- Competitive/professional	–	3 (15)	
Final follow-up	10 (71)	22 (73)	1.00
- Recreational	10 (100)	19 (86)	
- Competitive/professional	–	3 (14)	

N (%) is given. HTO: high tibial osteotomy; KJD: knee joint distraction. *P*-values were calculated with Fisher's exact test.

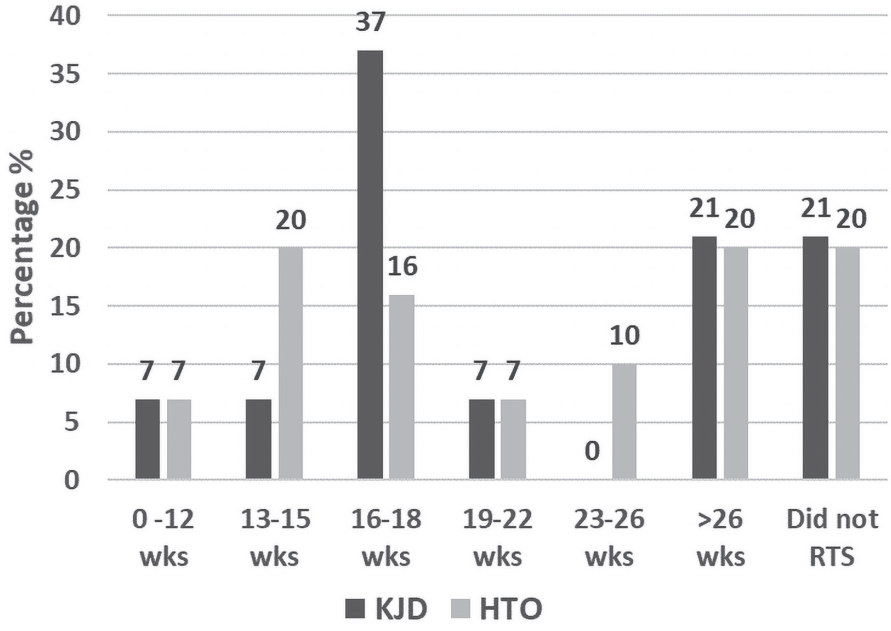

Figure 3: Time to return to sport (RTS) for the 2 groups. HTO: high tibial osteotomy; KJD: knee joint distraction.

Table 3: Sports frequency, participation, and level of impact for both groups

	Presymp		1 year preop		1 year postop		Final follow-up	
	KJD (n=14)	HTO (n=30)	KJD (n=14)	HTO (n=30)	KJD (n=14)	HTO (n=30)	KJD (n=14)	HTO (n=30)
*Sports frequency, times/wk**								
No participation	–	–	2 (14)	4 (13)	5 (36)	9 (30)	4 (29)	8 (27)
≤1	1 (7)	4 (13)	1 (7)	9 (30)	2 (14)	11 (37)	3 (22)	11 (37)
2	1 (7)	6 (20)	6 (43)	8 (27)	5 (36)	4 (13)	3 (22)	7 (23)
3	5 (36)	8 (27)	4 (29)	6 (20)	2 (14)	2 (7)	2 (14)	2 (7)
≥4	7 (50)	12 (40)	1 (7)	3 (10)	–	4 (13)	2 (14)	2 (7)
*Sports participation, hrs/wk**								
No participation	–	–	2 (14)	4 (13)	5 (36)	9 (30)	4 (29)	8 (27)
0 – 2	3 (22)	3 (10)	5 (36)	11 (37)	4 (29)	9 (30)	4 (29)	11 (37)
3 – 4	2 (14)	6 (20)	4 (29)	4 (13)	3 (21)	8 (27)	2 (14)	7 (23)
5 – 6	2 (14)	10 (33)	2 (14)	11 (37)	2 (14)	4 (13)	3 (21)	2 (7)
>6	7 (50)	11 (37)	1 (7)	–	–	–	1 (7)	2 (7)
Level of impact								
Low	38 (37)	67 (34)	23 (58)	41 (47)	21 (66)	42 (55)	25 (66)	43 (61)
Intermediate	28 (28)	81 (41)	11 (27)	33 (38)	9 (28)	31 (41)	12 (32)	23 (32)
High	35 (35)	49 (25)	6 (15)	13 (15)	2 (6)	3 (4)	1 (3)	5 (7)
Total sports	101 (–)	197 (–)	40 (–)	87 (–)	32 (–)	76 (–)	38 (–)	71 (–)

N (%) is given. *Due to rounding sum score can be >100%. hrs: hours; HTO: high tibial osteotomy; KJD: knee joint distraction; postop: postoperative; preop: preoperative; presymp: presymptomatic; wk: week

Compared to the patient's best sports ability in their lifetime, all KJD patients (100%) reported worse or much worse sports ability at final follow-up, compared to worse or much worse in 25 HTO patients (83%), unchanged in 1 HTO patient (3%) and improved or much improved in 4 HTO patients (13%) (n.s.). In the KJD group, the median Tegner score decreased from 5.0 (IQR 4.0–5.0) presymptomatically to 3.5 (3.0–4.0) 1 year postoperatively (p=0.02). In the HTO group, the median Tegner score decreased from 5.0 (IQR 4.0–7.0) presymptomatically to 3.0 (2.0–4.0) 1 year postoperatively (p<0.001). The median ΔTegner score was -1.0 (IQR -2.0 to 0) in the KJD group, compared to -1.0 (-3.0 to 0) in the HTO group (n.s.). The mean Lysholm score at follow-up was 67 (SD 10) in the KJD group compared to 65 (23) in the HTO group (n.s.).

Work-related outcomes

In the KJD group, 16 patients (100%) were working before the onset of restricting knee symptoms, and 3 months preoperatively 15 patients (94%) were still working. In the HTO group, 32 out of 35 patients (91%) were working before the onset of knee symptoms, and 3 months preoperatively 29 patients (83%) were still working. Postoperatively, 15 out of 16 KJD patients (94%) returned to work, compared to 31 out of 32 HTO patients (97%; n.s.). The RTW rate within 2 months was 27% in the KJD group and 45% in the HTO group (n.s.). The RTW rate within 4 months was 53% in the KJD group and 72% in the HTO

group (n.s.), and the RTW rate within 6 months was 91% in the KJD group and 87% in the HTO group (Figure 4; n.s.).

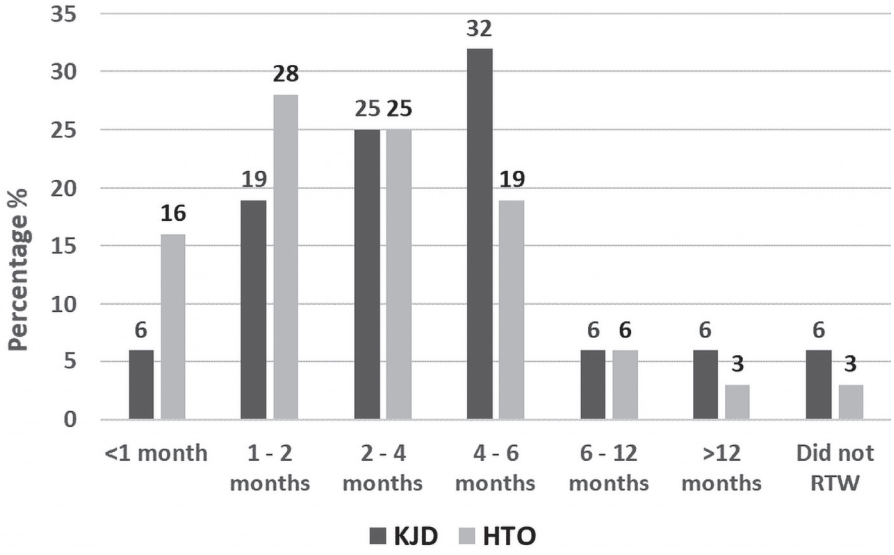

Figure 4: Time to return to work (RTW) for the 2 groups. HTO: high tibial osteotomy; KJD: knee joint distraction.

None of the KJD patients and 1 HTO patient-reported knee complaints as the reason for no RTW. The presymptomatic workload, preoperative workload and changes in postoperative workload did not significantly differ between both groups (Table 4). The number of working hours also did not significantly differ between both groups 3 months preoperatively, 1 year postoperatively and at final follow-up (Supplementary Table S3).

Table 4: Presymptomatic and preoperative workload, and postoperative change in workload, for both groups

Workload	Presymp HTO	Presymp KJD	Preop HTO	Preop KJD	Postop change in workload	HTO	KJD
Light	62	44	66	47	Lighter	–	7
Intermediate	19	19	17	13	Equal	91	93
High	19	37	17	40	Higher	9	–
P-value	0.36		0.25			0.19	

% Of patients is given. HTO: high tibial osteotomy, KJD: knee joint distraction; postop: postoperative; preop: preoperative; presymp: presymptomatic. *P*-values were calculated with Fisher's exact test.

The improvement (Δ) in mean WORQ scores from preoperatively to postoperatively was higher in the HTO group (16 (SD 16)) than in the KJD group (6 (13); p=0.04). For the KJD group, most patients experienced severe difficulty with kneeling (44%), clambering (38%) and walking on rough terrain preoperatively (38%; Figure 5a). The largest postoperative improvements were reported for walking on rough terrain (-25% reporting extreme difficulty), clambering (-19%) and kneeling (-19%; Figure 5a). For the HTO group, ≥50% of patients experienced severe difficulty with kneeling, crouching, clambering and taking the stairs 3

months preoperatively (Figure 5b). The largest postoperative improvements were reported for taking the stairs (-38%), clambering (-32%) and kneeling (-29%) (Figure 5b).

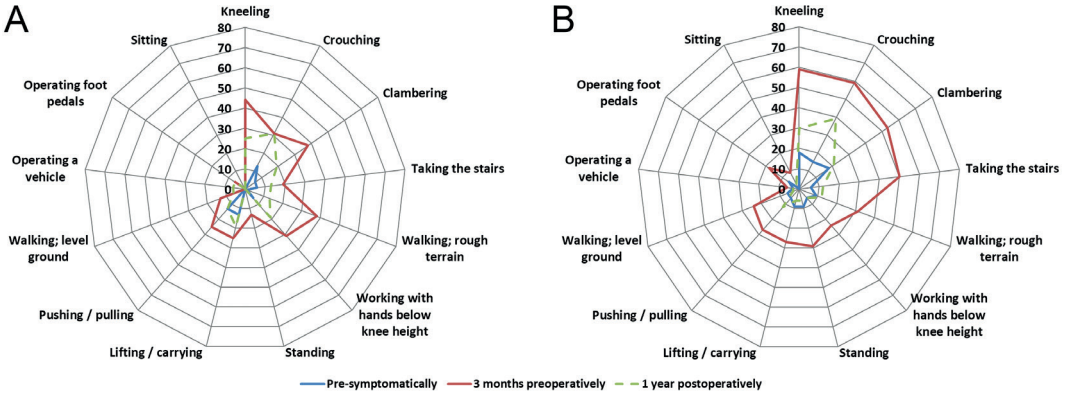

Figure 5: Reported difficulty with 13 work-related activities for the knee joint distraction group (A) and high tibial osteotomy group (B) at 3 time points. The percentage of patients that experienced severe difficulty is depicted for each task.

Discussion

The present survey among patients who previously participated in an RCT comparing KJD with HTO showed similar sport- and work-related outcomes for both groups. The RTS rate was 79% in the KJD group, compared to 80% in the HTO group. The RTW rate was 94% in the KJD group compared to 97% in the HTO group. Overall, 7 out of 10 patients returned to sports within 6 months and 9 out of 10 patients returned to work within 6 months. Time to RTS and RTW did not differ between both groups. The improvement in mean WORQ score from pre- to postoperative was slightly higher in the HTO group. Thus, our initial findings, the first RTS/RTW data in KJD patients, may support the hypothesis that KJD might result in comparable postoperative sport- and work participation, compared to HTO, although larger cohorts are clearly warranted to verify this hypothesis.

No data exist on RTS after KJD, but the present RTS rates of 79% after KJD and 80% after HTO are in line with the RTS rate of 85% after HTO that was found in a meta-analysis.[21] Although the overall time to RTS did not differ, we did observe a trend of more HTO patients returning within 4 months (33% *versus* 18%), which was likely not statistically significant due to the small sample size. A possible explanation for the lower percentage of KJD patients that RTS ≤4 months is the distraction device.[26] Interestingly, no KJD patients reported improved sports ability at follow-up compared to 13% of HTO patients. Still, the median Tegner score was 3.5 in the KJD group compared to 3.0 in the HTO group, which could indicate somewhat higher mean postoperative activity levels for the KJD group. For both groups, the postoperative Tegner scores were lower than the reported presymptomatic Tegner scores. Eleven previous

studies on HTO reported median postoperative Tegner scores ranging from 2.5 to 5.9, where the latter was found in a specific population (athletes).[21] Next, participation in low-, intermediate- and high-impact sports did not differ either. Here, we observed the same trend of lower postoperative participation in intermediate- and high-impact sports that was described previously after distal femoral osteotomy, HTO and KA.[22,36,37] Lastly, sports participation in terms of level, times per week and hours per week showed similar trends between both groups, namely postoperative participation at a lower level and less frequently. This decline is also in line with previous findings after HTO and KA.[21,37] Still, at final follow-up patients reported sports participation levels and frequencies comparable to 1 year postoperatively, indicating a sustained treatment effect over 5 years. Thus, our initial findings appear to be in line with previous studies on RTS after joint-sparing surgery for knee OA.

The reported RTW rates for KJD and HTO (94% resp. 97%) were higher than expected, since a systematic review found a pooled estimate of 85% RTW after HTO.[21] For KJD, this was the first study to report RTW, hampering comparison with existing literature. Still, 94% RTW is an encouraging finding, possibly facilitated by maintaining the native knee joint, as well as removing all external material after 6 weeks, compared to plate removal after 1–2 years in the HTO group. Again, larger cohort studies are mandatory to verify RTW rates after KJD. Next, time to RTW did not differ overall, although 53% of KJD patients returned after ≤4 months compared to 72% in the HTO group. As stated, this difference might be explained by the 6-week period of knee immobilization for KJD, which limits rehabilitation and thus slows the return to work activities. RTW outcomes should be further analyzed in adequately powered studies, since slower RTW after KJD may be clinically meaningful to the patient, and also has a negative societal impact given the financial consequences of slower RTW. Next, the improvement in WORQ scores was significantly higher in the HTO group (16 points *versus* 6 points), compared to KJD. While Kievit *et al.* reported a difference of 13 points for the WORQ to be clinically meaningful to the patient[33], a difference of 10 points in favor of HTO may certainly indicate a better postoperative ability to perform knee-demanding activities, compared to KJD. Additionally, the mean WORQ score of 73 in the HTO group was above the satisfaction threshold of 71[33], while the mean score of 69 in the KJD group was slightly below this threshold. In comparison, Kievit *et al.* reported mean WORQ scores of 71 after total KA (TKA) and 77 after unicompartmental KA (UKA).[38] As expected, kneeling and crouching presented most difficulty for both groups postoperatively. Yet, both groups appeared to experience less postoperative difficulty with these activities compared to TKA and UKA patients[38], although this comparison is hampered by the difference in mean age (50 years in our cohort *versus* 60 years in the KA cohort). Thus, regarding work-related outcome measures, HTO showed better outcomes than KJD in the present study.

Although KJD has shown promise in the treatment of knee OA, the current scientific basis remains small and literature on long-term outcomes is lacking.[39] Therefore, patient counseling should include these existing uncertainties, and the fact that TKA showed an overall better response in clinical outcome parameters at 2 years, including the total KOOS, VAS pain and EQ-5D, compared to KJD in the only RCT to date.[28] Yet, 15 out of 18 patients in the KJD group, who were initially indicated for TKA, had still not undergone TKA at 5 years follow-up.[26] Based on these findings, the authors concluded that KJD should not be considered a TKA replacement but rather a new treatment option to possibly postpone primary TKA.[26,28] Regarding sport and work participation, a significantly increased revision risk has been reported in younger, active TKA patients.[6,7] Clearly, maintaining the native knee joint decreases the future risk of prosthesis wear and associated revision procedures if KA is eventually performed. Thus, for patients with invalidating knee OA who wish to return to sport and work activities, KJD may become a viable treatment option and a possible alternative to HTO. Yet, much work remains to be done in order to provide a broader scientific basis for KJD.

In the only RCT to date, KJD and HTO showed similar clinical outcomes.[27,28] However, 13 KJD patients (59%) developed pin tract infections, the most frequent complication after KJD.[27] Nine patients were treated with oral antibiotics, while 3 patients were administered intravenous antibiotics and 2 patients required surgical debridement. In contrast, only 2 HTO patients (4%) developed wound infections, treated with oral and intravenous antibiotics respectively. Also, KJD patients experienced more discomfort with activities of daily living the first postoperative weeks due to the distraction device.[40] While KJD patients require standard surgical removal of the distraction device 6 weeks postoperatively, up to 71% of HTO patients require hardware removal, i.e. a new operation with its associated risks, due to hardware irritation.[41] Obviously, all the above should be discussed with the patient when considering KJD and HTO as treatment options for invalidating knee OA.

The most important limitation of the present study is the small group size for KJD, which limited statistical power for comparisons between the HTO- and KJD group. However, this was expected given that only 103 KJD cases have been described in prospective studies worldwide.[39] Therefore, our findings may be considered a general indication of the expected RTS and RTW after KJD, and no definite conclusions can be drawn yet. Another limitation is our retrospective design. Preferably, future prospective studies on KJD should include sport- and work outcome measures to control for this limitation. Finally, the small group size also complicates the generalizability and thus external validity of the present findings. Especially for KJD, distinct eligibility criteria as well as long-term outcome data clearly need to be established prior to broader implementation of this novel technique.

In conclusion, in the present first albeit small cohort study, knee joint distraction in patients indicated for high tibial osteotomy resulted in comparable postoperative participation in

sport and work, compared to high tibial osteotomy. Overall time to RTS and RTW did not differ in our cohort, and HTO patients were slightly more satisfied with their performance of knee-demanding activities. These findings should be confirmed in larger cohort studies, to further define the role of knee joint distraction in the treatment algorithm for the challenging population of 'young' knee OA patients.

References

1. Kurtz SM, Lau E, Ong K, *et al*. Future young patient demand for primary and revision joint replacement: National projections from 2010 to 2030. Clinical Orthopaedics and Related Research. 2009;467(10):2606–12.
2. Otten R, van Roermund PM, Picavet HSJ. Trends in the number of knee and hip arthroplasties: Considerably more knee and hip prostheses due to osteoarthritis in 2030. Nederlands Tijdschrift voor Geneeskunde. 2010;154(20):A1534.
3. Culliford D, Maskell J, Judge A, *et al*. Future projections of total hip and knee arthroplasty in the UK: Results from the UK Clinical Practice Research Datalink. Osteoarthritis and Cartilage. 2015;23(4):594–600.
4. Nilsdotter AK, Toksvig-Larsen S, Roos EM. Knee arthroplasty: Are patients' expectations fulfilled? A prospective study of pain and function in 102 patients with 5-year follow-up. Acta Orthopaedica. 2009;80(1):55–61.
5. Witjes S, van Geenen RC, Koenraadt KL, *et al*. Expectations of younger patients concerning activities after knee arthroplasty: Are we asking the right questions? Quality of Life Research. 2017;26(2):403–17.
6. Bayliss LE, Culliford D, Monk AP, *et al*. The effect of patient age at intervention on risk of implant revision after total replacement of the hip or knee: A population-based cohort study. The Lancet. 2017 Apr 8;389(10077):1424–30.
7. Santaguida PL, Hawker GA, Hudak PL, *et al*. Patient characteristics affecting the prognosis of total hip and knee joint arthroplasty: A systematic review. Canadian Journal of Surgery. 2008;51(6):428–36.
8. Lange JK, Lee YY, Spiro SK, *et al*. Satisfaction rates and quality of life changes following total knee arthroplasty in age-differentiated cohorts. Journal of Arthroplasty. 2018;33(5):1373–8.
9. Parvizi J, Nunley RM, Berend KR, *et al*. High level of residual symptoms in young patients after total knee arthroplasty knee. Clinical Orthopaedics and Related Research. 2014;472(1):133–7.
10. Khan M, Adili A, Winemaker M, *et al*. Management of osteoarthritis of the knee in younger patients. CMAJ. 2018;190(3):E72–9.
11. Arnold MP, Hirschmann MT, Verdonk PCM. See the whole picture: Knee preserving therapy needs more than surface repair. Knee Surgery, Sports Traumatology, Arthroscopy. 2012;20(2):195–6.
12. Orth P, Gao L, Madry H. Microfracture for cartilage repair in the knee: A systematic review of the contemporary literature. Knee Surgery, Sports Traumatology, Arthroscopy. 2020;28(3):670–706.
13. de Windt TS, Vonk LA, Brittberg M, *et al*. Treatment and prevention of (early) osteoarthritis using articular cartilage repair – Fact or fiction? A Systematic Review. Cartilage. 2013;4(3 SUPPL.).
14. Harris JD, Siston RA, Pan X, *et al*. Autologous chondrocyte implantation: A systematic review. Journal of Bone and Joint Surgery. 2010;92(12):2220–33.
15. Zitsch BP, Stannard JP, Worley JR, *et al*. Patient-reported outcomes for large bipolar osteochondral allograft transplantation in combination with realignment osteotomies for the knee. Journal of Knee Surgery. 2020 May;
16. Stannard JP, Cook JL. Prospective assessment of outcomes after primary unipolar, multisurface, and bipolar osteochondral allograft transplantations in the knee: A comparison of 2 preservation methods. American Journal of Sports Medicine. 2020 May;48(6):1356–64.
17. Brusalis CM, Greditzer HG, Fabricant PD, *et al*. BioCartilage augmentation of marrow stimulation procedures for cartilage defects of the knee: Two-year clinical outcomes. Knee. 2020;27(5):1418–25.
18. Seil R, van Heerwaarden R, Lobenhoffer P, *et al*. The rapid evolution of knee osteotomies. Knee Surgery, Sports Traumatology, Arthroscopy. 2013;21(1):1–2.
19. Price A, Beard D, Thienpont E. Uncertainties surrounding the choice of surgical treatment for "bone on

bone" medial compartment osteoarthritis of the knee. Knee. 2013;20(SUPPL.1):S16–20.

20. Kim J-H, Kim H-J, Lee D-H. Survival of opening *versus* closing wedge high tibial osteotomy: A meta-analysis. Scientific Reports. 2017 Dec 4;7(1):7296.
21. Hoorntje A, Witjes S, Kuijer PPFM, *et al*. High Rates of return to sports activities and work after osteotomies around the knee: A systematic review and meta-analysis. Sports Medicine. 2017;47(11):2219–44.
22. Hoorntje A, Kuijer PPFM, van Ginneken BT, *et al*. Prognostic factors for return to sport after high tibial osteotomy: A directed acyclic graph approach. American Journal of Sports Medicine. 2019;47(8):1854–62.
23. Hoorntje A, Kuijer PPFM, van Ginneken BT, *et al*. Predictors of return to work after high tibial osteotomy: The importance of being a breadwinner. Orthopaedic Journal of Sports Medicine. 2019;7(12):1–10.
24. Wiegant K, van Heerwaarden R, van der Woude JAD, *et al*. Knee Joint distraction as an alternative surgical treatment for osteoarthritis: Rationale and design of two randomized controlled trials (*vs* high tibial osteotomy and total knee prosthesis). International Journal of Orthopaedics. 2015 Aug 23;2(4):353–60.
25. Intema F, van Roermund PM, Marijnissen ACA, *et al*. Tissue structure modification in knee osteoarthritis by use of joint distraction: An open 1-year pilot study. Annals of the Rheumatic Diseases. 2011 Aug 1;70(8):1441–6.
26. van der Woude JAD, Wiegant K, van Roermund PM, *et al*. Five-year follow-up of knee joint distraction: Clinical benefit and cartilaginous tissue repair in an open uncontrolled prospective study. Cartilage. 2017;8(3):263–71.
27. van der Woude JAD, Wiegant K, van Heerwaarden RJ, *et al*. Knee joint distraction compared with high tibial osteotomy: A randomized controlled trial. Knee Surgery, Sports Traumatology, Arthroscopy. 2017;25(3):876–86.
28. Jansen MP, Besselink NJ, van Heerwaarden RJ, *et al*. Knee Joint distraction compared with high tibial osteotomy and total knee arthroplasty: Two-year clinical, radiographic, and biochemical marker outcomes of two randomized controlled trials. Cartilage. 2019 Feb 13;194760351982843.
29. Brinkman J-M, Lobenhoffer P, Agneskirchner JD, *et al*. Osteotomies around the knee. Journal of Bone and Joint Surgery British. 2008;90-B(12):1548–57.
30. Miniaci A, Ballmer FT, Ballmer PM, *et al*. Proximal tibial osteotomy: A new fixation device. Clinical Orthopaedics and Related Research. 1989;(246):250–9.
31. Vail TP, Mallon WJ, Liebelt RA. Athletic activities after joint arthroplasty. Sports Medicine and Arthroscopy Review. 1996;4(3):298–305.
32. Eshuis R, Lentjes GW, Tegner Y, *et al*. Dutch translation and cross-cultural adaptation of the lysholm score and tegner activity scale for patients with anterior cruciate ligament injuries. Journal of Orthopaedic and Sports Physical Therapy. 2016;46(11):976–83.
33. Kievit AJ, Kuijer PPFM, Kievit R, *et al*. A reliable, valid and responsive questionnaire to score the impact of knee complaints on work following total knee arthroplasty: The WORQ. Journal of Arthroplasty. 2014;29(6):1169–75.
34. Kuijer PPFM, van der Molen HF, Frings-Dresen MHW. Evidence-based exposure criteria for workrelated musculoskeletal disorders as a tool to assess physical job demands. Work. 2012;41(suppl.1):3795–7.
35. Proper KI, van den Heuvel SG, de Vroome EM, *et al*. Dose-response relation between physical activity and sick leave. British Journal of Sports Medicine. 2006;40(2):173–8.
36. Hoorntje A, van Ginneken BT, Kuijer PPFM, *et al*. Eight respectively nine out of ten patients return to sport and work after distal femoral osteotomy. Knee Surgery, Sports Traumatology, Arthroscopy. 2019;27(7):2345–53.
37. Witjes S, Gouttebarge V, Kuijer PPFM, *et al*. Return to sports and physical activity after total and unicondylar

knee arthroplasty: A systematic review and meta-analysis. Sports Medicine. 2016;46(2):1–24.

38. Kievit AJ, Kuijer PPFM, de Haan LJ, *et al*. Patients return to work sooner after unicompartmental knee arthroplasty than after total knee arthroplasty. Knee Surgery, Sports Traumatology, Arthroscopy. 2020;28(9):2905–16.
39. Goh EL, Lou WCN, Chidambaram S, *et al*. The role of joint distraction in the treatment of knee osteoarthritis: A systematic review and quantitative analysis. Orthopedic Research and Reviews. 2019;11:79–92.
40. van der Woude JAD, Wiegant K, van Heerwaarden RJ, *et al*. Knee joint distraction compared with total knee arthroplasty: A randomised controlled trial. Bone and Joint Journal. 2017;99-B(1):51–8.
41. Duivenvoorden T, van Diggele P, Reijman M, *et al*. Adverse events and survival after closing- and opening-wedge high tibial osteotomy: A comparative study of 412 patients. Knee Surgery, Sports Traumatology, Arthroscopy. 2017;25(3):895–901.

SUPPLEMENTARY DATA

Supplementary Table S1: Inclusion and exclusion criteria for the original randomized controlled trial
Inclusion criteria
Age <65 years
Radiological joint damage: Kellgren and Lawrence score >2 (as indicated by orthopedic specialist)
Intact knee ligaments
Normal range of motion (minimum of 120 degrees flexion)
Normal stability
Body mass index <35 kg/m^2
Patients with medial tibiofemoral compartmental OA considered for HTO according to regular clinical practice
Exclusion criteria
Psychological inabilities or difficult to instruct
Not able to undergo MRI examination (standard protocol)
Inflammatory or rheumatoid arthritis present or in history
Posttraumatic fibrosis due to fracture of the tibial plateau
Bone-to-bone contact in the joint (absence of any joint space on radiograph)
Surgical treatment of the involved knee
Primary patellofemoral OA
Mechanic varus axis deviation of more than 10 degrees
Contralateral knee OA that needs treatment
HTO: high tibial osteotomy; MRI: magnetic resonance imaging; OA: osteoarthritis.

Supplementary Table S2: Low-, intermediate-, and high-impact sports activities included in the questionnaire, and the total number of participants for each sport at 4 time points

Level of impact	Sport	Presymp	1 year preop	1 year postop	At final FU
Low	Nordic walking	3	0	0	0
Low	Cycling	35	26	28	32
Low	Bike racing	13	6	6	6
Low	Swimming	21	16	16	18
Low	Aqua aerobics	3	1	1	1
Low	Cross-country skiing	5	2	1	1
Low	Golf	3	3	2	3
Low	Table tennis	3	2	2	0
Low	Dancing	11	3	2	3
Low	Sailing	5	3	2	0
Low	Rowing	3	2	3	4
Intermediate	Inline skating	5	3	1	0
Intermediate	Hiking	19	6	7	10
Intermediate	Mountain climbing	3	2	1	1
Intermediate	Mountain biking	4	6	4	4
Intermediate	Fitness/weight training	20	13	16	13
Intermediate	Aerobics	8	1	1	1
Intermediate	Gymnastics	4	0	0	0
Intermediate	Downhill skiing	13	3	3	2
Intermediate	Snowboarding	2	0	0	0
Intermediate	Ice skating	17	3	2	2
Intermediate	Tennis (doubles)	10	5	2	1
Intermediate	Horse riding	4	2	3	1
High	Jogging	20	6	0	2
High	Ice hockey	0	0	0	0
High	Tennis (singles)	13	5	1	1
High	Squash	7	1	0	0
High	Badminton	6	2	2	0
High	Soccer	13	2	1	1
High	Handball	4	0	0	0
High	Volleyball	7	1	0	0
High	Baseball	0	0	0	0
High	Martial arts	6	1	1	1
High	Water skiing	2	0	0	0
High	Basketball	4	0	0	0
High	Hockey	0	0	0	0
High	Rugby	2	0	0	0

Level of impact according to Vail et al.[31] FU: follow-up; postop: postoperative; presymp: presymptomatic; preop: preoperative.

Supplementary Table S3: Working hours at 3 time points for both groups

Working hours	Preop HTO	Preop KJD	1 year postop HTO	1 year postop KJD	Final FU HTO	Final FU KJD
0–8 h						
9–16 h	3		4		4	
17–24h	14	13	9	20	12	25
25–32h	28	20	30	27	27	8
33–40h	38	47	37	40	42	50
>40 h	17	20	20	13	15	17
P-value	0.98		0.94		0.74	

FU: follow-up; HTO: high tibial osteotomy; KJD: knee joint distraction; OA: osteoarthritis; post-op: postoperative; presymp: presymptomatic; preop: preoperative. *P*-values were calculated with Fisher's exact test.

CHAPTER 6

Knee joint distraction in regular care for treatment of knee osteoarthritis

A comparison with clinical trial data

M.P. Jansen
S.C. Mastbergen
R.J. van Heerwaarden
S. Spruijt
M.D. van Empelen
E.C. Kester
F.P.J.G. Lafeber & R.J.H. Custers

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Abstract

Background: Knee joint distraction (KJD) has been evaluated as a joint-preserving treatment to postpone total knee arthroplasty in knee osteoarthritis patients in 3 clinical trials. Since 2014 the treatment is used in regular care in some hospitals, which might lead to a deviation from the original indication and decreased treatment outcome. In this study, baseline characteristics, complications and clinical benefit are compared between patients treated in regular care and in clinical trials.

Methods: In our hospital, 84 patients were treated in regular care for 6 weeks with KJD. Surgical details, complications, and range of motion were assessed from patient hospital charts. Patient-reported outcome measures were evaluated in regular care before and 1 year after treatment. Trial patients (n=62) were treated and followed as described in literature.

Results: Patient characteristics were not significantly different between groups, except for distraction duration (regular care 45.3 (SD 4.3); clinical trials 48.1 (8.1) days; p=0.019). Pin tract infections were the most occurring complication (70% regular care; 66% clinical trials), but there was no significant difference in treatment complications between groups (p>0.1). The range of motion was recovered within a year after treatment for both groups. WOMAC questionnaires showed statistically and clinically significant improvement for both groups (both p<0.001 and >15 points in all subscales) and no significant differences between groups (all differences p>0.05). After 1 year, 70% of patients were responders (regular care 61%, trial 75%; p=0.120). Neither regular care compared to clinical trial, nor any other characteristic could predict clinical response.

Conclusion: KJD as joint-preserving treatment in clinical practice, to postpone arthroplasty for end-stage knee osteoarthritis patient below the age of 65, results in an outcome similar to that thus far demonstrated in clinical trials. Longer follow-up in regular care is needed to test whether also long-term results remain beneficial and comparable to trial data.

Introduction

Knee osteoarthritis (OA) is characterized by articular cartilage degeneration and is an important cause of pain and disability in adults.[1,2] While total knee arthroplasty (TKA) is a widely accepted intervention for end-stage knee OA, it poses a major healthcare burden when placed in younger patients, since they have a higher risk of needing a costly and less effective revision surgery later in life.[3–6]

Knee joint distraction (KJD) is a joint-preserving treatment for knee OA for younger patients, where the knee joint is temporarily fully unloaded by distraction of tibia and femur, using an external fixation frame.[7] In an open prospective study (OPS) between 2006 and 2008, 20 knee OA patients below the age of 60, indicated for TKA were treated for 8 weeks with KJD.[8] These patients showed long-term, in the first 2 years progressive, significant clinical benefit and cartilage tissue regeneration. In over 3 quarters of the patients, TKA could be postponed for over 5 years, and half of the patients was still without prosthesis 9 years after treatment.[8–11] After this trial the distraction period was shortened to 6 weeks, as this was considered sufficient.[12] Between 2011 and 2014, the 6-week KJD was studied in comparison to TKA or to high tibial osteotomy (HTO) in 2 separate randomized controlled trials (RCTs). In both trials combined, 41 KJD patients gained significant clinical and structural benefit in the first year, which was shown to be maintained up to at least 2 years after treatment. Both trials demonstrated that KJD was non-inferior to the alternative treatment.[13–15] Since 2014, KJD is offered as a regular care treatment in a limited number of hospitals for knee OA patients under the age of 65.

Often when a new treatment proceeds from clinical trial to regular care, indications for treatment broaden and treatment outcome weakens. As such, treatment and surgery details, baseline characteristics, complications during treatment, and treatment efficacy of KJD in regular care were compared with clinical trial (OPS/RCT) conditions.

Methods

Patients

In regular care, at the department of Orthopedic Surgery in our hospital patients are offered KJD in case they are considered for TKA but still younger than 65. According to local guidelines for treating patients with TKA, patients have had sufficient conservative treatment, but with insufficient success and a Kellgren-Lawrence grade (KLG) of at least 2. Patients with presence or history of inflammatory joint condition, joint prosthesis elsewhere in the body (potential risk of prosthetic joint infection), or physical or social conditions that do not support a 6-week distraction period, are ineligible. The standard procedure at the department of orthopedics is that patients are asked for consent to use their anonymized data for future research purposes,

which all patients in the present study provided. Official ethical approval was ruled as not required by the medical ethical review committee of the University Medical Center Utrecht (protocol number 17-005C) and all patients give written informed consent.

In the open prospective study (OPS) and the 2 randomized controlled trials (RCTs), inclusion criteria were: medial tibiofemoral compartmental OA; intact knee ligaments; normal range-of-motion (min. of 120° flexion); normal stability; BMI <35; visual analogue scale of pain ≥60 mm, radiographic signs of joint damage and tibiofemoral OA (radiological joint damage KLG >2 as judged by the orthopedic surgeon). Exclusion criteria were (among others): presence or history of inflammatory or septic arthritis; severe knee malalignment (>10°) requiring surgical correction; psychological inabilities or difficult to instruct; joint prosthesis elsewhere in the body; not able to undergo MRI examination; post traumatic fibrosis due to fracture of the tibial plateau; surgical treatment of the involved knee <6 months ago; contra-lateral knee OA that needs treatment; primary patellofemoral OA. For the OPS the age was <60 years, for the RCTs <65 years. For the OPS and RCT *versus* TKA, all patients had to be considered for TKA. For the RCT *versus* HTO, all patients had to be considered for HTO, with medial compartmental knee OA with a varus deviation of <10°. All inclusion aspects have been described in detail for all 3 studies, previously.[8,13,14,16] All trials were granted ethical approval by the medical ethical review committee of the University Medical Center Utrecht (protocol numbers 04/086, 10/359/E, and 11/072) and registered in the Netherlands Trial Register (trial numbers NL419, NL2761 and NL2680). All patients gave written informed consent.

Knee joint distraction treatment

KJD was performed by fixating an external distraction device to the femur and tibia using 8 half pins according to a standardized surgical procedure. In all patients, a device was used consisting of 2 distraction tubes with internal springs, 1 placed medially and 1 laterally of the knee joint (Figure 1). The half pins (self-drilling, 5 mm diameter) used to fixate the distraction tubes were placed in pairs at 4 different locations (tibia/femur and medial/lateral), all placed outside the knee joint area to prevent complications during a potential future prosthesis surgery.[17] The medial femoral pins were positioned parallel to the knee joint line in an approximately 10° dorsomedial-ventrolateral direction (10° angulation to the frontal plane) to minimize interference of the half pins with the quadriceps muscles. The lateral femoral pins were placed parallel to the knee joint line, perpendicular to the tibial bone axis, and approximately in the frontal plane. The medial tibial half pins were positioned parallel to the knee joint space, and if possible perpendicular to tibial bone axis and the anteromedial tibial face, approximately at 35° to the frontal plane. The lateral tibial half pins used the same slope of approximately 35° to the frontal plane. Proper positioning and depth, with slight protrusion of the half pin (of the pointed tip only) through the second cortex, was checked using fluoroscopy (C-arm). After positioning the half pins and distraction tubes, according to standardized surgical procedures,

a distraction distance of 2 mm was provided intra-operatively. All this was performed under general or spinal anesthesia, depending on the surgeon's and patient's preference.

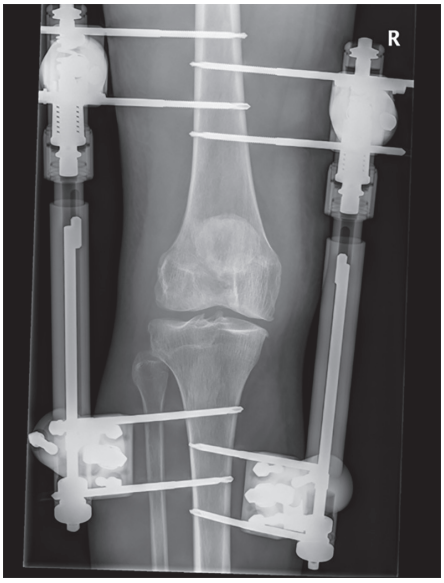

Figure 1: Representative radiograph of the external distraction frame in use.

In regular care

In regular care, the average intervention time (the time between the first incision and the surgeon being finished) was 53 (range 31–79) minutes. Blood loss during surgery was in all cases negligible. After surgery, patients generally stayed in the hospital for another 2 to 3 days, during which the tubes were gradually distracted until 5 mm distraction was reached. At completion, the distraction distance was checked on weight-bearing radiographs and adapted if needed. During the distraction period weight-bearing, supported with crutches if needed, was allowed and encouraged. This provides intra-articular fluid pressure changes, considered relevant for nutrition of the cartilage, because of 3 mm axial displacement under 80 kg of weight-bearing of the internal springs.[18,19] Patients received low molecular weight heparin for 6 weeks and a standard prescription for 7 days of oral antibiotics (flucloxacillin). If patients suspected a pin tract infection, based on consulting their physician, a course of flucloxacillin was started. During the distraction period, patients visited the outpatient clinic once for a general evaluation. After 6 weeks, the distraction frame was removed and knee manipulation (flexion-extension) was performed under general or spinal anesthesia at day-treatment. The total frame removal time in regular care was 16 minutes (range 7–36) and patients were discharged the same day.

Under trial conditions

The above described treatment was used for all patients included in the RCTs as well. However, the patients treated in the OPS received 8 instead of 6 weeks of distraction and returned to the hospital every 2 weeks, where the tubes were temporarily removed and the knee was flexed and extended by use of continuous passive motion device for 3 to 4 hours. Pain at the pin sites determined the maximum degree of flexion (mean 25°; range 15°–80°).[8]

Follow-up

In regular care, weight-bearing PA radiographs were taken and the range of motion (ROM) was measured presurgery and at 4 and 12 months after frame removal in the outpatient clinic. A standard registry for all orthopedic patients provided data on patient-reported outcome measures (PROMs). Patients were requested to fill out several PROMs by questionnaires, before surgery and 3, 6, and 12 months after surgery, and every year thereafter. This is done automatically by e-mail, without reminder, causing relatively high numbers of missing data.

Trial patients were seen at comparable time points (6 and 12 months after frame placement) where the ROM was measured and questionnaires were filled out on paper, causing limited missing data. One-year follow-up results have been published previously for each trial separately.[8,13,14]

No standardized radiographs were made in regular care and for that reason in clinical practice, the in previous trials reported cartilaginous tissue repair could only be confirmed quantitatively. Since this outcome is a major benefit of the distraction treatment, 2 representative sets of pre- and 1 year post-treatment radiographs of a regular care patient and clinical trial patient have been provided.

Data collection

All regular care KJD patients treated in our hospital before 2018 were included and thus provided 1-year follow-up. Electronic charts of these patients were evaluated to check essential baseline characteristics. The ROM, measured by the orthopedic surgeon, and complications as a result of treatment had been registered for these patients, data which was also available from the OPS and RCT patients.

Only data collected for both regular care and clinical trial patients were compared. The Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC, version 3.1) questionnaire was used for evaluation of clinical efficacy, as this questionnaire was available for all patient groups. Since regular care patients filled out their questionnaires online, a relatively large amount of missing data is expected. To limit bias, only patients who filled out the questionnaires both before and 1 year after treatment were included in the analysis of clinical

efficacy, and characteristics of these patients were compared to the entire group of regular care patients.

Statistical analysis

Characteristics were compared between regular care and clinical trial patients using independent *t*-tests or, in case of categorical variables, chi-square tests. WOMAC data before and 1 year after treatment was compared for both groups separately, using paired samples *t*-tests. The 1-year WOMAC values were compared and tested between groups for clinical significance, defined as a difference of more than 15 WOMAC points[20], and for statistical significance using linear regression, corrected for baseline values and possible significantly different baseline or treatment characteristics. The influence of different baseline characteristics on the 1-year change in total WOMAC score, corrected for baseline WOMAC, was identified using linear regression. Being a responder to KJD treatment was analyzed according to the Outcome Measures in Rheumatology-Osteoarthritis Research Society International (OMERACT-OARSI) responder criteria, defined as an increase of ≥50% and ≥20 points in WOMAC pain or function scales, or a ≥20% and ≥10-point improvement in both scales, and potential predictors identified.[21]

For all values, mean and standard deviations (SD) are given, and for all changes over time the mean change and 95% confidence interval (95%CI) are shown. *P*-values <0.05 were considered statistically significant. IBM SPSS Statistics version 25 (IBM Corp; Armonk, NY) was used for all statistical analyses.

Results

Baseline characteristics

Before 2018, 84 patients were treated with KJD in regular care in our hospital and all accepted to participate in the orthopedic standard registry. Between 2006 and 2014, 62 patients were treated in the 3 trials combined. The baseline characteristics of both groups are shown in Table 1, showing a different distraction duration between both groups, which was longer for clinical trial patients (48.1 (SD 8.1) days; regular care 45.3 (4.3); p=0.019), but shorter when excluding the OPS patients who received distraction for 8 instead of 6 weeks (RCT 42.8 (2.3); regular care 45.3 (4.3); p<0.001).

In 1 patient in the regular care group compartment syndrome occurred and the distraction frame was removed after 2 days. This patient was excluded from the distraction duration in Table 1, since no full treatment was applied.

Table 1: Baseline characteristics of patients treated with knee joint distraction in regular care and in clinical trials

	Regular care (n=84)	Clinical trial (n=62)	*P*-value
Age (years)	53.1 (6.9)	51.5 (6.9)	0.173
Male sex, n (%)	52 (62)	36 (58)	0.639*
BMI (kg/m^2)	27.9 (3.7)	28.2 (3.7)	0.639
Left index knee, n (%)	43 (51)	26 (42)	0.268*
Range of motion (degrees)	124.2 (17.8)	122.7 (14.7)	0.602
Leg axis (degrees)	4.3 (5.1)	4.9 (4.4)	0.556
Varus/valgus, n (%)	57 (68) / 16 (19)	28 (45) / 3 (5)	0.140*
Kellgren-Lawrence grade, n (%)			0.401*
- Grade 0	0 (0)	0 (0)	
- Grade 1 or 2	19 (23)	18 (29)	
- Grade 3 or 4	64 (76)	44 (71)	
Distraction duration (days)	45.3 (4.3)	48.1 (8.1)	**0.019**

Mean and standard deviation or n (%) are given. *P*-values are calculated with independent *t*-tests and for categorical variables with chi-square tests (indicated with *). Bold *p*-values indicate statistical significance ($p<0.05$). BMI: body mass index.

Cartilaginous tissue repair

Radiographs of a representative regular care patient and a trial patient pre-treatment and 1 year post-treatment are shown in Figure 2.

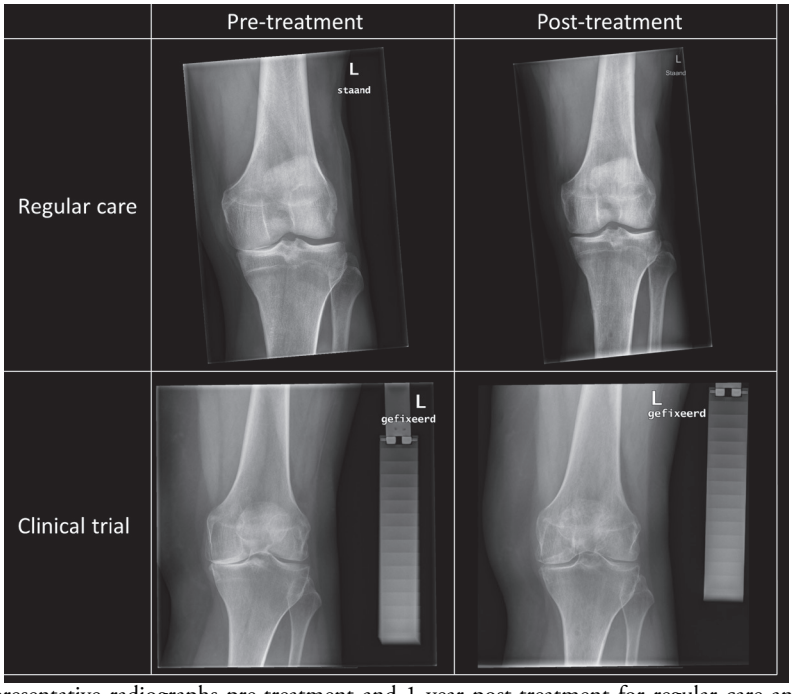

Figure 2: Representative radiographs pre-treatment and 1 year post-treatment for regular care and clinical trial patient. Note the aluminum step wedge needed for joint space width quantification as used in clinical trials.

In both cases, despite the absence of quantification of the joint space widening in clinical practice, a clear increase in joint space width is demonstrated, in previous studies clearly related to cartilage thickening using MRI and biochemical markers.[9,10,15]

Complications

All treatment-related complications that occurred are summarized in Table 2. Pin tract infections occurred most often and in 86% of cases were successfully treated with oral antibiotics. A combination of intravenous and oral antibiotics was necessary in 14% of pin tract infections. OPS patients had significantly more pin tract infections than RCT patients (OPS 85%; RCT 57%; p=0.030). There was no significant difference in pin tract infections between regular care patients and any of the trial patient groups (OPS/RCT, OPS or RCT; all p>0.1). Patients experiencing osteomyelitis (6 patients) were treated with additional surgical cleaning of pin tract wounds and a combination of intravenous (2 weeks) and oral (4 weeks) antibiotics according to a local standardized treatment protocol for osteomyelitis. Pin loosening (3 patients) or breaking (1 patient, reason unknown) was treated by tightening or refixation of the pins at either the emergency room or the outpatient clinic, while the 1 patient experiencing pin tract bleeding received a pressure bandage at the emergency room. Both deep venous thrombosis (2 patients) and pulmonary embolisms (3 patients) were treated with extra anticoagulation, which in case of a pulmonary embolism included hospitalization. For the patient experiencing a suspected compartment syndrome, the frame was immediately removed and a fasciotomy was performed, while the 1 patient who had pneumonia received intravenous antibiotics.

Of patients with complications, 15 experienced them after frame removal. Ten were post-distraction infections, treated with oral antibiotics (3 patients) or a combination with intravenous antibiotics (7 patients), and 1 was a postoperative foot drop, successfully treated with an ankle-foot orthosis. The cause has been discussed previously.[14] Flexion limitation (3 patients) was treated with manipulation under anesthesia and in 1 case arthroscopic arthrolysis, while the corpus liberum (a loose piece of cartilage/bone) present in 1 patient after treatment was arthroscopically removed.

The decrease in ROM shortly after distraction as observed in regular care (-26.5° (95%CI -32.0 to -21.0); p<0.001) and the clinical trials (-20.1 (-26.6 to -13.6); p<0.001) was largely regained within 4 months. Compared to baseline ROM, the regular care patients showed a statistically significant decrease at 4 months (-5.8 (-10.2 to -1.4); p=0.011), but not at 12 months (-2.3 (-6.3 to 1.8); p=0.263), as shown in Figure 3. Clinical trial patients showed no statistically significant difference at 4 months (-3.5 (-7.4 to 0.5); p=0.085) and 12 months (+2.7 (-0.6 to 6.0); p=0.112). When correcting for baseline ROM and distraction duration, there was a statistically significant difference between regular care and clinical trial patients for the 12-month change (p=0.013), but not the 4-month change (p=0.232).

Table 2: Complications during and after treatment with knee joint distraction in regular care and in clinical trials

	Regular care (n=84)	Clinical trial (n=62)
Pin tract skin infection	59 (70)	41 (66)
Oral antibiotics	51 (61)	35 (56)
Hospital admission + intravenous antibiotics	8 (10)	6 (10)
Osteomyelitis	5 (6)	1 (2)
Confirmed osteomyelitis	2 (2)	1 (2)
Infection treated as osteomyelitis	3 (4)	0 (0)
Pin loosening	4 (5)	
Flexion limitation	2 (2)	1 (2)
Deep venous thrombosis	2 (2)	
Pulmonary embolism	1 (1)	2 (3)
Pin tract bleeding	1 (1)	
Compartment syndrome	1 (1)	
Pneumonia	1 (1)	
Corpus liberum	1 (1)	
Postoperative foot drop		1 (2)
Breaking of bone pin		1 (2)

N (%) is given.

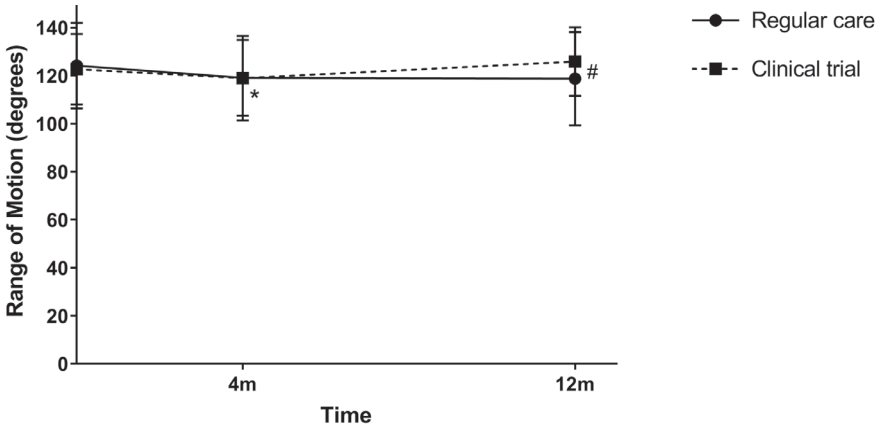

Figure 3: Range of motion before and after treatment with knee joint distraction. Statistically significant differences compared to baseline are indicated with * for regular care patients (non-existent for clinical trial patients); statistically significant differences between regular care and clinical trial patients are indicated with #. Mean and standard error are shown.

Clinical benefit

In total 41 regular care patients and 61 clinical trial patients completed both baseline and 1-year follow-up WOMAC questionnaires, 43 regular care patients were missing because they did not respond to the electronic requests to fill out the questionnaires by E-mail. One RCT patient was missing at 1-year follow-up after undergoing additional treatment. The baseline characteristics of the patients who completed both WOMAC questionnaires are shown in

Table 3, showing a significant difference only in distraction duration, which again was longer for clinical trial patients (48.2 (SD 8.2) days; regular care 45.5 (4.2); p=0.032), but shorter when excluding the OPS patients (RCT 42.8 (2.3); regular care 45.5 (4.2); p=0.001).

No statistical significant differences between the 43 regular care patients without and 41 patients with 1 year follow-up data were observed.

Table 3: Baseline characteristics of patients treated with knee joint distraction in regular care and in clinical trials, who completed both WOMAC baseline and 12-month follow-up questionnaires

	Regular care (n=41)	**Clinical trial (n=61)**	***P*-value**
Age (years)	54.0 (6.9)	51.7 (6.8)	0.102
Male sex, n (%)	23 (56)	35 (57)	0.898*
BMI (kg/m^2)	27.5 (3.9)	28.1 (3.7)	0.508*
Left index knee, n (%)	19 (46)	26 (43)	0.711
Range of motion (degrees)	125.4 (14.1)	122.7 (14.9)	0.362
Leg axis (degrees)	4.6 (4.7)	4.8 (4.4)	0.879
Varus/valgus, n (%)	33 (80) / 6 (15)	27 (44) / 3 (5)	0.510*
Kellgren-Lawrence grade, n (%)			0.152*
- Grade 0	0 (0)	0 (0)	
- Grade 1 or 2	7 (17)	18 (30)	
- Grade 3 or 4	34 (83)	43 (70)	
Distraction duration (days)	45.5 (4.2)	48.2 (8.2)	**0.032**
WOMAC Total (0–100)	47.5 (14.9)	49.8 (15.7)	0.464
WOMAC Pain (0–100)	46.3 (16.9)	49.8 (15.7)	0.293
WOMAC Stiffness (0–100)	39.3 (23.1)	45.4 (18.3)	0.141
WOMAC Function (0–100)	48.9 (15.2)	51.0 (16.2)	0.498

Mean and standard deviation or n (%) are given. *P*-values of continuous variables are calculated with independent *t*-tests and for categorical variables with chi-square tests (indicated with *). Bold *p*-values indicate statistical significance. BMI: body mass index; WOMAC: Western Ontario and McMaster Universities Osteoarthritis Index.

As shown in Table 4 and Figure 4, the total WOMAC (Figure 4A) and pain (Figure 4B), stiffness (Figure 4C), and function (Figure 4D) subscales increased statistically and clinically significantly for the 41 regular care patients and 61 clinical trial patients that completed the questionnaires (all p<0.001). Although there was a tendency towards better results for the clinical trial patients, no clinically or statistically significant differences in 1-year changes between regular care and trial patients were observed (all p>0.068). Similar data were found for OPS and RCT patients separately, although for OPS patients slightly, but not statistically significantly, better results were obtained.

After 1 year, 70% of patients were OMERACT-OARSI responders (regular care 61%, clinical trial 75%; p=0.120).

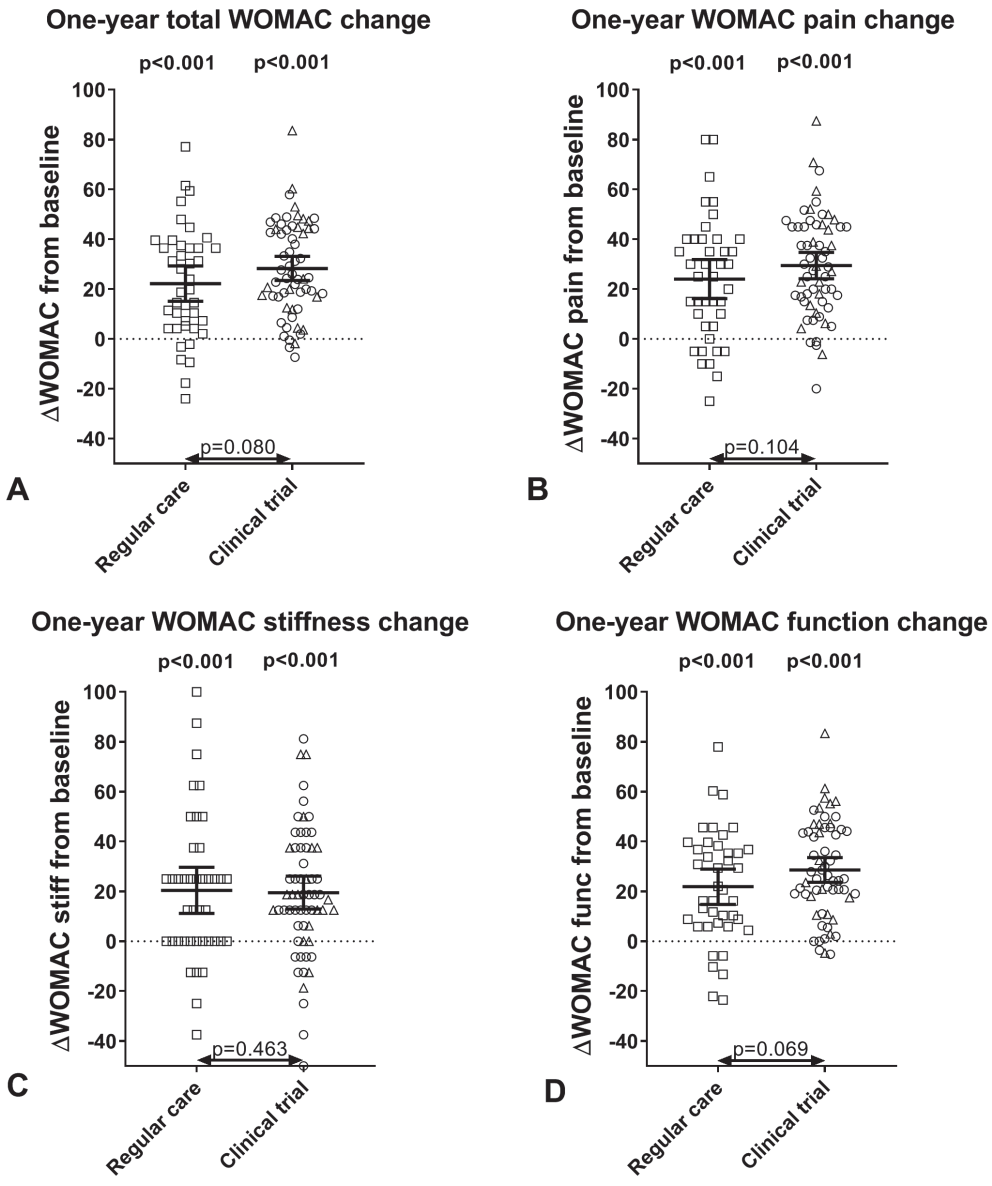

Figure 4: One-year change in Western Ontario and McMaster Universities Osteoarthritis Index for patients treated with knee joint distraction, for (A) the total score, and (B) the pain, (C) stiffness, and (D) function subscales for patients treated with knee joint distraction in regular care and in OPS/RCT clinical trials (OPS: open prospective study; RCT: randomized controlled trial). *P*-values above groups indicate significant changes at 1 year compared to baseline while *p*-values between groups indicate the significance of differences between groups, corrected for baseline values and distraction duration. Bold *p*-values indicate statistical significance ($p<0.05$). Each dot represents a patient (for trial patients: triangles represent OPS patients and circles RCT patients); bars represent mean and 95% confidence interval.

Neither regular care *versus* trial treatment nor any of the other baseline characteristics had a significant influence on the 1-year change in total WOMAC score, neither in univariable nor multivariable models, or on being a responder. Experiencing pin tract infections or complications in general did not have a significant influence on 1-year WOMAC change or being a responder (all $p>0.2$).

Table 4: Clinical outcome for patients treated with knee joint distraction in regular care and in clinical trials

	Regular care (n=41)	Clinical trial (n=61)	*P*-value
WOMAC Total	22.2 (15.1–29.3)*	28.3 (23.5–33.1)*	0.080
WOMAC Pain	24.0 (16.2–31.9)*	29.5 (24.2–34.7)*	0.104
WOMAC Stiffness	20.4 (11.2–29.7)*	19.5 (12.9–26.1)*	0.463
WOMAC Function	21.9 (14.8–29.0)*	28.6 (23.7–33.6)*	0.069

Mean change and 95% confidence interval are given. Significant 1-year changes are calculated with paired *t*-tests indicated with * while the *p*-values indicate differences in 1-year changes between regular care and clinical trial patients, calculated with linear regression, corrected for baseline Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) and distraction duration.

Discussion

Knee joint distraction is a relatively new, joint-preserving treatment for knee OA that after several clinical trials is now used in clinical practice to postpone a first TKA. This enabled evaluation if patients treated in regular care still have a similar indication profile, viz. similar characteristics as those treated in clinical trials and if KJD is still as clinically effective in regular care as it was shown to be in the trials.

Despite the fact that regular care usually does not use selection criteria as strictly as clinical trials do, this study showed that the 84 patients treated with KJD in regular care between 2014 and 2018 had in general the same characteristics as the patients included in clinical trials the years before. Only the distraction duration was shorter in the regular care patients, which was expected because of the different protocol (eight weeks distraction instead of 6 weeks) used in the OPS. The fact that the distraction duration in regular care is longer than in clinical trials when excluding the OPS is probably a result of the dependence on OR planning in regular care and the difference, being on average 2.7 days on 6-week protocol, was limited.

With an average intervention time of 53 minutes placing and 16 minutes removing the frame, the operative time is comparable to HTO and about half of the average time reported in literature for a TKA.[22–25] Complications were also described as similar to HTO and TKA[13–15], with pin tract infections, a common complication of external fixation in general[26], being the most prevalent complication in KJD. Complications of treatment were comparable between KJD patients treated in regular care and those treated in trials. With 70% of patients experiencing pin tract infections based on oral antibiotic use, they occurred more often than

was previously seen in the RCTs, where around half of patients experienced infections.[13–15] This could be because in regular practice patients receive a standard antibiotics prescription and do not have to visit the hospital before starting their course, which makes it likely that antibiotics are also used in case of doubtful infection. Pin tract infections had no significant influence on the clinical outcome at 1 year follow-up. Furthermore, despite the high occurrence of pin tract infections, patients undergoing TKA surgery several years after KJD have not experienced additional complications or diminished clinical efficacy.[17] Nevertheless, it is a major burden and effort should be made to reduce pin tract infections further. A new joint distraction device (KneeReviver) has been developed, which makes pin care easier. A clinical trial to evaluate this new device is currently ongoing. Additionally, new care protocols are encouraging, appearing to decrease the number of pin tracts significantly.

Not only pin tract infections, but complications in general did not significantly influence the clinical response. Complications other than pin tract infections did not occur with a frequency allowing statistical evaluation. However, the 17 patients who received full KJD treatment in regular care and experienced other complications than pin tract infections all returned to the outpatient clinic after treatment and 14 of them (82%) were satisfied with their KJD treatment and indicated that they had less OA complaints than before treatment. Only the other 3 patients (1 who experienced pneumonia and flexion limitation, 1 a corpus liberum and 1 a broken bone pin) did not report success of the treatment. Clearly, there is room for improvement to decrease complications of the treatment to further improve the balance of benefit over burden.

A decrease in range of motion was seen as adverse effect previously in the clinical trials. In both regular care and clinical trials, the decrease that was seen shortly after KJD, recovered within months and normalized after a year, with the observed changes being minimal and less than the minimally detectable difference reported in literature.[27] As such, the differences are considered not to be clinically relevant and within variation of measurement.

The clinical benefit that was demonstrated previously in all clinical trials was also observed in regular care. In the clinical trials, the clinical benefit seemed slightly better, which was partly due to slightly better effects of the OPS treated patients. Although all not statistically significant, this may be the benefit of subtle differences in patient selection as well as the small difference in distraction duration (in favor of the OPS patients), as has been discussed before.[12] Moreover, no difference in the percentage of responders according to OMERACT-OARSI criteria at 1 year was observed either.

Neither being a patient from a clinical trial or regular care, nor any of the other baseline data predicted clinical outcome.

Unfortunately, while radiographs were performed in regular care to judge OA severity pre-treatment, a KLG of 2 or higher being a treatment prerequisite according to local guideline, these radiographs were not performed in standardized way, and neither were follow-up radiographs (amongst other including an aluminum step wedge for quantification of density and distances). Therefore JSW widening could not be quantified. In the 3 clinical trials, it has previously been shown that KJD causes a significant increase in radiographic JSW during the years after treatment, which has been related to cartilaginous tissue repair based on additional MRI evaluation and biochemical marker analyses.[8,9,13–15] Since no significant differences in patient characteristics and clinical benefit were found between regular care and trial patients, KJD in regular care may be expected to cause a similar structural response as supported by the representative pre- and post-treatment images shown.

This study had a number of limitations. First, around half of patients treated in regular care could not be used in the evaluation of clinical efficacy, as they did not fill out the questionnaires before and 1 year after treatment. As the regular care patients in this study were evaluated retrospectively, this could unfortunately not be solved. This might have caused a bias or misrepresentation of clinical results, although it was shown that the regular care patients who filled out the questionnaires did not differ in patient and treatment characteristics from those who did not. Furthermore, for 93% of all regular care patients it is known they did not receive a TKA within a year, as they did attend the 1-year outpatient clinic visit and/or filled out electronic questionnaires more than 1 year after treatment.

The second limitation of this study was that all regular care patients were treated in the same hospital. While other hospitals provide KJD treatment as well, they only started recently and clinical data was available only from our hospital. The patients from the clinical trials were treated in 3 different hospitals, however, and there were no statistically significant differences in patients' clinical benefit between these hospitals. This would therefore not be expected in regular care either.

This study did not include a control group of non-surgically treated patients. However, in the stage patients are considered for KJD they should be considered for TKA, but aged below 65 with persistent pain, a KLG of 2 or higher, and sufficient history of conservative treatment without sufficient success. As such, any good control group receiving no treatment would not be ethically sound for this population.

Despite the absence of statistically significant differences between patients treated in regular care and in clinical trials, patient selection and treatment conditions in regular care remain crucial for this novel joint saving treatment. The maximal effect regarding clinical benefit and structural repair has in all trials been obtained around 1-year follow-up, sustaining for many years thereafter.[10,11] Therefore the 1-year follow-up comparison with regular care outcome is

considered predictive of the long-term outcome in regular care. Nevertheless, longer follow-up in regular care with larger number of patients is still warranted to proof this assumption. Moreover, such studies may benefit from standardized radiographs or MRI evaluation to evaluate joint tissue repair as well. Follow-up of more patients in regular care with proper data management may potentially provide treatment efficacy predictors, refining patient selection. Regardless, KJD as a regular care treatment results in significant clinical benefit 1 year post-treatment similar to that demonstrated in the clinical trials that have demonstrated sustainability of this initial effect. As such KJD, can be a joint-preserving of choice in relatively young patients with end stage knee OA.

References

1. Hernández-Díaz C, van Schoor N, Khalil AAF. Osteoarthritis. Comorbidity in Rheumatic Diseases. 2017;386:197–206.
2. Tonge DP, Pearson MJ, Jones SW. The hallmarks of osteoarthritis and the potential to develop personalised disease-modifying pharmacological therapeutics. Osteoarthritis and Cartilage. 2014;22(5):609–21.
3. Patel A, Pavlou G, Mújica-Mota RE, *et al*. The epidemiology of revision total knee and hip arthroplasty in England and Wales: A comparative analysis with projections for the United States. a study using the national joint registry dataset. The Bone and Joint Journal. 2015 Aug;97-B(8):1076–81.
4. Birk M V., Iacovides I, Johnson D, *et al*. The false dichotomy between positive and negative affect in game play. Proceedings of the 2015 Annual Symposium on Computer-Human Interaction in Play. 2015; 799–804.
5. Weinstein AM, Rome BN, Reichmann WM, *et al*. Estimating the burden of total knee replacement in the United States. Journal of Bone and Joint Surgery. 2013 Mar 6;95(5):385–92.
6. Bayliss LE, Culliford D, Monk AP, *et al*. The effect of patient age at intervention on risk of implant revision after total replacement of the hip or knee: A population-based cohort study. The Lancet. 2017 Apr 8;389(10077):1424–30.
7. van der Woude JAD, Nair SC, Custers RJH, *et al*. Knee joint distraction compared to total knee arthroplasty for treatment of end stage osteoarthritis: Simulating long-term outcomes and cost-effectiveness. PLOS ONE. 2016 May 12;11(5):e0155524.
8. Intema F, van Roermund PM, Marijnissen ACA, *et al*. Tissue structure modification in knee osteoarthritis by use of joint distraction: An open 1-year pilot study. Annals of the Rheumatic Diseases. 2011 Aug 1;70(8):1441–6.
9. Wiegant K, van Roermund PM, Intema F, *et al*. Sustained clinical and structural benefit after joint distraction in the treatment of severe knee osteoarthritis. Osteoarthritis and Cartilage. 2013 Nov;21(11):1660–7.
10. van der Woude JAD, Wiegant K, van Roermund PM, *et al*. Five-year follow-up of knee joint distraction: Clinical benefit and cartilaginous tissue repair in an open uncontrolled prospective study. Cartilage. 2017;8(3):263–71.
11. Jansen MP, van der Weiden GS, van Roermund PM, *et al*. Initial tissue repair predicts long-term clinical success of knee joint distraction as treatment for knee osteoarthritis. Osteoarthritis and Cartilage. 2018;26(12):1604–8.
12. van der Woude JAD, van Heerwaarden RJ, Spruijt S, *et al*. Six weeks of continuous joint distraction appears sufficient for clinical benefit and cartilaginous tissue repair in the treatment of knee osteoarthritis. Knee. 2016 Oct 1;23(5):785–91.
13. van der Woude JAD, Wiegant K, van Heerwaarden RJ, *et al*. Knee joint distraction compared with total knee arthroplasty: A randomised controlled trial. The Bone and Joint Journal. 2017;99-B(1):51–8.
14. van der Woude JAD, Wiegant K, van Heerwaarden RJ, *et al*. Knee joint distraction compared with high tibial osteotomy: A randomized controlled trial. Knee Surgery, Sports Traumatology, Arthroscopy. 2017;25(3):876–86.
15. Jansen MP, Besselink NJ, van Heerwaarden RJ, *et al*. Knee joint distraction compared with high tibial osteotomy and total knee arthroplasty: Two-year clinical, radiographic, and biochemical marker outcomes of two randomized controlled trials. Cartilage. 2019 Feb 13;194760351982843.
16. Wiegant K, van Heerwaarden RJ, van der Woude JAD, *et al*. Knee joint distraction as an alternative surgical treatment for osteoarthritis: Rationale and design of two randomized controlled trials (*vs* high tibial osteotomy and total knee prosthesis). International Journal of Orthopaedics. 2015 Aug 23;2(4):353–60.
17. Wiegant K, van Roermund PM, van Heerwaarden RJ, *et al*. Total knee prosthesis after knee joint distraction

treatment. Journal of Surgery and Surgical Research. 2015 Nov 5;1(3):066–71.

18. Lafeber F, Veldhuijzen JP, Vanroy JL, *et al*. Intermittent hydrostatic compressive force stimulates exclusively the proteoglycan synthesis of osteoarthritic human cartilage. British Journal of Rheumatology. 1992 Jul;31(7):437–42.
19. van Valburg AA, van Roy HL, Lafeber FP, *et al*. Beneficial effects of intermittent fluid pressure of low physiological magnitude on cartilage and inflammation in osteoarthritis: An in vitro study. Journal of Rheumatology. 1998 Mar;25(3):515–20.
20. Escobar A, Quintana JM, Bilbao A, *et al*. Responsiveness and clinically important differences for the WOMAC and SF-36 after total knee replacement. Osteoarthritis and Cartilage. 2007 Mar;15(3):273–80.
21. Escobar A, Gonzalez M, Quintana JM, *et al*. Patient acceptable symptom state and OMERACT-OARSI set of responder criteria in joint replacement: Identification of cut-off values. Osteoarthritis and Cartilage. 2012 Feb;20(2):87–92.
22. Liabaud B, Patrick DA, Geller JA. Higher body mass index leads to longer operative time in total knee arthroplasty. Journal of Arthroplasty. 2013 Apr 1;28(4):563–5.
23. Noble JW, Moore CA, Liu N. The value of patient-matched instrumentation in total knee arthroplasty. Journal of Arthroplasty. 2012 Jan;27(1):153–5.
24. Siman H, Kamath AF, Carrillo N, *et al*. Unicompartmental knee arthroplasty *vs* total knee arthroplasty for medial compartment arthritis in patients older than 75 years: Comparable reoperation, revision, and complication rates. Journal of Arthroplasty. 2017 Jun;32(6):1792–7.
25. Hoell S, Suttmoeller J, Stoll V, *et al*. The high tibial osteotomy, open *versus* closed wedge: A comparison of methods in 108 patients. Archives of Orthopaedic and Trauma Surgery. 2005 Nov 15;125(9):638–43.
26. Jennison T, McNally M, Pandit H. Prevention of infection in external fixator pin sites. Acta Biomaterialia. 2014 Feb 1;10(2):595–603.
27. Hancock GE, Hepworth T, Wembridge K. Accuracy and reliability of knee goniometry methods. Journal of Experimental Orthopaedics. 2018 Oct 19;5(1):46.

CHAPTER 7

User-friendliness of a dedicated orthopedic device for knee joint distraction
Experiences from clinical practice

M.P. Jansen & T. Struik
J. Jaspers
S.C. Mastbergen & R.J.H. Custers

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Abstract

Background: Knee joint distraction (KJD) is a surgical technique for treatment of severe knee osteoarthritis at a relatively young age. In the absence of devices intended for KJD, this procedure has only been performed with devices with another intended use. In collaboration with patients, clinicians and medical device experts, a dedicated distraction (DD) device intended for KJD was developed. In this study, user-friendliness is compared between this DD device and a previously used concept distraction (CD) device.

Methods: Patients were treated with either of the devices (n=22 *versus* n=22). The intervention duration and treatment complications were registered. After treatment, patients filled out a questionnaire about user-friendliness of the device during treatment, containing questions on difficulties performing activities regarding clothing, sleeping, pin care, daily activities, mobility, and complications. Results were compared between the 2 groups.

Results: Intervention duration was on average 56 *versus* 44 minutes ($p<0.001$) for CD and DD device, respectively. Pin tract infections were the most prevalent complication (73% of CD patients *versus* 55% of DD patients; $p=0.210$). 34 patients filled out the questionnaire (16 CD device *versus* 18 DD device). User-friendliness was better for the DD device for 6/25 questions (all $p<0.05$) and not different between devices for remaining questions (all $p>0.1$).

Conclusion: The DD device intended for KJD reduces surgery time and improves user-friendliness compared to the CD device. As such, the DD device contributes to implementation of KJD treatment in regular care.

Introduction

Knee joint distraction (KJD) is a joint-preserving surgical technique for treatment of severe tibiofemoral osteoarthritis (OA) in younger patients who are indicated for total knee arthroplasty (TKA).[1] Performing a TKA in this relatively young population (<65 years) brings an increased risk of a complex and costly revision surgery later in life.[2–4] This is specifically the case for male patients, who encounter an almost doubled risk for revision compared to female patients.[2] Joint-preserving therapies, such as KJD, aim to delay TKA in this population and possibly prevent a revision surgery.[5,6] Data from multiple clinical trials showed clinical improvement and cartilage regeneration of the affected joint in patients treated with KJD.[7–11] Also, it was shown that a primary TKA could be postponed for a clinically relevant period of 5 years in over 70% of the patients up to even 9 years in around half of the patients.[12,13] The best results have been described in males (72% survival after 9 years), who also show the highest risk for revision of a primary TKA, making KJD worth considering in treatment of severe knee OA.[2,13]

During KJD, the affected joint is temporarily and fully mechanically unloaded by increasing the joint space with a distraction device, which is rigidly connected with half pins to the femur and tibia. The most common fixation and distraction technique is performed bilaterally with 8 extra-articular half pins and 5 millimeters distraction for a period of 6 to 7 weeks.[14,16]

In the absence of a dedicated device intended for KJD, this procedure has been performed in clinical trials with external fixation devices that are applied for various indications including stabilization of fractures and limb lengthening.[1] This broad range of applications comes with unrequired features when these devices are used for KJD, and limitations in terms of complexity of surgery, procedure time, alignment of the device and ease of use for all users including surgeons and patients. The treatment burden might be reduced when a dedicated device for KJD with optimized specifications for its intended use, e.g. the size, weight, and application method, is used. The continued use of existing external devices in daily care outside intended use, is not allowed under EU Medical Device Regulations (MDR), motivating the development of a specific device for KJD. This KJD device might also reduce the risk of misuse, ultimately leading to a safer and more efficient procedure.[17]

The clinical demand for a dedicated KJD device originated from the clinical benefits that were achieved with KJD treatment in clinical trials.[10,12] In a multi-disciplinary setting with clinicians, patients, and medical device experts, a device intended for KJD was developed and made available for clinical application. Device characteristics that were defined and incorporated in the dedicated device are given in Table 1. In this study, user-friendliness is compared between the newly developed dedicated distraction (DD) device and the previously used device that served as a proof-of-concept distraction (CD) device for KJD (Figure 1); clinical efficacy and tissue structure repair are beyond the scope of this study.

Table 1: Overview of characteristics of the dedicated knee distraction device
Device weight is below 1500 grams.
Surgery can be performed within 45 minutes.
Bone pins are positioned extra-articular, not compromising the area for primary TKA.
Bone pins are positioned perpendicularly to longitudinal axis of tibia.
System can be adjusted in case of complications (soft tissue swelling/infection).*
No protruding parts are present above the most proximal and below the most distal bone pins.
Protruding bone pins are shielded for minimal interference during treatment.
The pin tracts are accessible for pin tract care.*
The distraction direction and method is visually indicated.
5 millimeter distraction is applied in the longitudinal axis of the tibia.
Within the distraction, 3 millimeter deflection is present at full weight-bearing.

Italics indicate characteristics that are new with respect to the concept distraction device; * indicate characteristics that have been improved with respect to the concept device. TKA: total knee arthroplasty.

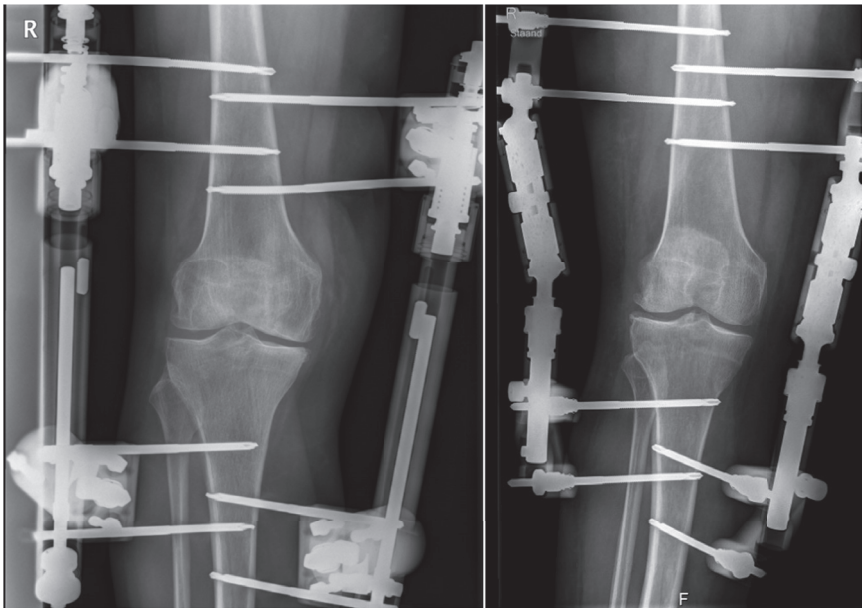


Figure 1: Radiographs of the concept (CD) device (left) and dedicated distraction (DD) device (right) in use. The surgical procedure for fixation of both devices is equal and performed with similar half pins.

Methods

Groups and patient selection

44 Patients were treated for severe knee OA with KJD either with the CD device (n=22) (Monotube Triax, Stryker GmbH, Selzach, Switzerland; the most often used KJD device reported on in previous studies) or with the DD device (n=22) (KneeReviver, BAAT Medical BV, Hengelo, The Netherlands). The criteria for study participation were equal for the 2 groups (Table 2).

Table 2: Inclusion and exclusion criteria for knee joint distraction treatment in this study

Inclusion criteria	Exclusion criteria
Age <65 years	Varus/valgus malalignment >10 degrees
BMI <35 kg/m^2	History of inflammatory or septic arthritis
VAS pain >40 mm	Primary patellofemoral OA
Kellgren & Lawrence grade ≥2	Surgical intervention within past 6 months prior to KJD
Persistent medication and conservative treatment resistant tibiofemoral pain	Osteopenia hampering proper pin fixation
	Physiological inabilities to cope with the treatment
	Arthroplasty of other joints, or expected need within 6 months
	Flexion contracture
	Vascular and/or soft-tissue abnormalities
	Body mass >130 kg

BMI: body mass index; KJD: knee joint distraction; OA: osteoarthritis; VAS: Visual Analogue Scale.

The 2 device types generally require the same anatomical sites and method of fixation as described previously, except for device specific differences.[1] In short, the external fixation device was surgically fixated to the femur and tibia using 8 self-drilling, 5 mm half pins. The CD device consisted of two rigid distraction tubes (Monotubes, see above), while the DD device (KneeReviver) was non-rigid to allow more user-friendly positioning around the joint (Figure 1). Both devices contain internal springs. After positioning of the pins and frame, 2 mm distraction distance was provided intra-operatively and extended with 1 mm per day to reach 5 mm distraction, confirmed radiographically. Afterwards, patients were discharged from the hospital and allowed full weight-bearing, supported with crutches if needed, and after 6 weeks of distraction the frame and pins were removed.

All patients were treated within the University Medical Center Utrecht, Utrecht, The Netherlands (UMC Utrecht), where ethical approval was obtained from the ethical committee for a prospective study design (protocol number 17-293). No randomization of patients between the 2 devices was allowed, since the DD device for KJD was available for standard care at the start of the study. It was anticipated in advance that the DD device was of added value, therefore, the ethical committee considered that randomization to an inferior device (viz. the CD device) would be non-ethical. As such, patients that had been treated with the CD device previously with written permission for future use of their data in retrospect, were included for analysis. The study was performed in accordance with the ethical principles from the Declaration of Helsinki and all patients gave written informed consent.

Data collection

As a measure for user-friendliness of the devices for the orthopedic surgeons, the duration of the intervention was collected from the surgery reports in the electronic medical records, defined as the time between the first incision and the end of the procedure as registered in clinical practice. Complications as a result of KJD treatment were assessed from medical records as well. After treatment, patients filled out a customized questionnaire, composed with a patient

panel, on the user-friendliness of the distraction device as experienced during treatment. Device characteristics relevant for analysis of user-friendliness and therewith for improvement of KJD treatment were incorporated in the questionnaires. The questionnaire consisted of 25 questions on difficulties performing activities regarding clothing, sleeping, wound care, general daily activities, and complications and were equal for the 2 devices (supplementary file I and Table 4). The effect of complications on the experienced user-friendliness was part of the analysis.

Within the cohort available for analysis, 3 patients were treated with both the CD device and the DD device. These patients received a questionnaire for a direct comparison of experiences during treatment between the CD and the DD device (supplementary file II).

Statistical analysis

Baseline characteristics were compared between groups using independent *t*-tests or, in case of categorical variables, chi-square tests. Statistical testing for significance of all outcome parameters was performed with independent *t*-tests and results are displayed using mean and standard deviations (SD). In case of non-normal distribution, Mann-Whitney *U* tests were used instead of independent *t*-tests and results are displayed using median and interquartile range (IQR). For categorical variables with only 2 categories (questions 21 and 22; Table 4), chi-square test were used and the number of occurrences (and % of the total amount of patients) are given. *P*-values <0.05 were considered statistically significant. IBM SPSS Statistics version 25 (IBM Corp; Armonk, NY) was used for all statistical analyses.

Results

Patients

The patients' baseline characteristics are presented in Table 3. There were no statistically significant differences between the 2 groups regarding these baseline characteristics. Patient age ranged from 46–63 years in the CD group and 38–63 years in the DD group.

Table 3: Baseline characteristics of patients treated with knee joint distraction in this study

	CD device (n=22)	DD device (n=22)	*P*-value
Age (years)	54.8 (4.8)	52.0 (6.7)	0.123
Male sex, n (%)	14 (64)	11 (50)	0.361*
BMI (kg/m^2)	58.3 (3.9)	27.5 (2.9)	0.501
Left leg, n (%)	12 (55)	9 (41)	0.365*

Mean and standard deviation or n (%) are given. *P*-values of continuous variables are calculated with independent *t*-tests and for categorical variables with chi-square tests (indicated with *). BMI: body mass index; CD: concept distraction; DD: dedicated distraction; SD: standard deviation.

Intervention duration

The intervention duration was on average 56 (SD 10) minutes for the CD device and 44 (8) minutes for the DD device (p<0.001), showing a statistically significant reduction of 12 minutes (21% reduction) for the DD device (Figure 2).

Intervention duration is defined as the time between the first incision and the end of the procedure. Each dot represents a patient/procedure. Lines indicate mean ± standard deviation. The p-value indicates statistical significance of the differences between groups (bold indicating statistical significance, p<0.05).

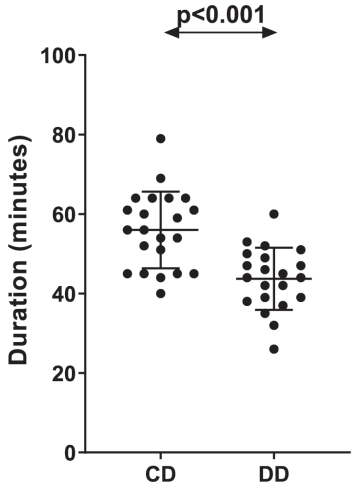


Figure 2: The registered intervention duration for the concept (CD) device *versus* the dedicated distraction (DD) device. Dots represent individual patients while lines represent group means and standard deviation.

Complications

The most frequently seen complications were pin tract skin infections, occurring somewhat more often in the CD patients (16/22; 73%) than the DD patients (13/22; 59%) but showing no statistically significant difference between devices (p=0.210). In the CD group, 3 patients required hospitalization and intravenous antibiotics for their pin tract infections, as did 1 patient who experienced osteomyelitis and 1 patient who experienced osteomyelitis and septic arthritis along with their pin tract infections. Also, 1 patient in the CD group had a broken bone pin (which was replaced) and 1 patient experienced a flexion limitation that required knee manipulation under anesthesia. In the DD group none of the patients required intravenous antibiotics and apart from the pin tract infections, 1 person experienced thrombosis and was treated with anticoagulation.

Questionnaires

Out of the 44 included patients, 34 filled out the questionnaire (16/22 patients with the

CD device *versus* 18/22 patients with the DD device). Baseline characteristics did not differ significantly between patients who did or did not fill out the questionnaire in each group. Results per question are provided in Table 4.

Table 4: Overview of user-friendliness questionnaire results per question for the concept distraction device and the dedicated distraction device

#	Aspect	CD device	DD device	*P*-value
Clothing and dressing (treated leg)				
1	Changing clothes	7.0 (4.5)	8.5 (5.3)	0.281
2	Clothes catching on device	6.0 (3.8)	8.5 (4.3)	0.070
3	Finding suitable/fitting clothes	5.0 (4.5)	10.0 (3.0)	**0.003**
Sleeping and night rest				
4	Sleeping in desired position	3.0 (3.0)	2.0 (4.0)	1.000
5	Disturbance of night rest	4.5 (2.0)	6.0 (8.0)	0.463
6	Damage to bedding	6.0 (6.0)	10.0 (0.0)	**0.002**
Pin care and device handling				
7	Performing pin care	4.0 (4.0)	9.0 (6.0)	**<0.001**
8	Understanding pin care instructions	8.0 (3.0)	10.0 (3.3)	0.274
9	Extending the device	8.0 (5.0)	10.0 (5.0)	0.791
10	Understanding extension instructions	9.0 (5.0)	9.0 (6.0)	1.000
Daily activities				
11	Getting caught / bumping during daily activities	6.0 (5.0)	5.5 (3.3)	0.484
12	Getting in and out of chair	5.0 (7.0)	6.0 (9.0)	0.135
13	Performing daily activities	4.0 (2.0)	4.0 (4.0)	0.198
14	Harm to the other leg	7.5 (3.5)	10.0 (6.0)	**0.003**
15	Loosening/losing shielding caps from bone pins	7.0 (7.0)	8.5 (7.0)	0.735
Mobility				
16	Walking without crutches	4.0 (3.0)	5.5 (6.3)	0.403
17	Resume daily domestic activities	3.0 (5.0)	4.0 (2.0)	**0.042**
18	Resume paid activities (job)	1.0 (0.0)	1.0 (4.0)	0.116
19	Daily traveled distance	3.0 (7.0)	4.0 (2.3)	0.175
Complications				
20	Antibiotic courses started, n (n per patient)	29 (1.8)^	29 (1.6)^	0.463
21	Patients with pin tract infection, n (%)	14 (88)^	10 (56)^	**0.041***
	Total pin tract infections, n (n per patient)[$]	77 (4.8)^	66 (3.7)^	0.237
22	Doctor visits related to the device, n (%)	10 (63)^	7 (39)^	0.169*
Other aspects				
23	Need for new clothing	8.0 (3.0)	7.0 (2.8)	0.325
24	Importance of signs of previous use	1.0 (5.3)^	4.5 (5.3)^	0.102
25	Importance of device color	1.0 (0.0)^	1.0 (2.0)^	0.597

Median and interquartile range are given unless otherwise indicated. In all cases a higher value represents the best (most desirable) answer, except for values marked with ^. *P*-values were calculated using Mann-Whitney *U* Tests; for categorical parameters (indicated with *) chi-square tests were used instead. Statistically significant differences between devices ($p<0.05$) are indicated in bold. The original questionnaire is provided in the supplementary data file I. $: defined as the total number of pin tract infections over the course of the treatment for all patients with every infected pin tract counting separately; a pin tract be infected multiple times during a treatment period. CD: concept distraction; DD: dedicated distraction.

As most of the answers were not normally distributed, Mann-Whitney *U* tests and mean with IQR were used for all parameters. For 6/25 (24%) of the questions a statistically significant difference in favor of the DD device is seen. For all other questions, scores were all in the direction of benefit for the DD device, but not statistically different between both devices (all $p>0.05$).

Based on responses of patients included in this study and on predetermined DD device characteristics (Table 1), 3 questionnaire aspects were identified as most relevant in experiencing user-friendliness: the incidence of clothes catching the device (question 2), the pin care (question 7), and the harm to the contralateral leg (question 14). These were aspects that patients specifically indicated as important with respect to user-friendliness during treatment when they completed their questionnaire. Moreover, these items were also considered as points that were likely important in reducing treatment burden during the development of the device. Detailed results on these aspects are provided in Figure 3 demonstrating favor for the DD with the latter 2 aspects statistically significant (both $p<0.004$).

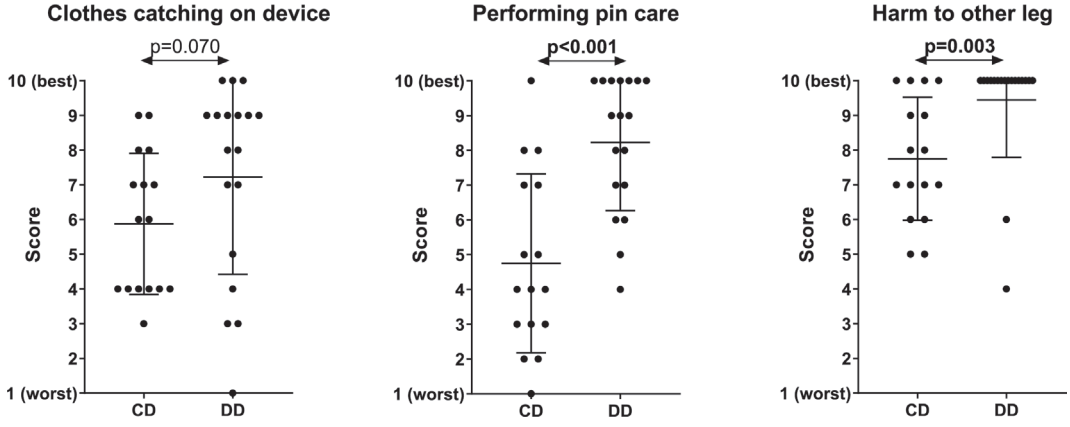


Figure 3: Individual patients' user-friendliness scores for the 3 aspects considered the most relevant by included patients. Each dot represents a patient's given score, with 10 the best score with respect to user-friendliness, while the lines indicate mean and standard deviation. The *p*-values indicate statistical significance of the differences between groups (bold values indicate statistical significance, $p<0.05$). CD: concept distraction; DD: dedicated distraction.

A statistically significant difference was found for the ease of performing pin care between patients with (median 5.0, IQR 2.3) and without (median 9.5, IQR 2.3) developed pin tract infections ($p=0.001$).

Data for direct comparison of the CD device and the DD device based on the response of 3 patients who were treated over time with both devices is given in Figure 4. The overall performance of the DD device appears to be somewhat better compared to the CD device for questions regarding device characteristics, as the 3 patients more often indicated that the DD

was better or slightly better than the CD than the other way around, but no statistical testing was performed because of the small size of this group (n=3).

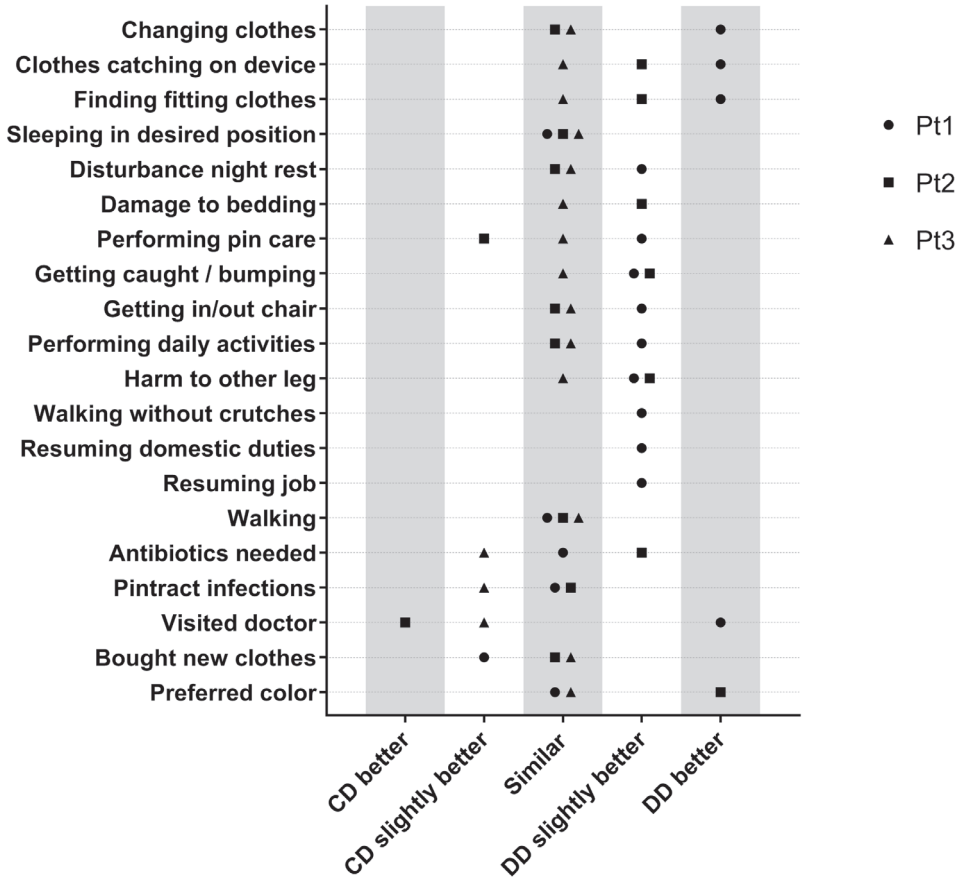


Figure 4: Questionnaire results from patients that received treatment with both devices. Statistical testing was not opportune for this small number of responders (n=3). CD: concept distraction; DD: dedicated distraction.

Discussion

The performance of a DD device for KJD, in terms of user-friendliness, was evaluated against a CD device in clinical practice amongst the primary intended users, viz. surgeons and patients. The development of the DD device focused on optimization of use-related aspects that had no direct effect on the safety of the device, with essential characteristics kept equal to the CD device. As such, the DD device was introduced according to the applicable regulations without a study on clinical efficacy. It was found that the DD device for KJD provides improved user-friendliness for both clinicians (reduced surgery time) and patients as compared to the CD device. Independently of the user-friendliness of the device, it remains to be evaluated whether the DD device has similar clinical efficacy as the CD device.

The shortened surgical procedure (21% time reduction) is considered not only beneficial for the surgeon, but also for the patient (shorter sedation, reducing risks for complications, e.g. surgical wound infection) and reduces healthcare costs by shortening the operating room occupation. The time difference is not considered attributable to a learning curve from the CD device as the surgeon performing the surgeries with the DD device already had extensive experience with the CD device following a similar surgical procedure. As such, the time difference is considered to result from improved user-friendliness for the DD device.

It was noticeable that the incidence of pin tract infections was lower in the DD device group, although the difference was statistically significant only in patients who filled out the user-friendliness questionnaire and not in the whole group. The total number of complications seemed somewhat less in the DD group as well, although because of the low occurrence of complications other than pin tract infections and limited sample size this outcome could be influenced by coincidence. Pin tract infections are considered a significant and well-known burden of treatment with external fixator devices, as is the case in KJD.[18] The reduced number of patients with pin tract infections in the DD group fits with the patients' experience that pin tract care is easier in the DD device compared to the CD device , which means the DD device seems to be successful in making pin tracts are accessible for pin tract care. This might indicate that difficulties in performing pin care increase the risk of pin tract infection development. On the other hand, the effect is could be related to differences in patient instructions for performing pin tract care as well. However, despite the reduction, the incidence is still high and extra attention in future developments towards improvement of treatment is demanded.

In general, all parameters related to patient user-friendliness were in favor of the DD device, some reaching statistically significance. For the 3 aspects that patients reported as most relevant for user-friendliness, the questions concerning harm to the contralateral leg and the pin tract care showed statistically significant improvement for the DD device, while the 22% improvement regarding the aspect of catching clothes was not statistically significant on group level. The latter aspect is likely inherent to the use of any externally fixated distraction device, regardless of minimization of protruding parts. Still, like the question concerning harm to the other leg, the significantly improved scores of finding suitable/fitting clothes and damage to bedding seen for the DD device are likely the result of the fact that no protruding parts are present above the most proximal and below the most distal bone pin and protruding bone pins are shielded. The fact that patients using the DD device indicated they could better resume daily activities seems to be the result of a combination of improvements in device characteristics as described in Table 1. Further improvement of the system should involve critical analysis of the defined device characteristics including clinical experiences from this study. Specifically, characteristics that may have high impact on patients during treatment should be carefully considered for evolvement of the device. In this respect, especially the items 'providing pin

care' and 'harm to other leg' appear to be relevant for increasing user-friendliness for patients.

The 3 patients who were treated with both the CD and DD device generally rated user-friendliness higher for the DD device, but there was clearly a lot of variation between their answers. Comparison of these outcomes should be interpreted with care, and only considered suggestive. Besides the fact that the group of patients that were treated with both devices is limited in size, data is likely to be influenced as a result of the period between the treatments.

This study had several limitations. First, this evaluation of user-friendliness would ideally have been performed in a randomized study. However, this was considered unethical by the responsible ethical committee due to the fact that the DD device was already available in clinical practice at the start of the study, which is why the current study setup was chosen. Second, the number of patients evaluated in this study was limited. Once further introduction of the DD device is established and more data becomes available, further evaluation is recommended to see if the current findings hold. Although longitudinal clinical and structural results with the DD device are expected to be similar to results seen in patients who received treatment with the CD device, this should be evaluated as well. Lastly, the patient questionnaire that was used to evaluate user-friendliness was not a validated questionnaire. Due to a lack of validated outcome measures relevant for evaluating the CD against the DD device, the current questionnaire was made based on demands and wishes as judged by the multidisciplinary team of patients, clinicians and medical device experts before development of the DD device. As such, the current questionnaire does incorporate aspects that are considered important by key users, but using a validated patient questionnaire would have been preferable.

In conclusion, the DD device provides a surgical instrument intended for KJD which reduces surgery time and improves user-friendliness compared to the CD device. Furthermore, it was demonstrated that incorporating patients as end-users in the development process of the DD device increases insights in user-friendliness, which potentially may further reduce treatment burden and facilitate implementation in regular care. Taken together, the DD device contributes to implementation of KJD for severe knee OA at a relatively young age.

References

1. Intema F, van Roermund PM, Marijnissen ACA, *et al*. Tissue structure modification in knee osteoarthritis by use of joint distraction: An open 1-year pilot study. Annals of the Rheumatic Diseases. 2011 Aug 1;70(8):1441–6.
2. Bayliss LE, Culliford D, Monk AP, *et al*. The effect of patient age at intervention on risk of implant revision after total replacement of the hip or knee: A population-based cohort study. The Lancet. 2017 Apr 8;389(10077):1424–30.
3. Kurtz SM, Lau E, Ong K, *et al*. Future young patient demand for primary and revision joint replacement: National projections from 2010 to 2030. Clinical Orthopaedics and Related Research. 2009;467(10):2606–12.
4. Julin J, Jämsen E, Puolakka T, *et al*. Younger age increases the risk of early prosthesis failure following primary total knee replacement for osteoarthritis: A follow-up study of 32,019 total knee replacements in the Finnish Arthroplasty Register. Acta Orthopaedica. 2010 Aug;81(4):413–9.
5. Mastbergen SC, Saris DBF, Lafeber FPJG. Functional articular cartilage repair: Here, near, or is the best approach not yet clear? Nature Reviews Rheumatology. 2013 May;9(5):277–90.
6. Lafeber FP, Intema F, van Roermund PM, *et al*. Unloading joints to treat osteoarthritis, including joint distraction. Current Opinion in Rheumatology. 2006 Sep;18(5):519–25.
7. Wiegant K, van Roermund PM, Intema F, *et al*. Sustained clinical and structural benefit after joint distraction in the treatment of severe knee osteoarthritis. Osteoarthritis and Cartilage. 2013 Nov;21(11):1660–7.
8. van der Woude JAD, Wiegant K, van Heerwaarden RJ, *et al*. Knee joint distraction compared with total knee arthroplasty: A randomised controlled trial. The Bone and Joint Journal. 2017;99-B(1):51–8.
9. van der Woude JAD, Wiegant K, van Heerwaarden RJ, *et al*. Knee joint distraction compared with high tibial osteotomy: A randomized controlled trial. Knee Surgery, Sports Traumatology, Arthroscopy. 2017;25(3):876–86.
10. Jansen MP, Besselink NJ, van Heerwaarden RJ, *et al*. Knee joint distraction compared with high tibial osteotomy and total knee arthroplasty: Two-year clinical, radiographic, and biochemical marker outcomes of two randomized controlled trials. Cartilage. 2019 Feb 13;194760351982843.
11. Jansen MP, Maschek S, van Heerwaarden RJ, *et al*. Changes in cartilage thickness and denuded bone area after knee joint distraction and high tibial osteotomy – Post-hoc analyses of two randomized controlled trials. Journal of Clinical Medicine. 2021;10(2):368
12. van der Woude JAD, Wiegant K, van Roermund PM, *et al*. Five-year follow-up of knee joint distraction: Clinical benefit and cartilaginous tissue repair in an open uncontrolled prospective study. Cartilage. 2017;8(3):263–71.
13. Jansen MP, van der Weiden GS, van Roermund PM, *et al*. Initial tissue repair predicts long-term clinical success of knee joint distraction as treatment for knee osteoarthritis. Osteoarthritis and Cartilage. 2018;26(12):1604–8.
14. Wiegant K, van Heerwaarden R, van der Woude JAD, *et al*. Knee joint distraction as an alternative surgical treatment for osteoarthritis: Rationale and design of two randomized controlled trials (*vs* high tibial osteotomy and total knee prosthesis). International Journal of Orthopaedics. 2015 Aug 23;2(4):353–60.
15. Struik T, Jaspers JEN, Besselink NJ, *et al*. Technical feasibility of personalized articulating knee joint distraction for treatment of tibiofemoral osteoarthritis. Clinical Biomechanics. 2017 Nov 1;49:40–7.
16. Jansen MP, Boymans TAEJ, Custers RJH, *et al*. Knee joint distraction as treatment for osteoarthritis results in clinical and structural benefit: A systematic review and meta-analysis of the limited number of studies and patients available. Cartilage. July 2020:194760352094294.

17. van Delft EAK, Schepers T, Bonjer HJ, *et al*. Safety in the operating room during orthopedic trauma surgery – Incidence of adverse events related to technical equipment and logistics. Archives of Orthopaedic and Trauma Surgery. 2018 Apr 1;138(4):459–62.
18. Jennison T, McNally M, Pandit H. Prevention of infection in external fixator pin sites. Acta Biomaterialia. 2014 Feb 1;10(2):595–603.

SUPPLEMENTARY DATA

Supplementary file I: User-friendliness questionnaire

Date of filling out questionnaire: |__|__|-|__|__|-|__|__|__|__|

Date of surgery: |__|__|-|__|__|-|__|__|__|__|

Treated knee:

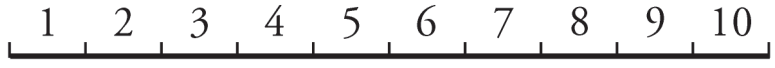
☐ Left

☐ Right

Please put a cross on the line at the 'score' that best fits your situation.

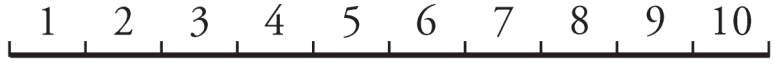
Clothing

1. During the distraction period of 6 weeks, did you have trouble getting clothes on and off over the knee distractor?



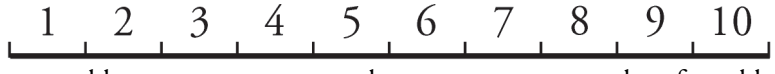
never sometimes regularly often

2. During the distraction period of 6 weeks, did your clothes ever catch on your knee distractor?



never sometimes regularly often

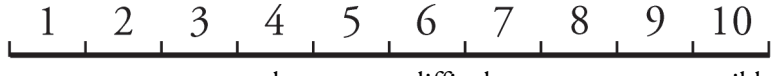
3. During the distraction period of 6 weeks, have you had trouble finding fitting clothing because of the knee distractor?



no trouble went okay lot of trouble

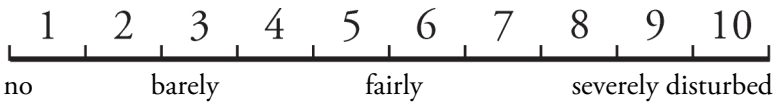
Sleeping

4. During the distraction period of 6 weeks, were you able to sleep in your desired sleeping position?

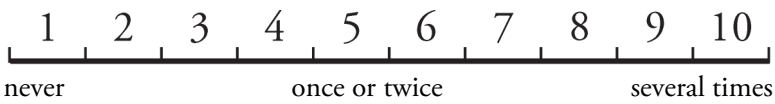


yes went okay difficult not possible

5. During the distraction period of 6 weeks, was your sleeping very disturbed by the knee distractor?

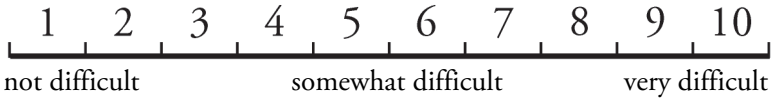


6. During the distraction period of 6 weeks, did the knee distractor damage your bedding?

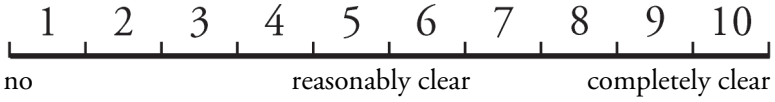


Care/use

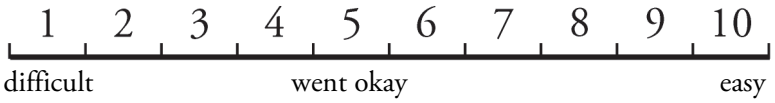
7. During the distraction period of 6 weeks, was it difficult to take care of the pin tracts well?



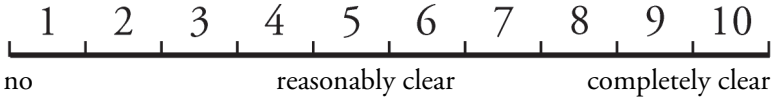
8. Was the manual for taking care of pin tracts clear for you?



9. How easy was it to extend the knee distractor with the thumb wheel?

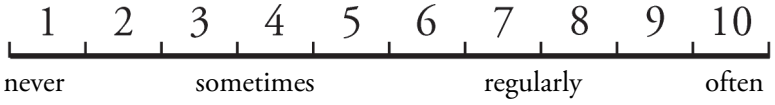


10. Was the manual for extending the knee distractor clear for you?

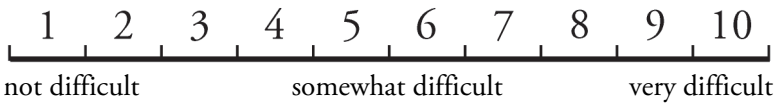


Daily activities

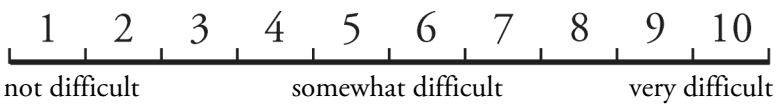
11. During the distraction period of 6 weeks, did your knee distractor ever get caught on something or did you ever bump the knee distractor against something during daily activities?



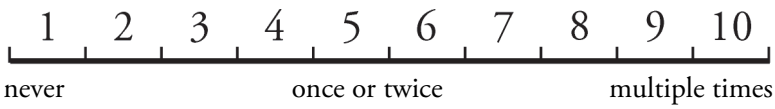
12. During the distraction period of 6 weeks, how was it to get in and out of a chair?



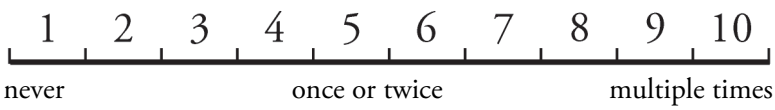
13. During the distraction period of 6 weeks, how was it to carry out your daily activities?



14. During the distraction period, did you ever hurt your other leg on the knee distractor?

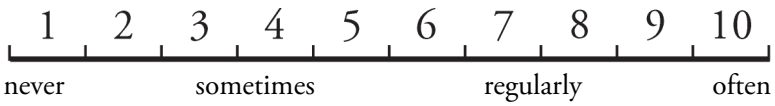


15. During the treatment, did the shielding caps of pin ends ever get loose/lost?

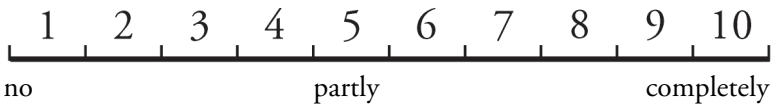


Freedom of movement

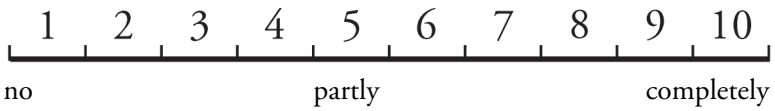
16. During the distraction period of 6 weeks, did you walk without the help of crutches?



17. During the distraction period of 6 weeks, were you able to resume your daily domestic activities?



18. During the distraction period of 6 weeks, were you able to resume your (paid) activities (job)?



19. During the distraction period of 6 weeks, how many meters do you think you walked on average **per day** with the knee distractor?

1	2	3	4	5	6	7	8	9	10

none 500m 1000m (1km) 2500m (2.5km)

Complications

20. How many antibiotics courses did you start during the distraction period of 6 weeks? Circle the correct number.

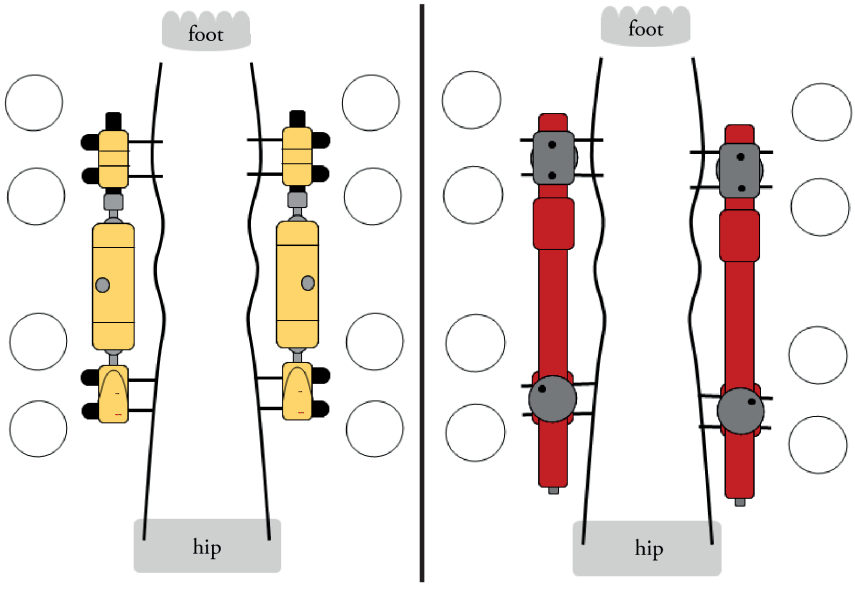
0	1	2	3	4

21. How many pin tract infections for which antibiotics have been prescribed did you have during the distraction period of 6 weeks, and at which pens?

Please enter the number of pin tract infections for each in the pens in the circles. Note: the picture is drawn from your own viewing direction (so you look at your foot).

Right leg / left leg (please cross out)

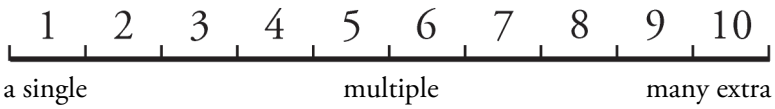
(note: the left picture was used for patients who received treatment with the dedicated device (yellow frame) while the right picture was used for patients who received treatment with the proof-of-concept device (red frame))



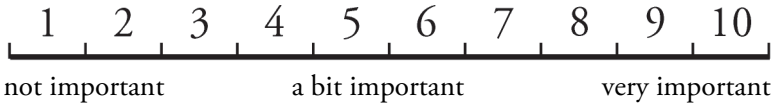
22. During the distraction period of 6 weeks, did you have to visit your doctor due to problems with the distractor (please circle)?

Yes, because …….
No

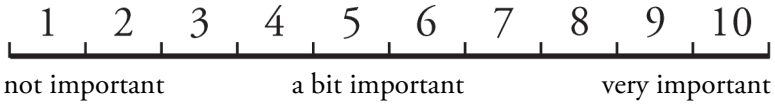
23. How many new clothes have you had to adjust or purchase in order to wear over the knee distractor?



24. Is it important to you that the knee distractor (which is reused) does not show any damage (e.g. scratches) at the beginning of the treatment?



25. How important is the color of the knee distractor for you?



26. Do you have any suggestions for improvements to the knee distractor? Yes / No

If yes, please write down below

……
……
……
……
……
……
……
……
……

Supplementary file II: Comparison CD and DD questionnaire

Date of filling out questionnaire: |__|__|-|__|__|-|__|__|__|__|

Date of birth: |__|__|-|__|__|-|__|__|__|__|

Which of your knees was treated with:

Proof-of-concept (red frame) distractor Left / Right (cross out what does not apply)

KneeReviver (yellow frame) Right / Left (cross out what does not apply)

Please circle the best fitting answer to the following questions

Clothing

1. With which knee distractor have you had the most trouble putting on and taking off clothes over the knee distractor during the distraction period?

only the red one / mostly the red one / both / mostly the yellow one / only the yellow one

2. On which knee distractor did your clothes get caught during the distraction period?

only the red one / mostly the red one / both / mostly the yellow one / only the yellow one

3. With which knee distractor did you have trouble finding fitting clothing during the distraction period?

only the red one / mostly the red one / both / mostly the yellow one / only the yellow one

Sleeping

4. With which knee distractor could you not sleep well in your desired sleeping position during the distraction period?

only the red one / mostly the red one / both / mostly the yellow one / only the yellow one

5. With which knee distractor was your sleep disturbed during the distraction period?

only the red one / mostly the red one / both / mostly the yellow one / only the yellow one

6. Which knee distractor damaged your bedding during the distraction period (if not damaged then do not circle anything)?

only the red one / mostly the red one / both / mostly the yellow one / only the yellow one

Care/use

7. With which knee distractor was it difficult to take care of the pin tracts well (if not difficult then do not circle anything)?

only the red one / mostly the red one / both / mostly the yellow one / only the yellow one

Daily activities

8. With which knee distractor did you get caught on something or did you bump the knee distractor against something during daily activities?

only the red one / mostly the red one / both / mostly the yellow one / only the yellow one

9. With which knee distractor was it difficult to get in and out of a chair during the distraction period?

only the red one / mostly the red one / both / mostly the yellow one / only the yellow one

10. With which knee distractor was it difficult to carry out your daily activities during the distraction period?

only the red one / mostly the red one / both / mostly the yellow one / only the yellow one

11. With which knee distractor did you ever hurt your other leg on the knee distractor during the distraction period?

only the red one / mostly the red one / both / mostly the yellow one / only the yellow one

Freedom of movement

12. With which knee distractor were you able to walk without crutches during the distraction period (if not walked without crutches then do not circle anything)?

only the red one / mostly the red one / both / mostly the yellow one / only the yellow one

13. With which knee distractor were you able to resume your daily domestic activities during the distraction period (if not able to resume then do not circle anything)?

only the red one / mostly the red one / both / mostly the yellow one / only the yellow one

14. With which knee distractor were you able to resume your (paid) activities (job) during the distraction period (if not able to resume then do not circle anything)?

only the red one / mostly the red one / both / mostly the yellow one / only the yellow one

15. With which knee distractor did you walk during the distraction period?

only the red one / mostly the red one / both / mostly the yellow one / only the yellow one

Complications

16. With which knee distractor did you need antibiotics during the distraction period?

only the red one / mostly the red one / both / mostly the yellow one / only the yellow one

17. With which knee distractor have you had pin tract infections during the distraction period?

only the red one / mostly the red one / both / mostly the yellow one / only the yellow one

18. With which knee distractor did you have to visit your doctor due to problems with the distractor during the distraction period?

only the red one / mostly the red one / both / mostly the yellow one / only the yellow one

19. Have you had to adjust or purchase new clothing to wear over the knee distractor?

only the red one / mostly the red one / both / mostly the yellow one / only the yellow one

20. Which knee distractor did you think had the nicest color?

only the red one / mostly the red one / both / mostly the yellow one / only the yellow one

CHAPTER 8

Reduction of pin tract infections during external fixation using cadexomer iodine

M.P. Jansen
N. van Egmond
E.C. Kester
S.C. Mastbergen
F.P.J.G. Lafeber
R.J.H. Custers

Published in the Journal of Experimental Orthopaedics, December 2020;7:88

Abstract

Background: Knee joint distraction (KJD) is a joint-preserving treatment for younger osteoarthritis patients. KJD has shown positive results in regular care, but the external fixation frame often caused pin tract skin infections. Therefore, the use of cadexomer iodine was included in the wound care protocol. The goal of this cross-sectional study was to evaluate whether use of this ointment reduced the number of patients with infections during KJD treatment.

Methods: Patients treated with KJD in regular care were included if they gave consent for use of their data and completed treatment with the newest distraction device before 2020. All patients followed a wound care protocol, which since March 2019 included using cadexomer iodine ointment. The number of patients experiencing pin tract infections was compared between patients who did (March 2019–December 2019) and did not (November 2017–March 2019) use the ointment.

Results: 67 Patients were included; 34 patients used cadexomer iodine and 33 patients did not. Patient who did not use cadexomer iodine experienced twice as many infections (64% *versus* 32%; p=0.010). There was a significant difference in the number of patients with serious infections, requiring more antibiotics than the standard 7-day oral antibiotics (30% without *versus* 6% with cadexomer iodine; p=0.009).

Conclusion: The use of cadexomer iodine ointment during KJD results in a significant reduction of the number of patients experiencing pin tract infections during treatment. Use of this ointment should be considered standard protocol during KJD treatment and could be of value in general external fixator usage as well.

Introduction

Knee joint distraction (KJD) is a joint-preserving treatment for younger (<65 years) patients with severe knee osteoarthritis (OA). KJD aims to postpone total knee arthroplasty (TKA) and decrease the chance of a revision TKA later in life.[1]

In KJD, the tibia and femur are placed at 5 mm distance for 6 weeks using an external fixation frame, fixed to the bones using 8 trans-cutaneous half pins. KJD has shown clinical benefit similar to TKA or osteotomy, as well as cartilage repair activity.[1–7] Effects can last for years, evaluated up to 9 years thus far.[8] Despite positive results that were observed in trials and regular care, the treatment can be a 6-week burden for patients when pin tract skin infections occur.[9] Pin tract infections are often seen in external fixation devices, and while a small number of studies have been published on how to prevent these infections, literature on this topic is limited.[10–14] Although in KJD the infections did not seem to have an influence on the patients' clinical benefit, prevention could decrease the burden of this promising treatment.[9] Updating the wound care protocol (see: Methods) in between clinical trials revealed a positive effect in decreasing infections, reducing pin tract infections from 85% to 57% of patients.[9] However, further reduction was clearly desirable.[6] Therefore, the use of cadexomer iodine ointment was included in the KJD wound care protocol in regular care. The objective of this study was to evaluate whether using cadexomer iodine ointment reduced the number of patients with pin tract infections during KJD treatment.

Methods

Patients

In the UMC Utrecht, knee OA patients with an indication for TKA, but younger than 65 years old, were offered KJD treatment in regular care. Specific considerations and criteria for KJD treatment in regular care have been described previously.[9]

As standard procedure, all patients treated at the department of orthopedics are asked written consent for use of their anonymized data for future research purposes (protocol number 17-005). Ethical approval for this study was waived by the medical ethical review board of the University Medical Center Utrecht (protocol number 20-128/C). While KJD has been performed in regular care since 2014, a new dedicated distraction device (KneeReviver®; ArthroSave, Culemborg, The Netherlands) was introduced in November 2017, which was developed to better facilitate pin care and showed a significant reduction in pin tract infections.[15] To prevent bias, only patients who received the full KJD treatment with the KneeReviver® and had their frame removed before 2020 were included in the current cross-sectional study. All included patients gave written informed consent.

Treatment

The treatment protocol in regular care has been extensively described.[9] In short, the tibia and femur were distracted for at least 5 mm for 6 to 7 weeks, using an external fixation frame (KneeReviver®) that consisted of 2 distraction tubes, 1 placed medially and 1 laterally of the knee joint. The tubes were fixed to the bones using 8 trans-cutaneous half pins, placed in pairs at 4 locations (medial/lateral and tibia/femur), as shown in Figure 1. Distraction was obtained gradually over the course of 3 days, and after radiographic confirmation, patients were discharged from the hospital with a standard prescription for 7 days of oral antibiotics (flucloxacillin; 3 times per day 500 mg) only to be used in case of infection (not as prophylaxis). In case a patient suspected a pin tract infection, they consulted their physician and based on the physician's judgment started their 7-day antibiotic course. If this standard course was not enough or more infections occurred during the distraction period or shortly thereafter, patients received additional antibiotic courses as necessary. During treatment, full weight-bearing was encouraged, supported by crutches if necessary.

After 4 weeks patients returned to the outpatient clinic for a general evaluation, and after 6 to 7 weeks the distraction frame was removed in daycare.

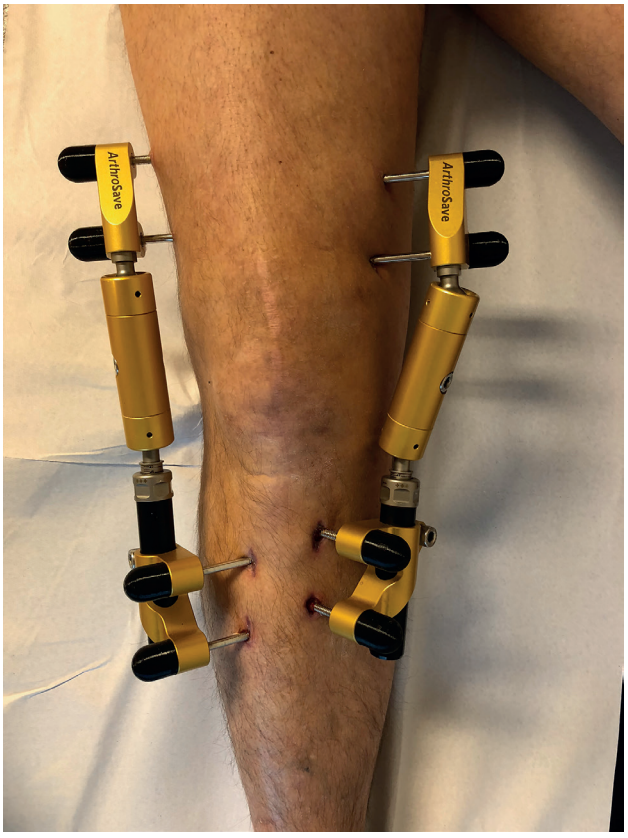


Figure 1: The external fixation frame used for knee joint distraction treatment.

Cadexomer iodine (Iodosorb®, Smith & Nephew)

Since March 2019, patients treated with KJD receive antimicrobial ointment to use on pin tracts during the distraction period. Iodosorb® (Smith & Nephew, Watford, United Kingdom) ointment consists of small cadexomer (polysaccharide) beads containing 0.9% iodine that can absorb wound exudate, pus and debris.[16,17] The absorption causes the beads to swell, allowing a sustained release of iodine. As more iodine is released, the color gradually changes from brown to white/gray, indicating the ointment is no longer effective and wound care should be performed.

Wound care protocol

Except for the use of Iodosorb®, the advised wound care protocol was identical for all patients. Patients were instructed to perform the following wound care every 1 to 3 days: first, the distraction frame is cleaned using non-sterile water (for example in the shower) and the gauze around all pins is removed. If the patient used Iodosorb®, the old ointment is removed from the wounds. The skin around the pins is massaged, freeing it from the pin and causing any accumulation of exudate to surface. After, the pins are cleaned using 70% alcohol, moving from the skin upwards. The skin around the pins is cleaned by dabbing it with chlorhexidine 0.5% (in alcohol 70%), using clean gauze. If the patient is using Iodosorb®, fresh ointment is subsequently reapplied to the wounds; if the wounds are clean and dry, application is not needed. Finally, clean gauze is applied around the pins and fixed with plasters.

After removal of the KneeReviver, Iodosorb® was not applied anymore.

Statistical analyses

Patients who used Iodosorb® during their KJD treatment (March 2019–December 2019) were compared with patients who did not use Iodosorb® during treatment (November 2017–March 2019). Baseline age, sex, BMI, diabetes mellitus, smoking status and treated leg (left/right) were compared between the 2 groups using independent 2-tailed *t*-tests for continuous variables and chi-square tests for nominal variables. Diabetes mellitus and smoking status were included because they, like age and sex, are known risk factors for infections during fixation.[18,19] All data was extracted from patients' electronic records; no missing data was expected since all data was required before treatment could be performed.

Outcome parameters were the number of patients requiring antibiotics for pin tract infections, the number of patients requiring more than 1 standard 7-day oral antibiotic course (indicating a more serious infection), and the number of patients with infections after frame removal. All 3 outcome parameters were compared between groups using chi-square tests. *P*-values <0.05 were considered statistically significant. IBM SPSS Statistics version 25 (IBM Corp; Armonk, NY) was used for all statistical analyses.

Results

Patients

Before 2020, a total of 73 patients were treated with the latest distraction device, of whom 68 gave permission for use of their data. In 1 patient full treatment was not carried out (frame was removed within a week because of pain), while the other 67 patients received full KJD treatment. Of these, 34 patients used Iodosorb® during treatment, while the other 33 patients did not. The baseline characteristics of both groups are shown in Table 1, showing no significant differences between groups. There was no missing data.

Table 1: Baseline characteristics of knee joint distraction patients with or without cadexomer iodine (Iodosorb®)

	Without Iodosorb®	**With Iodosorb®**	
	(n=33)	**(n=34)**	***P*-value**
Age (years)	52.0 (7.0)	52.9 (7.6)	0.624
Male sex, n (%)	14 (42)	19 (56)	0.271*
BMI (kg/m^2)	27.0 (3.0)	27.9 (2.8)	0.259
Diabetes mellitus, n (%)	1 (3)	1 (3)	0.983*
Smoking status, n (%)			0.921*
- Never	20 (61)	19 (56)	
- Former	12 (36)	14 (41)	
- Current	1 (3)	1 (3)	
Left leg, n (%)	11 (33)	16 (47)	0.252*

Mean and standard deviation or n (%) are given. BMI: body mass index. P-values were calculated with independent *t*-tests or with chi-square tests for categorical variables (indicated with *).

Infections

The number of patients who experienced infections during and after treatment are shown in Table 2 for both groups. During treatment, patients who did not use Iodosorb® experienced twice as many infections as patients who used the ointment (64% *versus* 32%; p=0.010).

Table 2: Infections during and after treatment with and without use of cadexomer iodine (Iodosorb®) during treatment.

	Without Iodosorb®	**With Iodosorb®**	
	(n=33)	**(n=34)**	***P*-value**
Patients with pin tract infections during treatment	21 (64)	11 (32)	**0.010**
Patients with >1 7-day antibiotics course	10 (30)	2 (6)	**0.009**
Patients with infections after treatment	2 (6)	3 (9)	0.667

N (%) is given. Bold p-values indicate statistical significance (p<0.05) calculated with chi-square tests.

Also, there was a significant difference in the number of patients with more serious infections, requiring more antibiotics than the standard 7-day antibiotic prescription (30% without Iodosorb® *versus* 6% with Iodosorb®; p=0.009). In all cases, the additional antibiotics consisted of multiple courses or 1 longer course of oral antibiotics; none of the patients required hospital admission or intravenous antibiotics during treatment.

The number of patients experiencing infections after frame removal did not differ significantly between groups (6% without Iodosorb® *versus* 9% with Iodosorb®; p=0.667). After frame removal, in the group without Iodosorb®, 1 patient received intravenous antibiotics while admitted to the hospital because of suspected osteomyelitis, and the other 1 received 1 7-day course of oral antibiotics for pin tract infection. In the group with Iodosorb®, after frame removal, 1 patient received intravenous antibiotics while admitted to the hospital because of suspected osteomyelitis, a second patient was admitted to the hospital and treated with intravenous antibiotics for a postoperative abscess and a third patient received 1 standard course of oral antibiotics because a pin tract wound was not completely healed.

Discussion

The most important finding of the present study was that for patients treated with KJD, incorporating the use of cadexomer iodine ointment in the wound care protocol significantly reduces the prevalence of pin tract infections. The number of patients experiencing pin tract infections decreased with 50% by using Iodosorb®. This is a clinically relevant reduction that implicates a significant decrease in treatment burden of patients. An even bigger difference was seen in the number of patients requiring more than a 7-day course of oral antibiotics. The number of patients with these more frequent or serious infections was reduced by 80%. It can be expected that this influences the patient's general physical and mental health during treatment. The use of cadexomer iodine during KJD treatment did not seem to have an effect on the number of patients experiencing infections after removal of the distraction frame. This may be related to ceasing application of the ointment too early.

None of the patients in either group required hospital admission and intravenous antibiotics during treatment. This is a remarkable difference with the previously reported complications experienced in KJD patients treated in regular care, where intravenous antibiotics were necessary for 14% of patients.[9] The fact that in the current study this number was reduced to zero does not seem to be a result of cadexomer iodine use, but may be because of the use of the ArthroSave KneeReviver® frame as compared to the Stryker Dynamic Monotubes used in previous studies, considered by patients to be advantageous with respect to wound care.[15]

The number of patients experiencing pin tract infections in this study was based on how many patients required antibiotics. In regular care, when patients have complaints of their pin tract wound and suspect an infection, they consult their physician. If the physician decides that it is an infection, based on the patient's complaints of pain around the pin tract as well as redness, warmth and pus presence, the patient can start their prescription of antibiotics. As a result, these infections are not confirmed by, for example, positive bacterial cultures. Although it has been shown that swab cultures in pin tract infections are not very helpful[20], it is possible that

some patients started antibiotics without actually having a pin tract infection, in which case the amount of pin tract infections might be lower than presented in this study. While this was a limitation of the current study, all patients taking antibiotics experienced infection-like symptoms and received antibiotics according to regular care protocol, so the significant reduction experienced after use of cadexomer iodine is clearly relevant in clinical practice and has direct implications for both patient wellbeing and general antibiotic use. It may, however, have been useful to not only compare the number of patients experiencing infections, but also the number of infected pins, as is often done in other studies. We did not collect this data, or different outcomes such as systemic biomarker levels to evaluate the effect of the ointment on general physiological functions, as this was a retrospective analysis.

Another limitation of the current study was that it was not set up as a randomized controlled trial. Ideally, patients receiving cadexomer iodine would be compared to patients using a placebo ointment in a randomized controlled trial. Nevertheless, the 2 patient groups seem similar and do not show any statistically significant differences in baseline characteristics, including known risk factors for infections during fixation. At present, a randomized trial while knowing the difference in infections between both groups would be ethically unsound. However, an interesting future study may be a randomized controlled trial comparing Iodosorb® to 1 or more other agents or methods for pin tract infection prevention.

Despite significant reductions in patients with infections, still a third of KJD patients experience pin tract infections. Further reduction of pin tract infections, which might be achieved by additional changes in the surgical technique, equipment (pins) or wound care protocol, is required to further reduce antibiotic use and the patients' treatment burden during KJD. Literature on preventing pin tract infections associated with external fixators is limited, and studies that evaluated factors such as cleansing solutions, prophylactic antibiotic use, different types of dressings, pin coating, and pin care frequency generally found no significant effects.[10–12,21,22] However, combined with cadexomer iodine use, implementing other changes might result in a further reduction of pin tract infections. Although it was previously shown infections do not have an influence on clinical benefit, and patients undergoing TKA several years after KJD did not experience additional complications or decreased clinical benefit, prevention of pin tract infections could still have positive effects in decreasing the patients' treatment burden during the fixation period.[9,23]

While the use of cadexomer iodine in patients has been evaluated and shown positive results, these studies were all performed in patients with ulcers.[17,24,25] Based on the significant results found in the current study, the use of cadexomer iodine in other treatments that use external fixation frames could be considered and evaluated as well, as it is likely that these results are not specific to only KJD.

In conclusion, the use of cadexomer iodine ointment during KJD results in a significant reduction of the number of patients experiencing pin tract infections during treatment in regular care. Use of this ointment may be considered as standard protocol during KJD treatment and could be of value in general external fixator usage as well.

References

1. Intema F, van Roermund PM, Marijnissen ACA, *et al*. Tissue structure modification in knee osteoarthritis by use of joint distraction: An open 1-year pilot study. Annals of the Rheumatic Diseases. 2011 Aug 1;70(8):1441–6.
2. Wiegant K, van Roermund PM, Intema F, *et al*. Sustained clinical and structural benefit after joint distraction in the treatment of severe knee osteoarthritis. Osteoarthritis and Cartilage. 2013 Nov;21(11):1660–7.
3. van der Woude JAD, Wiegant K, van Roermund PM, *et al*. Five-year follow-up of knee joint distraction: Clinical benefit and cartilaginous tissue repair in an open uncontrolled prospective study. Cartilage. 2017;8(3):263–71.
4. van der Woude JAD, Wiegant K, van Heerwaarden RJ, *et al*. Knee joint distraction compared with total knee arthroplasty: A randomised controlled trial. The Bone and Joint Journal. 2017;99-B(1):51–8.
5. van der Woude JAD, Wiegant K, van Heerwaarden RJ, *et al*. Knee joint distraction compared with high tibial osteotomy: A randomized controlled trial. Knee Surgery, Sports Traumatology, Arthroscopy. 2017;25(3):876–86.
6. Jansen MP, Besselink NJ, van Heerwaarden RJ, *et al*. Knee joint distraction compared with high tibial osteotomy and total knee arthroplasty: Two-year clinical, radiographic, and biochemical marker outcomes of two randomized controlled trials. Cartilage. 2019 Feb 13;194760351982843.
7. Jansen MP, Maschek S, van Heerwaarden RJ, *et al*. Knee joint distraction is more efficient in rebuilding cartilage thickness in the more affected compartment than high tibial osteotomy in patients with knee osteoarthritis. Osteoarthritis and Cartilage. 2019 Apr;27(1):S330–1.
8. Jansen MP, van der Weiden GS, van Roermund PM, *et al*. Initial tissue repair predicts long-term clinical success of knee joint distraction as treatment for knee osteoarthritis. Osteoarthritis and Cartilage. 2018;26(12):1604–8.
9. Jansen MP, Mastbergen SC, van Heerwaarden RJ, *et al*. Knee joint distraction in regular care for treatment of knee osteoarthritis: A comparison with clinical trial data. PLOS ONE. 2020 Jan 22;15(1):e0227975.
10. Kazmers NH, Fragomen AT, Rozbruch SR. Prevention of pin site infection in external fixation: a review of the literature. Strategies in Trauma and Limb Reconstruction. 2016;11(2):75–85.
11. Lethaby A, Temple J, Santy-Tomlinson J. Pin site care for preventing infections associated with external bone fixators and pins. Cochrane Database of Systematic Reviews. 2013 Dec 3;2013(12).
12. Iobst C, Liu R. A systematic review of incidence of pin track infections associated with external fixation. Journal of Limb Lengthening and Reconstruction. 2016;2(1):6.
13. Antoci V, Ono CM, Antoci V, *et al*. Pin-tract infection during limb lengthening using external fixation. American journal of orthopedics. 2008;37(9).
14. Mahan J, Seligson D, Henry SL, *et al*. Factors in pin tract infections. Orthopedics. 1991 Mar 1;14(3):305–8.
15. Jansen MP, Struijk T, Mastbergen SC, *et al*. User-friendliness of a novel dedicated knee joint distraction device: Experiences from clinical practice. Osteoarthritis and Cartilage. 2020 Apr 1;28:S474.
16. Edwards-Jones V. Essential microbiology for wound care. 1st ed. Oxford University Press; 2016.
17. Malone M, Johani K, Jensen SO, *et al*. Effect of cadexomer iodine on the microbial load and diversity of chronic non-healing diabetic foot ulcers complicated by biofilm in vivo. Journal of Antimicrobial Chemotherapy. 2017 Jul 1;72(7):2093–101.
18. Kortram K, Bezstarosti H, Metsemakers WJ, *et al*. Risk factors for infectious complications after open fractures: A systematic review and meta-analysis. International Orthopaedics. 2017 Oct 1;41(10):1965–82.
19. Egol KA, Paksima N, Puopolo S, *et al*. Treatment of External fixation pins about the wrist. Journal of Bone

and Joint Surgery. 2006 Feb;88(2):349–54.

20. Guerado E, Cano JR, Fernandez-Sanchez F. Pin tract infection prophylaxis and treatment. Injury. 2019 Jun 1;50:S45–9.
21. Fragomen AT, Miller AO, Brause BD, *et al*. Prophylactic postoperative antibiotics may not reduce pin site infections after external fixation. HSS Journal. 2017 Jul 27;13(2):165–70.
22. W-Dahl A, Toksvig-Larsen S. Infection prophylaxis: A prospective study in 106 patients operated on by tibial osteotomy using the hemicallotasis technique. Archives of Orthopaedic and Trauma Surgery. 2006 Sep 21;126(7):441–7.
23. Wiegant K, van Roermund PM, van Heerwaarden RJ, *et al*. Total knee prosthesis after knee joint distraction treatment. Journal of Surgery and Surgical Research. 2015 Nov 5;1(3):066–71.
24. Raju R, Kethavath SN, Sangavarapu SM, *et al*. Efficacy of cadexomer iodine in the treatment of chronic ulcers: A randomized, multicenter, controlled trial. Wounds. 2019;31(3):85–90.
25. Angel D, Morey J, Storey J, *et al*. The great debate over iodine in wound care continues: a review of the literature. Wound Practice and research. 2008;16(1):6–21.

CHAPTER 9

Prospective one-year follow-up of clinical efficacy of knee distraction as treatment for knee osteoarthritis by use of the KneeReviver

M.P. Jansen
S.C. Mastbergen
R.J.H. Custers
R.W. Brouwer
R.C.I. van Geenen
C.H.W. Heusdens
P.J. Emans
P.M. van Roermund
S. Spruijt
R.J. van Heerwaarden
F.P.J.G. Lafeber

Abstract

Background: Knee joint distraction (KJD) has shown clinical efficacy and cartilage restoration in several clinical osteoarthritis (OA) studies. Recently, a user-friendly dedicated KJD frame was developed (KneeReviver) and a prospective multicenter clinical trial was started to evaluate this frame. The goal of this interim analysis was primarily to evaluate its 1-year clinical efficacy and secondarily to evaluate non-inferiority with respect to the previously used frame (Dynamic Monotubes).

Methods: 65 young (<65 years) severe knee OA patients received KJD with the KneeReviver in 5 hospitals. Data of 39 patients previously treated with Dynamic Monotubes was available, so in this interim analysis 1-year data of 39 KneeReviver patients was used (1:1 ratio). Sample size calculations showed this was enough for both objectives. Before and 1 year after treatment, patients filled out the WOMAC questionnaire and standardized radiographs were taken to measure joint space width (JSW). Changes over time were calculated with paired *t*-tests. Non-inferiority limits were 10 for the WOMAC and 0.56 for JSW, based on literature and on no deterioration, respectively.

Results: The total WOMAC, all subscales (all >27 points; $p<0.001$) and JSW (0.4 mm; $p=0.013$) showed significant improvement in KneeReviver patients. The change in total WOMAC (difference 1.3; 95% confidence interval -6.6 to 9.2) and JSW (-0.20; -0.52 to 0.13) were non-inferior for the KneeReviver. Corrected for baseline, the change in JSW was non-inferior (-0.06; -0.35 to 0.24) while the WOMAC change was inconclusive (-7.5; -14.9 to -0.1).

Conclusion: KJD with the KneeReviver results in significant clinical efficacy, comparable to that with Dynamic Monotubes.

Introduction

Knee joint distraction (KJD) is a relatively novel joint-preserving surgical technique indicated for end-stage osteoarthritis by which the 2 bony ends of the knee joint are placed at around 5 mm distance for at least 6 weeks using an external distraction device.[1] This treatment, as an alternative for placement of a total knee arthroplasty (TKA) at a young age (<65 years), has been evaluated in several small studies: a retrospective study[2], a controlled trial[3], a long-term follow-up cohort study[4–7], and in 2 randomized controlled trials (RCTs) against TKA and high tibial osteotomy (HTO)[8–10]. In the retrospective study and controlled trial, customized frames or Ilizarov circular frames were used (Figure 1). In the cohort study and RCTs, Dynamic Monotubes (Stryker; Figure 1) were used. All studies demonstrated clear and prolonged clinical benefit and joint tissue repair.[2,3,7,10] Most importantly, the treatment was demonstrated to postpone the initially indicated TKA for over 5 years in 3 quarter of patients up to even 9 years in half of the patients.[6,7] With that, this joint-preserving treatment, delaying a first prosthesis, is considered to prevent the need for costly and less effective prosthesis revision surgery.[11]

Recently, a new, dedicated KJD device was developed by the UMC Utrecht to facilitate surgeons and patients, the KneeReviver (ArthroSave; Figure 1). This device has comparable mechanical properties and makes use of the same pin fixation positions as the Dynamic Monotubes, but has specifications optimized for its intended use, such as a reduced size and weight, and easy pin placement and fixation.[12,13] To evaluate this device, a prospective, multicenter clinical trial with 5 years of follow-up was started. Inclusion and treatment of 65 patients was completed at the end of 2019. The treatment protocol in this prospective study was identical to that used in the RCTs performed with the Dynamic Monotubes. In both these studies, KJD patients showed clinical improvement and cartilaginous tissue repair (increased radiographic joint space width; JSW) at 1 year of follow-up.[8,9]

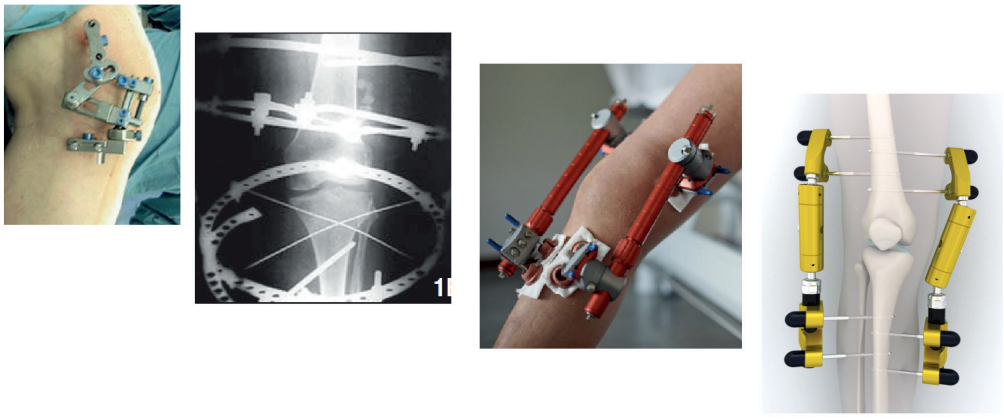


Figure 1: Different frames used for knee joint distraction. From left to right: custom articulated distraction device (Deie *et al.* 2007)[2]; Ilizarov circular frame (Aly *et al.* 2011)[3]; Dynamic Monotubes (Van der Woude *et al.* 2017)[6]; KneeReviver (Jansen *et al.* 2020)[12,14].

The objective of this current study was to evaluate the 1-year results of treatment with the KneeReviver. The primary hypothesis is that KJD using the KneeReviver is clinically effective in the treatment of end-stage knee osteoarthritis below the age of 65 years, based on an increase in both clinical and structural (radiographic JSW) parameters at 1 year as compared to baseline. The secondary hypothesis is that the clinical efficacy and structural repair by KJD using the KneeReviver at 1 year of follow-up is non-inferior to the benefit obtained by using the Dynamic Monotubes in the previously performed RCT studies.

Methods

Sample size calculation

The KneeReviver prospective follow-up study is a registered study with 5 years of follow-up and a sample size calculation based on previous 5-year results (Netherlands Trial Register NL7986). For this interim 1-year analysis, the required sample size was recalculated and based on the 1-year changes over time in the previous RCTs as well as to have the possibility to show non-inferiority. To ensure the primary and secondary hypothesis could be tested reliably, 4 sample size calculations were performed: 1 for both hypotheses and for both the primary clinical and the structural parameter. Primary parameters were the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) for clinical analysis and minimum radiographic joint space width (JSW) for structural analysis.

For the changes over time (first hypothesis), G-Power 3.1.9.7 was used with a 2-tailed analysis, an alpha of 0.05, and power of 80%. The input was based on the previous 1-year RCT results for the WOMAC and JSW. For the total WOMAC, this meant a baseline mean of 53.8 points (SD 15.6) and 1-year mean of 80.0 (15.5), with a correlation of 0.397 between the 2 variables. This resulted in a minimal required sample size of 6 patients required to show a change in total WOMAC. For the minimum JSW this number was 22 patients, calculated with a baseline minimum JSW of 0.54 mm (0.95), a 1-year minimum JSW of 1.09 (0.86) and a correlation of 0.556.

For the non-inferiority (second hypothesis), the Sealed Envelope online power calculator was used with an alpha of 0.05, power of 80%, and standard deviation (SD) based on the 1-year changes in WOMAC and JSW in the previous RCTs. Based on the WOMAC non-inferiority test, 2/3 of the minimal clinically important difference (MCID) was chosen as non-inferiority limit, viz. 10 points for the WOMAC; the required sample size was 37 patients per group, calculated with a SD of 17.1 for the WOMAC change over time that resulted from the RCT patients. The RCT patients showed a 1-year minimum JSW change of 0.56 mm, which was used as the non-inferiority limit (so at least no worsening of JSW), and a standard deviation of

0.86. This resulted in a required sample size of 30 patients per group.

From the 4 sample size calculations, the highest required number of patients was 37 for the WOMAC and 30 for the minimum JSW. Since the number of available patients with complete datasets treated in the RCTs with the Monotubes was 39, it was decided to include the first 39 KneeReviver patients with complete datasets in this analysis. As such, the sample size was large enough for all primary analyses, and a 1:1 ratio could be used between the 2 groups.

Patients

Relatively young patients with end-stage knee osteoarthritis, defined by persisting, conventional treatment-resistant pain with cartilage tissue damage in general practice considered for total (or compartmental) knee arthroplasty or high tibial osteotomy (with limited axis deviation), were offered knee joint distraction by the orthopedic surgeon as alternative joint-preserving treatment. Patients in the KneeReviver study were included in 5 different hospitals: the Martini Hospital Groningen, University Medical Center Utrecht, Amphia Hospital Breda, Antwerp University Hospital, and Maastricht University Medical Center.

The following criteria were applied for both the prospective KneeReviver study as well as the 2 RCTs. In order to be eligible to participate in this study, patients had to meet all inclusion criteria: adults ≤65 years of age; BMI <35 kg/m2 with max 110 kg body weight; normal-good physical condition (arbitrarily defined by orthopedic surgeons); sufficient knee joint stability (arbitrarily defined by orthopedic surgeons); sufficient range of motion (arbitrarily defined by orthopedic surgeons); radiographic signs of joint damage (Kellgren-Lawrence grade 2–4); Visual Analogue Scale (VAS) pain >40/100 (conservative treatment resistant).

Patients that would not be considered for arthroplasty or osteotomy because of psychosocial condition were excluded, as were those meeting any of the exclusion criteria: comorbidities that would compromise the efficacy of knee joint distraction (arbitrarily defined by orthopedic surgeons); history of inflammatory or septic arthritis; knee malalignment of more than 10 degrees; previous surgical interventions of the index knee <6 months ago; absence of any radiographic joint space width on both sides (medial and lateral); presence of an endoprostheses elsewhere.

The prospective KneeReviver trial and both RCTs were granted ethical approval by the medical ethical review committee of the University Medical Center Utrecht (protocol numbers 17-293, 10/359, and 11/072) and registered in the Netherlands Trial Register (trial numbers NL7986, NL2680, and NL2761). All patients in all trials gave written informed consent.

Treatment

KJD was performed according to a standardized surgical protocol.[12,15] In short: fixating the external distraction device to the femur and tibia medially and laterally using bone pins, placed in pairs at 4 different locations (tibia/femur and medial/lateral).

After positioning, a distraction distance of 2 mm was applied intra-operatively. After surgery, patients stayed in the hospital for another 2 to 3 days, during which the device was gradually distracted further until 5 mm distraction was reached. Afterwards, the distraction distance was checked on weight-bearing radiographs and adapted if needed. During the 6-week distraction period weight-bearing was encouraged, supported by crutches if needed. After 6 weeks, the distraction frame was removed and knee manipulation (flexion-extension) was performed at day-treatment. Procedures were identical for the KneeReviver prospective study and the 2 RCTs using the Dynamic Monotubes.

Clinical and radiographic evaluation

For this interim analysis data was collected for included patients at screening, directly before placement of the KJD frame, and 1 year after treatment. At all 3 time points, patients filled out the Knee injury and Osteoarthritis Outcome Score (KOOS) and VAS of pain. The Short-Form 36 (SF-36) was filled out at screening and 1 year after treatment. The KOOS questionnaire was used to calculate the total WOMAC scale and its subscales (pain, function, stiffness). From the SF-36, the physical component scale (PCS) and mental component scale (MSC) were calculated for quality of life analysis. For the KOOS/WOMAC and VAS, the results at screening and directly before frame placement were averaged to obtain the baseline clinical results. For the WOMAC, KOOS and SF-36, higher values indicate a better condition, while for the VAS lower values indicate a better condition.

Standardized weight-bearing, semi-flexed posterior-anterior radiographs were performed according to the Buckland-Wright protocol at screening and at 1-year follow-up.[16,17] Images of all included patients were checked in pairs for consistency of acquisition between baseline and 1 year follow-up by 2 observers (MJ, FL; blinded to any data) and excluded in case of considerable inconsistencies. The most affected compartment (MAC) and least affected compartment (LAC) were determined visually from the radiographs. Images were evaluated using knee images digital analysis (KIDA) software to analyze the JSW; an aluminum step wedge was used as a reference standard.[18] Calculated JSW parameters were the minimum JSW, the MAC JSW and LAC JSW, and the mean joint JSW. All image analyses were performed by a single, experienced observer, blinded to patient characteristics, and the intra-observer variation of this measurement method was shown to be good (for all different parameters ICC = 0.73–0.99).[18]

Data collection and evaluation were identical for the KneeReviver prospective study and the 2 RCTs.

Statistical analysis

Independent *t*-tests, or chi-square tests in case of categorical parameters, were used to compare baseline characteristics between groups. Primary outcomes were the total WOMAC and minimum JSW; secondary outcomes were the SF-36 and VAS pain; tertiary outcomes were the MAC radiographic JSW, the LAC JSW and the mean joint JSW. Paired *t*-tests were used to calculate changes at 1 year compared to pre-treatment for all parameters. Differences between groups in 1-year changes were calculated with linear regression, correcting for baseline values. Non-inferiority was calculated using linear regression, using the unstandardized *B* coefficient as mean difference and 90% confidence interval (90%CI). For the clinical outcome parameters, 2/3 of the minimal clinically important difference (MCID) was chosen as non-inferiority limit, viz. 10 points for the WOMAC, 7 points for the SF-36, and 2 points for the VAS pain.[19–21] For the minimum JSW, the 1-year change observed in the previously treated RCT patients was used as the non-inferiority limit; viz. not accepting a decrease in JSW.

A p-value <0.05 was considered statistically significant. IBM SPSS 25 was used for all analyses.

Results

Patients

The baseline characteristics of the 39 included patients per group are shown in Table 1. In both groups, 1 patient underwent a total or unilateral knee arthroplasty within 1 year after treatment, and as such was not included in these analyses. Also, in both groups, 1 patient showed a significant technical difference in radiographic acquisition (positioning) between baseline and 1-year follow-up that was judged to provide unreliable KIDA data. Therefore, these JSW measurement results were excluded from analysis, and JSW results are based on a total of 38 patients per group.

Patients treated with the KneeReviver had a clinically (pain and function) worse condition than the Dynamic Monotube treated patients as they had statistically significantly worse baseline clinical scores as reflected by lower scores of WOMAC total and all WOMAC subscales, higher VAS pain, and lower SF-36 PCS (all p<0.025). Contrarily, the KneeReviver patients had less severe radiographic joint damage with a higher, though not statistically significant, minimum and MAC radiographic JSW (p=0.091 and p=0.169, respectively). Lastly, KneeReviver patients had a significantly lower LAC JSW (p<0.038). The baseline parameters of the 39 KneeReviver patients included in this interim analysis did not differ statistically significantly from the whole group of 65 KneeReviver patients (all p>0.15); JSW parameters were not compared since radiographs were analyzed in pairs (baseline and 1 year) and as such were not available for the patients not included in this interim analysis.

Table 1: Baseline parameters of both patient groups

	KneeReviver (n=39)	Dynamic Monotubes (n=39)	*P*-value
BMI (kg/m^2)	27.6 (3.0)	27.2 (3.5)	0.532
Age (years)	52.4 (7.0)	53.7 (6.6)	0.407
Male sex, n (%)	22 (56)	23 (59)	0.819*
WOMAC pain (0–100)	41.0 (16.0)	52.0 (16.0)	**0.003**
WOMAC stiffness (0–100)	32.7 (18.2)	47.3 (18.4)	**0.001**
WOMAC function (0–100)	42.2 (15.1)	55.1 (16.0)	**<0.001**
WOMAC total (0–100)	41.2 (14.9)	53.8 (15.6)	**<0.001**
VAS pain (10–0)	6.9 (1.2)	6.0 (2.2)	**0.024**
SF-36 PCS (0–100)	31.5 (6.8)	35.9 (8.2)	**0.012**
SF-36 MCS (0–100)	53.6 (9.3)	54.7 (8.2)	0.573
JSW minimum (mm)*	1.0 (1.2)	0.5 (0.9)	0.091
JSW (mm) MAC*	2.7 (1.8)	2.2 (1.8)	0.169
JSW (mm) LAC*	7.4 (2.0)	8.4 (2.0)	**0.038**
JSW (mm) mean*	5.0 (1.2)	5.2 (1.2)	0.497

Mean and standard deviation or n (%) are given of all 39 patients (* 38 patients) with full data and images sets (for the KneeReviver patients, these were the first 39 patients with complete data sets). *P*-values were calculated with independent *t*-tests, or chi-square tests for categorical variables (indicated with *). Bold *p*-values indicate statistical significance ($p<0.05$). BMI: body mass index; JSW: joint space width; LAC: least affected compartment; MAC: most affected compartment; MCS: mental component scale; PCS: physical component scale; SF-36: short-form 36; VAS: Visual Analogue Scale; WOMAC: Western Ontario and McMaster Universities Osteoarthritis Index.

Complications

The complications that occurred in the 39 KneeReviver patients are summarized in Table 2. The number of complications and the number of pin tract infections in these 39 patients were not statistically significantly different from the whole group of 65 KneeReviver patients (both $p>0.4$). Because of differences in registration of complications, no direct comparison between patients treated with the Dynamic Monotubes and patients treated with the KneeReviver can be made. Complications occurring during and after treatment with the Dynamic Monotubes have been previously described.[8–10,22]

One-year outcomes

In the KneeReviver treated patients, the total WOMAC and minimum JSW both showed a statistically significant 1-year increase (both $p<0.014$), as shown in Table 3 and Figure 2 for these primary outcomes. Also, all WOMAC subscales, the VAS pain, and SF-36 PCS improved significantly upon treatment with the KneeReviver (all $p<0.001$), while the SF-36 MCS as expected showed no significant 1-year change ($p=0.778$). The other JSW parameters increased statistically significantly after treatment with the KneeReviver as well (all $p<0.05$). There were no statistically significant differences in 1-year changes between centers of the KneeReviver trial (all $p>0.06$).

Table 2: Complications after knee joint distraction treatment with the KneeReviver

During distraction period	
Pin tract infections	28 (72)
- Oral antibiotics	26 (67)
- Wound cleaning + oral antibiotics	1 (3)
- Hospital admission + intravenous antibiotics	1 (3)
Pain/discomfort	12 (26)
- Sudden joint pain/discomfort	1 (3)
- Sustaining periarticular pain	11 (28)
- Hospital admission	2 (5)
Frame complications	4 (10)
- Frame repositioned	1 (3)
- Deviated distraction distance	2 (5)
- Loosened pins	1 (3)
Thrombosis	1 (3)
- Hospital admission	1 (3)
Within 1 year after distraction surgery	
Limited knee flexion	1 (3)
Sustained periarticular pain with hydrops	2 (5)
- Hospital admission	1 (2)
Pin tract discomfort	1 (3)
Antibiotic treatment	1 (3)
Defect in tibia cortex	1 (3)

N (%) is given.

Table 3: One-year changes upon treatment with the KneeReviver compared with those of the Dynamic Monotubes

	KneeReviver		**Dynamic Monotubes**		**Difference**
	Change	***P*-value**	**Change**	***P*-value**	***P*-value**
WOMAC pain	27.8 (18.9 to 36.6)	**<0.001**	28.1 (21.9 to 34.2)	**<0.001**	0.051
WOMAC stiffness	27.2 (18.1 to 36.4)	**<0.001**	19.4 (10.7 to 28.1)	**<0.001**	0.249
WOMAC function	27.4 (19.8 to 35.1)	**<0.001**	26.4 (20.9 to 31.9)	**<0.001**	0.119
WOMAC total	27.5 (19.7 to 35.3)	**<0.001**	26.2 (20.6 to 31.7)	**<0.001**	0.094
VAS pain	-3.1 (-3.9 to -2.3)	**<0.001**	-3.0 (-4.0 to -2.0)	**<0.001**	0.225
SF-36 PCS	9.6 (6.3 to 13.0)	**<0.001**	8.0 (5.3 to 10.7)	**<0.001**	0.911
SF-36 MCS	0.3 (-2.1 to 2.7)	0.778	-1.1 (-3.8 to 1.7)	0.438	0.754
JSW minimum	0.4 (0.1 to 0.6)	**0.013**	0.6 (0.3 to 0.8)	**<0.001**	0.749
JSW MAC	0.6 (0.1 to 1.0)	**0.015**	0.8 (0.4 to 1.2)	**<0.001**	0.929
JSW LAC	0.3 (0.0 to 0.7)	**0.042**	0.1 (-0.3 to 0.6)	0.607	0.516
JSW mean	0.5 (0.2 to 0.7)	**0.003**	0.4 (0.2 to 0.7)	**0.004**	0.806

Mean change and 95% confidence interval are given. *P*-values for the 1-year change are given for both groups, calculated with paired *t*-tests. The final column shows *p*-values of the comparison of 1-year changes between the 2 groups, corrected for baseline values using linear regression. Bold *p*-values indicate statistical significance ($p<0.05$). JSW: joint space width; LAC: least affected compartment; MAC: most affected compartment; MCS: mental component scale; PCS: physical component scale; SF-36: Short-form 36; VAS: Visual Analogue Scale; WOMAC: Western Ontario and McMaster Universities Osteoarthritis Index.

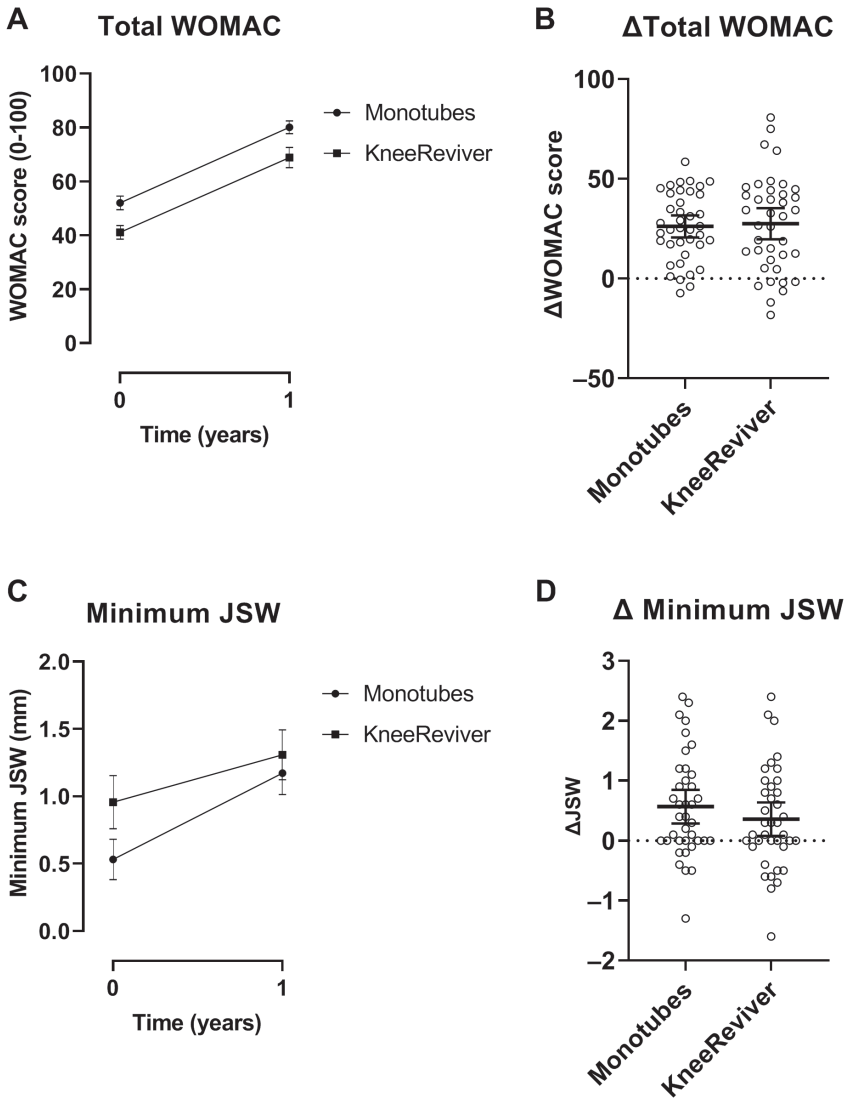


Figure 2: One-year changes in the primary outcome parameters for the 2 patient groups. (A) and (B) show the 1-year total Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) change while (C) and (D) show the 1-year minimum joint space width (JSW) change. (A) and (C) show the mean and standard error of the mean (SEM); (B) and (D) show each individual patient as well as the mean change with 95% confidence interval. All increases in primary outcome measures were statistically significant, whereas these changes were not statistically significantly different between both groups (see Table 2).

For the retrospective evaluation of the 1-year follow-up of patients treated with the Dynamic Monotubes, the observed changes over time were similar to those of the KneeReviver with no statistically significant differences for the 1-year changes between the 2 groups, as shown in Table 3 and Figure 2.

Non-inferiority

Both primary parameters (WOMAC and minimum JSW) were shown to be non-inferior for patients treated with the KneeReviver compared to the Monotubes, as shown in Figure 3. When correcting for baseline values, the minimum JSW change was still non-inferior for the KneeReviver, but (non-) inferiority of the 1-year total WOMAC change was inconclusive (Table 3) as the outer limit of the 90% confidential interval crossed the 10-point non-inferiority level.

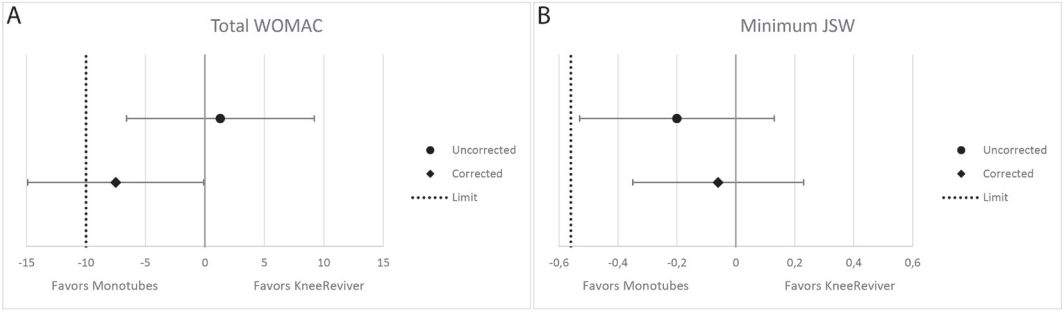


Figure 3: Non-inferiority tests for the KneeReviver compared to the Dynamic Monotubes, for the change in (A) the total Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) and (B) the minimum joint space width (JSW). Results are shown both uncorrected (circle) and corrected (diamond) for baseline values. Mean differences with 90% confidence interval are shown. The dotted line indicates the non-inferiority limit.

All secondary parameters (VAS pain, SF-36 PCS and MCS) were shown to be non-inferior for the KneeReviver compared to the Dynamic Monotubes, even when corrected for baseline values, as shown in Table 4.

Table 4: Non-inferiority results of the KneeReviver compared to the Dynamic Monotubes for 1-year changes in primary and secondary outcome parameters

	Non-inferiority limit	Baseline correction	Difference	Conclusion
WOMAC total	-10	Uncorrected	1.3 (-6.6 to 9.2)	Non-inferior
		Corrected	-7.5 (-14.9 to -0.1)	Inconclusive
JSW minimum	-0.56	Uncorrected	-0.20 (-0.52 to 0.13)	Non-inferior
		Corrected	-0.06 (-0.35 to 0.24)	Non-inferior
VAS pain	-2	Uncorrected	-0.1 (-1.2 to 1.0)	Non-inferior
		Corrected	0.7 (-0.3 to 1.6)	Non-inferior
SF-36 PCS	-7	Uncorrected	1.7 (-1.8 to 5.2)	Non-inferior
		Corrected	0.2 (-3.3 to 3.8)	Non-inferior
SF-36 MCS	-7	Uncorrected	1.4 (-1.6 to 4.4)	Non-inferior
		Corrected	0.5 (-2.2 to 3.2)	Non-inferior

Difference is shown with mean and 95% confidence interval. JSW: joint space width; MCS: mental component scale; PCS: physical component scale; SF-36: Short-form 36; VAS: Visual Analogue Scale; WOMAC: Western Ontario and McMaster Universities Osteoarthritis Index.

Discussion

As hypothesized, patients treated with KJD using the KneeReviver, which was developed with input of surgeons, patients, and engineers and with CE certification and the intended use 'knee joint distraction', showed significant clinical benefit 1 year after treatment. Almost all evaluated parameters, both regarding clinical outcome measures and tissue structure repair, showed a statistically significant improvement at 1-year follow-up. Effects were not statistically significantly different when compared to patients previously treated with the Dynamic Monotubes (originally designed for trauma surgery). The only parameter that did not show a significant change in both groups was the mental component scale of the SF-36. This is anticipated since this parameter is insensitive to knee OA treatments in general, as HTO or TKA did not induce a change in this parameter either.[8–10] Although the 1-year results between the 2 frames were not statistically significantly different, the second hypothesis could only partially be confirmed as the total WOMAC, being 1 of the primary outcome parameters for which the study was powered, was inconclusive when corrected for baseline in the non-inferiority evaluation. Changes in all other outcome parameters 1 year after treatment, including minimum JSW as the other primary outcome parameter, were shown to be non-inferior for patients treated with the KneeReviver as compared to the Dynamic Monotubes. However, it should be mentioned that the difference between the 2 treatments in minimum JSW change was in favor of the Dynamic Monotubes and the non-inferiority level was taken quite liberally.

Complications were not directly compared between trials, but as reported previously in patients treated with the Dynamic Monotubes, pin tract infections were the most occurring complication and a relatively high number of patients experienced them.[22] In order to decrease treatment burden, this number should be reduced as much as possible. One option may be including the use of cadexomer iodine ointment in the wound care protocol during treatment, as this has shown a significant reduction in pin tract infections in patients treated with KJD.[23]

While these first analyses show positive results for the KneeReviver, the long-term results will become the most interesting. Previous analyses have shown that the first-year increase in minimum radiographic JSW is predictive of long-term survival of KJD treatment (viz. the duration till TKA after KJD). The chance of being without a prosthesis 9 years after KJD treatment was significantly higher for patients with a larger initial JSW increase. None of the patients with a first-year minimum JSW increase of less than 0.5 mm had their native knee 9 years later.[7] Patients treated with the KneeReviver showed a smaller average minimum JSW increase in the 1st year, 0.4 mm compared to 0.6 mm for the Dynamic Monotubes. It has also been shown that more severely affected joints show a better tissue repair response.[24] Compared to patients treated with the Dynamic Monotubes, the KneeReviver patients seem to have less affected joints with respect to baseline JSW with 1 mm *versus* 0.5 mm for the minimum JSW and 2.7 mm *versus* 2.2 mm for the MAC JSW, both nearing statistical significance. As such,

long-term results will be critical in order to fully determine the clinical effectiveness as well as tissue structure repair and non-inferiority of the KneeReviver in comparison with other devices.

A clear limitation of this study is that the 2 patient groups were not randomized. In fact, almost all baseline clinical scores were significantly worse for the KneeReviver patients, which would indicate that they had a higher clinical disease activity. However, baseline radiographic JSW measurements indicate the opposite, showing less severe joint tissue damage. While the LAC JSW was statistically significantly lower in patients treated with the KneeReviver, their MAC JSW and minimum JSW were clearly higher, in case of the minimum JSW even double. Apparently, different types of patients were included in the 2 studies, with patients treated in the open prospective study with the KneeReviver experiencing more complaints but less joint damage, and those treated in the RCTs with the Dynamic Monotubes showing an opposite profile with more joint damage and less pain. The difference between complaint-driven patients in the KneeReviver group and damage-driven patients in the Monotubes group can only be speculated on. The patients treated with the Dynamic Monotubes were randomized against alternative surgical treatments with significant impact in contrast to those in the open prospective KJD study without randomization. As such, these patients may have had more advanced joint damage, despite the same inclusion criteria, enough to considered a demanding surgical treatment in regular care as alternative. It might have been that the indication TKA or HTO in the 2 RCTs has resulted in large baseline differences. However, when comparing the KneeReviver patients to the 2 groups treated with the Dynamic Monotubes (those indicated for HTO and for TKA) separately, the KneeReviver patients at baseline show in both cases more complaints (total WOMAC: KneeReviver 41.2 (SD 14.9); Monotubes from the TKA trial 50.3 (11.1); Monotubes from the HTO trial 56.5 (18.1)) and also in both cases less joint damage (minimum JSW: KneeReviver 1.0 (1.2); Monotubes from the TKA trial 0.6 (1.2); Monotubes from the HTO trial 0.5 (0.8)). So, the difference in baseline characteristics between the 2 RCTs is not explanatory, as both show the same differences compared to the patients in the KneeReviver study. The difference may be related to the gradual change in considerations of the orthopedic surgeon which patient to include changing gradually from a more tissue structure damage driven OA to a more pain driven OA, specifically for the latter without proven effective alternative treatments, in contrast to the earlier included patients where TKA or, in case of axis deviation, a HTO were good alternatives. This remarkable difference in patients characteristics between the 2 RCTs with the Dynamic Monotubes and the open prospective KneeReviver study would likely not have been introduced in case a randomized study between both devices would have been performed. However, the ethical committee of the UMC Utrecht did not allow such a direct comparison since the KneeReviver was considered and later shown to be more user friendly.[12] Long-term results might indicate whether the different type of patients included matters or not, and conclusions on the long-term

effectiveness of KJD treatment with the KneeReviver should take into account the difference in patient population. In any case, these results stress the importance of defining clear inclusion criteria, and ensuring these criteria are met when selecting patients for treatment with KJD.

In conclusion, the newly developed user-friendly KneeReviver device enables successful KJD treatment and is broadly spoken non-inferior compared to the previously used Dynamic Monotubes. Based on the first-year data, long-term follow-up and analyses are warranted and necessary to further conclude whether the KneeReviver can postpone a TKA as the Dynamic Monotubes frame has shown thus far.

References

1. Jansen MP, Boymans TAEJ, Custers RJH, *et al*. Knee Joint distraction as treatment for osteoarthritis results in clinical and structural benefit: A systematic review and meta-analysis of the limited number of studies and patients available. Cartilage. 2020 Jul 22;194760352094294.
2. Deie M, Ochi M, Adachi N, *et al*. A new articulated distraction arthroplasty device for treatment of the osteoarthritic knee joint: a preliminary report. Arthroscopy. 2007;23(8):833–8.
3. Aly TA, Hafez K, Amin O. Arthrodiatasis for management of knee osteoarthritis. Orthopedics. 2011;34(8):e338–43.
4. Intema F, van Roermund PM, Marijnissen ACA, *et al*. Tissue structure modification in knee osteoarthritis by use of joint distraction: An open 1-year pilot study. Annals of the Rheumatic Diseases. 2011 Aug 1;70(8):1441–6.
5. Wiegant K, van Roermund PM, Intema F, *et al*. Sustained clinical and structural benefit after joint distraction in the treatment of severe knee osteoarthritis. Osteoarthritis and Cartilage. 2013 Nov;21(11):1660–7.
6. van der Woude JAD, Wiegant K, van Roermund PM, *et al*. Five-year follow-up of knee joint distraction: Clinical benefit and cartilaginous tissue repair in an open uncontrolled prospective study. Cartilage. 2017;8(3):263–71.
7. Jansen MP, van der Weiden GS, van Roermund PM, *et al*. Initial tissue repair predicts long-term clinical success of knee joint distraction as treatment for knee osteoarthritis. Osteoarthritis and Cartilage. 2018;26(12):1604–8.
8. van der Woude JAD, Wiegant K, van Heerwaarden RJ, *et al*. Knee joint distraction compared with total knee arthroplasty: A randomised controlled trial. The Bone and Joint Journal. 2017;99-B(1):51–8.
9. van der Woude JAD, Wiegant K, van Heerwaarden RJ, *et al*. Knee joint distraction compared with high tibial osteotomy: A randomized controlled trial. Knee Surgery, Sports Traumatology, Arthroscopy. 2017;25(3):876–86.
10. Jansen MP, Besselink NJ, van Heerwaarden RJ, *et al*. Knee joint distraction compared with high tibial osteotomy and total knee arthroplasty: Two-year clinical, radiographic, and biochemical marker outcomes of two randomized controlled trials. Cartilage. 2019 Feb 13;194760351982843.
11. van der Woude JAD, Nair SC, Custers RJH, *et al*. Knee Joint distraction compared to total knee arthroplasty for treatment of end stage osteoarthritis: Simulating long-term outcomes and cost-effectiveness. PLOS ONE. 2016 May 12;11(5):e0155524.
12. Jansen MP, Struijk T, Mastbergen SC, *et al*. User-friendliness of a novel dedicated knee joint distraction device: Experiences from clinical practice. Osteoarthritis and Cartilage. 2020 Apr 1;28:S474.
13. van Heerwaarden RJ, Verra W. Knee joint distraction in the treatment of severe osteoarthritis. Arthroskopie. 2020 Dec 1;33(1):10–4.
14. ArthroSave. KneeReviver. https://www.arthrosave.com/. 2020.
15. Wiegant K, van Heerwaarden R, van der Woude JAD, *et al*. Knee joint distraction as an alternative surgical treatment for osteoarthritis: Rationale and design of two randomized controlled trials (*vs* high tibial osteotomy and total knee prosthesis). International Journal of Orthopaedics. 2015 Aug 23;2(4):353–60.
16. Buckland-Wright JC, Wolfe F, Ward RJ, *et al*. Substantial superiority of semiflexed (MTP) views in knee osteoarthritis: a comparative radiographic study, without fluoroscopy, of standing extended, semiflexed (MTP), and schuss views. Journal of Rheumatology. 1999 Dec;26(12):2664–74.
17. Buckland-Wright JC, Ward RJ, Peterfy C, *et al*. Reproducibility of the semiflexed (metatarsophalangeal) radiographic knee position and automated measurements of medial tibiofemoral joint space width in a multicenter clinical trial of knee osteoarthritis. Journal of Rheumatology. 2004 Aug;31(8):1588–97.

18. Marijnissen ACA, Vincken KL, Vos PAJM, *et al*. Knee Images Digital Analysis (KIDA): A novel method to quantify individual radiographic features of knee osteoarthritis in detail. Osteoarthritis and Cartilage. 2008 Feb 1;16(2):234–43.
19. Escobar A, Quintana JM, Bilbao A, *et al*. Responsiveness and clinically important differences for the WOMAC and SF-36 after total knee replacement. Osteoarthritis and Cartilage. 2007 Mar;15(3):273–80.
20. Lee JS, Hobden E, Stiell IG, *et al*. Clinically important change in the visual analog scale after adequate pain control. Academic Emergency Medicine. 2003 Oct;10(10):1128–30.
21. Ehrich EW, Davies GM, Watson DJ, *et al*. Minimal perceptible clinical improvement with the Western Ontario and McMaster Universities Osteoarthritis Index questionnaire and global assessments in patients with osteoarthritis. Journal of Rheumatology. 2000 Nov 1;27(11):2635–41.
22. Jansen MP, Mastbergen SC, van Heerwaarden RJ, *et al*. Knee joint distraction in regular care for treatment of knee osteoarthritis: A comparison with clinical trial data. PLOS ONE. 2020 Jan 22;15(1):e0227975.
23. Jansen MP, van Egmond N, Kester EC, *et al*. Reduction of pin tract infections during external fixation using cadexomer iodine. Journal of Experimental Orthopaedics. 2020 Dec 7;7(1):88.
24. van der Woude JAD, Welsing PM, van Roermund PM, *et al*. Prediction of cartilaginous tissue repair after knee joint distraction. The Knee. 2016 Oct;23(5):792–5.

PART 2

Joint processes and working mechanisms

CHAPTER 10

Joint distraction for osteoarthritis
Clinical evidence and molecular mechanisms

M.P. Jansen
S.C. Mastbergen

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Abstract

Joint distraction has emerged as a joint-preserving treatment for end-stage osteoarthritis, with a gradually growing promise for implementation in regular clinical practice. This review focuses on distraction of the knee, showing prolonged symptomatic improvement in combination with cartilaginous tissue repair in degenerated knee joints, and supporting the concept of cartilage repair translating into real clinical benefit. The reversal of the tissue degenerative process could be the result of any of the supposed mechanisms involved – a combination of partial unloading, synovial fluid pressure oscillation, subchondral mechanical and biochemical bone changes, joint-derived stem cells, and a changed molecular joint milieu. The overall picture that emerges from this combined evidence is relevant for joint distraction as well as translation to other joint-preserving techniques. It remains to be elucidated whether optimizing the biomechanical conditions during distraction can actually cure the disease instead of only providing temporarily relief, but even in the latter case it may be of relevance for society and patients, as it will delay placement of a prosthesis at an early age and with that prevent revision surgery later in life. Most importantly, a better insight in the underlying mechanisms may provide new leads to more targeted treatment options.

Introduction

With an aging and increasingly obese population, there is a growing demand for joint-preserving treatments for osteoarthritis (OA), a degenerative joint disease characterized by pain and disability due to joint tissue damage. OA gives rise to a huge societal problem, as the disease affects over 10% of the adult population.[1] Joint preservation is especially relevant in case of relatively young, middle aged, physically still active patients, as it postpones irreversible surgical treatments such as joint arthroplasty. With that, it prevents complex and costly revision surgery later in life. More and more options for joint-preserving treatments are subject of study, with multiple reviews addressing joint distraction specifically as one of these options.[2–4] Over the past 30 years, joint distraction has emerged as a joint-preserving treatment for (end-stage; considered for joint replacement surgery) OA, with a gradually growing promise for implementation in regular clinical practice. For joint distraction, the two bony ends of a joint are placed at a certain distance, for a certain time, using an external fixation frame.[5] In the 1990s, this treatment was first described for the hip, ankle, and foot joints.[6–9] Since then, joint distraction has been applied for the knee and thumb-base as well.[10–12] In 2013, an evaluation of distraction studies was covered in a review on cartilage repair strategies in this journal.[2] Data showed predominantly positive results, with patients experiencing significant improvements in pain and mobility, as well as evidence of cartilage and bone tissue repair activity.[2] Despite this clinical promise, the mechanisms behind the observed quite unique tissue regenerative process were still unknown. Over the past years, more research has been performed on these (molecular) mechanisms behind distraction treatment, specifically for the knee, to support the structural changes seen upon treatment. This includes research into synovial fluid markers, stem cell involvement, and animal studies showing tissue repair mechanisms. Moreover, since 2013 more extensive clinical trials have been performed, with distraction also being applied in regular care for the knee, although still in small numbers.[13]

Compared to other joints, more extensive research has been performed on distraction on the knee, especially with respect to the working mechanisms. This review therefore focuses specifically on distraction of the knee, with the first part describing the increased clinical evidence with respect to patient-reported symptomatic outcomes as well as cartilaginous tissue repair. This part is followed by discussing different concepts of potential underlying molecular mechanisms. Finally, the overall picture emerging from the combined evidence and the possible future approaches, with regard to joint distraction and translation to other joint-preserving techniques is discussed.

Clinical evidence

Several clinical trials have been performed in which patients were treated with knee joint distraction (KJD), in some cases combined with other treatment modalities. While there are

differences between the trials with regard to the distraction technique and treatment protocol, the general principle remains the same. In all cases, an external frame is placed around the knee joint using bone pins on the medial and lateral sides of the femur and tibia, after which the two joint surfaces are placed at a certain distance for several weeks after which the frame is removed, with in general no imposed follow-up treatment. The frames used are shown in Figure 1 and discussed below.

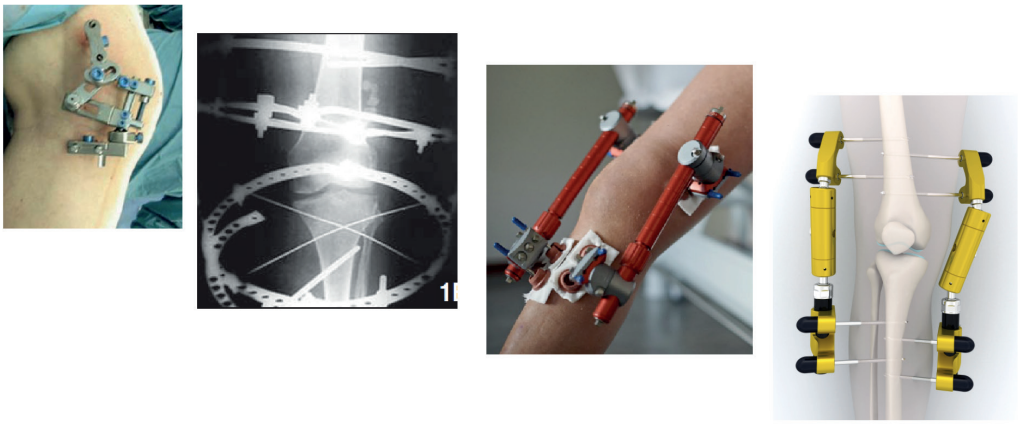

Figure 1: Different type of frames used for knee joint distraction. From left to right: custom articulated distraction device (Deie *et al.*, 2007)[14]; Ilizarov circular frame (Aly *et al.*, 2011)[15]; Dynamic Monotubes (Van der Woude *et al.*, 2017)[16]; KneeReviver.[17,18]

An overview of the presently performed and (to our knowledge) ongoing KJD clinical trials is given in Table 1. The search strategy used to find these studies is summarized in the 'review criteria' box.

Review criteria
To find the studies summarized in Table 1, the MEDLINE, EMBASE, and Web of Science libraries were searched for relevant articles. Search terms were (distraction OR arthrodiatasis OR arthrodiastasis) AND (knee OR tibiofemoral OR tibiofibular), and were applied on title and abstract and, in Web of Science, Keywords+. Only full-text publications about clinical studies in which knee joint distraction with external fixation was applied and the primary outcomes were patient-reported outcomes and/or cartilaginous tissue restoration were included in Table 1. Studies that were found but did not fully meet the criteria were used throughout the text where relevant. The studies in progress with no results published yet were included based on personal communication.

The first trial in 2007 was a retrospective study with 6 OA patients who were treated with a combination of hinged KJD and bone marrow stimulation, using a customized frame for 2–3 months.[14] Subsequently, in 2010 a case report was published, where 1 patient with an osteochondral defect was treated with hinged distraction and an artificial bone graft using the same customized frame for 3 months.[19] These studies indicate a beneficial effect of the distraction with respect to clinical outcome as well as joint tissue repair including cartilage.

Table 1: Overview of knee joint distraction clinical studies

Study	Design	Number, type of patients	Age (years)	Treatment	Follow-up	Outcomes
Deie *et al.* (2007)[14] & (2010)[20]	Retrospective	n=6 generalized OA	51.7 (SD 7.8)	Hinged customized distraction + BMS, 2–3 mths	Mean 2.5 yrs (range 14–51 mths)	PROMs, radiographs, arthroscopy
Abouheif *et al.* (2010)[19]	Case report	n=1 osteo-chondral defect	18	Hinged customized distraction + bone graft, 3 mths	4.5 yrs	Radiographs, arthroscopy, MRI
Intema *et al.* (2011);[21] Wiegant *et al.* (2013);[22] Van der Woude *et al.* (2017);[16] Jansen *et al.* (2018)[23]	Prospective	n=20 OA indication TKA	48.5 (SEM 1.3)	Dynamic Monotubes distraction, 2 mths	3, 6, 9 and 12 mths; 18 and 24 mths; 5 yrs; 9 yrs	PROMs, radiographs, MRI, systemic biomarkers
Aly *et al.* (2011)[15]	Controlled trial (*vs* debridement)	n=19 OA	Range 39–65	Ilizarov distraction + debridement; 4 wks	Mean 5.5 yrs (range 58–82 mths)	PROMs, radiographs
Van der Woude *et al.* (2017);[24] Jansen *et al.* (2019)[25]	RCT (*vs* HTO)	n=22 OA indication HTO	51.2 (SEM 1.1)	Dynamic Monotubes distraction, 6 wks	3, 6, 9, and 12 mths; 2 yrs	PROMs, radiographs, MRI, systemic biomarkers
Van der Woude *et al.* (2017);[26] Jansen *et al.* (2019)[25]	RCT (*vs* TKA)	n=20 OA indication TKA	54.9 (SEM 1.8)	Dynamic Monotubes distraction, 6 wks	1 yr; 2 yrs	PROMs, radiographs, MRI, systemic biomarkers
Jansen *et al.* (2020)[13]	Retrospective	n=84/41* OA	53.1 (SD 6.9)	Dynamic Monotubes distraction, 6 wks	1 yr	PROMs
Studies in progress, no results published yet						
Jansen	Prospective	n=65 OA		KneeReviver	1 yr	PROMs; radiographs
Pandit	RCT	n=172 OA indication (T)KA		Multiple devices	To be started	PROMs; radiographs

In case not all patients in the trial were evaluated on outcome measures (yet), the number of evaluated patients is indicated with *. BMS: bone marrow stimulation; HTO: high tibial osteotomy; OA: osteoarthritis; PROMs: patient-reported outcome measures; RCT: randomized controlled trial; SD: standard deviation; SEM: standard error of the mean; TKA: total knee arthroplasty.

In 2011, the first open prospective study was published in which 20 knee OA patients were treated with Dynamic Monotubes (Stryker) resulting in immobilization of the knee joint during the 2 months distraction.[21] In the same year a controlled study was published in which 19 OA patients were treated with an Ilizarov distraction frame for 4 weeks (also immobilizing the joint during distraction) in combination with debridement.[15] Both these studies demonstrated a clear clinical as well tissue structure improvement upon treatment. In the meantime, two randomized studies (RCTs) were initiated using 6-week distraction with

the Dynamic Monotubes, the first-year results reported in 2017. In one RCT, 22 medial compartmental OA patients indicated for high tibial osteotomy (HTO) were treated with KJD and compared with HTO treatment.[24] In another RCT, 20 OA patients indicated for total knee arthroplasty (TKA) were treated with the same type of 6-week distraction and compared with TKA treatment.[26] Both studies showed clinical improvement and tissue structure repair upon KJD. Lastly, a retrospective study on 84 OA patients treated with distraction in regular care using the Dynamic Monotubes was published in 2020.[13] Of 41 of these patients patient-reported outcome measures (PROMs) were available one year after treatment and showed also in regular care a clear improvement.

Most recently a prospective study was started, in which 65 patients were treated with distraction using the KneeReviver frame (ArthroSave) and will be followed for 5 years. A preliminary analysis showed that the first 39 patients reaching one year of follow-up showed significant improvement in clinical parameters and tissue structure repair, which was generally shown to be comparable and non-inferior to results obtained with 39 patients treated with the Dynamic Monotubes (personal observation based upon interim analyses).[27] Lastly, in the UK a national multicenter study (KARDS) initiated by the NIHS, in which 344 patients will be randomized in a 1:1 ratio to KJD or knee arthroplasty using different distraction devices, has started 2021 (personal communication with Prof H Pandit, Leeds, United Kingdom).

Throughout the studies, different distraction techniques and postoperative rehabilitation protocols (if imposed) were used. Only Deie *et al.* and Abouheif *et al.* used hinged distraction, allowing flexion and extension of the knee joint, and continuous passive motion was applied for two weeks after placement of the distraction device.[14,19] All other studies used distraction frames that did not allow joint flexion, although in the study of Intema *et al.* the frame was removed every two weeks and continuous passive motion was applied for 3-4 hours, after which the frame was replaced and distraction was installed again.[21] In this study the clinical effects and tissue structure repair were slightly better than in the following RCTs.[28] This could have been related to the flexion (see below), although also the baseline characteristics and the total distraction duration differed between these studies. It should be noticed that for the knee also a personalized hinged device was developed and mechanically approved feasible[29]; however, clinical feasibility could not be demonstrated, mainly due to painful motion of soft tissues along the bone pins.[30] The distraction duration varied from 4 weeks to 3 months.[15,19] The distraction distance, i.e. the number of millimeters the bones are separated, was not clearly described by Deie *et al.* and Abouheif *et al.*, while Aly *et al.* described a distraction of one mm/day for four weeks. All other KJD studies used a fixed distance of 5 mm. However, it remains unclear how this distance was exactly measured, e.g. bone to bone distance or increase above the original bone to bone distance. Also, correction of the mechanical leg axis has been performed during distraction, providing more distance at either side in case of predominantly

unicompartmental knee OA. None of the studies provided a reasoning for their choices on the amount of distraction or the distraction duration. For the RCTs it was explained that the distraction time was shortened from 2 months to 6 weeks to decrease treatment burden. A separate published post-hoc analysis (insufficiently powered) demonstrated that there were no significant differences in outcome between patients treated with 6 weeks versus 2 months distraction, although the patients treated with 2 months distraction did show somewhat better results.[28,31]

Each KJD study evaluated several different outcome parameters after KJD treatment, as shown in Table 1. These are summarized in the next sections, divided into patient-reported (clinical) outcomes and outcomes related to cartilaginous tissue repair.

Patient-reported outcomes

All studies evaluated patient-reported outcome measures (PROMs) before and after treatment, except for Abouheif *et al,* who only mentioned their patient had knee pain pre-treatment and was pain-free post-treatment.[19] All other studies statistically evaluated a change in pain, using a Visual Analogue Scale (VAS) of pain[14], a four-point Likert scale for pain[15], the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) pain subscale[13,16,21–26], and/or the Intermittent and Constant Osteoarthritis Pain (ICOAP) questionnaire.[24–26] For all pain parameters, as well as follow-up moments varying from three months to nine years (table 1), patients experienced significantly less pain after treatment compared to pre-treatment values. In fact, all symptom-related PROMs (walking capacity or stair climbing, the Japanese Osteoarthritis (JOA) knee score, or the WOMAC or Knee Injury and Osteoarthritis Outcome Score (KOOS) and all of their subscales, which evaluate stiffness, function, symptoms, sport, and quality of life) in all studies show a (statistically) significant improvement of around 40-60% at every time point between one and nine years after treatment.[13,14,32,15,16,19,22–26] Interestingly, it was shown that even patients who underwent a TKA several years after their KJD, still reported increased total WOMAC scores of on average 20 points before undergoing the TKA.[23] This increase is higher than the 15-point change considered the minimal clinically important difference and neared statistical significance (p=0.067).[33] Apparently, other considerations besides the symptomatic complaints are important for patients to stay satisfied with their treatment (e.g. a relative worsening with the alternative option for TKA). Important to notice is that studies were retrospective, prospective cohorts, or small size RCTs. The quality of especially retrospective and prospective studies without a control group may provide bias, with clinical improvement comprising in part a placebo effect.

Some studies also evaluated quality of life (EuroQol (EQ)-5D and Short Form (SF)-36 questionnaires). A statistically significant improvement in EQ-5D and in the physical components scale (PCS) of the SF-36 was observed.[24–26] The mental component scale (MCS)

of the SF-36 did not show any change.

A few studies compared KJD with control groups. Aly *et al.* compared 19 patients treated with KJD and debridement with 42 patients treated with debridement alone. Contrary to KJD patients, those treated with debridement alone did not show a significant improvement in pain or walking capacity.[15] In the KJD *vs* HTO RCT, 22 KJD patients were compared with 45 HTO patients, and results were generally comparable between the two groups.[24,25] Return to sports and work five years after treatment was comparable between the groups as well.[34] In the other RCT, 20 KJD patients were compared with 36 TKA patients. While after one year there were no significant differences between the two groups, the patients treated with TKA after 2 years showed significantly better results than the KJD patients in almost all PROMs.[25,26] TKA is generally accepted as a treatment that results in highly significant improvements in PROMs, however, because of wear and tear and loosening of the prosthesis a revision surgery later in life may be needed. The odds of needing this revision are much higher in younger patients, aged <65 years, who show a lifetime risk of revision between 15 and 35%, compared to older patients with a lifetime risk of on average ~5%.[35] Therefore, it is specifically this population of relatively young and still active patients that is indicated for KJD. The average age in all studies fits this consideration (Table 1), although not much data is present on the effects of KJD in the older population. Also, a repeated KJD treatment with several years interval has for the knee never been studied, although this was anecdotally found to be effective for the ankle in case of a second distraction.

Cartilaginous tissue restoration

The most evaluated parameter for cartilage restoration was radiographic joint space width (JSW), measured on weight-bearing radiographs, as a surrogate measure for cartilage thickness change. While Abouheif *et al.* only mentions joint space preservation after 4.5 years[19], the other studies quantified this by measuring the mean or minimum JSW.[14–16,21–26] All studies showed a group average increase in JSW measurements after KJD treatment, at all measured time points, and almost all were statistically significant. The largest increase was seen in the study by Aly *et al.*, who measured a 2.5 mm average JSW pre-treatment and 4.3 mm at 5.5 years post-treatment.[15] The studies that evaluated multiple time points all showed the same general pattern: an initial significant one-year increase in JSW of around 0.5-1.0 mm, sustaining at a similar level over the second year of follow-up.[21,22,24–26] The first-year increase in minimum JSW was reported in a post-hoc analysis to predict long-term survival of KJD treatment to postpone TKA.[23] At five and seven years after treatment, the JSW was still increased compared to baseline, statistically significantly in case of the minimum JSW but not the mean JSW of the most affected compartment.[16,23] Apparently, the advantage of the initial one- to two-year increase in JSW is maintained, despite the fact that natural OA progression is taking over again.

The use of radiographic JSW does not provide a direct measure for cartilage thickness. E.g. partial meniscus extrusion may normalize because of the temporary increase in JSW, enabling the meniscus to reposition, resulting in an increased JSW but not cartilage thickening per se. Actual cartilaginous tissue repair is supported by MRI or post-treatment arthroscopy evaluation. The studies by Deie *et al.* and Abouheif *et al.* evaluated the treated knees arthroscopically, and showed hyaline-like cartilage being formed after treatment, confirmed on an MRI scan in the study by Abouheif *et al.*[14,19] In most studies arthroscopy was not used, as to not disturb the joint and the processes occurring, and since patients are reluctant to interfere with the well-functioning joint. MRI evaluation by Intema *et al.* showed that the average cartilage thickness measured by quantitative MRI evaluation of the most affected compartment increased significantly from 2.4 mm pre-treatment to 3.0 mm post-treatment.[21] As for the first-year radiographic JSW change, the first-year cartilage thickness change (when corrected for baseline) was shown to predict long-term survival.[23] Also, the percentage of denuded bone area, i.e. the percentage of subchondral bone without cartilage, decreased from 22% to 5%.[21] Two years after treatment these beneficial changes were still significant, and while they prolonged to five years after treatment, they were no longer significant at that point.[16] When the five-year changes were compared to natural progression from matched patients from the Osteoarthritis Initiative (OAI), who showed a significant five year deterioration in both MRI parameter (and in the radiographic JSW parameters), patients treated with KJD showed significantly better five-year results.[16] Even if long-term cartilage restoration results are no longer significantly improved, patients treated with KJD apparently still respond significantly better than if they would not have been treated conventionally with natural OA progression instead. KJD patients from the RCTs have been evaluated by MRI showing a two-year increase in cartilage thickness and decrease in denuded bone area in the most affected compartment.[36] Lastly, preliminary long-term results in the prospective study of Intema *et al.* show that, while after an initial increase one and two years after treatment the cartilage thickness gradually decreased, even ten years after treatment it was still increased compared to pre-treatment in both the tibia and femur.[37] Unfortunately, the two most recent (ongoing) KJD studies have not included MRI scans as a primary outcome in their protocol because of the costs related to repeated scanning of these patients' knees.

With respect to the quality of the cartilage regenerated after KJD, data are limited. In the prospective study and both RCTs, systemic collagen type II biomarkers (serum N-propeptide of type IIA procollagen (PIIANP) as synthesis marker, and urinary C-telopeptide of type II collagen (CTXII) as degradation marker) were evaluated. A ratio between the two showed that the net collagen type II synthesis was significantly decreased in the first months after treatment (i.e. more degradation than synthesis), but slowly increased to significance two years after treatment, in all studies.[21,22,25] This suggests that the regenerated tissue may be of hyaline nature.[38] From a subgroup of patients from the two RCTs, the change in cartilage

quality after KJD treatment using delayed gadolinium-enhanced magnetic resonance imaging of cartilage (dGEMRIC), which indicates glycosaminoglycans (GAG) concentration in the cartilage, and T2-mapping data, representing collagen structure of the cartilage, were gathered. No significant change in dGEMRIC or T2 signal values, when volume increased, up to two years after treatment was found, suggesting the cartilage quality did not change.[39] In other words, the newly formed cartilage (as previously shown with JSW increase and MRI cartilage thickening) was likely of a similar quality as before treatment and not of fibrocartilage quality.

In case compared with control groups, KJD generally performed similarly or better in structural results. Aly *et al* showed that, unlike patients treated with KJD and debridement, those treated with debridement only did not show a JSW increase.[15] In the RCT, HTO patients showed one- and two-year JSW increases that were not significantly different from those shown by KJD patients.[24,25] Since in TKA the knee joint is replaced, KJD could not be compared with TKA in cartilage restoration parameters. Lastly, MRI results from two RCTs showed that, contrary to KJD, HTO patients presented a significant deterioration in cartilage thickness and denuded bone area and results in severe OA patients were significantly better for KJD than for HTO.[40] There was no difference between KJD and HTO with regard to dGEMRIC and T2 measurements.[39]

Adverse events

These beneficial results regarding PROMS and tissue structure repair come at the expense of side-effects during the distraction treatment, because of the external fixation. All studies reported occurrence of complications, except for Abouheif *et al.* who reported no complication.[19] In all other trials, pin tract skin infections occurred frequently. While in the studies of Deie *et al.* only two of the six patients (30%) experienced skin infections, in the other studies this percentage was much higher, ranging from around 60% in both RCTs to 85% in the prospective study.[21,24,26] It might be that the low skin infection rate is due to the positioning and type of pins, with Deie *et al.* placing the frame more closely to the joint with less soft tissue involvement and thinner pins (k-wires). Aly *et al.* reports contradictory results of first 18% and then 74% of patients experiencing skin infections. Regardless, the vast majority (~86%) of all pin tract infections could be treated with oral antibiotics, and they did not have a significant influence on one-year PROMs.[13] Furthermore, despite the high occurrence of these infections, patients undergoing TKA surgery years after KJD did not experience additional complications or decreased clinical effect.[41] Superficial skin infections should not be trivialized with respect to burden for the patient and risk of more serious deeper infections. Efforts should be made to decrease the number. Development of a dedicated frame like the KneeReviver might be a way to realize this.[17] Also, care protocols like the use of cadexomer iodine ointment during distraction treatment demonstrating a significant decrease in pin tract infections (from 64% to 32%) might be of help.[42]

Complications other than pin tract skin infections occurred only sporadically (all less than 5% of the 172 patients included in the published studies of table 1). The two most occurring ones were osteomyelitis (6 patients, 3%), treated with pin tract wound cleaning and a combination of oral and intravenous antibiotics, as a result of too late or inappropriately treated skin infections, and deep venous thrombosis (4 patients, 2%), treated with additional anticoagulation (in addition to the preventive anticoagulation which is considered important and standard for distraction treatment). This percentage of more serious complications is similar to alternative treatments like HTO and TKA.[25]

Possible mechanisms of joint repair

Despite the fact that joint distraction is studied for over 20 years, the mechanisms involved in the observed benefit are largely speculative. Only recently literature touching this specific subject has emerged.[43–45] To date, several concomitant occurring underlying mechanisms have been postulated to be involved in the clinical and structural benefit observed after joint distraction (see also Figure 2).

Firstly, joint distraction results in temporary relief of mechanical stress (strain and shear) on the cartilage, which prevents further wear and tear of the cartilage. Secondly, maintained nutrition of the cartilage during mechanical unloading is considered of importance. Joint fluid pressure oscillation remains present as a result of loading and unloading during distraction due to the resilience in/of the external device. A third mechanism is transient periarticular osteopenia developed during the distraction. Mechanical stresses on the bone within the distraction frame are taken over by the frame. This results in permanent diminished subchondral sclerosis and with that diminished mechanical impact on the cartilage. Significant changes in bone turnover during and after distraction may provide growth factors. Bone is a storage of growth factors that have been demonstrated to facilitate cartilage repair. Moreover, stem cells from the different joint tissues, including the synovial tissue and fluid, are facilitated by the distraction environment, mechanically and biochemically, to restore cartilage tissue. Lastly, the altered molecular milieu during mechanical unloading of the normally mechanically loaded tissue results in a reset of the balance between anabolism and catabolism in the joint.

Mechanical unloading and maintenance of synovial fluid pressure oscillation

OA is influenced in its early and late phases by joint mechanics (loading) and thereby its effect on joint metabolism.46 The mechanical properties of the joint at the macro and micro environment are severely disturbed in OA. Especially in the more advanced disease stage, overloading of the cartilage and bone are a continuous stimulus for progressive joint degeneration. As such it is logical that creating a favorable mechanical environment is a prerequisite to enable repair activity. Unloading the joint might be a first rational to provide such a condition. There is a clear

reasoning behind the role of unloading in the clinical and structural benefit of distraction (and other partial unloading techniques). The actual strain magnitudes on cartilage are important for the fate of cartilage and the chondrocyte response. During normal activities, diurnal strains range from 0–10%[47,48], post activity strains range from 5–15%[49–52], and dynamic strains during activity range from 15–35%.[53,54] At higher nominal strain magnitudes (50–70%), mechanical compression can cause injury[55–57], eventually inducing cell death via necrosis and apoptosis at strains of the highest levels (70–90%).[58,59] Effects of different loading conditions influence the chondrocyte function. Static loading decreases cartilage metabolic activity[60], physiologic levels of dynamic loading can be anabolic or anti-inflammatory[61–64], while hyper physiologic levels of dynamic loading and injurious-loading can induce catabolic or pro-inflammatory responses.[62,65,66] Moreover, controlled impact experiments on cartilage tissue indicated that shear stress, rather than impact force, is the strongest predictor for the occurrence of cartilage damage (fissures).[67] The damaged cartilage in OA might result in a disturbed perception of normal weight-bearing and thereby direct chondrocytes to further dedifferentiation resulting in further degeneration. This all suggests that treatments where the strain magnitude and shear stress shift from severe and are (temporarily) reduced, result in a favorable mechanical environment to allow repair.

With joint distraction, loading of cartilage and bone is reduced. The most recent insight made clear that the intended mechanical unloading is only partial. During treatment patients are encouraged to walk and load their distracted joint. In most instances there will be most likely contact between the articular surfaces during loading of the joint due to resilience in the distraction frames (personal observations from mechanical bench testing of different devices; manuscript in preparation). This is supported by a previous study demonstrating that the joint surfaces of cadaveric ankles undergoing distraction contact in case of 5 mm distraction under 70 kg loading.[68] Irrespective, a condition is created where mechanical overload (strain and shear), an important driving force of joint degeneration, is temporally neutralized. Moreover, in case of non-articulating devices, shear stresses will be fully absent. This absence of mechanical wear and tear on the cartilage is considered to be of importance. Chondrocytes are sensitive to mechanical stimuli to maintain cartilage integrity.[69] This means that complete immobilization and absence of any chondrocyte mechanical stimulation may be ineffective. At present it is unknown to which degree (force and frequency) mechanical contact of both cartilage surfaces during loading of the distracted joint is a prerequisite or parameter to facilitate cartilage tissue repair. More or less deviated from an optimal condition may be related to more or less or less or more repair. The exact force and frequency will be highly variable between patients in daily practice and may be an explanation for the variable joint tissue repair activity seen in the clinical studies. Future studies, taking this parameter into account by recording and controlling resilience in the distraction device, weight of the patients, and actual loading of the joint during distraction are warranted to get a grip on this parameter and potentially improving repair activity in case an optimum can be reached for each patient.

It should be noted that with this variation in resilience in the devices, joint distraction creates a condition different from complete immobilization, like obtained by casting. As mentioned, during distraction, loading of the affected joint is encouraged. This will not only result in partial mechanical contact between the cartilage surfaces, but also in joint fluid pressure oscillations because of the stiffness of the joint capsule when the two bone ends are nearing each other during loading. The combination of loading and resilience of the distraction frame and the stiffness of the joint capsule provides fluctuation of the intra-articular fluid pressure as naturally occurring during normal loading and unloading of a joint.[7] Not only is this intermittent fluid pressure oscillation considered essential in nourishment of the cartilage, it also plays a role as mechanical stimulus of the chondrocytes in the anisotropic cartilage extracellular matrix. In vitro, it has been demonstrated that these fluid pressure changes are beneficial specifically to OA cartilage.[70] Normal healthy cartilage seems less sensitive. Moreover, these fluid pressure changes are able to diminish the inflammatory activity of OA synovial cells.[71] Production of catabolic cytokines such as interleukin (IL)-1 and tumor necrosis factor (TNF)-a were decreased. Other joint-saving techniques with partial unloading such as tibial osteotomy or unicompartmental load absorbing implants (Atlas system) show clinical[72] and even structural beneficial changes.[73–75] Both techniques significantly reduce (medial) compartment contact pressure and peak contact pressure[76,77] and maintain joint fluid pressure oscillations as well. Clearly, more research is needed which exact (hydro)mechanical condition during (and after) distraction treatment is the most favorable.

Periarticular bone changes

The significant bone changes during distraction, a process starting with inducing osteopenia followed post-treatment by normalization of bone characteristics, are considered another important promoter of cartilage repair. Moreover, bone changes may be a key factor relating to the observed pain relief. The mechanical stresses during distraction are taken over by the distraction frame connected to the bone pins and fixing both bone ends. This will result in osteopenia during distraction even during loading and unloading the joint during distraction because the bone within the outer bone pins will remain mechanically (partially) unloaded.[78] A study where advanced post-traumatic OA patients were treated with ankle distraction indicated an overall decrease of subchondral bone density, which persisted over at least two years.[32,79] Pre-treatment, the subchondral bone demonstrated regions of cystic (relatively low density) and sclerotic (relatively high density) areas. While overall density decreased, density in cystic lesions increased, representing an overall normalization of bone density. Similar results were reported for KJD, where a decrease and normalization in bone density was reported.[21] The mechanism for the disappearance of the cystic areas might relate to the changes in mechanical and biochemical environment induced by distraction. Cysts represent regions of bone necrosis[80], and have the potential to not only increase but also diminish over time.[81] Decreased surrounding sclerosis and subsequently less stiff bone, may allow mechanical stimuli to reach the cystic area and

induce bone formation. This combination with an overall increase in bone turnover might be the necessary circumstance under which cystic areas can be repaired. So far, no clear relations have been found between clinical improvement and overall bone changes. However, when specifically looking at the resolution of the cysts in relation to clinical improvement in case of ankle distraction, as determined by patient-reported outcome, a rather good correlation was demonstrated.[32] Cyst-related joint pain might be caused by increased pressure and fluid flow in the subchondral bone. During loading, compression of cartilage forces fluid into the bone through the damaged subchondral plate.[82] The hydraulic conductance of osteochondral tissue has been shown to be higher in OA patients.[83] When cysts and defects in the subchondral plate diminish, the subchondral bone is less subject to increased fluid flow and pressure decreasing joint pain. Cystic pores within the cortical plate close to the joint surface result in an increase in hydraulic conductance which might be responsible for joint pain. Bone cysts, as well as bone surface attrition, seem to evolve in regions of bone marrow lesions and are suggested to be the next level of bone marrow pathology.[84] The relationship between bone marrow lesions as seen on MRI and clinical symptoms is well-established, and it could also be explained by increased pressure within the bone in areas of excessive loading and mechanically compromised trabecular structure[84,85], as such providing a rational for the deceased pain as a result of KJD.

In addition to the mechanical effect, the significant changes in bone turnover inflicted by the osteopenia and later normalization most likely result in release of growth factors resided in large amounts in the bone. Bone is known to be a storage of factors that have been demonstrated to play a role in cartilage tissue repair.[86–88] These mechanical and biochemical interactions might not only be causative in the clinical and structural benefit of KJD (and joint distraction in general) but may also be valid to explain the tissue repair as observed by osteotomy, as this is an intervention which is accompanied by strong bone turnover as well. As the exact factors are not yet identified in the context of KJD (and HTO), we might learn a lot in the advances of understanding distraction histogenesis, a distraction technique which is successfully applied to overcome difficult orthopedic conditions such as limb deformities, non-union, and segmental bone defects. Though differently applied, it has been demonstrated that both local and systemic responses triggered by distraction contribute to bone regeneration and include bone morphogenetic proteins[89], inflammatory factors[90], and mechanotransduction signals (e.g, Hippo and Wnt signaling pathways)[91], amongst others. Moreover, an animal study further supports the involvement of bone in the cartilage repair process under influence of KJD.[92] In this study, aimed to demonstrate the beneficial structural effect of KJD in dogs, an additional group was included in which only an external fixated frame without distraction was applied. Remarkably, this treatment group with clear bone turnover changes showed a moderate beneficial effect on the cartilage, as defined by an improved histology and cartilage proteoglycan turnover as compared to the untreated OA group, though inferior to the group treated with KJD. The improvement in this 'frame non-distraction' group might be due to the partial unloading with maintained joint mobility. The quadruple dogs loaded their treated

joints less as a result of the frame without distraction. Nonetheless, the actual distraction was superior in this study. This supports that it is more likely that a combination of (hydro) mechanical changes on cartilage as well as bone turnover is needed to obtain the observed effects of distraction.

Stem cells and joint milieu

An impressive result of KJD is the significant reduction of denuded bone areas as determined by MR imaging, where the gaps were filled in with tissue with a similar signal intensity as the original cartilage. [21,36] It is difficult to envision that this effect is solely due to an increased extracellular matrix synthesis of chondrocytes surrounding the gap. It is postulated that resident mesenchymal stem cells (MSCs) in the joint[93–95] are important for the intra-articular repair activity. The identification of MSCs in the different tissues such as synovium, cartilage, and synovial fluid of the joint supports this hypothesis.[93] The exact contribution is not clear and potentially consist of metabolic stimulation of existing chondrocytes or differentiation in a chondrogenic manner into new chondrocytes. Nonetheless, more recently the first studies of MSCs and mediators released in the context of distraction have emerged.

It was demonstrated that OA synovial fluid (SF), as well as purified high molecular weight hyaluronic acid (HA MW), inhibited adhesion of synovial fluid derived MSCs (SF-MSCs).[43] Treatment with hyase of the OA SF could increase this attachment four-fold. This hints that during OA the MSCs are coated with a layer of HA, preventing the cells to attach to the site of injury. Moreover, using the canine KJD model, it was demonstrated that under the influence of distraction MSCs were able to attach to the damaged cartilage, and that this was dependent on the MW of the HA. This supports that under influence of distraction, SF-MSCs can attach, considered key to MSC mediated colonization, differentiation, and cartilage repair.

Though the exact mechanisms involved are largely unknown, endogenous subchondral bone (SB) MSCs and SF-MSCs have been suggested as potential contributors to structural improvement and cartilage repair following unloading.[66,96,97] Studying gene expression of SF-MSCs derived from OA patients showed that these cells express lower levels of ossification- and hypothropy-related genes, parathyroid hormone 1 receptor, and runt-related transcription factor than SB-MSCs of these patients did.[44] This might indicate a greater cartilage remodeling ability of the OA SF-MSCs, as compared with SB-MSCs. Interestingly, joint unloading by KJD resulted in a sustained and significant increase in SF-MSC colonies sizes and densities. Also, an upregulation of the key cartilage core protein aggrecan as well as a decrease in the pro-inflammatory C-C motif chemokine ligand 2 (CCL2) expression during the distraction period was noticed.[44] The first 3 weeks of the distraction treatment were marked by significant increases in MSC chondrogenic commitment markers such as gremlin 1, and growth differentiation factor 5 (GDF5) , markers associated with an healthy cartilage homeostasis.[98–101] These results indicate that the transcriptomes differ between joint-resident MSCs depending

on the biomechanical environment, viz. fluid vs bone, and that temporarily unloading leads to transcriptional changes in SF-MSCs that may be of importance to cartilage repair.

In addition to the reported MSC changes, a different study reported on the molecular profile of SF changes upon KJD. 20 patients who underwent KJD had SF sampled at baseline, midpoint, and endpoint of distraction, in which 10 predefined mechanosensitive molecules were measured.[45] 6/10 markers showed statistically significant changes between pre-treatment and 6 weeks (endpoint): activin A, transforming growth factor beta (TGFβ), monocyte chemoattractant protein 1 (MCP-1), IL-6, fibroblast growth factor 2 (FGF2), and Latent-transforming growth factor beta-binding protein 2 (LTBP2). Of these, five showed a predominant increase in levels and one (activin A) mainly a decrease (to within normal range for most individuals). For most analytes, changes were detectable at 3 weeks of distraction (midpoint). For some analytes such as LTBP2, there was diversity of response. The remaining four markers IL-8, matrix metalloproteinase-3 (MMP3), tissue inhibitor of metalloproteinases 1 (TIMP1), TNF-inducible gene 6 protein (TSG-6) did not change significantly over 6 weeks, but two (IL-8, TIMP1) were significantly different at the 3-week midpoint. Although the study lacked power to test in full an association between the marker change and clinical outcome, some indicative associations between changes in markers and subsequent changes in KOOS at 12 months post treatment were seen. Patients achieving the minimum clinically important difference of 10 points of KOOS over a 6-month period showed greater increases in FGF2 and TGFβ than those who did not. An increase in IL-8 during the 6-week treatment period was associated with a significantly greater improvement in KOOS over 12 months. Moreover, these increased FGF2 and TGFβ levels might be related to the enhanced expressed TGFβ receptor 1 and 2 seen in SF MSCs early during KJD[44], which may signify a enrichment in TGFβ-responsive MSCs during these early stages of the treatment. As seen with the SF-MSCs study[44], detectable, significant molecular changes are observed in SF upon joint distraction, providing additional clues for the clinical and structural changes found. Though new clues are emerging also puzzling effects occur, especially regarding some of the SF pro-inflammatory mediators. The SF MSC study[44] indicated lower expression of the proinflammatory chemokines CCL2/MCP1, whereas the IL-6 and MCP1 SF levels were found increased following KJD.[45] MCP1 is associated with chondrocyte degeneration, synovial inflammation, and implicated in joint pain.[102,103] These results contrast also effects found in animals studies in which KJD was applied and a significant effect on joint inflammation was documented.[92,96] An interesting thought might be that a mechanically-induced response results in both catabolic and reparative responses which are initiated at the moment the joint surfaces are distracted but needs prolonged time to fully shift to a reparative status. Such a thought is supported by the response of the collagen type II synthesis marker (PIIANP) and breakdown marker (CTXII) in patients treated with KJD which indicate a shift from breakdown towards synthesis between 6 and 12 months after treatment.[22,25] This is in line with recent preliminary research[104] in which it was demonstrated that the shift from a catabolic to an anabolic state occurs within the weeks after

joint distraction, as indicated by collagen type II markers, proteoglycan (PG) turnover and a catabolic transcription profile using a canine animal KJD model. This hints that not only during distraction but also the post-distraction period seems to be essential. It is obvious that larger studies are needed, both clinical as preclinical, with multiple time points, both during and post-treatment focusing on broader sets of markers and transcripts to further expand and value the effects found thus far.

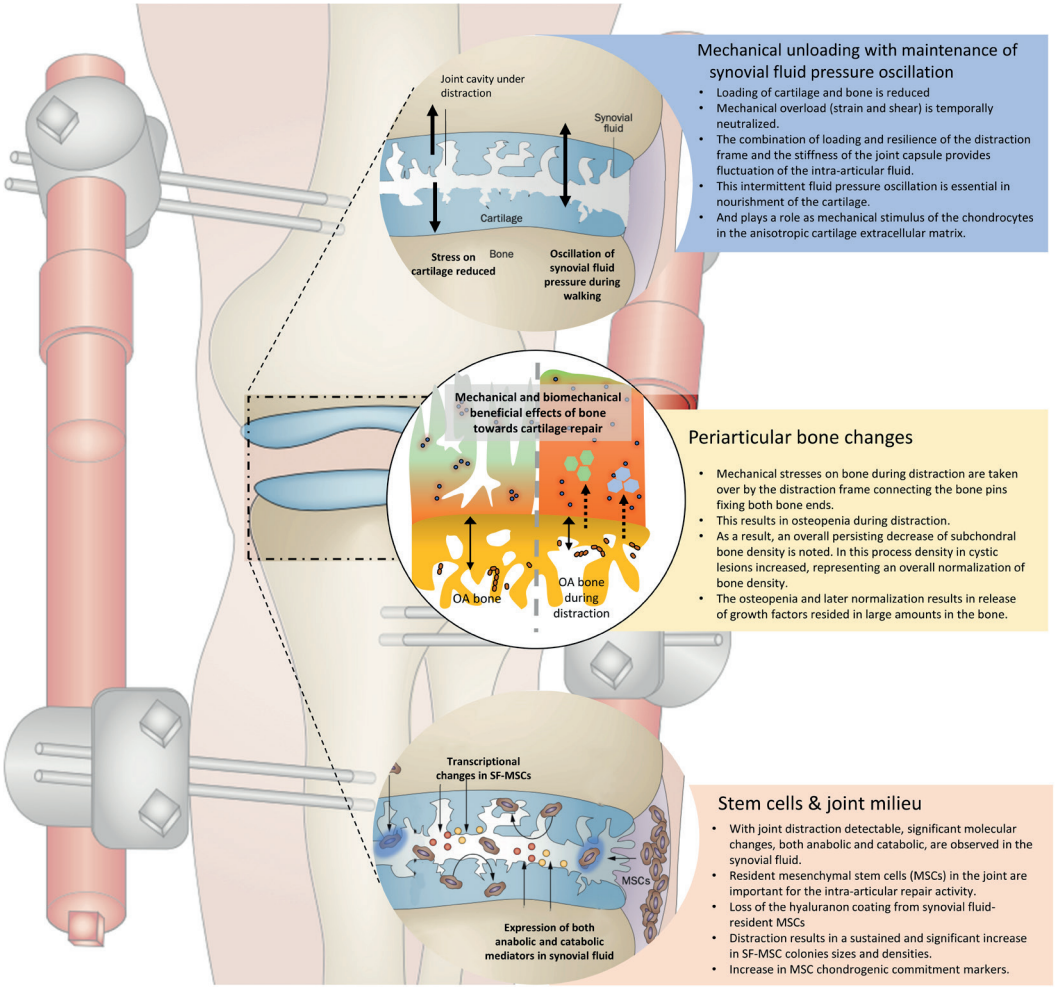

Figure 2: Overview of joint processes/molecular mechanisms during/after distraction. Distraction changes the OA-related joint homeostasis. The reduced mechanical (over)load on the articular cartilage surfaces prevents wear and tear and might initiate intrinsic cartilage repair activity (upper part of figure). Resilience in the distraction frame causes synovial fluid pressure changes during loading and unloading of the joint, improving nutrition of cartilage and stimulating chondrocytes. Distraction also results in considerable periarticular bone changes (middle part of figure). Altered activity of bone cells may add to release of trophic factors to support cartilage repair. Restoration of the mechanical and the biochemical environment of the joint, including the loss of the hyaluranon coating from synovial fluid-resident MSCs, might therefore provide a window of opportunity in which joint-resident MSCs can attach and repair tissues (lower part). MSCs: mesenchymal stem cells; SF-MSCs: synovial fluid derived MSCs.

Future directions

KJD is able to improve clinical results and promote tissue restoration, and more and more is known about the underlying molecular mechanisms, but there are several steps that could and should be taken in the future (Table 2).

While on a group level patients show significant and long-lasting clinical improvement, it is important to realize that individually not all patients respond well. Better KJD treatment response has been shown in male patients and those with more severely affected joints, but might also be related to processes or characteristics not yet known or investigated. Improving patient selection before treatment is crucial to increase the chance patients respond well to the treatment. Also, more patient-specific treatment alterations or combinations with other remedies could be considered. Furthermore, more wide implementation in regular clinical care is required. Thus far, KJD has been applied almost exclusively in trial conditions, and has been used in regular care conditions only in a limited number of hospitals in The Netherlands. Internationally, both patients and surgeons are interested in KJD, but implementing a new treatment in a more widespread clinical setting is a slow and challenging process. Some steps have been made, such as the development of a dedicated device for KJD treatment, but necessary future advances include defining an ideal and official treatment and rehabilitation protocol and arranging treatment reimbursement.

Despite the developments in recent years, still a better understanding of the working mechanisms is warranted. Our knowledge could be improved with use of more novel imaging techniques, such as 7T MRI scans using advanced protocols (e.g. gagCEST or sodium MRI scanning), ideally in combination with SF marker evaluation. These measures could improve patient selection as well. Also other local or systemic markers could be considered. More recently, the role of miRNAs and extracellular vesicles in relation to senescent cells in osteoarthritis is recognized[105]. It might well be that KJD also influences these processes and are part of the mechanism. Moreover, the role of unloading should be further studied implementing tools like advanced gait analysis during and after treatment and computational modeling. Also, the involvement of MSCs needs further studying. Though the first results were focused on involvement of synovial fluid derived MSCs, these cells might originate from the synovial tissue. Cartilage-resident progenitors could be involved as well and become activated and senescent/dying chondrocytes could be cleared upon such stimulation as well. Subsequently, the different components of KJD treatment and the joint processes that are observed as a result could be translated to other treatments that thus far have not shown the desired treatment result.

Table 2: Possible future directions

Future direction	How this can be achieved
Improved individual patient response	Better patient selection pre-treatment
	Patient-specific treatment alterations
Implementation in regular clinical care	Defining official treatment protocols
	Arranging treatment reimbursement
Further understanding of working mechanisms	Use of novel imaging techniques in combination with biomarkers
	Evaluating additional local or systemic markers
	Evaluating the role of other factors (e.g. miRNA, gait, MSC origin)
Using knowledge outside current treatment	Translating different components of KJD treatment and the resulting joint processes to other treatments

MSC: mesenchymal stem cell; miRNA: micro RNA.

Conclusion and future directions

Evidence is gradually accumulating that KJD results in prolonged relief of pain and that it indeed can reverse the tissue degenerative process. It remains to be elucidated whether optimizing the biomechanical conditions during distraction, can actually cure the disease instead of only providing temporarily relief. Even in the latter case it may be of societal and patient relevance as it will delay placement of a prosthesis at an early age and with that prevent revision surgery later in life. Most importantly, a better insight in the underlying mechanisms may provide new leads to more targeted treatment options. E.g., MSC enrichment under the proper joint milieu maybe even without the need for distraction treatment (and its burden) provide sufficient repair activity, although the mechanical condition (temporary absence of wear and tear, with the bone turnover) might be assumed essential.

Providing the right joint milieu mechanically and biologically has the potential to repair the joint. The difference with the many trial-and-error treatment attempts is that we can learn from distraction and (just) need to unravel the mechanisms that lead to this repair.

References

1. Hunter DJ, Bierma-Zeinstra S. Osteoarthritis. The Lancet. 2019 Apr 27;393(10182):1745–59.
2. Mastbergen SC, Saris DBF, Lafeber FPJG. Functional articular cartilage repair: Here, near, or is the best approach not yet clear? Nature Reviews Rheumatology. 2013 May;9(5):277–90.
3. Palmer JS, Monk AP, Hopewell S, et al. Surgical interventions for symptomatic mild to moderate knee osteoarthritis. Cochrane Database of Systematic Reviews. 2019 Jul 19;7(7):CD012128.
4. Jatinder Singh L, Salim AL H, Suwailim AL G. Surgical options for treating knee osteoarthritis - A concise review. Journal of Musculoskeletal Disorders and Treatment. 2020 Aug 21;6(3):084.
5. Lafeber FP, Intema F, van Roermund PM, et al. Unloading joints to treat osteoarthritis, including joint distraction. Current Opinion in Rheumatology. 2006 Sep;18(5):519–25.
6. Aldegheri R, Trivella G, Saleh M. Articulated distraction of the hip: Conservative surgery for arthritis in young patients. Clinical Orthopaedics and Related Research. 1994;301:94–101.
7. van Valburg AA, van Roermund PM, Lammens J, et al. Can Ilizarov joint distraction delay the need for an arthrodesis of the ankle? A preliminary report. Journal of Bone and Joint Surgery British Volume. 1995 Sep 1;77(5):720–5.
8. Van Valburg AA, Van Roermund PM, Marijnissen ACA, et al. Joint distraction in treatment of osteoarthritis: A two-year follow-up of the ankle. Osteoarthritis and Cartilage. 1999 Sep 1;7(5):474–9.
9. Bain GI, Mehta JA, Heptinstall RJ, et al. Dynamic external fixation for injuries of the proximal interphalangeal joint. Journal of Bone and Joint Surgery British Volume. 1998;80(6):1014–9.
10. DeVries JG, Amiot RA, Cummings P, et al. Freiberg's infraction of the second metatarsal treated with autologous osteochondral transplantation and external fixation. Journal of Foot and Ankle Surgery. 2008 Nov 27;47(6):565–70.
11. Spaans AJ, Minnen LP van, Braakenburg A, et al. Joint distraction for thumb carpometacarpal osteoarthritis: A feasibility study with 1-year follow-up. Journal of Plastic Surgery and Hand Surgery. 2017 Jul 4;51(4):254–8.
12. Jansen MP, Boymans TAEJ, Custers RJH, et al. Knee joint distraction as treatment for osteoarthritis results in clinical and structural benefit: A systematic review and meta-analysis of the limited number of studies and patients available. Cartilage. 2020 Jul 22;194760352094294.
13. Jansen MP, Mastbergen SC, van Heerwaarden RJ, et al. Knee joint distraction in regular care for treatment of knee osteoarthritis: A comparison with clinical trial data. PLOS ONE. 2020 Jan 22;15(1):e0227975.
14. Deie M, Ochi M, Adachi N, et al. A new articulated distraction arthroplasty device for treatment of the osteoarthritic knee joint: A preliminary report. Arthroscopy. 2007;23(8):833–8.
15. Aly TA, Hafez K, Amin O. Arthrodiatasis for management of knee osteoarthritis. Orthopedics. 2011;34(8):e338-43.
16. van der Woude JAD, Wiegant K, van Roermund PM, et al. Five-year follow-up of knee joint distraction: Clinical benefit and cartilaginous tissue repair in an open uncontrolled prospective study. Cartilage. 2017;8(3):263–71.
17. Jansen MP, Struijk T, Mastbergen SC, et al. User-friendliness of a novel dedicated knee joint distraction device: Experiences from clinical practice. Osteoarthritis and Cartilage. 2020 Apr 1;28:S474.
18. ArthroSave. KneeReviver. https://www.arthrosave.com/. 2020.
19. Abouheif MM, Nakamura M, Deie M, et al. Repair of a large osteochondral defect in the knee joint using autologous and artificial bone graft combined with motion preserving distraction arthroplasty: A case report. Archives of Orthopaedic and Trauma Surgery. 2010 Feb;130(2):231–6.
20. Deie M, Ochi M, Nakamae A, et al. Knee articulated distraction arthroplasty for the middle-aged osteoarthritic

knee joint. Techniques in Knee Surgery. 2010 Jun;9(2):80–4.

21. Intema F, van Roermund PM, Marijnissen ACA, et al. Tissue structure modification in knee osteoarthritis by use of joint distraction: An open 1-year pilot study. Annals of the Rheumatic Diseases. 2011 Aug 1;70(8):1441–6.
22. Wiegant K, van Roermund PM, Intema F, et al. Sustained clinical and structural benefit after joint distraction in the treatment of severe knee osteoarthritis. Osteoarthritis and Cartilage. 2013 Nov;21(11):1660–7.
23. Jansen MP, van der Weiden GS, van Roermund PM, et al. Initial tissue repair predicts long-term clinical success of knee joint distraction as treatment for knee osteoarthritis. Osteoarthritis and Cartilage. 2018;26(12):1604–8.
24. van der Woude JAD, Wiegant K, van Heerwaarden RJ, et al. Knee joint distraction compared with high tibial osteotomy: A randomized controlled trial. Knee Surgery, Sports Traumatology, Arthroscopy. 2017;25(3):876–86.
25. Jansen MP, Besselink NJ, van Heerwaarden RJ, et al. Knee joint distraction compared with high tibial osteotomy and total knee arthroplasty: Two-year clinical, radiographic, and biochemical marker outcomes of two randomized controlled trials. Cartilage. 2019 Feb 13;12(2):181–91.
26. van der Woude JAD, Wiegant K, van Heerwaarden RJ, et al. Knee joint distraction compared with total knee arthroplasty: A randomised controlled trial. Bone and Joint Journal. 2017;99-B(1):51–8.
27. Jansen MP. Prospective one-year follow-up of clinical efficacy of knee distraction as treatment for knee osteoarthritis by use of the KneeReviver. In: Knee joint distraction: moving forward. 2021. p. 167–82.
28. van der Woude JAD, van Heerwaarden RJ, Spruijt S, et al. Six weeks of continuous joint distraction appears sufficient for clinical benefit and cartilaginous tissue repair in the treatment of knee osteoarthritis. Knee. 2016 Oct 1;23(5):785–91.
29. Struik T, Jaspers JEN, Besselink NJ, et al. Technical feasibility of personalized articulating knee joint distraction for treatment of tibiofemoral osteoarthritis. Clinical Biomechanics. 2017 Nov 1;49:40–7.
30. Struik T, Custers RJH, Jaspers JEN, et al. Clinical feasibility of personalized articulating knee joint distraction. Submitted.
31. Wiegant K, van Heerwaarden R, van der Woude JAD, et al. Knee joint distraction as an alternative surgical treatment for osteoarthritis: Rationale and design of two randomized controlled trials (*vs* high tibial osteotomy and total knee prosthesis). International Journal of Orthopaedics. 2015 Aug 23;2(4):353–60.
32. Intema F, Thomas TP, Anderson DD, et al. Subchondral bone remodeling is related to clinical improvement after joint distraction in the treatment of ankle osteoarthritis. Osteoarthritis and Cartilage. 2011 Jun 1;19(6):668–75.
33. Escobar A, Quintana JM, Bilbao A, et al. Responsiveness and clinically important differences for the WOMAC and SF-36 after total knee replacement. Osteoarthritis and Cartilage. 2007 Mar;15(3):273–80.
34. Hoorntje A, Kuijer PPFM, Koenraadt KLM, et al. Return to sport and work after randomization for knee distraction versus high tibial osteotomy: Is there a difference? Journal of Knee Surgery. 2020 Nov 23.
35. Bayliss LE, Culliford D, Monk AP, et al. The effect of patient age at intervention on risk of implant revision after total replacement of the hip or knee: A population-based cohort study. The Lancet. 2017 Apr 8;389(10077):1424–30.
36. Jansen MP, Maschek S, van Heerwaarden RJ, et al. Changes in cartilage thickness and denuded bone area after knee joint distraction and high tibial osteotomy – Post-hoc analyses of two randomized controlled trials. J Clin Med. 2021 Jan 19;10(2):368.
37. Jansen MP, Mastbergen SC, Turmezei TD, et al. Knee joint distraction results in MRI cartilage thickness increase up to ten years after treatment. Submitted.

38. van Spil WE, DeGroot J, Lems WF, et al. Serum and urinary biochemical markers for knee and hip-osteoarthritis: A systematic review applying the consensus BIPED criteria. Osteoarthritis and Cartilage. 2010 May;18(5):605–12.

39. Besselink NJ, Vincken KL, Bartels LW, et al. Cartilage quality (dGEMRIC index) following knee joint distraction or high tibial osteotomy. Cartilage. 2018;11(1):19–31.

40. Jansen MP, Maschek S, Van Heerwaarden RJ, et al. Knee joint distraction is more efficient in rebuilding cartilage thickness in the more affected compartment than high tibial osteotomy in patients with knee osteoarthritis. Osteoarthritis and Cartilage. 2019 Apr;27(1):S330–1.

41. Wiegant K, van Roermund PM, van Heerwaarden RJ, et al. Total knee prosthesis after knee joint distraction treatment. Journal of Surgery and Surgical Research. 2015 Nov 5;1(3):066–71.

42. Jansen MP, van Egmond N, Kester EC, et al. Reduction of pin tract infections during external fixation using cadexomer iodine. Journal of Experimental Orthopaedics. 2020 Dec 7;7(1):88.

43. Baboolal TG, Mastbergen SC, Jones E, et al. Synovial fluid hyaluronan mediates MSC attachment to cartilage, a potential novel mechanism contributing to cartilage repair in osteoarthritis using knee joint distraction. Annals of the Rheumatic Diseases. 2016;75(5):908–15.

44. Sanjurjo-Rodriguez C, Altaie A, Mastbergen S, et al. Gene Expression signatures of synovial fluid multipotent stromal cells in advanced knee osteoarthritis and following knee joint distraction. Frontiers in Bioengineering and Biotechnology. 2020 Oct 14;8:1178.

45. Watt FE, Hamid B, Garriga C, et al. The molecular profile of synovial fluid changes upon joint distraction and is associated with clinical response in knee osteoarthritis. Osteoarthritis and Cartilage. 2020 Jan;28(3):324–33.

46. Griffin TM, Guilak F. The role of mechanical loading in the onset and progression of osteoarthritis. Exercise and Sport Sciences Reviews. 2005;33(4):195–200.

47. Widmyer MR, Utturkar GM, Leddy HA, et al. High body mass index is associated with increased diurnal strains in the articular cartilage of the knee. Arthritis and Rheumatism. 2013;65(10):2615–22.

48. Coleman JL, Widmyer MR, Leddy HA, et al. Diurnal variations in articular cartilage thickness and strain in the human knee. Journal of Biomechanics. 2013;46(3):541–7.

49. Eckstein F, Tieschky M, Faber SC, et al. Effect of physical exercise on cartilage volume and thickness in vivo: MR imaging study. Radiology. 1998;207(1):243–8.

50. Eckstein F, Hudelmaier M, Putz R. The effects of exercise on human articular cartilage. Journal of Anatomy. 2006;208(4):491–512.

51. Eckstein F, Tieschky M, Faber S, et al. Functional analysis of articular cartilage deformation, recovery, and fluid flow following dynamic exercise in vivo. Anatomy and Embryology. 1999;200(4):419–24.

52. Sutter EG, Widmyer MR, Utturkar GM, et al. In vivo measurement of localized tibiofemoral cartilage strains in response to dynamic activity. American Journal of Sports Medicine. 2015;43(2):370–6.

53. Liu F, Kozanek M, Hosseini A, et al. In vivo tibiofemoral cartilage deformation during the stance phase of gait. Journal of Biomechanics. 2010;43(4):658–65.

54. Van De Velde SK, Bingham JT, Hosseini A, et al. Increased tibiofemoral cartilage contact deformation in patients with anterior cruciate ligament deficiency. Arthritis and Rheumatism. 2009;60(12):3693–702.

55. Kurz B, Jin M, Patwari P, et al. Biosynthetic response and mechanical properties of articular cartilage after injurious compression. Journal of Orthopaedic Research. 2001;19(6):1140–6.

56. Patwari P, Cheng DM, Cole AA, et al. Analysis of the relationship between peak stress and proteoglycan loss following injurious compression of human post-mortem knee and ankle cartilage. Biomechanics and Modeling in Mechanobiology. 2007;6(1–2):83–9.

57. Patwari P, Cook MN, DiMicco MA, et al. Proteoglycan degradation after injurious compression of bovine

and human articular cartilage in vitro: Interaction with exogenous cytokines. Arthritis and Rheumatism. 2003;48(5):1292–301.

58. Stolberg-Stolberg JA, Furman BD, William Garrigues N, et al. Effects of cartilage impact with and without fracture on chondrocyte viability and the release of inflammatory markers. Journal of Orthopaedic Research. 2013;31(8):1283–92.
59. Natoli RM, Scott CC, Athanasiou KA. Temporal effects of impact on articular cartilage cell death, gene expression, matrix biochemistry, and biomechanics. Annals of Biomedical Engineering. 2008;36(5):780–92.
60. Guilak F, Meyer BC, Ratcliffe A, et al. The effects of matrix compression on proteoglycan metabolism in articular cartilage explants. Osteoarthritis and Cartilage. 1994;2(2):91–101.
61. Ng KW, Mauck RL, Wang CCB, et al. Duty cycle of deformational loading influences the growth of engineered articular cartilage. Cellular and Molecular Bioengineering. 2009;2(3):386–94.
62. Nam J, Aguda BD, Rath B, et al. Biomechanical thresholds regulate inflammation through the NF-κB pathway: Experiments and modeling. PLoS ONE. 2009;4(4):e5262.
63. Mauck RL, Nicoll SB, Seyhan SL, et al. Synergistic action of growth factors and dynamic loading for articular cartilage tissue engineering. Tissue Engineering. 2003;9(4):597–611.
64. Torzilli PA, Bhargava M, Chen CT. Mechanical loading of articular cartilage reduces IL-1-induced enzyme expression. Cartilage. 2011;2(4):364–73.
65. Chan PS, Schlueter AE, Coussens PM, et al. Gene expression profile of mechanically impacted bovine articular cartilage explants. Journal of Orthopaedic Research. 2005;23(5):1146–51.
66. Ashwell MS, Gonda MG, Gray K, et al. Changes in chondrocyte gene expression following in vitro impaction of porcine articular cartilage in an impact injury model. Journal of Orthopaedic Research. 2013;31(3):385–91.
67. Atkinson TS, Haut RC, Altiero NJ. An investigation of biphasic failure criteria for impact-induced fissuring of articular cartilage. Journal of Biomechanical Engineering. 1998;120(4):536–7.
68. Fragomen AT, McCoy TH, Meyers KN, et al. Minimum distraction gap: How much ankle joint space is enough in ankle distraction arthroplasty? HSS Journal. 2014;10(1):6–12.
69. Sanchez-Adams J, Leddy HA, McNulty AL, et al. The mechanobiology of articular cartilage: Bearing the burden of osteoarthritis. Current Rheumatology Reports. 2014;16(10):451.
70. Lafeber F, Veldhuijzen JP, Vanroy JL, et al. Intermittent hydrostatic compressive force stimulates exclusively the proteoglycan synthesis of osteoarthritic human cartilage. British Journal of Rheumatology. 1992 Jul;31(7):437–42.
71. van Valburg AA, van Roy HL, Lafeber FP, et al. Beneficial effects of intermittent fluid pressure of low physiological magnitude on cartilage and inflammation in osteoarthritis: An in vitro study. The Journal of Rheumatology. 1998 Mar;25(3):515–20.
72. Slynarski K, Walawski J, Smigielski R, et al. Two-year results of the PHANTOM high flex trial: A single-arm study on the atlas unicompartmental knee system load absorber in patients with medial compartment osteoarthritis of the knee. Clinical Medicine Insights: Arthritis and Musculoskeletal Disorders. 2019;12.
73. Jung WH, Takeuchi R, Chun CW, et al. Second-look arthroscopic assessment of cartilage regeneration after medial opening-wedge high tibial osteotomy. Arthroscopy - Journal of Arthroscopic and Related Surgery. 2014 Jan;30(1):72–9.
74. Slynarski K, Lipinski L. Treating early knee osteoarthritis with the Atlas® unicompartmental knee system in a 26-year-old ex-professional basketball player: A case study. Case Reports in Orthopedics. 2017;2017:1–5.
75. Spahn G, Klinger HM, Harth P, et al. Knorpelregeneration nach valgisierender Tibiakopfosteotomie. Ergebnisse einer arthroskopischen studie. Zeitschrift fur Orthopadie und Unfallchirurgie. 2012;150(3):272–9.
76. Bode G, Kloos F, Feucht MJ, et al. Comparison of the efficiency of an extra-articular absorber system and

high tibial osteotomy for unloading the medial knee compartment: An in vitro study. Knee Surgery, Sports Traumatology, Arthroscopy. 2017;25(12):3695–703.

77. Slynarski K, Walawski J, Smigielski R, et al. Feasibility of the atlas unicompartmental knee system load absorber in improving pain relief and function in patients needing unloading of the medial compartment of the knee: 1-year follow-up of a prospective, multicenter, single-arm pilot study (PHANTOM high flex trial). Clinical Medicine Insights: Arthritis and Musculoskeletal Disorders. 2017 Sep 26;10.
78. Bikle DD, Halloran BP. The response of bone to unloading. Journal of Bone and Mineral Metabolism. 1999;17(4):233–44.
79. Marijnissen ACA, Vincken KL, Viergever MA, et al. Ankle images digital analysis (AIDA): Digital measurement of joint space width and subchondral sclerosis on standard radiographs. Osteoarthritis and Cartilage. 2001;9(3):264–72.
80. Pouders C, De Maeseneer M, Van Roy P, et al. Prevalence and MRI-anatomic correlation of bone cysts in osteoarthritic knees. American Journal of Roentgenology. 2008;190(1):17–21.
81. Tanamas SK, Wluka AE, Pelletier JP, et al. The association between subchondral bone cysts and tibial cartilage volume and risk of joint replacement in people with knee osteoarthritis: A longitudinal study. Arthritis Research and Therapy. 2010;12(2):R58.
82. van Dijk CN, Reilingh ML, Zengerink M, et al. The natural history of osteochondral lesions in the ankle. Instructional course lectures. 2010;59:375–86.
83. Hwang J, Bae WC, Shieu W, et al. Increased hydraulic conductance of human articular cartilage and subchondral bone plate with progression of osteoarthritis. Arthritis and Rheumatism. 2008;58(12):3831–42.
84. Carrino JA, Blum J, Parellada JA, et al. MRI of bone marrow edema-like signal in the pathogenesis of subchondral cysts. Osteoarthritis and Cartilage. 2006;14(10):1081–5.
85. Hunter DJ, Gerstenfeld L, Bishop G, et al. Bone marrow lesions from osteoarthritis knees are characterized by sclerotic bone that is less well mineralized. Arthritis Research and Therapy. 2009;11(1).
86. Caldwell KL, Wang J. Cell-based articular cartilage repair: The link between development and regeneration. Osteoarthritis and Cartilage. 2015;23(3):351–62.
87. Funck-Brentano T, Cohen-Solal M. Crosstalk between cartilage and bone: When bone cytokines matter. Cytokine and Growth Factor Reviews. 2011;22(2):91–7.
88. Yuan XL, Meng HY, Wang YC, et al. Bone-cartilage interface crosstalk in osteoarthritis: Potential pathways and future therapeutic strategies. Osteoarthritis and Cartilage. 2014;22(8):1077–89.
89. Yazawa M, Kishi K, Nakajima H, et al. Expression of bone morphogenetic proteins during mandibular distraction osteogenesis in rabbits. Journal of Oral and Maxillofacial Surgery. 2003 May;61(5):587–92.
90. Claes L, Recknagel S, Ignatius A. Fracture healing under healthy and inflammatory conditions. Nature Reviews Rheumatology. 2012 Jan;8(3):133–43.
91. Song J, Ye B, Liu H, et al. Fak-Mapk, Hippo and Wnt signalling pathway expression and regulation in distraction osteogenesis. Cell Proliferation. 2018 Aug;51(4).
92. Wiegant K, Intema F, Roermund PM, et al. Evidence of cartilage repair by joint distraction in a canine model of osteoarthritis. Arthritis and Rheumatology. 2015 Feb 28;67(2):465–74.
93. McGonagle D, Baboolal TG, Jones E. Native joint-resident mesenchymal stem cells for cartilage repair in osteoarthritis. Nature Reviews Rheumatology. 2017;13(12):719–30.
94. Jones BA, Pei M. Synovium-derived stem cells: A tissue-specific stem cell for cartilage engineering and regeneration. Tissue Engineering – Part B: Reviews. 2012;18(4):301–11.
95. Jones EA, Crawford A, English A, et al. Synovial fluid mesenchymal stem cells in health and early osteoarthritis: Detection and functional evaluation at the single-cell level. Arthritis and Rheumatism. 2008;58(6):1731–40.

96. Chen Y, Sun Y, Pan X, et al. Joint distraction attenuates osteoarthritis by reducing secondary inflammation, cartilage degeneration and subchondral bone aberrant change. Osteoarthritis and Cartilage. 2015 Oct 1;23(10):1728–35.

97. Sánchez M, Delgado D, Sánchez P, et al. Combination of intra-articular and intraosseous injections of platelet rich plasma for severe knee osteoarthritis: A pilot study. BioMed Research International. 2016;2016:4868613.

98. Kouroupis D, Sanjurjo-Rodriguez C, Jones E, et al. Mesenchymal stem cell functionalization for enhanced therapeutic applications. Tissue Engineering - Part B: Reviews. 2019;25(1):55–77.

99. Kania K, Colella F, Riemen AH, et al. Expression of growth and differentiation factor 5 during joint repair and osteoarthritis. Osteoarthritis and Cartilage. 2020;28:S34.

100. Kania K, Colella F, Riemen AHK, et al. Regulation of Gdf5 expression in joint remodelling, repair and osteoarthritis. Scientific Reports. 2020;10(1):157.

101. Leijten JCH, Bos SD, Landman EBM, et al. GREM1, FRZB and DKK1 mRNA levels correlate with osteoarthritis and are regulated by osteoarthritis-associated factors. Arthritis Research and Therapy. 2013;15(5):R126.

102. Raghu H, Lepus CM, Wang Q, et al. CCL2/CCR2, but not CCL5/CCR5, mediates monocyte recruitment, inflammation and cartilage destruction in osteoarthritis. Annals of the Rheumatic Diseases. 2017;76(5):914–22.

103. Miotla Zarebska J, Chanalaris A, Driscoll C, et al. CCL2 and CCR2 regulate pain-related behaviour and early gene expression in post-traumatic murine osteoarthritis but contribute little to chondropathy. Osteoarthritis and Cartilage. 2017;25(3):406–12.

104. Teunissen M, Popov-Celeketic J, Coeleveld K, et al. Knee joint distraction-induced shift from catabolic to anabolic state occurs after the distraction period. Osteoarthritis and Cartilage. 2020;28:S76–7.

105. Jeon OH, Wilson DR, Clement CC, et al. Senescence cell-associated extracellular vesicles serve as osteoarthritis disease and therapeutic markers. JCI Insight. 2019 Apr;4(7).

CHAPTER 11

Performance of Knee Image Digital Analysis of radiographs of patients with severe end-stage knee osteoarthritis

M.P. Jansen
P.M.J. Welsing
K.L. Vincken
S.C. Mastbergen

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Abstract

Background: Knee Image Digital Analysis (KIDA) is standardized radiographic analysis software for measuring osteoarthritis (OA) characteristics. It was validated in mild OA patients, but often used for severe OA as well. The goal of this study was to evaluate the performance of KIDA in severe OA patients.

Methods: Of 103 patients, standardized radiographs were performed before and 1 and 2 years after treatment for severe OA. All radiographs were evaluated on subchondral bone density, joint space width (JSW), osteophytes, eminence height, and joint angle, twice within years by the same observer. Part of the radiographs were randomly selected for reevaluation twice within 1 month. The intraclass correlation coefficient (ICC), smallest detectable difference (SDD) and coefficient of variation (CV) were calculated; the SDD and CV were compared to those in mild OA patients. The relation of severity with KIDA parameters and with intra-observer differences was calculated with linear regression models.

Results: ICCs were higher in the 98 severe radiographs reanalyzed within 1 month (all >0.8) than the 293 reanalyzed within years (all >0.5; most >0.8). SDDs and CVs were smaller when reanalyzed within a month and generally comparable to those in previous mild OA patients. Some parameters showed significant bias between readings. Severity showed a significant relation with especially osteophytes and JSW parameters, and with the intra-observer variation in these parameters (all $p<0.02$).

Conclusion: KIDA is a well-performing tool also for severe OA. In order to decrease variability and SDDs, images should be analyzed in a limited time frame and randomized order.

Introduction

Osteoarthritis (OA) is a degenerative joint disease characterized by structural changes such as cartilage degeneration, osteophyte formation, and subchondral bone changes.[1] In knee OA, these characteristics are usually evaluated on radiographs, frequently taken in weight-bearing position and in anterior-posterior or posterior-anterior (PA) direction.[2] Although the use of imaging techniques such as magnetic resonance imaging (MRI) is increasing, radiography remains the primary technique for the diagnosis and monitoring of knee OA. With the exception of joint space width (JSW) as a measure of cartilage thickness, radiography based knee OA characteristics are most often evaluated using a grading system, such as the Kellgren & Lawrence (KL) grade and the Altman score.[3,4] While these grading systems have been validated and proven useful, stepwise scoring of OA-related parameters makes results less sensitive to small changes over time. This was 1 of the main motivations for the development of the Knee Images Digital Analysis (KIDA) software in 2008.[5] Using KIDA, the individual radiographic knee OA features of JSW, subchondral bone density, osteophytes, tibial eminence height, and knee joint angle can be measured objectively and quantitatively resulting in continuous variables. The usefulness and validity of the KIDA parameters was initially demonstrated for patients with relatively mild knee OA, as indicated by their average KL grade of 1.3, and measurements were shown to distinguish these patients from healthy controls. Indeed, such distinction in mild OA is key for early detection of presence and progression of radiographic changes. Both the inter- and intra-observer variability were proven to be relatively low, and the smallest detectable difference (SDD) for the different parameters showed good results as well.[5] Since then, KIDA has been used in observational cohorts with patients with relatively mild knee OA, such as the CHECK and APPROACH cohorts.[6,7] However, KIDA parameters have also been used as endpoints in studies including patients with significantly more severe OA. End-stage OA patients treated with knee joint distraction (KJD) or high tibial osteotomy (HTO) were evaluated with KIDA before and up to 9 years after treatment.[8–11] For these severe knee OA cases KIDA has not been evaluated. The goal of the present study was to evaluate the performance of KIDA in patients with severe knee OA.

Methods

Patients

Patients were included from 3 different clinical studies. Twenty (20) patients with end-stage knee OA, in regular care indicated for total knee arthroplasty (TKA) and relatively young (age <60 years), were included in an open prospective study and treated with KJD. In a randomized controlled trial (RCT), where KJD was compared with TKA, 20 end-stage knee OA patients indicated for TKA were treated with KJD. In a separate RCT, KJD was compared with HTO, and another 22 and 45 patients indicated for HTO were treated with KJD or HTO,

respectively. For all patients, the KL grade was determined before treatment.

All details with regard to inclusion criteria and treatment have been described in detail previously for all 3 studies.[12–15] All trials were approved by the medical ethical review committee of the University Medical Center Utrecht (protocol numbers 04/086, 10/359/E, and 11/072) and registered in the Netherlands Trial Register (trial numbers NL419, NL2680, and NL2761). All patients gave written informed consent, which included further use of their data for additional research.

Radiography

Standardized, semi-flexed PA radiographs were performed under full weight-bearing according to the Buckland-Wright protocol.[16,17] An aluminum step wedge was placed alongside the knee, against the detector and within the field of exposure, in order to quantify bone density and determine the pixel size corrected for possible magnification. Radiographs were taken pre-treatment (baseline) and 1 and 2 years post-treatment.

KIDA analysis

The KIDA analysis method has not changed since the original publication in 2008.[5]

First the aluminum step wedge is identified by the user by indicating the 4 corners of the wedge, after which the program automatically draws the outline of the entire wedge and the different steps (Figure 1). From this, it calculates the pixel size and the reference mm aluminum equivalent (mm Al eq) with which subchondral bone density can be expressed. Next, the user places a framework of 4 lines around the joint, that touch on the medial and lateral side of the joint (2 longest vertical lines), and on the distal femur and proximal tibia (horizontal lines; Figure 1). From these last 2 lines, perpendiculars are calculated, 4 on each area (medial and lateral femur and tibia) at predefined calculated positions; 1 circle along each perpendicular can be moved by the user to place the edge of the circle at the bone-'cartilage' interface (16 smallest circles in Figure 1). The distance between each pair of circles is calculated to measure the JSW in mm, at 4 locations of the medial and the lateral compartment. These 4 distances can be averaged to obtain a mean medial and mean lateral JSW, and all 8 distances can be averaged for a mean JSW of the whole joint, all in mm. The mean intensity in each circle is calculated as well, and can be averaged to obtain the subchondral bone density at the medial and lateral tibia and femur, expressed in mm Al eq.

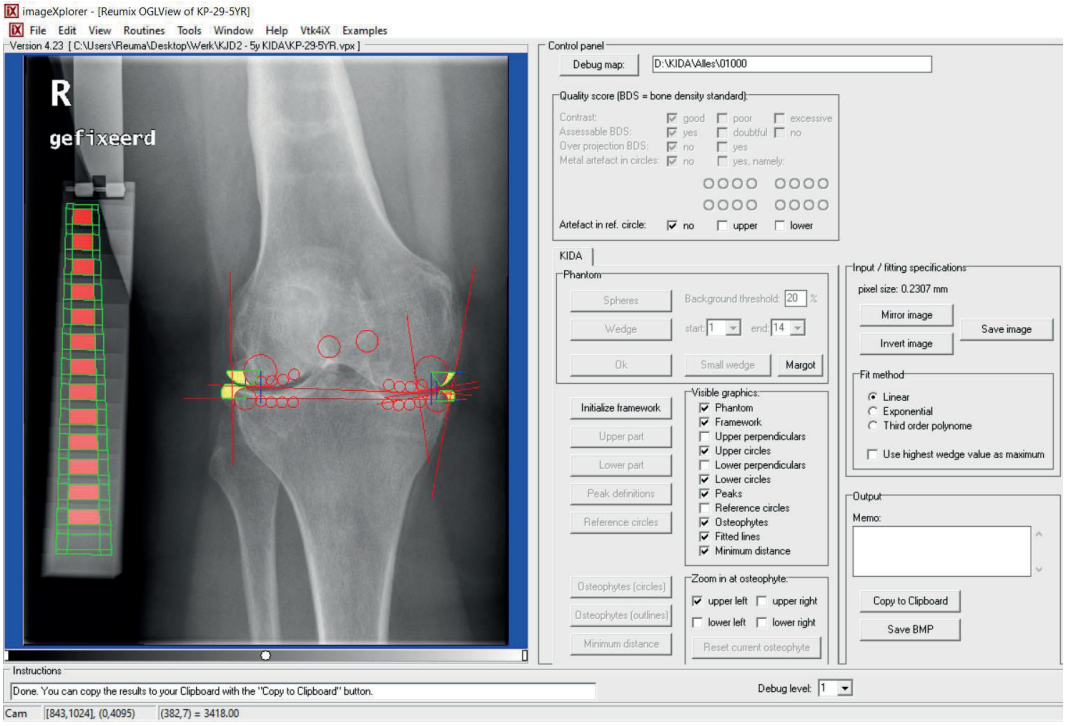


Figure 1: Example of KIDA analysis.

The height of the medial and lateral tibial eminence is determined by placing 2 circles on the top of the eminences; the program calculates the distance in mm from the bottom of these circles to the line at the proximal tibia (Figure 1). Next, the user positions 4 circles, 1 at each corner of the joint, following the original bone lines (Figure 1). The user then indicates the outer osteophyte borders; only the borders within a quadrant (blue/green lines in Figure 1) are included. The program then calculates the osteophyte area in mm^2 for each of the 4 areas (yellow in Figure 1). Using the middle 8 small circles at the bone-cartilage interface, a new line is generated for both the bone edges of the femur and the tibia separately (not displayed in Figure 1); these 2 lines are used to calculate the joint angle in degrees. A negative angle indicates medial joint space narrowing. Lastly, the program gives a vertical line at the narrowest point between these 2 lines, within the joint edges, suggesting the location of the minimum JSW. Since the bone edges are not fully straight, the user can manually adjust the lines to indicate the actual minimum JSW (this does not affect the joint angle). The program then calculates the distance between the 2 horizontal lines at the location of the vertical line as a measure of minimum JSW in mm.

Additional details of the analysis process can be found in the original publication.[5]

Data collection

Since the first KIDA publication in 2008, all KIDA evaluations have been performed by the same observer. The radiographs from the 3 previously performed studies (described under *patients*) that we evaluate in the current analysis were all analyzed for the first time between 2013 and 2015. More recently (2017–2018) all radiographs at baseline, and 1 and 2 years for these 3 studies, were reanalyzed by the same reader. As such, almost all radiographs had duplicate readings, which could be used for determining the intra-observer variability and as such for an evaluation of measurement properties and performance of KIDA in these patients with severe OA.

Since there were multiple years between the first and second analysis, which might influence results, 100 of the radiographs were randomly selected to be evaluated again twice with maximum 1 month in between. The selection was made randomly to ensure that the subset was generalizable to the full set of radiographs. These 200 images (100 radiographs analyzed twice) were randomly ordered and divided in 4 batches of 50; every week 1 batch was analyzed by the same observer (MM) completely blinded to patient characteristics. This data set was additionally used to make a comparison with the dataset from the original KIDA publication, which consisted of mild OA patients with duplicate readings with limited timespan in between both readings.[5] Moreover, the relevance of the in-between reading time, months *versus* years, could be evaluated.

Statistical analysis

The intra-observer variability was calculated for the 2 groups of severe radiographs separately: the total group with radiographs analyzed with a larger and varying time period (years) between 2 observations, and the 100 radiographs analyzed within 1 month.

The intra-observer variation was, for all KIDA parameters separately, displayed with Bland-Altman plots in which the difference between the first and second result was plotted against the mean of the 2 observations.[18] In accordance with the original publication, the mean and standard deviation (SD) of all measurements were calculated, as were the mean, SD and 95% confidence interval (95%CI) of the differences between the duplicate readings; the SDD was defined as 1.96 times the SD of the differences. The intraclass correlation coefficient (ICC) was calculated for single measures using a 2-way random model with absolute agreement. ICCs were interpreted according to the definitions of Koo and Li: an ICC <0.50 was considered poor, 0.50< ICC >0.75 was moderate, 0.75< ICC >0.90 was good, and ICC >0.90 was excellent.[19]

The mean, SD (of the difference), and SDD were compared between the 3 groups of radiographs: total group with severe OA radiographs analyzed with a larger period between 2 observations, the 100 severe OA radiographs analyzed within 1 month, and the results from the mild OA patients from the original publication. Since the SD and with that the SDD may

depend on the mean absolute values which may influence the comparison of these absolute values between mild and severe OA patients, the coefficient of variation (CV), a measure expressing variability relatively to the average value of the measurements, was calculated as well, by dividing the SD of the differences between observations by the mean value of both observations and multiplying that by 100 (%).

To compare KIDA parameters with the most frequently used grading system for OA, individual KIDA parameters were compared to the overall KL grade. This was done using separate linear regression models, using only 1 (the most recent) analysis result for each of the radiographs analyzed with a larger time period (years).

As an additional explorative analysis, the influence of the mean of the measurements (of the 2 observations) and of the KL grade (both separately, as measure for severity) on the absolute intra-observer difference between 2 measurements was analyzed for all parameters. For this, linear regression was used on the data of severe OA patients re-analyzed within 1 month (to ensure that results will not be biased by a long period of time between analyses); a p-value <0.05 was considered statistically significant.

Results

Patients

In total, 293 radiographs with double KIDA readings were available, taken at baseline (n=103), 1-year follow-up (n=98), and 2-year follow-up (n=92). The radiographs were taken of 103 different patients, of whom 61 were treated with KJD and 42 with HTO. The mean KL grade of the patients was 2.7. The median time difference between the first and second analysis was 50 months (interquartile range 39–52 months).

Of the 100 radiographs that were reanalyzed within 1 month, it was discovered that for 2 radiographs the process of randomization was not correct and, as a result, they were not included for analysis twice. As such, these were excluded, and double analysis results within 1 month were available for a total of 98 radiographs. These were images of patients treated with KJD (n=56) and HTO (n=42) and taken at baseline (n=37), 1 year (n=29) and 2 years (n=32). The average KL grade was 2.6.

Results for all severe radiographs reanalyzed within a large period of time

The Bland-Altman plots for 3 relevant example parameters evaluated in all 293 radiographs are shown in Figure 2. Plots for all other parameters of these patients can be found in Supplementary Figures S1–5.

All bone densities (Figure 2A and S1), eminence height (Figure S4), and joint angle (Figure S5) plots did not show any large systematic differences between the 2 readings. However, the minimum JSW (Figure 2B and S2) and osteophyte plots (Figure 2C and S3) showed a floor effect, where measurements resulted in 0 in 1 analysis, but not in the other (as indicated by the straight line of dots starting from around 0).

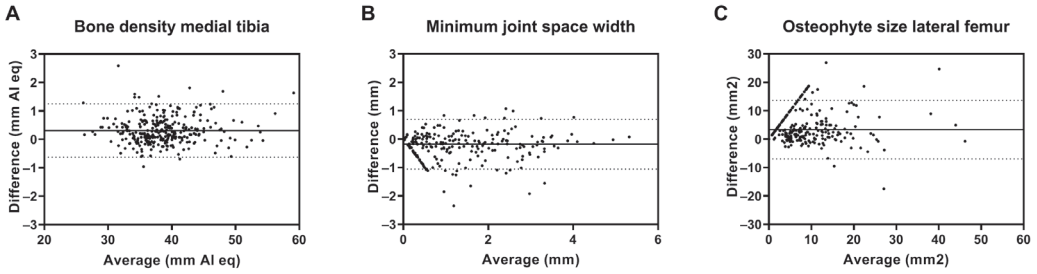


Figure 2: Bland-Altman plots for all 293 available radiographs that were analyzed twice, for (A) the bone density of the medial tibia in mm aluminum equivalent (mm Al eq), (B) the minimum joint space width in mm and (C) the osteophyte area of the lateral femur in mm^2.

The ICC, mean and SD of all measurements, mean of the differences between 2 analysis moments, SD and 95%CI of the difference, and the SDD are shown in Table 1.

Table 1: Intra-observer results for all severe radiographs reanalyzed within a large period of time

	Mean (SD)	Mean Δ	SD Δ	95%CI Δ	SDD	ICC
Bone density (all in mm Al eq)						
Femur mean lateral	33.0 (4.6)	-0.05	0.31	-0.09 to -0.02	0.61	0.998
Femur mean medial	37.3 (5.1)	0.17	0.33	0.13 to 0.21	0.65	0.997
Tibia mean lateral	33.7 (5.2)	-0.59	1.41	-0.75 to -0.43	2.76	0.958
Tibia mean medial	38.6 (5.0)	0.32	0.50	0.26 to 0.38	0.98	0.993
JSW (all in mm)						
Mean	5.2 (1.1)	0.37	0.59	0.30 to 0.44	1.16	0.821
Mean lateral	7.7 (1.9)	0.66	1.03	0.54 to 0.77	2.02	0.816
Mean medial	2.7 (1.7)	0.09	0.39	0.04 to 0.13	0.76	0.973
Minimum	1.0 (1.1)	-0.18	0.45	-0.23 to -0.13	0.88	0.915
Osteophytes (all in mm^2)						
Femur lateral	7.6 (7.5)	3.32	5.26	2.72 to 3.93	10.31	0.716
Femur medial	7.1 (8.0)	5.44	6.84	4.66 to 6.23	13.41	0.579
Tibia lateral	10.0 (10.0)	2.49	4.77	1.94 to 3.03	9.35	0.867
Tibia medial	7.6 (5.9)	2.46	6.24	1.74 to 3.18	12.23	0.532
Other (mm, mm, degrees)						
Eminence lateral	12.5 (2.3)	0.59	1.13	0.46 to 0.72	2.21	0.864
Eminence medial	13.3 (1.8)	0.30	0.94	0.19 to 0.41	1.84	0.860
Joint angle	-6.1 (3.4)	-0.66	1.19	-0.80 to 0.52	2.33	0.924

95%CI Δ: 95% confidence interval of mean differences between the 2 observations; ICC: intraclass correlation coefficient; mean Δ: mean difference between the 2 observations of all radiographs; mm Al eq: mm aluminum equivalent; SD Δ: standard deviation of mean differences between the 2 observations; SDD: smallest detectable difference (1.96*SD of mean differences between the 2 observations).

The ICCs in most cases were good-excellent and the differences (Δ), SD and SDD were small compared to the overall means. However, for the osteophytes the ICCs were moderate (except for the lateral tibia with a good ICC) and the differences and SDDs were relatively high compared to the mean values. Furthermore, all parameters showed a systematic difference (bias) between readings, as indicated by the 95%CI of the difference. The direction of this bias differed and, except for osteophytes, was small relative to the absolute value.

Results for severe radiographs reanalyzed within one month

The Bland-Altman plots for the same set of 3 parameters as shown in Figure 2, but evaluated in the 98 radiographs that were reanalyzed within a month, are shown in Figure 3. All other plots for these 98 radiographs can be found in Supplementary Figures S6–10. For these analyses, none of the plots showed significant systematic differences between the 2 readings.

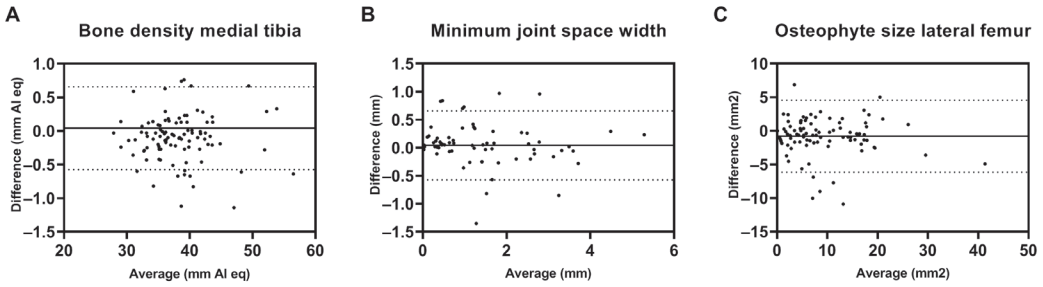


Figure 3: Bland-Altman plots the 98 radiographs that were analyzed twice within a month, for (A) the bone density of the medial tibia in mm aluminum equivalent (mm Al eq), (B) the minimum joint space width in mm and (C) the osteophyte area of the lateral femur in mm^2.

The analysis parameters for these radiographs are shown in Table 2. The ICCs were excellent for most parameters, for 4 parameters the ICC was good, 3 of them being osteophyte parameters. Again, in most cases, differences (Δ), SD and SDD were small compared to the overall means for all parameters, although not for the osteophytes. Clearly less parameters showed significant bias, as indicated by the 95%CI of the differences. Similar to the observed bias for comparisons over the longer time period, the tibia medial bone density, femoral osteophytes, and mean lateral JSW showed significant positive bias, while the joint angle showed negative bias.

Table 2: Intra-observer results for severe radiographs reanalyzed within 1 month

	Mean (SD)	Mean Δ	SD Δ	95%CI Δ	SDD	ICC
Bone density (all in mm Al eq)						
Femur mean lateral	32.6 (4.4)	0.02	0.21	-0.02 to 0.06	0.41	0.999
Femur mean medial	36.8 (5.1)	0.02	0.23	-0.02 to 0.07	0.45	0.999
Tibia mean lateral	32.9 (5.2)	-0.16	1.20	-0.40 to 0.08	2.35	0.973
Tibia mean medial	38.2 (5.2)	0.10	0.35	0.03 to 0.17	0.69	0.998
JSW (all in mm)						
Mean	5.3 (1.1)	0.07	0.39	-0.01 to 0.15	0.76	0.935
Mean lateral	7.7 (1.9)	0.17	0.73	0.03 to 0.32	1.43	0.923
Mean medial	2.9 (1.8)	-0.03	0.24	-0.08 to 0.02	0.47	0.992
Minimum	1.0 (1.2)	-0.04	0.31	-0.10 to 0.02	0.61	0.965
Osteophytes (all in mm^2)						
Femur lateral	8.6 (7.3)	0.80	2.73	0.25 to 1.34	5.35	0.928
Femur medial	11.1 (9.1)	2.04	5.69	0.90 to 3.18	11.15	0.806
Tibia lateral	11.8 (12.2)	0.77	5.90	-0.41 to 1.95	11.56	0.889
Tibia medial	8.5 (7.4)	0.01	5.58	-1.11 to 1.13	10.94	0.751
Other (mm, mm, degrees)						
Eminence lateral	12.7 (2.5)	0.17	1.14	-0.06 to 0.39	2.23	0.901
Eminence medial	13.3 (1.8)	0.06	0.89	-0.12 to 0.24	1.74	0.891
Joint angle	-6.0 (3.6)	-0.28	0.96	-0.47 to -0.08	1.88	0.962

95%CI Δ: 95% confidence interval of mean differences between the 2 observations; ICC: intraclass correlation coefficient; mean Δ: mean difference between the 2 observations of all radiographs; mm Al eq: mm aluminum equivalent; SD Δ: standard deviation of mean differences between the 2 observations; SDD: smallest detectable difference (1.96*SD of mean differences between the 2 observations).

Comparison of all 3 groups

The mean of the parameters, the SD of the differences, the SDD and CV are shown for the 3 groups (all 293 radiographs with severe OA reanalyzed within a large period of time, the 98 radiographs with severe OA reanalyzed within 1 month, and 55 radiographs with mild OA from the original publication analyzed within 1 month) in Table 3. Besides increasing the ICC (comparing Tables 1 and 2), reanalyzing the severe OA radiographs within 1 month seemed to decrease the SDD and CV for almost all parameters. Furthermore, the SDD and CV for severe OA patients analyzed within 1 month were comparable to and often even better than those for mild OA patients for most parameters. Compared to mild OA, the SDD for severe OA was especially high for osteophyte parameters, although the CV, which corrects the SD for the mean overall values, was more comparable. For the tibia lateral bone density, the difference remained high in SDD and CV.

Obviously, but importantly, all variables differed between mild and the severe OA in the expected direction, severe patients having a higher bone density, a smaller JSW, larger osteophytes, and higher eminetia.

Table 3: Intra-observer results for the 3 groups

	Mean			SDD			CV (%)		
	Severe OA (n=293)	Severe OA 1 month (n=98)	Mild OA (n=55)	Severe OA (n=293)	Severe OA 1 month (n=98)	Mild OA (n=55)	Severe OA (n=293)	Severe OA 1 month (n=98)	Mild OA (n=55)
Bone density (all in mm Al eq)									
Femur mean lateral	33.0	32.6	28.6	0.61	0.41	1.08	0.9	0.6	1.9
Femur mean medial	37.3	36.8	29.8	0.65	0.45	0.84	0.9	0.6	1.4
Tibia mean lateral	33.7	32.9	29.6	2.76	2.35	1.06	4.2	3.6	1.8
Tibia mean medial	38.6	38.2	31.3	0.98	0.69	0.84	1.3	0.9	1.4
JSW (all in mm)									
Mean	5.2	5.3	5.1	1.16	0.76	0.86	11.3	7.4	8.6
Mean lateral	7.7	7.7	6.1	2.02	1.43	1.53	13.4	9.5	12.8
Mean medial	2.7	2.9	4.2	0.76	0.47	0.67	14.4	8.3	8.1
Minimum	1.0	1.0	2.8	0.88	0.61	0.49	45.0	31.0	8.9
Osteophytes (all in mm^2)									
Femur lateral	7.6	8.6	5.4	10.31	5.35	6.78	69.2	31.7	64.1
Femur medial	7.1	11.1	3.7	13.41	11.15	3.21	96.3	51.3	44.3
Tibia lateral	10.0	11.8	6.4	9.35	11.56	8.06	47.7	50.0	64.2
Tibia medial	7.6	8.5	9.9	12.23	10.94	4.63	82.1	65.6	23.8
Other (mm, mm, degrees)									
Eminence lateral	12.5	12.7	10.0	2.21	2.23	2.47	9.0	9.0	12.6
Eminence medial	13.3	13.3	11.6	1.84	1.74	1.92	7.1	6.7	8.4
Joint angle*	6.4	6.3	3.0	2.35	1.86	2.02	18.8	15.1	34.3

*The joint angle here was defined as the absolute value (negative angles as a result of medial narrowing were taken as a positive value), as this was done in the original publication. CV: coefficient of variation (standard deviation of the differences between observations divided by the mean value of both observations and multiplied by 100); SDD: smallest detectable difference (1.96*standard deviation of mean differences between the 2 observations); mm Al eq: mm aluminum equivalent.

Comparison with Kellgren-Lawrence grade

The relation between all individual KIDA parameters and KL-grade are shown in Table 4. A smaller JSW and especially higher osteophytes were significantly associated with a higher KL-grade, as would be expected. A higher bone density in the medial femur showed a significant positive relation with KL-grade as well.

Table 4: Relation between KIDA parameters and Kellgren-Lawrence grade

	B	**β**	***P*-value**
Bone density (all in mm Al eq)			
Femur mean lateral	0.164	0.034	0.564
Femur mean medial	1.218	0.227	**<0.001**
Tibia mean lateral	0.314	0.056	0.324
Tibia mean medial	0.608	0.113	0.053
JSW (all in mm)			
Mean	-0.173	-0.142	**0.015**
Mean lateral	-0.049	-0.023	0.697
Mean medial	-0.298	-0.163	**0.005**
Minimum	-0.299	-0.247	**<0.001**
Osteophytes (all in mm^2)			
Femur lateral	2.995	0.340	**<0.001**
Femur medial	4.917	0.488	**<0.001**
Tibia lateral	4.677	0.402	**<0.001**
Tibia medial	2.325	0.325	**<0.001**
Other (mm, mm, degrees)			
Eminence lateral	0.097	0.038	0.520
Eminence medial	-0.016	-0.008	0.891
Joint angle	-0.358	-0.096	0.100

Separate linear regression models were used for all different parameters. β: standardized coefficient; *B*: unstandardized coefficient; mm Al eq: mm aluminum equivalent.

Influence of severity on intra-observer difference

The influence of the mean values and KL grade, both as a measure of severity, on the differences between measurements of severe radiographs reanalyzed within 1 month are shown in Table 5. Both medial osteophyte parameters and the lateral tibia osteophytes showed a statistically significant influence of the mean values and of the KL grade (all $p<0.02$); in all cases more severe OA (higher values) corresponded with a larger difference between measurements. Additionally, the tibia medial bone density and minimum JSW showed a significant positive influence of their mean values (both $p<0.03$), but not KL grade (both $p>0.32$).

Table 5: Influence of mean values and Kellgren-Lawrence grade on the intra-observer differences between measurements for severe radiographs analyzed within 1 month

	Mean value			Kellgren-Lawrence grade		
	B	**β**	***P*-value**	***B***	**β**	***P*-value**
Bone density (all in mm Al eq)						
Femur mean lateral	0.002	0.078	0.443	0.024	0.176	0.083
Femur mean medial	0.006	0.186	0.066	-0.013	-0.081	0.427
Tibia mean lateral	0.032	0.159	0.118	-0.060	-0.057	0.575
Tibia mean medial	0.011	0.223	**0.021**	0.025	0.100	0.326
JSW (all in mm)						
Mean	-0.028	-0.098	0.336	-0.025	-0.081	0.428
Mean lateral	0.011	0.032	0.755	-0.066	-0.104	0.309
Mean medial	-0.006	-0.067	0.515	0.016	0.093	0.365
Minimum	0.070	0.314	**0.002**	0.008	0.029	0.778
Osteophytes (all in mm²)						
Femur lateral	0.050	0.173	0.089	0.156	0.072	0.479
Femur medial	0.130	0.244	**0.016**	1.340	0.271	**0.007**
Tibia lateral	0.257	0.577	**<0.001**	1.783	0.325	**0.001**
Tibia medial	0.393	0.606	**<0.001**	1.375	0.285	**0.004**
Other (mm, mm, degrees)						
Eminence lateral	0.043	0.114	0.264	0.134	0.141	0.167
Eminence medial	0.021	0.059	0.564	-0.040	-0.059	0.565
Joint angle	-0.011	-0.048	0.639	-0.069	-0.084	0.413

Separate linear regression models were used the mean value and the Kellgren-Lawrence grade, for all different parameters. β: standardized coefficient; *B*: unstandardized coefficient; mm Al eq: mm aluminum equivalent.

Discussion

Based on the presented results, it is shown that KIDA is a useful tool for radiographic analysis of OA characteristics even in patients with severe OA. Notably, (re)analyzing images in a short time period increases reproducibility (decreases SDDs and CVs). Furthermore, the systematic bias between measurements decreases when images are reanalyzed within a short time period (1 month compared to years). This emphasizes the importance of performing the analyses required for a specific research question within a limited time period and randomized for time/ visit sequence.

The fact that some parameters showed significant differences between readings, even for the images reanalyzed within 1 month, can only be speculated on. For these parameters, the direction of this bias was the same for the images that were analyzed over years and over months, which implies that the bias is expectedly systematic and not coincidental (i.e. not because of subtly different conditions that may unconsciously affect measurement) and that it is not likely the result of recalling the first reading. For most consistent biases, the direction was positive. As such, changes over time for bone density, femoral osteophytes, and lateral JSW might be overstated in case images are analyzed in chronological order of acquisition over time

(visits). However, in general the bias is small compared to the mean values and treatment effect that has been observed thus far.[8–10] Moreover, this bias becomes irrelevant when comparing differences in changes over time between groups, e.g. treatment arms. Still, when analyzing changes over time, it is strongly recommended to randomize the chronological order in which radiographs are analyzed, so this bias will not be of relevance.

Although speculative, the systematic bias for bone density and osteophyte area may be caused by a gradual learning curve of the observer in identifying the outer and inner boundaries of the osteophytes and the edges of the bone 'cartilage' interface (black to white interface on the radiographs). Moving the small circles that determine JSW and bone density somewhat will likely not affect JSW significantly, but if the circle is placed slightly outside the actual (white) bone area, a small number of pixels could be dark-gray to black (background) and significantly impact the average gray value.

It is remarkable that for many parameters, the SDD was lower (better) for severe OA patients analyzed within a month in this study than for mild OA patients from the original publication. However, the differences are not very large. Again the explanation may be found in a learning curve by analyzing KIDA images over the past 12 years. In this case the experience is in favor of the technique (reproducibility), instead of the time-dependent bias.

The more important conclusion is that for most parameters, intra-observer variation is similar in severe OA patients compared to mild OA patients. Medial osteophyte areas seem to be the exception, and have a much bigger (worse) SDD for severe OA patients. For both medial osteophytes and lateral tibial osteophytes it was shown that the intra-observer variation depended on the osteophyte area, as bigger osteophytes, associated with more severe OA, and a higher KL grade results in a larger variation between measurements. This explains why, even if SDDs are not comparable between patients of different severities, the CVs are (as they are corrected for the mean osteophyte area, and with that partly for severity as well). Osteophytes did not only show a relatively high dependence on mean values, but also on whether the reanalysis was performed within a long or short period. All 4 osteophyte locations showed a clear floor effect in the complete dataset of 293 radiographs (Figure S3), which disappeared for the 98 radiographs reanalyzed within 1 month (Figure S8). This may also be explained by a learning curve, as these osteophytes were not recognized as osteophytes in the first reading (value 0) but were recognized as osteophytes in the second reading. Furthermore, while ICC improved for all parameters when reanalyzed within a month (compare Table 2 with Table 1), this effect was the most notable for the osteophyte measurements. Apparently the osteophytes are the parameters most sensitive to intra-observer variability. This may be explained by the fact that the values depend on a calculated area within a manually delineated boundary, a subjective action sensitive to a learning curve.

While the minimum JSW SDD is comparable between mild and severe OA, the CV shows a large difference, because the severe OA patients show a smaller mean value for minimum JSW. Surprisingly, for minimum JSW, a higher absolute difference between measurements was significantly associated with a higher mean values (and thus less severe OA), although this comparison could have been complicated by the extremely small values, as a result of a truncation effect (1-sided limitation at 0) and limitations with respect to pixel size. Nevertheless, also in these cases, performing the analyses in a short time frame greatly decreases this variability.

The SDDs calculated in this research indicate the smallest change that can be interpreted as a real change, as opposed to a measurement error, with $p<0.05$. It is important to note that the SDDs described in this research are relevant on an individual level. When using these SDDs on a group level, for example when evaluating groups of patients before and after treatment using KIDA analyses, the group SDD should be calculated by dividing the SDDs calculated here by the square root of the number of observations in the group.[20,21]

Apart from intra-observer differences between measurements, it was shown that also in more severe OA, osteophytes and JSW parameters were significantly associated with KL grade. As such, as for mild OA, also for severe OA KIDA is a valid method to evaluate radiographic characteristics of OA.

In conclusion, while the variability of some parameters may depend on severity, and without precautions bias may develop, KIDA has been shown to be a useful tool also in patients with severe OA. Its use, like most image analyses techniques, needs to be performed with caution. In order to decrease variability and be able to detect smaller differences, images should be analyzed in a limited time frame and randomized order.

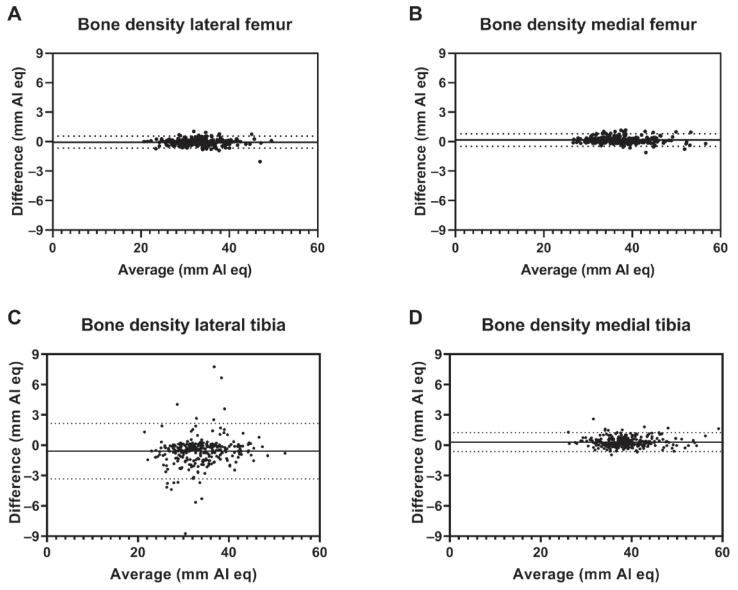
References

1. Buckwalter JA, Martin JA. Osteoarthritis. Advanced Drug Delivery Reviews. 2006 May 20;58(2):150–67.
2. Vignon E, Piperno M, Le Graverand MPH, *et al*. Measurement of radiographic joint space width in the tibiofemoral compartment of the osteoarthritic knee: Comparison of standing anteroposterior and Lyon schuss views. Arthritis and Rheumatism. 2003 Feb 1;48(2):378–84.
3. Kellgren JH, Lawrence JS. Radiological assessment of osteo-arthrosis. Annals of the Rheumatic Diseases. 1957 Dec 1;16(4):494–502.
4. Altman RD, Gold GE. Atlas of individual radiographic features in osteoarthritis, revised. Osteoarthritis and Cartilage. 2007 Jan 1;15(SUPPL. 1):1–56.
5. Marijnissen ACA, Vincken KL, Vos PAJM, *et al*. Knee Images Digital Analysis (KIDA): A novel method to quantify individual radiographic features of knee osteoarthritis in detail. Osteoarthritis and Cartilage. 2008 Feb 1;16(2):234–43.
6. Wesseling J, Boers M, Viergever MA, *et al*. Cohort profile: Cohort Hip and Cohort Knee (CHECK) study. International Journal of Epidemiology. 2016 Feb 1;45(1):36–44.
7. van Helvoort EM, van Spil WE, Jansen MP, *et al*. Cohort profile: The Applied Public-Private Research enabling OsteoArthritis Clinical Headway (IMI-APPROACH) study: A 2-year, European, cohort study to describe, validate and predict phenotypes of osteoarthritis using clinical, imaging and biochemical markers. BMJ Open. 2020 Jul 28;10(7):e035101.
8. Jansen MP, van der Weiden GS, van Roermund PM, *et al*. Initial tissue repair predicts long-term clinical success of knee joint distraction as treatment for knee osteoarthritis. Osteoarthritis and Cartilage. 2018;26(12):1604–8.
9. Jansen MP, Besselink NJ, van Heerwaarden RJ, *et al*. Knee Joint distraction compared with high tibial osteotomy and total knee arthroplasty: Two-year clinical, radiographic, and biochemical marker outcomes of two randomized controlled trials. Cartilage. 2019 Feb 13;194760351982843.
10. Jansen MP, Mastbergen SC, Watt FE, *et al*. Cartilage repair activity during joint-preserving treatment may be accompanied by osteophyte formation. Submitted.
11. Jansen MP, Boymans TAEJ, Custers RJH, *et al*. Knee joint distraction as treatment for osteoarthritis results in clinical and structural benefit: A systematic review and meta-analysis of the limited number of studies and patients available. Cartilage. 2020 Jul 22;194760352094294.
12. Intema F, van Roermund PM, Marijnissen ACA, *et al*. Tissue structure modification in knee osteoarthritis by use of joint distraction: An open 1-year pilot study. Annals of the Rheumatic Diseases. 2011 Aug 1;70(8):1441–6.
13. van der Woude JAD, Wiegant K, van Heerwaarden RJ, *et al*. Knee joint distraction compared with total knee arthroplasty: A randomised controlled trial. Bone and Joint Journal. 2017;99-B(1):51–8.
14. van der Woude JAD, Wiegant K, van Heerwaarden RJ, *et al*. Knee joint distraction compared with high tibial osteotomy: A randomized controlled trial. Knee Surgery, Sports Traumatology, Arthroscopy. 2017;25(3):876–86.
15. Jansen MP, Mastbergen SC, van Heerwaarden RJ, *et al*. Knee joint distraction in regular care for treatment of knee osteoarthritis: A comparison with clinical trial data. PLOS ONE. 2020 Jan 22;15(1).
16. Buckland-Wright JC, Ward RJ, Peterfy C, *et al*. Reproducibility of the semiflexed (metatarsophalangeal) radiographic knee position and automated measurements of medial tibiofemoral joint space width in a multicenter clinical trial of knee osteoarthritis. Journal of Rheumatology. 2004 Aug;31(8):1588–97.
17. Buckland-Wright JC, Wolfe F, Ward RJ, *et al*. Substantial superiority of semiflexed (MTP) views in knee osteoarthritis: a comparative radiographic study, without fluoroscopy, of standing extended, semiflexed

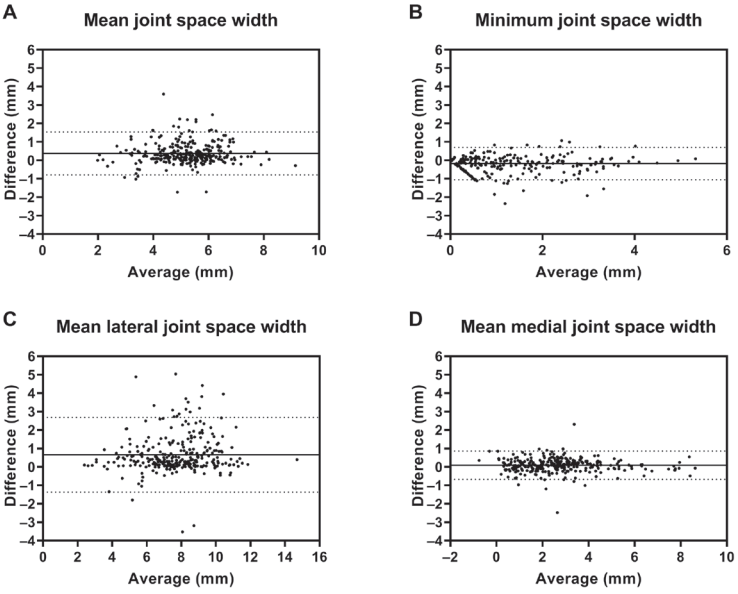
(MTP), and schuss views. Journal of Rheumatology. 1999 Dec;26(12):2664–74.

18. Martin Bland J, Altman DG. Statistical methods for assessing agreement between two methods of clinical measurement. The Lancet. 1986 Feb 8;327(8476):307–10.
19. Koo TK, Li MY. A guideline of selecting and reporting intraclass correlation coefficients for reliability research. Journal of Chiropractic Medicine. 2016 Jun;15(2):155.
20. De Vet HCW, Bouter LM, Dick Bezemer P, *et al*. Reproducibility and responsiveness of evaluative outcome measures: Theoretical considerations illustrated by an empirical example. International Journal of Technology Assessment in Health Care. 2001;17(4):479–87.
21. Terwee CB, Bot SDM, de Boer MR, *et al*. Quality criteria were proposed for measurement properties of health status questionnaires. Journal of Clinical Epidemiology. 2007 Jan 1;60(1):34–42.

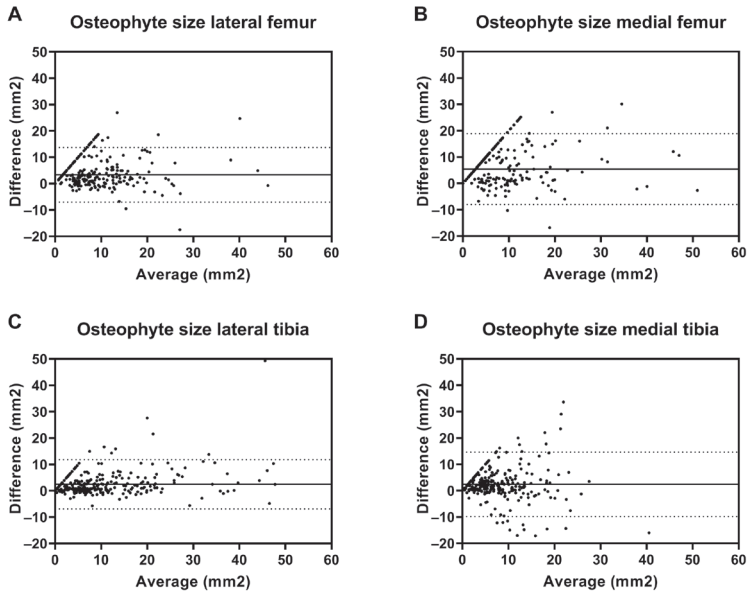
SUPPLEMENTARY DATA



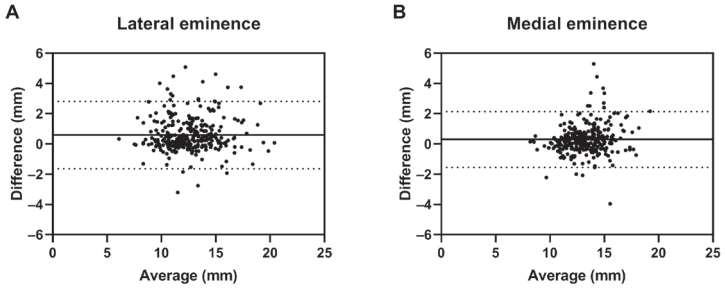
Supplementary Figure S1: Bland-Altman plots for all 293 available radiographs that were reanalyzed within a large period of time, for the bone density of (A) the lateral femur, (B) the medial femur, (C) the lateral tibia, and (D) the medial tibia, all in mm aluminum equivalent (mm Al eq).



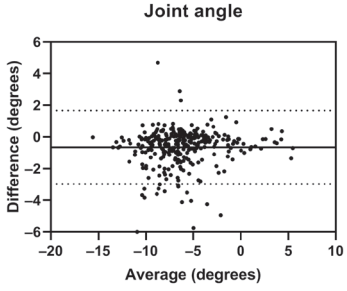
Supplementary Figure S2: Bland-Altman plots for all 293 available radiographs that were reanalyzed within a large period of time, for the (A) mean joint space width (JSW) of the whole joint, (B) the minimum JSW, (C) the mean lateral JSW, and (D) the mean medial JSW, all in mm.



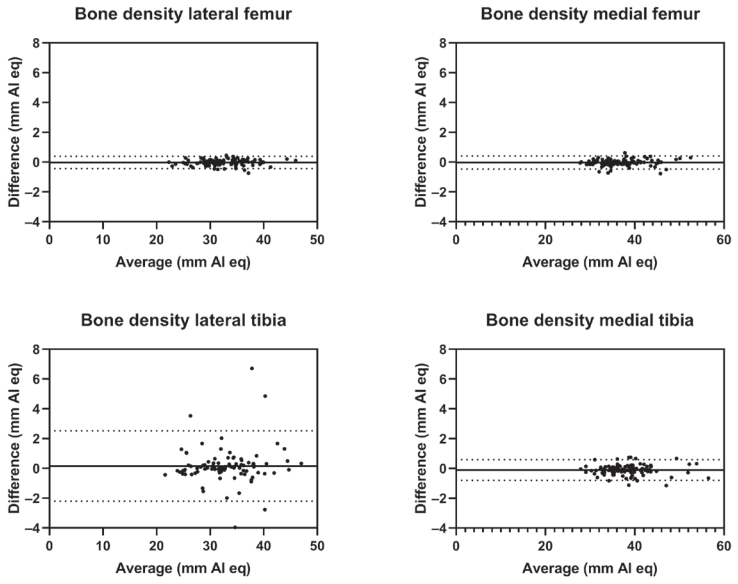
Supplementary Figure S3: Bland-Altman plots for all 293 available radiographs that were reanalyzed within a large period of time, for the osteophyte area of (A) the lateral femur, (B) the medial femur, (C) the lateral tibia, and (D) the medial tibia, all in mm^2.



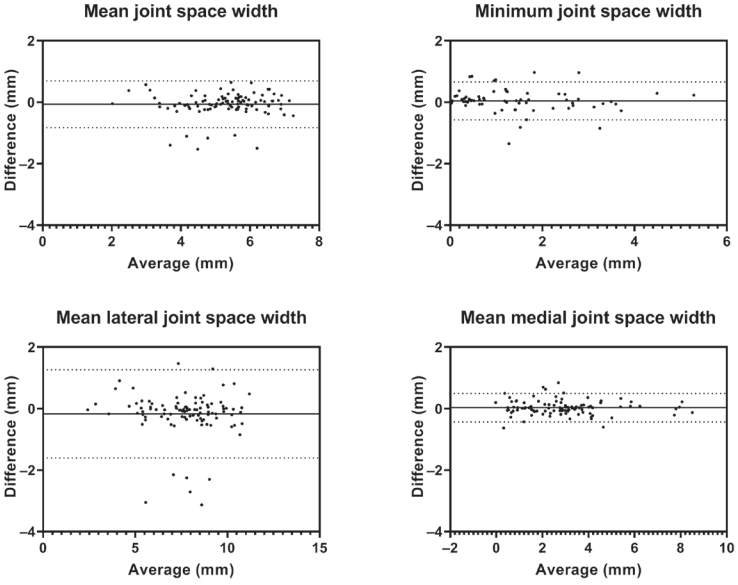
Supplementary Figure S4: Bland-Altman plots for all 293 available radiographs that were analyzed twice, for the (A) lateral and (B) medial eminence, both in mm.



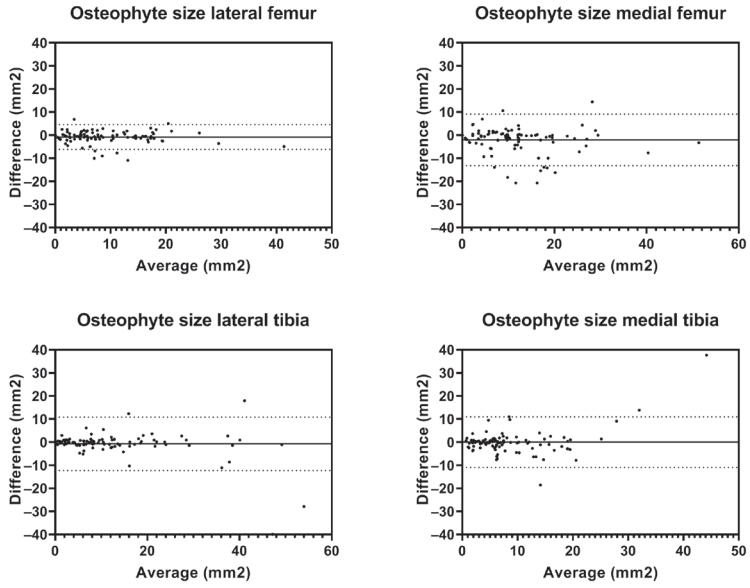
Supplementary Figure S5: Bland-Altman plots for all 293 available radiographs that were analyzed twice, for the tibia-femur joint angle in degrees.



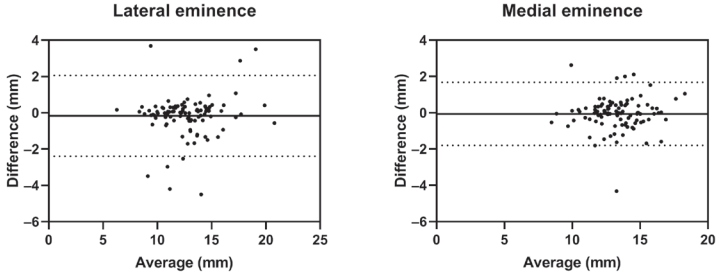
Supplementary Figure S6: Bland-Altman plots for the 98 radiographs that were analyzed twice within a month, for the bone density of (A) the lateral femur, (B) the medial femur, (C) the lateral tibia, and (D) the medial tibia, all in mm aluminum equivalent (mm Al eq).



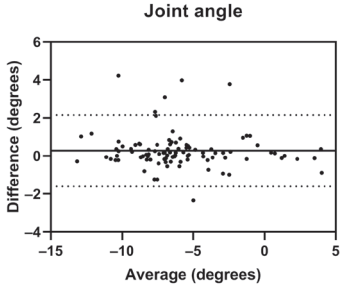
Supplementary Figure S7: Bland-Altman plots for the 98 radiographs that were analyzed twice within a month, for the (A) mean joint space width (JSW) of the whole joint, (B) the minimum JSW, (C) the mean lateral JSW, and (D) the mean medial JSW, all in mm.



Supplementary Figure S8: Bland-Altman plots for the 98 radiographs that were analyzed twice within a month, for the osteophyte area of (A) the lateral femur, (B) the medial femur, (C) the lateral tibia, and (D) the medial tibia, all in mm^2.



Supplementary Figure S9: Bland-Altman plots for the 98 radiographs that were analyzed twice within a month, for the (A) lateral and (B) medial eminence, both in mm.



Supplementary Figure S10: Bland-Altman plots for the 98 radiographs that were analyzed twice within a month, for the tibia-femur joint angle in degrees.

CHAPTER 12

Comparison between 2D radiographic weight-bearing joint space width and 3D MRI non-weight-bearing cartilage thickness measures in the knee using non-weight-bearing 2D and 3D CT as an intermediary

M.P. Jansen
S.C. Mastbergen
F. Eckstein
R.J. van Heerwaarden
S. Spruijt
F.P.J.G. Lafeber

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Abstract

Background: In knee osteoarthritis, radiographic joint space width (JSW) is frequently used as surrogate marker for cartilage thickness; however, longitudinal changes in radiographic JSW have shown poor correlations with those of MRI cartilage thickness. There are fundamental differences between the techniques: radiographic JSW represents 2D, weight-bearing, bone-to-bone distance, while on MRI 3D non-weight-bearing cartilage thickness is measured. In this exploratory study, CT was included as a third technique, as it can measure bone-to-bone under non-weight-bearing conditions. The objective was to use CT to compare the impact of weight-bearing *versus* non-weight-bearing, as well as bone-to-bone JSW *versus* actual cartilage thickness, in the knee.

Methods: Osteoarthritis patients (n=20) who were treated with knee joint distraction were included. Weight-bearing radiographs, non-weight-bearing MRIs, and CTs were acquired before and 2 years after treatment. The mean radiographic JSW and cartilage thickness of the most affected compartment were measured. From CT, the 3D median JSW was calculated and a 2D projectional image was rendered, positioned similarly and measured identically to the radiograph. Pearson correlations between the techniques were derived, both cross-sectionally and longitudinally.

Results: Fourteen patients could be analyzed. Cross-sectionally, all comparisons showed moderate-strong significant correlations (R=0.43–0.81; all p<0.05). Longitudinal changes over time were small; only the correlations between 2D CT and 3D CT (R=0.65; p=0.01) and 3D CT and MRI (R=0.62; p=0.02) were statistically significant.

Conclusion: The poor correlation between changes in radiographic JSW and MRI cartilage thickness appears to primarily result from the difference in weight-bearing, and less so from measuring bone-to-bone distance *versus* cartilage thickness.

Introduction

Knee osteoarthritis (OA) is a degenerative joint disease that is characterized by, among other factors, articular cartilage degeneration and subsequent thinning.[1] The gold standard for quantifying cartilage thinning has traditionally been measurements of the joint space width (JSW) on weight-bearing radiographs.[2] The radiographic JSW provides a 2-dimensional projectional estimate of the bone-to-bone distance and thus reflects, to a certain extent, articular cartilage thickness. Radiographic JSW is often required for evaluating the rate of cartilage degeneration/regeneration in clinical trials and, when managed well with a high degree of acquisition standardization, the reliability and reproducibility of JSW measurement techniques are considered to be high.[3–5] Because knee radiographs are generally taken in a weight-bearing position, quality of the cartilage (with respect to deformability of the tissue) may be an important factor in the assessment of radiographic JSW. However, representing only an indirect measure for cartilage thickness, JSW measurements can be influenced significantly by positioning, acquisition errors, focal cartilage degeneration, and changes in other joint tissues.[6,7] The meniscus, in particular, has been shown to substantially impact radiographic JSW measurements.[8,9]

A more recent method is the direct measurement of articular cartilage thickness on MRI scans. Using MRI, cartilage tissue itself can be visualized 3-dimensionally. Different quantitative measurements have been described and the average cartilage thickness generally shows high reproducibility.[10,11] However, unlike radiography, MRI images are taken in a non-weight-bearing position. As such, deformability of the cartilage tissue is not taken into account. Yet, it has been shown that knee OA affects the mechanical properties of cartilage, which influences the amount of deformation.[12]

Literature comparing both techniques for natural OA progression show moderate to strong correlations cross-sectionally.[13–15] In cross-sectional evaluation, differences in cartilage thickness between individuals are relatively large (millimeters) and as such in favor of finding these relations. However, when looking at longitudinal changes over time, changes are much less pronounced (tenths of millimeters), limiting the measurement window. In these longitudinal studies, no or at best weak correlations were found between the change in radiographic JSW and the change in MRI cartilage thickness.[16–20]

This may be the result of the various differences between the techniques described previously: weight-bearing *versus* non-weight-bearing, bone-to-bone distance *versus* cartilage thickness, and 2D *versus* 3D. In the present study we include CT as an imaging technique, as it is performed without weight-bearing, like MRI, but specifically visualizes the bone-to-bone distance, like radiographs. CT is a 3D imaging technique, but is also capable of creating a projectional image

for 2D measurements. By including CT in the comparison with radiographic JSW and MRI cartilage thickness, the impact of weight-bearing *versus* non-weight-bearing and of measuring bone-to-bone JSW *versus* cartilage thickness measurements can be elucidated.

Methods

Patients

Patients treated with a joint-preserving surgical technique demonstrating cartilaginous tissue repair, knee joint distraction[21,22], who had radiographs (x-rays), MRI scans, and CT scans before and 2 years after treatment were included for this study. Knee joint distraction has previously been reported to result in cartilaginous tissue repair by radiographic and MRI evaluation, making it a population explicitly suitable for the present evaluation.[23]

Patients were included from 2 independent randomized controlled trials (RCTs).[24,25] In both trials, a subgroup of patients (both n=10) was asked to participate in an extended imaging protocol that included additional MRI and CT scans, in addition to the radiographs all patients received in these trials. Only patients who had complete imaging datasets at baseline and 2-year follow-up were included in the current study. Both trials were granted ethical approval by the medical ethical review committee of the University Medical Center Utrecht (protocol numbers 10/359/E and 11/072) and registered in the Netherlands Trial Register (trial numbers NL2761 and NL2680). All patients gave written informed consent.

Knee joint distraction is a surgical treatment for end stage knee OA below 65 years of age to postpone the need for a knee prosthesis.[26] In- and exclusion criteria of the RCTs and treatment details have been described previously.[27,28] Before treatment, the most affected knee joint compartment (MAC) medial or lateral was determined for all patients.

Imaging and measurement methods

An overview of the different imaging techniques and key differences between them is shown in Figure 1.

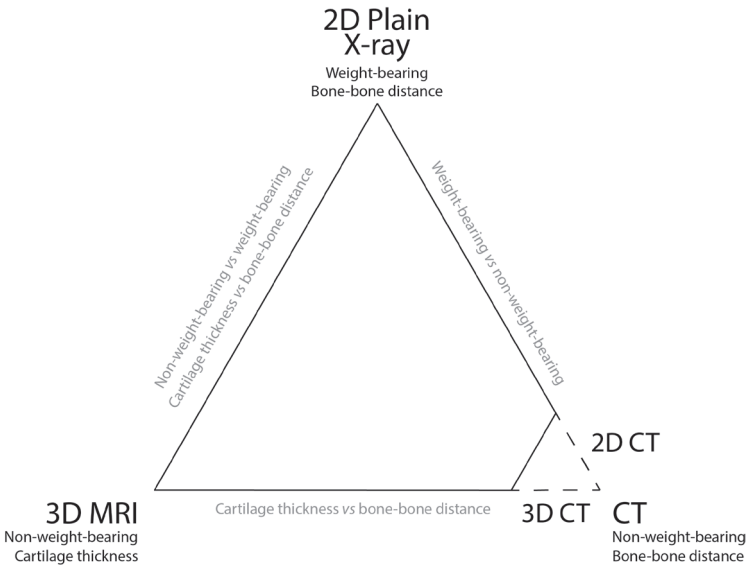


Figure 1: The 3 different imaging methods used for (in)direct cartilage quantification. The key characteristics are listed underneath each modality, and key differences between modalities are displayed in gray. For CT, both 3D and 2D joint space width measurements were used, for comparison with MRI and radiography respectively.

Radiography (x-rays)

Standardized weight-bearing, semi-flexed, posteroanterior (PA) radiographs were performed according to the Buckland-Wright protocol.[29,30] An aluminum step wedge was used as a reference standard to calculate the pixel size. For analysis of the radiographs, 'knee images digital analysis' (KIDA) software was used by 1 experienced observer, blinded to the acquisition order. The mean JSW of the most affected compartment (MAC) was calculated by averaging the tibia-femur distance at 4 locations of the MAC, which were determined automatically based on a framework of 4 lines placed manually around joint. A detailed explanation of the KIDA mathematical method has been provided in the original article.[31]

MRI

3T MRIs with 3D spoiled gradient recalled imaging sequence with fat suppression (SPGR-fs) were acquired for analysis of cartilage structure using Chondrometrics Works 3.0 software.[32] Experienced observers blinded to acquisition order segmented the tibiofemoral cartilage throughout the joint, which was averaged to calculate the mean cartilage thickness of the MAC.

CT

Axial CT scans of the knee were performed, from which coronal reconstructions with 2 mm slice thickness were rendered. A segmentation and 3D JSW measurement method was

developed in-house (for details see supplementary file). Bone segmentation was performed semi-automatically, after which the perpendicular distance from the tibia plateau to the femur was measured throughout the entire joint. Only tibial areas where the perpendiculars were 'reflected' back onto the tibia surface (i.e. the femoral perpendicular originating from the location where the tibial perpendicular meets the femoral surface, has to meet the tibial surface as well) were included, to only include joint space areas where mutual force transfer between the 2 bones can take place. The medial and lateral boundaries were determined similar as for KIDA evaluation: the width of the medial and lateral side of the joint are 3/20 of the total width of the joint, and the outer border of both sides is 2/15 of the total joint width away from the outer border of the joint, the latter was performed manually (MJ).[31] The median of the remaining perpendicular distances of the MAC was calculated to get the '3D CT' surface median JSW value. The median value instead of the mean value was used to exclude the influence of potentially artificially induced exceptionally large bone-bone distances, however outcome was almost identical in case mean values were used.

In addition to the bone-to-bone distance of the 3D image, the coronal CT scans were rotated semi-automatically to a standard position in order to match the position used for the (weight-bearing) radiographs. The tibia plateau was positioned parallel to the axial plane and the line through the back of the femoral condyles was positioned parallel to the coronal plane, viz the most optimal 2D image acquisition. The positioning of tibia in relation to femur was not changed (i.e. no artificial changes were made in the amount of flexion). Subsequently, an over-projection of the repositioned CT scan was created in the coronal plane, so that a non-weight-bearing 2D radiograph was mimicked. A wedge was added based on the current pixel size. These radiographs were then analyzed using the KIDA software, according to the same method and by the same observer as used for the weight-bearing radiographs. The '2D CT' MAC mean JSW was calculated.

A representative image of the 4 different techniques for the same patient is shown in Figure 2.

Statistical analyses

For patient characteristics and image analysis results, descriptive statistics were used.

Pearson *R* correlations were calculated between the techniques cross-sectionally, using all patient time points in 1 comparison. Additionally, Pearson *R* correlations between the techniques were calculated for the changes over time (2 years - baseline). To describe correlation strength, the guide for *R*-values suggested by Evans in 1996 was used: <0.2 very weak; 0.2–0.39 weak; 0.40–0.59 moderate; 0.60–0.79 strong; >0.8 very strong.[33] *P*-values <0.05 were considered statistically significant. IBM SPSS Statistics version 25 (IBM Corp; Armonk, NY) was used for all statistical analyses.

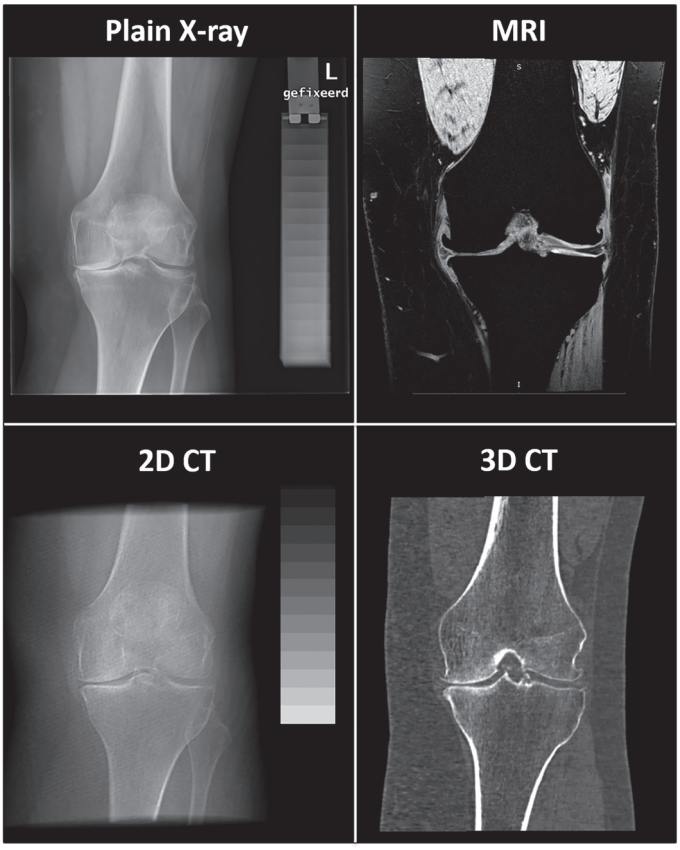


Figure 2: Representative image of the 4 techniques that are compared; all images are taken from the same patient before treatment (baseline). For MRI and 3D CT 1 slice is shown, since they are 3D imaging techniques. The 2D CT images is created by over-projecting the CT scan, after standardized positioning, in the coronal plane.

Results

Patients

Of the 20 patients originally included, 3 patients were lost to follow-up because they converted to a different treatment within 2 years after the original distraction treatment. Of 1 patient, no CT scan at baseline and 2 years was available. Of the remaining 16 patients, 2 had severe motion artifacts present in either of their 2 MRI scans disqualifying proper analyses. As such, 14 patients completed all imaging protocols at both time points and were used for evaluation.

The patient characteristics and image analysis results for the 14 included patients are shown in Table 1. Baseline parameters are comparable to those of the entire population of KJD patients from both original RCTs, as published before, so this small subpopulation seems representable for the entire KJD population.[27]

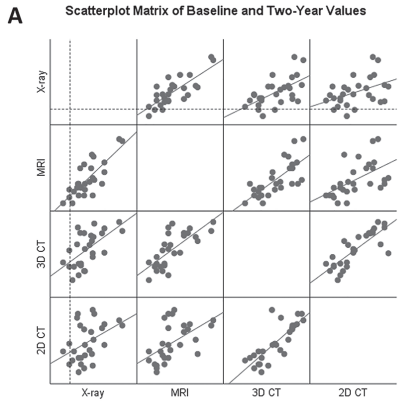
Table 1: Patient characteristics and image analysis (most affected compartment) results

Patient characteristics	All patients (n=14) Baseline		
Age (years)	53.9 (7.7)		
Weight (kg)	87.6 (13.7)		
BMI (kg/m^2)	27.6 (3.9)		
Male sex, n (%)	9 (64)		
Image analysis results	**Baseline**	**2 years**	**Δ2-year**
X-ray JSW (mm)	1.7 (1.9)	2.7 (1.6)	1.1 (1.3)
MRI cartilage thickness (mm)	2.0 (0.9)	2.2 (0.9)	0.2 (0.3)
3D CT JSW (mm)	4.4 (1.0)	4.6 (0.8)	0.2 (0.8)
2D CT JSW (mm)	4.2 (1.5)	4.2 (1.5)	0.0 (1.6)

Mean and standard deviation or n (%) are given. BMI: body mass index;; JSW: joint space width.

Correlations

The cross-sectional correlations between all 4 techniques, of the baseline and 2-year values combined, are shown in Figure 3. The scatterplot matrix (left panel) shows that correlations were present between all techniques, as confirmed by the Pearson *R* and *p*-values (right panel). All correlations were statistically significant (all $p<0.023$) and most were moderate or strong, with 2D CT and 3D CT showing a very strong correlation.



B

Correlations

		X-ray	MRI	3D CT	2D CT
X-ray	Pearson Correlation		.791**	.598**	.432*
	Sig. (2-tailed)		**.000**	**.001**	**.022**
MRI	Pearson Correlation	.791**		.733**	.541**
	Sig. (2-tailed)	**.000**		**.000**	**.003**
3D CT	Pearson Correlation	.598**	.733**		.806**
	Sig. (2-tailed)	**.001**	**.000**		**.000**
2D CT	Pearson Correlation	.432*	.541**	.806**	
	Sig. (2-tailed)	**.022**	**.003**	**.000**	

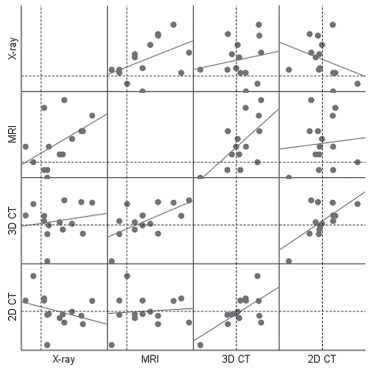
**. Correlation is significant at the 0.01 level (2-tailed).

*. Correlation is significant at the 0.05 level (2-tailed).

Figure 3: Cross-sectional correlations of combined baseline and 2-year values for all 4 techniques, displayed (A) visually as a scatterplot matrix and (B) with Pearson *R* and *p*-values. The dotted line in (A) indicates the origin (0). Bold *p*-values indicate statistical significance ($p<0.05$).

The correlations between the 2-year changes of all 4 techniques are shown in Figure 4. It can be seen in the scatterplot matrix that between most techniques, a clear correlation was absent. This was confirmed by the Pearson *R* and *p*-values.

A



B

Correlations

		X-ray	MRI	3D CT	2D CT
X-ray	Pearson Correlation	1	.484	.179	-.321
	Sig. (2-tailed)		.080	.541	.262
MRI	Pearson Correlation	.484	1	.619*	.087
	Sig. (2-tailed)	.080		**.018**	.767
3D CT	Pearson Correlation	.179	.619*	1	.651*
	Sig. (2-tailed)	.541	**.018**		**.012**
2D CT	Pearson Correlation	-.321	.087	.651*	1
	Sig. (2-tailed)	.262	.767	**.012**	

*. Correlation is significant at the 0.05 level (2-tailed).

Figure 4: Correlations of 2-year changes over time for all 4 techniques, displayed (A) visually as a scatterplot matrix and (B) with Pearson *R* and *p*-values. The dotted line indicates the origin (0). Bold *p*-values indicate statistical significance ($p<0.05$).

The change in radiographic (plain x-ray) mean JSW was not statistically significantly correlated with any of the other techniques, including the change in 2D CT JSW (Δ2D CT; correlation R=-0.321 and p=0.262) and the change in MRI cartilage thickness (ΔMRI; correlation R=0.484 and p=0.080). There was a statistically significant, strong correlation between the change in 3D CT median JSW (Δ3D CT) and Δ2D CT mean JSW (R=0.651; p=0.012) and between Δ3D CT JSW and ΔMRI cartilage mean thickness (R=0.619; p=0.018). None of the other correlations were statistically significant. In Figure 5 these Pearson *R* and *p*-values have been added to the triangle of imaging techniques as depicted in Figure 1.

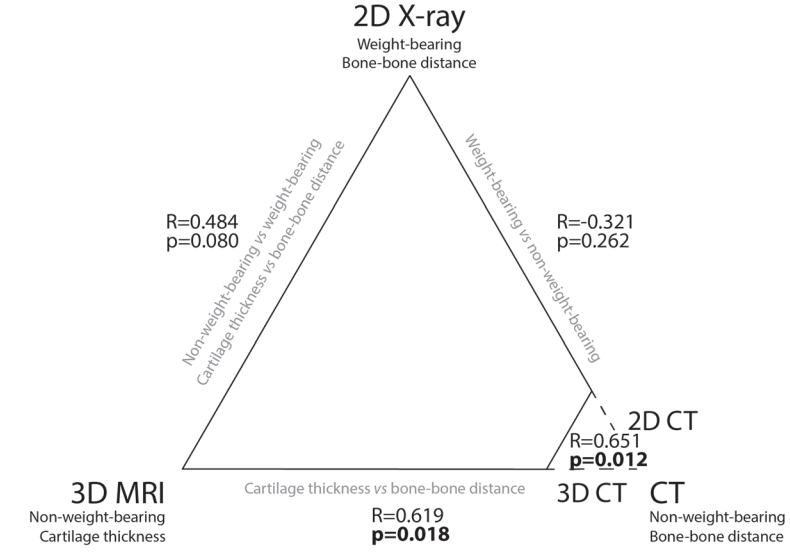


Figure 5: The 3 different imaging methods used for (in)direct cartilage quantification. The key characteristics are listed underneath each modality, and key differences between modalities are displayed in gray. For CT, both 3D and 2D joint space width measurements were used, for comparison with MRI and radiography respectively. Correlations (Pearson *R* and *p*-values) of the 2-year changes are shown between the techniques.

Discussion

Although cross-sectional evaluation provided a statistically significant correlation between plain radiographic mean JSW (bone-to-bone distance) and MRI surface mean cartilage thickness, no statistically significant correlation between these measures was found when evaluating the relatively small changes over 2 years follow-up. Similarly, there was no significant correlation between the 2-year change in plain radiographic mean JSW and 2D CT mean JSW, whereas cross sectional evaluation provided such a correlation. In contrast, the 2-year change in MRI surface mean cartilage thickness correlated strongly with 3D CT surface median bone-to-bone distance. Also, the 3D CT surface median JSW correlated strongly with the 2D mean JSW.

From this it is concluded that non-weight-bearing image acquisitions, independent of using evaluation of bone-to-bone distance measurements (CT) or cartilage thickness measurements (MRI), result in significant correlations between outcomes. In contrast, when a weight-bearing imaging technique (plain radiography) is compared to non-weight-bearing imaging techniques (MRI and CT) the correlation is lacking. It can therefore be concluded that weight-bearing image acquisition provides an independent characteristic of cartilage, that is not observed by non-weight-bearing techniques. Deformability of the cartilage (cartilage quality) may be involved in addition to the quantitative measurement of cartilage thickness. The position and morphology of the meniscus may also play a role, although visually scored meniscal extrusion (grade 0–3) did not seem to significantly influence the longitudinal correlation in this group of patients (data not shown).

The significant correlations found between the different imaging techniques when evaluating cross-sectional data, whereas such correlations are lost in case of relating more subtle changes in cartilage quantitative measures during (2-year) follow-up, fits the inconclusive literature on this topic.[14–21]

With the exception of radiographic JSW, the 2-year changes over time in our study were much smaller than the absolute baseline or 2-year values (at least 1 order of magnitude decrease), while the standard deviations stayed roughly the same (Table 1). Apparently, correlations are lost when weight-bearing image acquisition is compared to non-weight-bearing acquisition in case of small changes (over time), whereas they are maintained when bone-to-bone distance is compared to cartilage thickness in a 2D or 3D manner when the image acquisition is non-weight-bearing.

This argues for the use of weight-bearing image acquisition, such as weight-bearing CT or weight-bearing MRI. Both these techniques have been researched and have shown positive results, but use of both is mostly limited to research settings.[34–36] To further investigate the objectives of our study, a rotatable MRI scanner would be a valuable tool, since both cartilage thickness and JSW can be measured in weight-bearing and non-weight-bearing position using

the exact same imaging technique. Results of such future studies could help to better relate results obtained from MRI scans and radiographs to monitor OA progression or treatment response. An important consideration in using weight-bearing CT or MRI is that using such approaches need thorough concern of the relative contribution of weight and cartilage deformability. Also, the actual weight-bearing relative to the contra-lateral leg in case of uneven load distribution as well as preacquisition weight-bearing or exercise is a parameter to consider in such a study.[37]

A limitation of our study is the relatively small sample size, as only 14 of the originally 20 complete data sets were available. As a sensitivity analysis, the 2 patients that were excluded because of MRI motion artifacts were included in the evaluation of radiographic JSW, 2D CT JSW and 3D CT JSW. The significance of the correlations between these 3 techniques for these 16 patients did not change compared to the (for all images complete) dataset of 14 patients, neither for absolute (cross-sectional) values nor for changes over time. Also, scatterplot matrices of all calculated correlations were included, because *p*-values may be less conclusive in this small number of patients. Clearly the scatterplot matrices support the conclusions based on the Pearson *R* and *p*-values. Irrespectively, the present study is a post-hoc analysis and exploratory. More research with larger data sets, preferable using weight-bearing CT or MRI as additional variables, would validate the conclusion.

Another limitation of our study is that knee flexion is not taken into account. The weight-bearing radiographs are performed under slight flexion of the knee (7–10°). MRI and CT scans are not performed under a specific angle, but normally the leg is extended for as much as is allowed by, for example, a patient's possible extension limitation or the hardware setup. Although the 3D imaging techniques provide a mean or median surface value, the 2D rendering of the 3D CT has a potential knee flexion angle difference as compared to the plain radiograph. This difference might have influenced the correlation between both techniques and the effect of different knee flexion could be included in future research as well.

In conclusion, the cause of the generally weak correlation between changes in radiographic JSW and MRI cartilage thickness appears to primarily be the difference in weight-bearing conditions during imaging, and less so the difference in measuring bone-to-bone distance *versus* cartilage thickness directly. Further research on the effects of weight-bearing on cartilage thickness measurements is warranted and might provide an indirect measure for cartilage deformability in case of quantitative measurements, in addition to the measured thickness.

References

1. Buckwalter JA, Martin JA. Osteoarthritis. Advanced Drug Delivery Reviews. 2006 May 20;58(2):150–67.
2. Vignon E, Piperno M, Le Graverand MPH, *et al*. Measurement of radiographic joint space width in the tibiofemoral compartment of the osteoarthritic knee: Comparison of standing anteroposterior and Lyon schuss views. Arthritis and Rheumatism. 2003 Feb 1;48(2):378–84.
3. Buckland-Wright JC, Macfarlane DG, Lynch JA, *et al*. Joint space width measures cartilage thickness in osteoarthritis of the knee: High resolution plain film and double contrast macroradiographic investigation. Annals of the Rheumatic Diseases. 1995 Apr 1;54(4):263–8.
4. Kothari M, Guermazi A, von Ingersleben G, *et al*. Fixed-flexion radiography of the knee provides reproducible joint space width measurements in osteoarthritis. European Radiology. 2004 Sep 19;14(9):1568–73.
5. Piperno M, Hellio M-P, Graverand L, *et al*. Quantitative evaluation of joint space width in femorotibial osteoarthritis: Comparison of three radiographic views. Osteoarthritis and Cartilage. 1998 Jul;6(4):252–9.
6. Chan WP, Huang GS, Hsu SM, *et al*. Radiographic joint space narrowing in osteoarthritis of the knee: Relationship to meniscal tears and duration of pain. Skeletal Radiology. 2008 Oct 2;37(10):917–22.
7. Hunter DJ, Zhang YQ, Tu X, *et al*. Change in joint space width: Hyaline articular cartilage loss or alteration in meniscus? Arthritis and Rheumatism. 2006 Aug;54(8):2488–95.
8. Roth M, Emmanuel K, Wirth W, *et al*. Sensitivity to change and association of three-dimensional meniscal measures with radiographic joint space width loss in rapid clinical progression of knee osteoarthritis. European Radiology. 2018 May 1;28(5):1844–53.
9. Roth M, Wirth W, Emmanuel K, *et al*. The contribution of 3D quantitative meniscal and cartilage measures to variation in normal radiographic joint space width – Data from the Osteoarthritis Initiative healthy reference cohort. European Journal of Radiology. 2017 Feb 1;87:90–8.
10. Blumenkrantz G, Majumdar S. Quantitative magnetic resonance imaging of articular cartilage in osteoarthritis. European Cells and Materials. 2007 May;13:76–86.
11. Eckstein F, Cicuttini F, Raynauld JP, *et al*. Magnetic resonance imaging (MRI) of articular cartilage in knee osteoarthritis (OA): Morphological assessment. Osteoarthritis and Cartilage. 2006 Jan 1;14(suppl. 1):46–75.
12. Cotofana S, Eckstein F, Wirth W, *et al*. In vivo measures of cartilage deformation: Patterns in healthy and osteoarthritic female knees using 3T MR imaging. European Radiology. 2011 Jun;21(6):1127–35.
13. Gudbergsen H, Lohmander LS, Jones G, *et al*. Correlations between radiographic assessments and MRI features of knee osteoarthritis – A cross-sectional study. Osteoarthritis and Cartilage. 2013 Apr 1;21(4):535–43.
14. Lonza GC, Gardner-Morse MG, Vacek PM, *et al*. Radiographic-based measurement of tibiofemoral joint space width and magnetic resonance imaging derived articular cartilage thickness are not related in subjects at risk for post traumatic arthritis of the knee. Journal of Orthopaedic Research. 2019 May 1;37(5):1052–8.
15. Segal NA, Frick E, Duryea J, *et al*. Correlations of medial joint space width on fixed-flexed standing computed tomography and radiographs with cartilage and meniscal morphology on magnetic resonance imaging. Arthritis Care and Research. 2016 Oct 1;68(10):1410–6.
16. Cicuttini F, Hankin J, Jones G, *et al*. Comparison of conventional standing knee radiographs and magnetic resonance imaging in assessing progression of tibiofemoral joint osteoarthritis. Osteoarthritis and Cartilage. 2005 Aug 1;13(8):722–7.
17. Raynauld JP, Martel-Pelletier J, Berthiaume MJ, *et al*. Long term evaluation of disease progression through the quantitative magnetic resonance imaging of symptomatic knee osteoarthritis patients: Correlation with clinical symptoms and radiographic changes. Arthritis Research and Therapy. 2005 Dec 30;8(1):R21.
18. Pierre Raynauld J-, Martel-Pelletier J, Berthiaume M-J, *et al*. Quantitative magnetic resonance imaging

evaluation of knee osteoarthritis progression over two years and correlation with clinical symptoms and radiologic changes. Arthritis and Rheumatism. 2004 Feb 1;50(2):476–87.

19. Duryea J, Neumann G, Niu J, *et al*. Comparison of radiographic joint space width with magnetic resonance imaging cartilage morphometry: Analysis of longitudinal data from the osteoarthritis initiative. Arthritis Care and Research. 2010 Feb 23;62(7):932–7.
20. Bruyere O, Genant H, Kothari M, *et al*. Longitudinal study of magnetic resonance imaging and standard X-rays to assess disease progression in osteoarthritis. Osteoarthritis and Cartilage. 2007 Jan 1;15(1):98–103.
21. Jansen MP, Boymans TAEJ, Custers RJH, *et al*. Knee joint distraction as treatment for osteoarthritis results in clinical and structural benefit: A systematic review and meta-analysis of the limited number of studies and patients available. Cartilage. 2020 Jul 22;194760352094294.
22. Jansen MP, Maschek S, van Heerwaarden RJ, *et al*. Changes in cartilage thickness and denuded bone area after knee joint distraction and high tibial osteotomy – Post-hoc analyses of two randomized controlled trials. Journal of Clinical Medicine. 2021 Jan 19;10(2):368.
23. van der Woude JAD, Wiegant K, van Roermund PM, *et al*. Five-year follow-up of knee joint distraction: Clinical benefit and cartilaginous tissue repair in an open uncontrolled prospective study. Cartilage. 2017;8(3):263–71.
24. van der Woude JAD, Wiegant K, van Heerwaarden RJ, *et al*. Knee joint distraction compared with high tibial osteotomy: A randomized controlled trial. Knee Surgery, Sports Traumatology, Arthroscopy. 2017;25(3):876–86.
25. van der Woude JAD, Wiegant K, van Heerwaarden RJ, *et al*. Knee joint distraction compared with total knee arthroplasty: A randomised controlled trial. Bone and Joint Journal. 2017;99-B(1):51–8.
26. Jansen MP, van der Weiden GS, van Roermund PM, *et al*. Initial tissue repair predicts long-term clinical success of knee joint distraction as treatment for knee osteoarthritis. Osteoarthritis and Cartilage. 2018;26(12):1604–8.
27. Jansen MP, Besselink NJ, van Heerwaarden RJ, *et al*. Knee joint distraction compared with high tibial osteotomy and total knee arthroplasty: Two-year clinical, radiographic, and biochemical marker outcomes of two randomized controlled trials. Cartilage. 2019 Feb 13;194760351982843.
28. Jansen MP, Mastbergen SC, van Heerwaarden RJ, *et al*. Knee joint distraction in regular care for treatment of knee osteoarthritis: A comparison with clinical trial data. PLOS ONE. 2020 Jan 22;15(1).
29. Buckland-Wright JC, Ward RJ, Peterfy C, *et al*. Reproducibility of the semiflexed (metatarsophalangeal) radiographic knee position and automated measurements of medial tibiofemoral joint space width in a multicenter clinical trial of knee osteoarthritis. Journal of Rheumatology. 2004 Aug;31(8):1588–97.
30. Buckland-Wright JC, Wolfe F, Ward RJ, *et al*. Substantial superiority of semiflexed (MTP) views in knee osteoarthritis: a comparative radiographic study, without fluoroscopy, of standing extended, semiflexed (MTP), and schuss views. Journal of Rheumatology. 1999 Dec;26(12):2664–74.
31. Marijnissen ACA, Vincken KL, Vos PAJM, *et al*. Knee Images Digital Analysis (KIDA): A novel method to quantify individual radiographic features of knee osteoarthritis in detail. Osteoarthritis and Cartilage. 2008 Feb 1;16(2):234–43.
32. Wirth W, Eckstein F. A technique for regional analysis of femorotibial cartilage thickness based on quantitative magnetic resonance imaging. IEEE Transactions on Medical Imaging. 2008 Jun;27(6):737–44.
33. Evans JD. Straightforward statistics for the behavioral sciences. 1st ed. Pacific Grove: Pacific Grove: Brooks/ Cole Pub. Co.; 1996. p146.
34. Bruno F, Barile A, Arrigoni F, *et al*. Weight-bearing MRI of the knee: A review of advantages and limits. Acta Biomedica. 2018 Jan 1;89(Suppl 1):78–88.

35. Lintz F, Netto C de C, Barg A, *et al*. Weight-bearing cone beam CT scans in the foot and ankle. EFORT Open Reviews. 2018 May 1;3(5):278–86.

36. Tuominen EKJ, Kankare J, Koskinen SK, *et al*. Weight-bearing CT imaging of the lower extremity. American Journal of Roentgenology. 2013 Jan 14;200(1):146–8.

37. Kersting UG, Stubendorff JJ, Schmidt MC, *et al*. Changes in knee cartilage volume and serum COMP concentration after running exercise. Osteoarthritis and Cartilage. 2005 Oct 1;13(10):925–34.

CHAPTER 13

Knee joint distraction results in MRI cartilage thickness increase up to ten years after treatment

M.P. Jansen
S.C. Mastbergen
J.W. MacKay
T.D. Turmezei
F.P.J.G. Lafeber

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Abstract

Background: Knee joint distraction (KJD) has shown long-term clinical improvement and short-term cartilage restoration in young osteoarthritis (OA) patients. The current objective was to evaluate MRI cartilage thickness up to 10 years after KJD treatment, using a 3-dimensional surface-based approach.

Methods: Twenty end-stage knee OA patients were treated with KJD. 1.5T MRI scans were performed before and at 1, 2, 5, 7, and 10 years after treatment. Tibia and femur cartilage segmentation and registration to a canonical surface were performed semi-automatically. Statistical parametric mapping (SPM) with linear mixed models was used to analyze whole-joint changes. The influence of baseline patient characteristics was analyzed with SPM using linear regression. Relevant weight-bearing parts of the femur were selected to obtain the average cartilage thickness in the femur and tibia of the most (MAC) and least affected compartment (LAC). These compartmental changes over time were analyzed using repeated measures ANOVA; missing data was imputed. In all cases, $p<0.05$ was considered statistically significant.

Results: One- and 2-years post-treatment, cartilage in the MAC weight-bearing region was significantly thicker than pre-treatment, gradually thinning after 5 years, but still increased at 10 years post-treatment. Long-term results showed areas in the LAC were significantly thicker than pre-treatment. Male sex and more severe OA at baseline somewhat predicted short-term benefit ($p>0.05$). Compartmental analyses showed significant short- and long-term thickness increase in the tibia and femur MAC (all $p<0.05$).

Conclusion: KJD results in significant short- and long-term cartilage regeneration, up to 10 years post-treatment.

Introduction

End-stage knee osteoarthritis (OA) is often treated with a total knee arthroplasty (TKA), which generally shows improvement in knee pain and function.[1] However, in younger patients (<65 years), TKA treatment brings an increased risk of a complex and costly revision surgery later in life.[2] In these patients, a joint-preserving treatment could postpone a first TKA and possibly prevent a future revision surgery. One such joint-preserving surgical treatment is knee joint distraction (KJD). In distraction surgery, the 2 bony ends of a joint are temporarily placed at a small distance from each other by an external frame, which is fixed to the bones with bone pins.[3] KJD has been evaluated in a limited number of clinical studies, including 2 randomized controlled trials, where the treatment has shown good results comparable to those after alternative surgical treatments (TKA and high tibial osteotomy).[4–10] KJD has also been applied in regular care, where it has shown clinical improvement as well.[11] Besides clinical effects, cartilage restoration activity was demonstrated on radiographs and MRI scans, especially in the first 2 years after treatment.[12–16] The first long-term clinical analyses showed beneficial results up to 9 years after treatment, and MRI scans up to 5 years after treatment showed better results in patients treated with KJD than in untreated OA patients from the osteoarthritis initiative (OAI).[14,15] However, despite the many studies that have been performed, MRI scans have not been evaluated long-term more than 5 years after KJD. The objective of this study was to evaluate MRI cartilage thickness up to 10 years after KJD treatment, looking not only at (sub)regional cartilage thickness measurements, but primarily at the whole articular area in 3D using a surface-based approach.[17]

Methods

Patients

Between 2006 and 2008, 20 patients with end-stage knee OA were included in an open prospective study. Inclusion criteria were age <60 years old, Visual Analogue Scale of pain ≥60 mm, radiographic signs of joint damage, and primarily tibiofemoral OA. Exclusion criteria were severe symptoms in both knees, history of inflammatory or septic arthritis, and severe malalignment (>10°). Patients were in regular care indicated for TKA surgery but treated with KJD instead because of their young age.

KJD treatment was performed using an external fixation frame consisting of 2 monotubes (Stryker), fixed to the femur and tibia on the lateral and medial side of the joint with 4 pairs of bone pins. The joint was distracted 2 mm at surgery, and gradually extended by 1 mm per day over the next 3 days until 5 mm distraction was reached, confirmed radiographically. After full distraction was completed, patients were discharged from the hospital, and encouraged to load the distracted joint, using crutches if necessary. After 2 months, the frame and pins were

removed under anesthesia, after which patients were discharged the same day, without further imposed rehabilitation protocol.

The study was approved by the medical ethical review committee of the University Medical Center Utrecht (04/086). All patients gave written informed consent. As the current study was initiated long ago, patients were not included in the design of or recruitment to the study. However, in the past years a patient council was established and multiple meetings with KJD patients have been held, with the purpose of directly involving patients in research and gathering their input on the treatment and related research. Patients from all our OA research, including the current study, receive newsletters with updates on study results.

MRI analyses

1.5T MRI scans including a coronal 3D spoiled gradient recalled echo sequence with fat suppression (SPGR-fs) were acquired shortly before and at 1, 2, 5, 7, and 10 years after surgical treatment. A slice thickness of 1.5 mm, repetition time of 20 ms, echo time of 9 ms, flip angle of 15 degrees, acquisition matrix of 512x512 pixels, and pixel size of 0.31x0.31 mm were used. Images were imported into Stradview v6.0 (University of Cambridge Department of Engineering, Cambridge, UK, in-house developed software freely available at https://mi.eng.cam.ac.uk/Main/StradView), which was used for semi-automatic cartilage segmentation. Initial contours were drawn manually for the tibia and femur every 5 slices, from which a 3D isosurface was generated for the 2 bones separately. The inner and outer cartilage surfaces were measured automatically in every slice and checked manually. Data sampled along a vector at the normal to each vertex of the surface on the cartilage patches was used to calculate the distance between the inner and outer surface and with that obtain the cartilage thickness at each vertex via model-based deconvolution. This process was performed for every scan for patches of the femur, medial and lateral tibia separately, and has previously been described in more detail.[17]

The outer surface of all obtained patches were registered to representative canonical surfaces using an initial similarity transformation and subsequent thin-plate spline registration, performed in wxRegSurf v18 (University of Cambridge Department of Engineering, Cambridge, UK, in-house developed software freely available at http://mi.eng.cam.ac.uk/~ahg/wxRegSurf/) to allow comparing patches from multiple scans.

Initial analyses focused on the whole joint (patches). To analyze the average cartilage thickness on both sides of the joint separately, relevant medial and lateral weight-bearing parts of the femur were selected (cut out) from the canonical surface (and thus applied identically in all patients and time points) in wxRegSurf (Supplementary Figure S1). An average cartilage thickness for both the femur and tibia on both sides of the joint could be generated by averaging the thickness values of all vertices in the 4 parts separately.

Statistical analyses

Whole-joint analyses

MATLAB R2020a and the SurfStat MATLAB package (https://www.math.mcgill.ca/keith/surfstat/, modified for this specific application by Graham Treece of the University of Cambridge) were used for whole-joint, vertex-wise data analysis and visualization. The average cartilage thickness was displayed for each time point separately by averaging data of all available patients at each specific time point. Statistical parametric mapping (SPM) was used for analysis of changes over time. SPM uses all subject values at each vertex for testing between time points and delivers *p*-values corrected for multiple comparisons.[18] For differences at each follow-up moment compared to baseline, SPM with linear mixed models was used. The influence of baseline patient characteristics on the changes over time was also analyzed with SPM, using a separate linear regression model for each different patient characteristic and its influence on short-term (2-year) and long-term (ten-year) changes. In all cases, a threshold p-value <0.05 was considered statistically significant. Since KJD has previously shown significant results mostly in the patients' most affected compartment (MAC), patients were separated in 2 groups based on whether their MAC was the medial or lateral compartment.

Compartmental analyses

For each time point, the average cartilage thickness was calculated for the medial and lateral femur and tibia. Instead of analyzing changes over time for the medial and lateral side areas, changes over time were analyzed for the MAC (either medial of lateral) and least affected compartment (LAC; either lateral or medial). As such, the 4 different compartments analyzed at each time point were the MAC and LAC femur and tibia. Compartmental statistical analyses were performed in IBM SPSS Statistics 25. In case of missing data over the entire 10 years, for the statistical compartmental analyses (not for the whole-joint surface-based analyses) multiple imputation was performed for each compartment separately for all patients; missing data was replaced by the average of 5 imputations considering the data available before loss of follow-up data. This was considered valid, as previous data have shown that those patients that underwent arthroplasty after several years within the 10-year follow-up period had no significant change in clinical or structural radiographic outcome shortly before arthroplasty.[15] As a sensitivity analysis for imputation validity, patients with complete data sets were analyzed separately. Changes over time were analyzed using repeated measures ANOVA. Additionally, as patients filled out the Western Ontario McMaster Osteoarthritis Index (WOMAC) at the same time points MRI scans were performed, the influence of compartmental cartilage thickness changes over time on the change in total WOMAC over time was analyzed using linear mixed models, with total WOMAC as outcome variable, a random intercept at patient level and fixed effects of time and compartmental cartilage thickness. In case the cartilage thickness change in a compartment had a statistically significant influence, its influence on the change in WOMAC

subscales (pain, function and stiffness) was analyzed in separate models as well. In all cases, a *p*-value <0.05 was considered statistically significant.

Results

Patients

All 20 patients were treated successfully; their characteristics are summarized in Table 1.

Table 1: Patient characteristics

	KJD patients (n=20)
Age (years)	48.5 (5.7)
BMI (kg/m^2)	29.6 (3.5)
Male sex, n (%)	11 (55)
Kellgren- Lawrence grade, n (%)	
- Grade 0	0 (0)
- Grade 1	1 (5)
- Grade 2	3 (15)
- Grade 3	15 (75)
- Grade 4	1 (5)
Medial MAC, n (%)	18 (90)

Mean and standard deviation or n (%) are given. BMI: body mass index; KJD: knee joint distraction; MAC: most affected compartment.

No patients were lost to follow-up in the first 2 years. Between 2 and 5 years of follow-up, 3 patients were lost: 1 patient underwent a TKA; 2 patients underwent arthroscopy. Between 5 and 7 years, 5 patients were lost: 4 underwent TKA surgery; 1 refused further follow-up. Between 7 and 10 years, 4 patients were lost, all because of TKA surgery.

Whole-joint changes

The average cartilage thickness for the femur and the (medial and lateral) tibia of the 18 patients with a medial MAC are shown in Figure 1. The cartilage on the medial side of both the femur and tibia was thinner than the lateral side, as indicated by the red *versus* green-blue color. One and 2 years post-treatment, the cartilage in the medial weight-bearing region was on average thicker than pre-treatment (diminishing red intensity). Effects were clear at both the femur and tibia. After 2 years, the average medial cartilage thickness seemed to gradually decrease, though even at 10 years this did not yet seem lower than before treatment. On the lateral side, the cartilage thickness seemed to increase as well, especially long-term (increasing blue intensity). The average cartilage results for the 2 patients with a lateral MAC are shown in Supplementary Figure S2; these patients showed similar results, with the biggest changes seen on the lateral side of the joint.

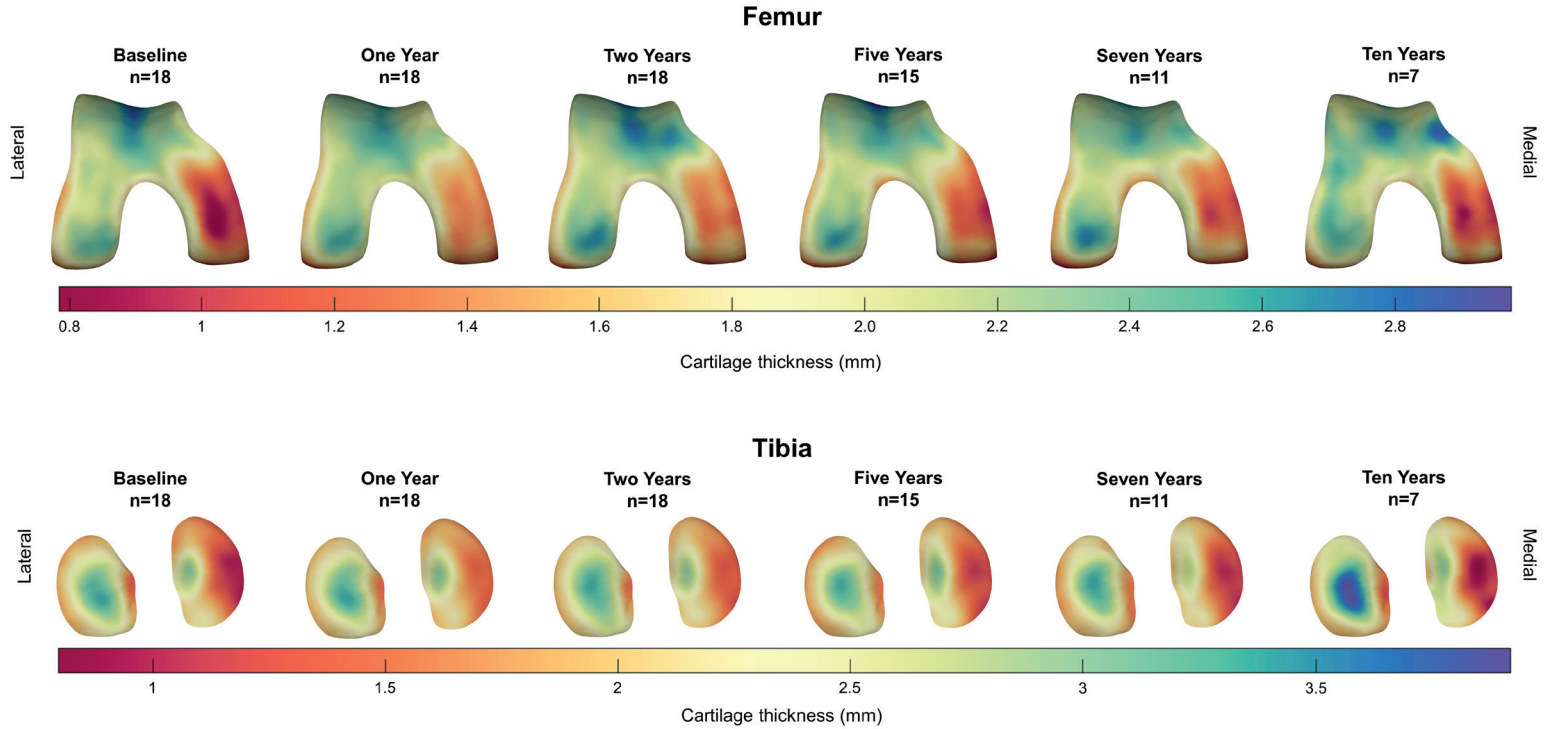


Figure 1: The average cartilage thickness of all patients whose medial compartment was the most affected, at baseline (n=18) and 1 (n=18), 2 (n=18), 5 (n=15), 7 (n=11) and 10 (n=7) years after treatment with knee joint distraction. Results are displayed on average right femur and tibia articular cartilage surfaces. The color range is based on the minimum and maximum average values of the femur (0.78–3.00) and tibia (0.80–3.92) separately.

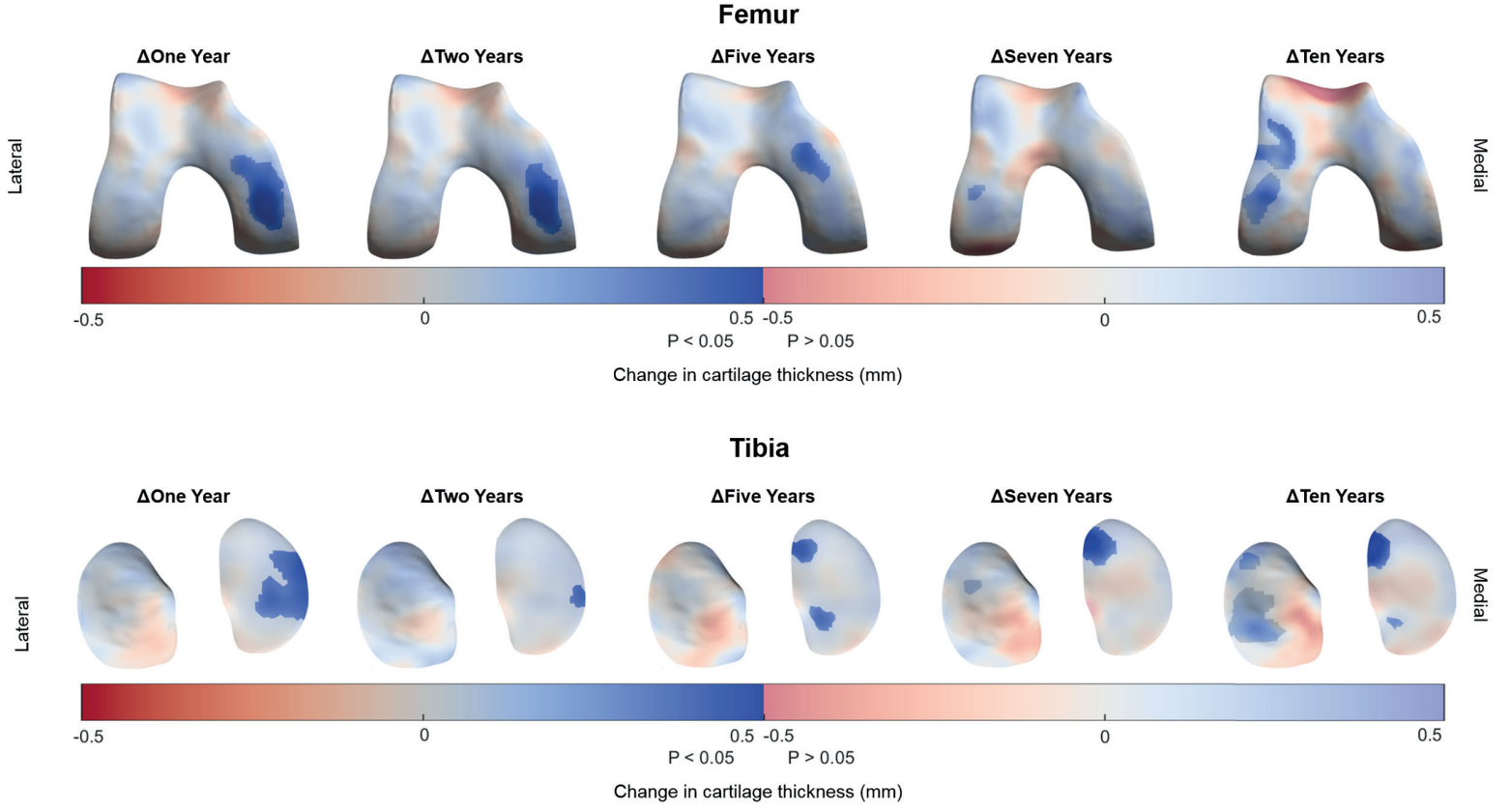


Figure 2: The change in cartilage thickness compared to baseline, for all patients whose medial compartment was the most affected, after 1 (n=18), 2 (n=18), 5 (n=15), 7 (n=11) and 10 (n=7) years after treatment with knee joint distraction. Statistically significant changes are indicated by the darker color map (p<0.05) while non-significant areas are shown with faded colors (p>0.05). Blue indicates an increase and red a decrease in cartilage thickness compared to baseline. Results are viewed on average right femur and tibia articular cartilage surfaces.

Changes in cartilage thickness compared to baseline for all patients with a medial MAC are shown in Figure 2. As indicated by the dark blue areas, the initial increase in medial cartilage thickness was largely statistically significant after 1 year and, especially for the femur, at 2 years. The medial tibia showed some smaller significantly thicker areas up to 10 years after treatment. Long-term results showed that areas in the lateral (least affected) compartment were significantly thicker than before treatment in both the femur and tibia. These statistical tests were not performed for patients with a lateral MAC, because of the small number of patients (n=2).

Compartmental changes

Figure 3 shows the results per compartment of the joint for all patients combined (for 18 of whom the MAC was the medial side and for 2 the lateral side). Both the MAC femur and tibia showed a significant increase over the 10-year period after treatment (both $p<0.02$), while the LAC femur and tibia did not (both $p>0.2$).

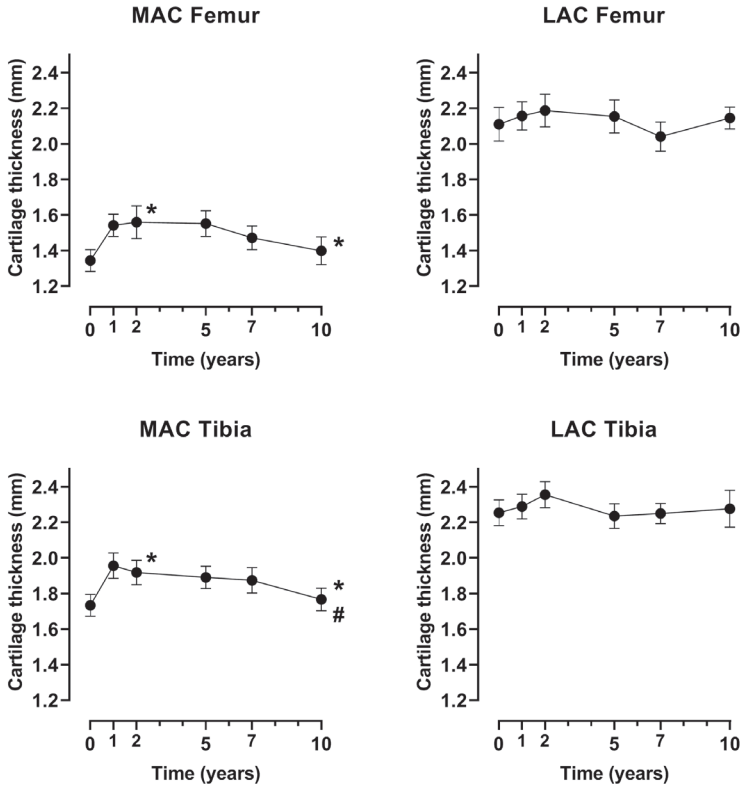


Figure 3: Change over time for the 4 compartments. Missing data was imputed (n=20 on all time points). * indicates significant ($p<0.05$) changes up until that time point from baseline: from baseline to 2 years and from baseline to 10 years. # indicates significant ($p<0.05$) changes from 2 years to 10 years. Mean and standard error are shown. LAC; least affected compartment; MAC: most affected compartment.

As for the whole-joint analyses, cartilage thickness of the 4 compartments showed a biphasic response after treatment: an initial cartilage prompt regeneration phase up to 2 years, statistically significant for MAC femur (baseline 1.3 (SD 0.3) – 2 years 1.6 (0.4); p=0.010) and MAC tibia (1.7 (0.3) – 1.9 (0.3); p=0.016), and a gradual degeneration phase between 2 and 10 years, statistically significant for MAC tibia (ten years 1.8 (0.3); p=0.044) but not the MAC femur (ten years 1.4 (0.3); p=0.072). The LAC femur (2.1 (0.4) – 2.2 (0.4); p=0.343) and LAC tibia (2.2 (0.3) – (2.4 (0.3); p=0.058) showed the same trend of an increase in the first 2 years, with some more variation in the years afterwards (both p>0.1). Since the MAC compartments clearly show lower cartilage thickness values even at baseline, Supplementary Figure S3 displays the compartmental cartilage thickness over time using separate Y-axis ranges for the subfigures, to better visualize the changes that occur in each compartment. The mean and 95% confidence interval (95%CI) of all data points are shown in Supplementary Table S1.

Because this analysis was performed with imputed data, a sensitivity analysis was performed only including the 8 patients with full data sets. Results are shown in Supplementary Figure S4, showing the same biphasic response.

Influence of baseline parameters

The influence of baseline parameters on the whole-joint 2- and 10-year changes are shown in Figure 4 for all patients with a medial MAC. Over the short-term (2 years), a higher age, lower BMI, male sex and a higher Kellgren-Lawrence grade seemed to result in a higher medial cartilage thickness increase. It should be noted 75% of patients had Kellgren-Lawrence grade 3, however, so these results are based on only a very small number of patients. Long-term results (ten years) generally showed the opposite, although for sex and Kellgren-Lawrence grade it is important to note that at 10 years only 1 female patient was left with grade 2 and 6 male patients all with grade 3. None of the results were statistically significant, although especially male sex and higher Kellgren-Lawrence grade seemed to have some positive influence on the 2-year change in the medial compartment.

Influence on clinical outcome

The influence of the compartmental cartilage thickness changes over time on the change in total WOMAC is shown in Table 2. As indicated, the 2-year cartilage thickness change did not have a significant influence on the 2-year change in total WOMAC for any of the compartments. However, the 10-year LAC tibia thickness change had a statistically significant influence on the 10-year total WOMAC change (p=0.031) with a relatively large effect estimate: 1 mm cartilage thickness increase could result in 24 points of total WOMAC increase. Looking at the WOMAC subscales separately, the 10-year LAC tibia thickness increase had a significant influence only on the WOMAC function scale (p=0.030; effect estimate 24.93 (95%CI 2.57–47.30)) but not on the other subscales (both p>0.05), although effect estimates were still relatively large (both >17.09).

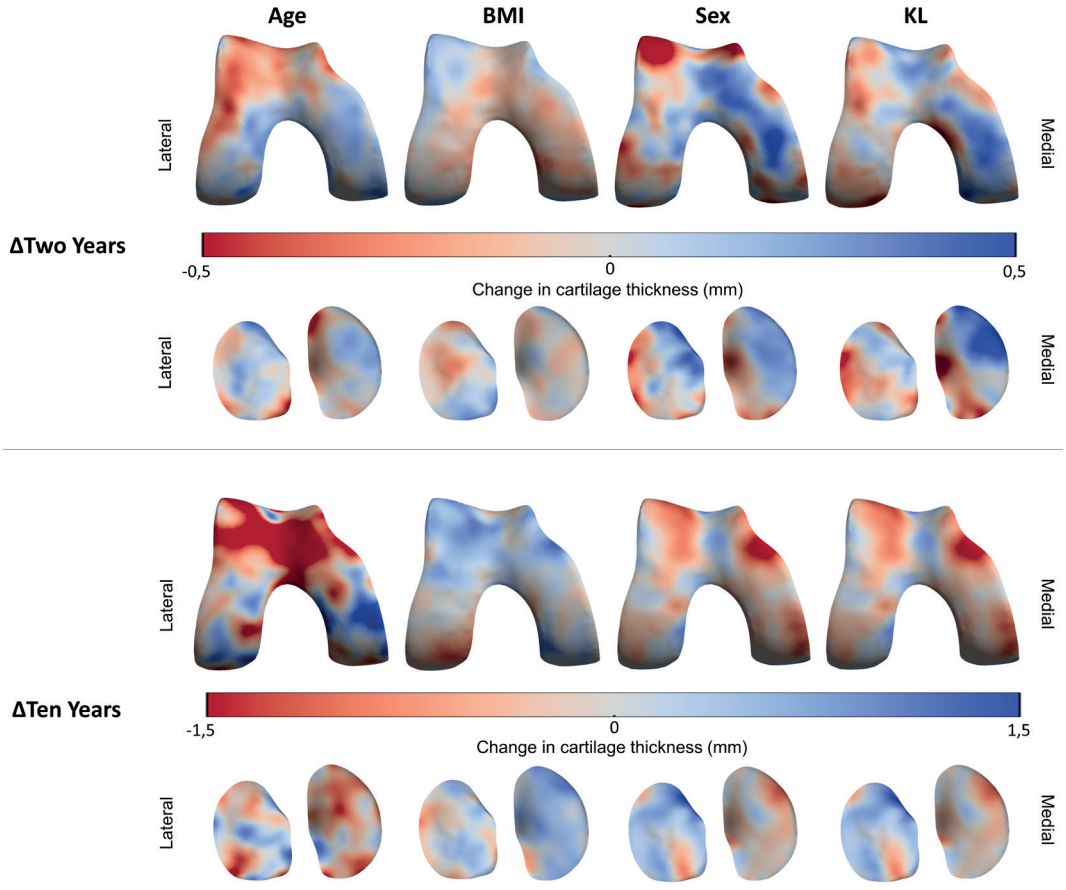


Figure 4: Influence of baseline parameters on the whole-joint 2-year (n=18) and 10-year (n=7) changes, for all patients with a medial most affected compartment. For continuous parameters (age and BMI) the color map indicates the change per standard deviation increase; for sex the color map indicates male sex compared to female sex; for Kellgren-Lawrence (KL) grade the color map indicates the change per category increase.

Table 2: Influence of cartilage changes on total WOMAC change

	Change over 2 years		Change over 10 years	
	Effect estimate	***P*-value**	**Effect estimate**	***P*-value**
MAC femur	-6.64 (-25.16 to 11.89)	0.476	1.28 (-16.11 to 18.67)	0.884
LAC femur	-4.16 (-22.72 to 14.40)	0.652	2.48 (-16.11 to 21.07)	0.789
MAC tibia	5.50 (-13.32 to 24.26)	0.562	4.79 (-13.76 to 23.35)	0.609
LAC tibia	13.16 (-8.64 to 34.97)	0.228	24.00 (2.29 to 45.69)	0.031

Estimates and 95% confidence interval are given. LAC: least affected compartment; MAC: most affected compartment.

Discussion

Ten years after treatment with KJD, in patients who did not convert to TKA, the beneficial effects of this treatment still appear visible, even in this relatively small cohort. In these end-stage knee OA patients, KJD treatment resulted in significant short-term (1 to 2 years) cartilage regeneration in the most affected compartment. While after 2 years this initial gain in cartilage thickness is gradually lost, 10 years after treatment the cartilage remains thicker than before treatment. This is seen in the whole-joint changes as indicated in Figure 1, but also compartmentally as seen in Figure 3 and Supplementary Figures 3 and 4. Even individually, all patients with data at 10 years showed an increase of at least 0.1 mm in one or more compartments, and 6 of 8 patients showed a 10-year increase when averaging all compartments (data not shown). The gradual decrease after 2 years is likely the result of natural progression in loss occurring again after the 2-year regenerative response, potentially in combination with normal or even increased weight-bearing and movement, as a result of successful treatment and the experienced clinical improvement shown previously.[15] However, as we have no untreated control group, this cannot be verified. A good control group for these patients is difficult to find, since purposefully not treating patients with an indication for TKA, especially over multiple years, is impractical and ethically unsound.

In the LAC, a delayed cartilage response seems to take place, with significantly increased cartilage thickness in the long term on the whole-joint analyses. This is surprising, since thus far it was concluded that KJD did not have a clear effect on the cartilage in the LAC.[16] The compartmental analyses did not show a significant long-term increase in the LAC, but only a minimal increase between 5 and 10 years after treatment. For the analyses in all patients these results could be affected by survivorship bias, but a similar effect was seen when looking only at patients with full 10-year data-sets. Apparently, the LAC areas with a significant long-term increase are compensated for by a decrease in the remaining space of the LAC, resulting in the LAC barely changing in the compartmental analyses. This highlights the value of analytical approaches which fully reflect the spatial distribution of changes in articular cartilage. Still, looking at Figures 1 and 3, the slight long-term increase in the LAC goes in parallel with a decrease in the MAC, which for the MAC tibia was statistically significant. This may indicate increased loading on the MAC and decreased loading on the LAC over time, allowing regeneration in the LAC, either in a delayed response to the processes in the joint initiated by KJD treatment (described previously[19,20]) or as a natural response that might occur even in untreated patients. It is also surprising that only the 10-year cartilage thickness change in the LAC tibia had a significant influence on the clinical outcome over 10 years. Previously, no association between clinical and structural changes was found, and it is unexpected that changes in the LAC instead of the MAC could be related to better clinical response. Importantly, these analyses should be repeated in a larger group of patients to verify these results, especially since the effect was not significant over the first 2 years after treatment.

This is the first time that the cartilage thickness changes after KJD treatment have been shown topographically and over such a long time span, and it seems that the most significant cartilage regeneration moves from the exterior side of the MAC initially to more interiorly long term. Short-term (2-year) subregional analyses in a different cohort have been performed after KJD before, and showed the most significant response on the exterior side of the MAC femur and tibia as well.[16] The exterior side of the MAC seems to be the most affected pre-treatment, meaning that perhaps the initial regenerative response takes place in the parts of the joint with thinner baseline cartilage and a slower response takes place in the less affected parts, including the LAC. In fact, baseline MAC cartilage thickness has previously been shown to significantly predict a short-term (2-year) cartilage thickness increase, as has Kellgren- Lawrence grade.[16] In the current study, Kellgren-Lawrence grade did not have a statistically significant influence. Fifteen of the 20 patients had Kellgren- Lawrence grade 3, so there were only very small groups for grade 1 (n=1), grade 2 (n=3) and grade 4 (n=1), hampering detection of statistically significant differences between the groups. Looking at the influence of Kellgren-Lawrence grade on the whole joint (Figure 3) a higher grade does seem to result in a higher 2-year MAC cartilage increase, but no strong conclusions can be drawn here because of the small sample size. In general, the baseline parameters showed opposing results for the 2- and 10-year change, indicating a distinction between a short- and long-term response, although in both cases the same beneficial effect. Performing short- and long-term MRI scans in a larger group of patients, ideally including for example biomarker analyses or MRI scans reflecting cartilage quality, could help drawing stronger conclusions on different responses between (types of) patients.

This study had several limitations. First, the sample size of n=20 was small and there was no control group. Despite the small sample size, results are clear and consistent with previously published short-term results in similar patients. In the current study, long-term MRI cartilage thickness after KJD treatment was evaluated for the first time, adding unique evaluations and conclusions not previously known. Another limitation is that only cartilage thickness was evaluated, not cartilage quality. It would be interesting to see whether the newly generated cartilage is of the same quality, and if the quality of the already present cartilage changes. While dGEMRIC and T2-mapping scans were performed in a different cohort, these were up to 2 years only (T2-mapping analyses being performed currently).[21] Thirdly, patients are lost over time, mostly due to the (delayed) placement of a joint prosthesis. The last data available before TKA have been included and represent the potential worsening of the joint, which remains the reference after data imputation. This may have resulted in underestimation of the cartilage thickness over time. On the other hand, imputation of data based on data available of survivors may have led to overestimation of the repair activity over time, although none of the compartments showed a difference in cartilage thickness changes over the first 2 or 5 years between patients who did and did not complete ten years of follow-up (data not shown;

all p>0.18). Also, the sensitivity analyses using the patients of whom all data were available demonstrated that the observed effects presented with imputed data of the whole group seem solid. Still, it remains important to remember that the long-term whole-group results may be an underestimation or, perhaps more likely, an overestimation of the actual cartilage regeneration effect, since patients were lost to follow-up because of additional surgery, making it likely that the remaining patients experienced greater treatment benefit. Lastly, as validation for the results of the current study, it could have been worthwhile to directly measure the cartilage thickness in the patients undergoing TKA. Unfortunately, in these patients the post-surgery material was not stored and no cartilage thickness was measured. Including this in the study protocol of future studies could give an opportunity for validation of results. Future studies could also include registration of data that could possibly bias the measured cartilage thickness, such as activity monitoring, to further improve reliability of the data.

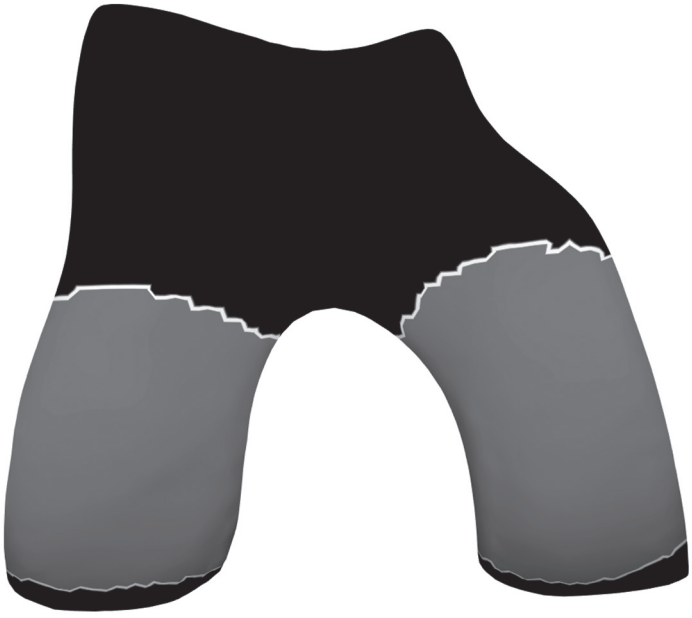
In conclusion, in these young end-stage knee OA patients, KJD treatment results in significant short-term cartilage regeneration in the most affected compartment, of which the effects can still be seen after 10 years. Apparently, an initial boost of cartilaginous tissue repair provides a long-term tissue structure benefit. In the less affected compartment, a delayed regenerative response seems to take place. Male sex and severity of joint damage may predict initial benefit, although this was lost over time. The observed intrinsic cartilage tissue repair activity upon KJD, specifically in the first 2 years, may be used to find the metabolic and mechanical drivers of intrinsic cartilage repair in general, providing novel leads for cartilage tissue repair strategies.

References

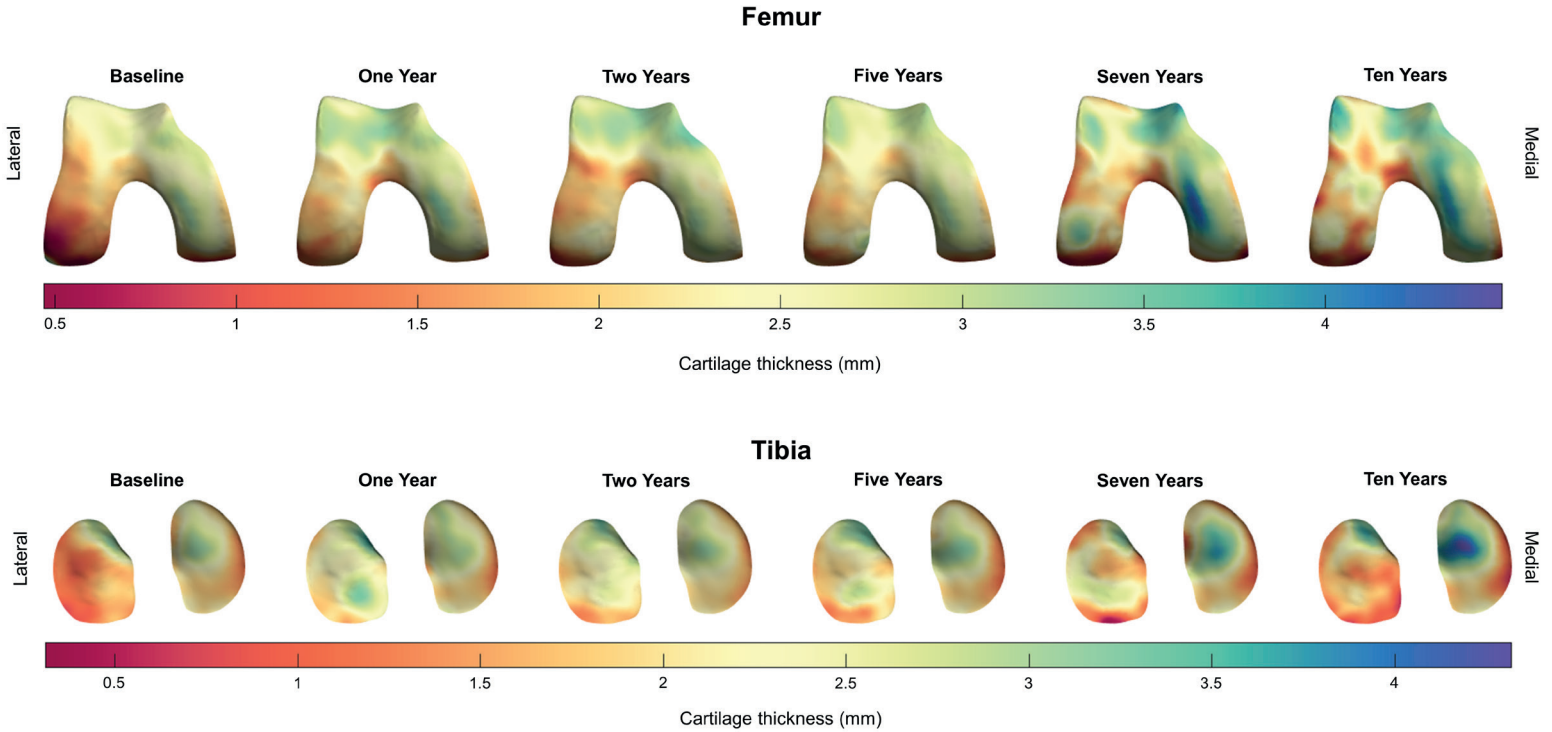
1. Nilsdotter AK, Toksvig-Larsen S, Roos EM. A 5 year prospective study of patient-relevant outcomes after total knee replacement. Osteoarthritis and Cartilage. 2009 May 1;17(5):601–6.
2. Bayliss LE, Culliford D, Monk AP, *et al*. The effect of patient age at intervention on risk of implant revision after total replacement of the hip or knee: A population-based cohort study. The Lancet. 2017 Apr 8;389(10077):1424–30.
3. Mastbergen SC, Saris DBF, Lafeber FPJG. Functional articular cartilage repair: Here, near, or is the best approach not yet clear? Nature Reviews Rheumatology. 2013 May;9(5):277–90.
4. Jansen MP, Boymans TAEJ, Custers RJH, *et al*. Knee joint distraction as treatment for osteoarthritis results in clinical and structural benefit: A systematic review and meta-analysis of the limited number of studies and patients available. Cartilage. 2020 Jul 22;194760352094294.
5. van der Woude JAD, Wiegant K, van Heerwaarden RJ, *et al*. Knee joint distraction compared with total knee arthroplasty: A randomised controlled trial. Bone and Joint Journal. 2017;99-B(1):51–8.
6. van der Woude JAD, Wiegant K, van Heerwaarden RJ, *et al*. Knee joint distraction compared with high tibial osteotomy: A randomized controlled trial. Knee Surgery, Sports Traumatology, Arthroscopy. 2017;25(3):876–86.
7. Jansen MP, Besselink NJ, van Heerwaarden RJ, *et al*. Knee joint distraction compared with high tibial osteotomy and total knee arthroplasty: Two-year clinical, radiographic, and biochemical marker outcomes of two randomized controlled trials. Cartilage. 2019 Feb 13;194760351982843.
8. Hoorntje A, Kuijer PPFM, Koenraadt KLM, *et al*. Return to sport and work after randomization for knee distraction *versus* high tibial osteotomy: Is there a difference? The Journal of Knee Surgery. 2020 Nov 23;
9. Deie M, Ochi M, Adachi N, *et al*. A new articulated distraction arthroplasty device for treatment of the osteoarthritic knee joint: A preliminary report. Arthroscopy. 2007;23(8):833–8.
10. Aly TA, Hafez K, Amin O. Arthrodiatasis for management of knee osteoarthritis. Orthopedics. 2011;34(8):e338–43.
11. Jansen MP, Mastbergen SC, Heerwaarden RJ van, *et al*. Knee joint distraction in regular care for treatment of knee osteoarthritis: A comparison with clinical trial data. PLOS ONE. 2020 Jan 22;15(1).
12. Intema F, van Roermund PM, Marijnissen ACA, *et al*. Tissue structure modification in knee osteoarthritis by use of joint distraction: An open 1-year pilot study. Annals of the Rheumatic Diseases. 2011 Aug 1;70(8):1441–6.
13. Wiegant K, van Roermund PM, Intema F, *et al*. Sustained clinical and structural benefit after joint distraction in the treatment of severe knee osteoarthritis. Osteoarthritis and Cartilage. 2013 Nov;21(11):1660–7.
14. van der Woude JAD, Wiegant K, van Roermund PM, *et al*. Five-year follow-up of knee joint distraction: Clinical benefit and cartilaginous tissue repair in an open uncontrolled prospective study. Cartilage. 2017;8(3):263–71.
15. Jansen MP, van der Weiden GS, van Roermund PM, *et al*. Initial tissue repair predicts long-term clinical success of knee joint distraction as treatment for knee osteoarthritis. Osteoarthritis and Cartilage. 2018;26(12):1604–8.
16. Jansen MP, Maschek S, van Heerwaarden RJ, *et al*. Changes in cartilage thickness and denuded bone area after knee joint distraction and high tibial osteotomy – Post-hoc analyses of two randomized controlled trials. Journal of Clinical Medicine. 2021 Jan 19;10(2):368.
17. MacKay JW, Kaggie JD, Treece GM, *et al*. Three-dimensional surface-based analysis of cartilage mri data in knee osteoarthritis: Validation and Initial clinical application. Journal of Magnetic Resonance Imaging. 2020 Oct 24;52(4):1139–51.

18. Turmezei TD, Treece GM, Gee AH, *et al*. Quantitative 3D analysis of bone in hip osteoarthritis using clinical computed tomography. European Radiology. 2016 Jul 1;26(7):2047–54.
19. Watt FE, Hamid B, Garriga C, *et al*. The molecular profile of synovial fluid changes upon joint distraction and is associated with clinical response in knee osteoarthritis. Osteoarthritis and Cartilage. 2020 Jan;28(3):324–33.
20. Sanjurjo-Rodriguez C, Altaie A, Mastbergen S, *et al*. Gene expression signatures of synovial fluid multipotent stromal cells in advanced knee osteoarthritis and following knee joint distraction. Frontiers in Bioengineering and Biotechnology. 2020 Oct 14;8:1178.
21. Besselink NJ, Vincken KL, Bartels LW, *et al*. Cartilage quality (dGEMRIC index) following knee joint distraction or high tibial osteotomy. Cartilage. 2018;1947603518777578.

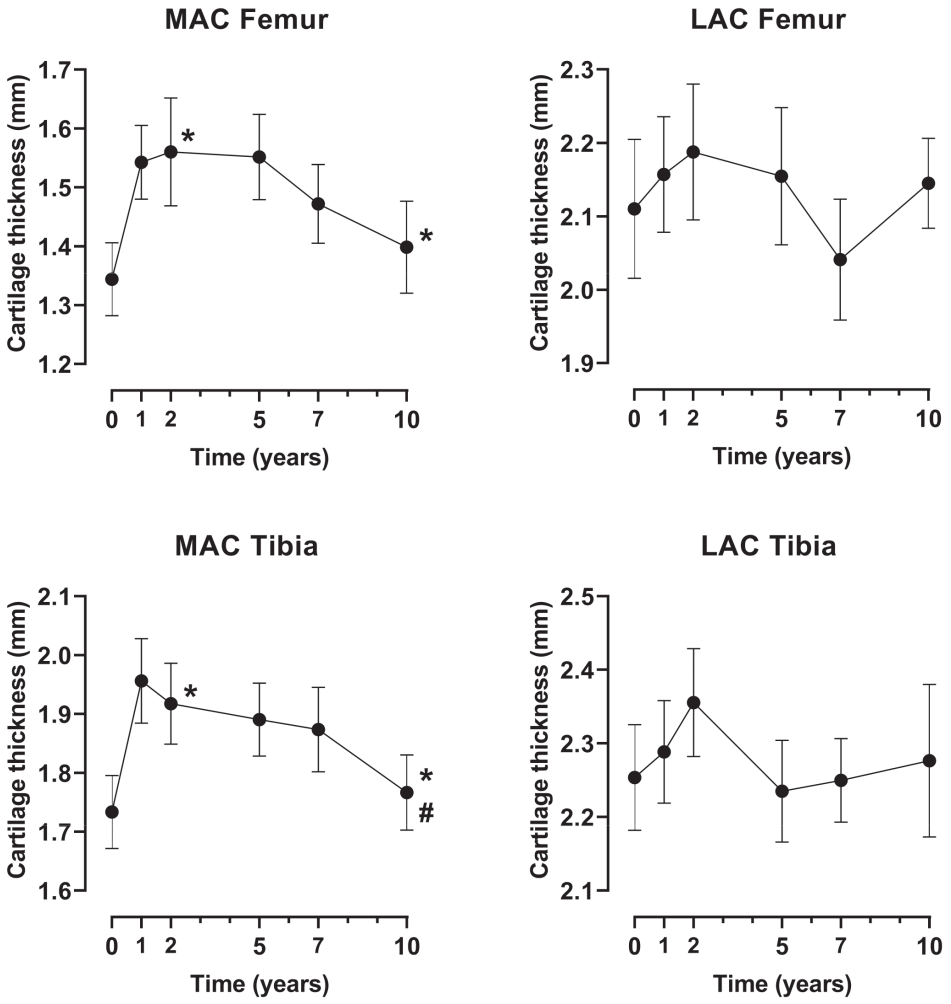
SUPPLEMENTARY DATA



Supplementary Figure S1: Selection of medial and lateral femoral compartment. Gray: included; black: excluded.



Supplementary Figure S2: The average cartilage thickness of all patients whose lateral compartment was the most affected, at baseline (n=2) and 1 (n=2), 2 (n=2), 5 (n=2), 7 (n=1) and 10 (n=1) years after treatment with knee joint distraction. Results are viewed on average right femur and tibia articular cartilage surfaces. The color range is based on the minimum and maximum average values of the femur (0.47–4.49) and tibia (0.31–4.32) separately.

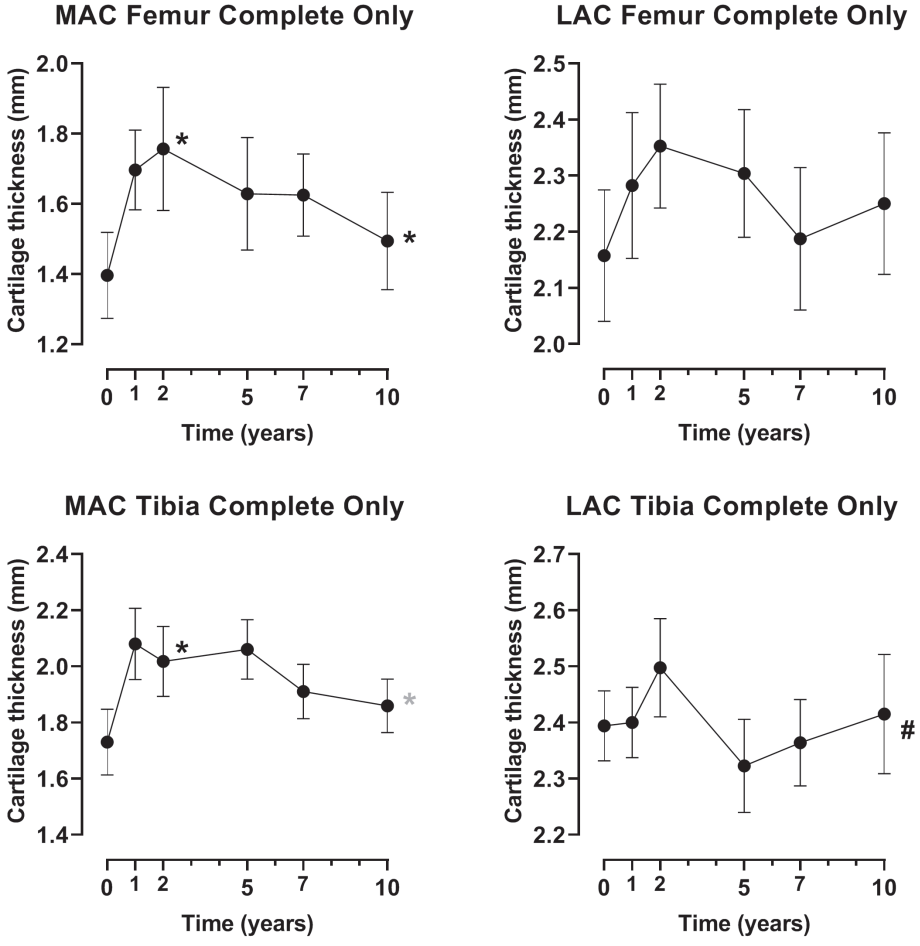


Supplementary Figure S3: Change over time for the 4 compartments, zooming in on each compartment separately (using inconsistent Y-axis ranges). Missing data was imputed (n=20 on all time points). * indicates significant ($p<0.05$) changes up from baseline to 2 years and from baseline to 10 years. # indicates significant changes from 2 years to 10 years. MAC: most affected compartment; LAC: least affected compartment. Mean and standard error are shown.

Supplementary Table S1: Compartmental average cartilage thickness before and after knee joint distraction treatment

	Baseline	1 year	2 years	5 years	7 years	10 years
MAC femur	1.34 (1.21–1.47)	1.54 (1.41–1.67)	1.56 (1.37–1.75)	1.55 (1.40–1.70)	1.47 (1.33–1.61)	1.40 (1.23–1.56)
LAC femur	2.11 (1.91–2.31)	2.16 (1.99–2.32)	2.19 (1.99–2.38)	2.15 (1.96–2.35)	2.04 (1.87–2.21)	2.15 (2.02–2.27)
MAC tibia	1.73 (1.60–1.86)	1.96 (1.81–2.11)	1.92 (1.77–2.06)	1.89 (1.76–2.02)	1.87 (1.72–2.02)	1.77 (1.63–1.90)
LAC tibia	2.25 (2.10–2.40)	2.29 (2.14–2.43)	2.36 (2.20–2.51)	2.24 (1.09–2.38)	2.25 (2.13–2.37)	2.28 (2.06–2.49)

LAC: least affected compartment; MAC: most affected compartment.



Supplementary Figure S4: Change over time for the four compartments for patients with complete datasets up to ten years (n=8). * indicates significant changes up until that time point ($p<0.05$; gray $p=0.05$): from baseline to 2 years and from baseline to 10 years. # indicates significant changes from 2 years to 10 years. LAC: least affected compartment; MAC: most affected compartment. Mean and standard error are shown.

CHAPTER 14

Changes in cartilage thickness and denuded bone area after knee joint distraction and high tibial osteotomy

Post-hoc analyses of two randomized controlled trials

M.P. Jansen
S. Maschek
R.J. van Heerwaarden
S.C. Mastbergen
W. Wirth
F.P.J.G. Lafeber & F. Eckstein

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Abstract

High tibial osteotomy (HTO) and knee joint distraction (KJD) are joint-preserving treatments that unload the more affected compartment (MAC) in knee osteoarthritis. This post-hoc study compares 2-year cartilage thickness changes after treatment with KJD *versus* HTO and identifies factors predicting cartilage restoration. Patients indicated for HTO were randomized to KJD (KJD_{HTO}) or HTO treatment. Patients indicated for total knee arthroplasty received KJD (KJD_{TKA}). Outcomes were the MRI mean MAC cartilage thickness and percentage of denuded bone area (dABp) change 2 years after treatment, with radiographic joint space width (JSW) as reference. Cohen's *d* was used for between-group effect sizes. Post-treatment, KJD_{HTO} patients (n=18) did not show significant changes. HTO patients (n=33) displayed a decrease in MAC cartilage thickness and increase in dABp, but increase in JSW. KJD_{TKA} (n=18) showed an increase in MAC cartilage thickness and JSW and decrease in dABp. Osteoarthritis severity was the strongest predictor of cartilage restoration. Kellgren-Lawrence grade ≥3 showed significant restoration ($p<0.01$) after KJD; grade ≤2 did not. Effect sizes between severe KJD and HTO patients were large for MAC MRI cartilage thickness ($d=1.09$; $p=0.005$) and dABp ($d=1.13$; $p=0.003$), but not radiographic JSW ($d=0.28$; $p=0.521$). This suggests that in knee osteoarthritis patients with high disease severity, KJD may be more efficient in restoring cartilage thickness.

Introduction

Knee osteoarthritis (OA) is the most prevalent form of OA and 1 of the most common causes of disability worldwide.[1] It poses a major global burden, anticipated to increase in the future.[2,3] End-stage knee OA is frequently treated with total knee arthroplasty (TKA), a generally effective and safe treatment.[4,5] However, in younger and more active patients it involves a risk of failure, and future revision surgery. In these cases a joint-preserving alternative may be a desired option.[6]

In case of predominantly unicompartmental knee OA, unicompartmental knee arthroplasty (UKA), high tibial osteotomy (HTO), and knee joint distraction (KJD) may be considered as (partly) joint-preserving treatment options.[7–11] As opposed to UKA, only HTO and KJD fully preserve the native joint tissue. HTO permanently unloads the more affected compartment (MAC) of the tibiofemoral joint by (over-) correcting the leg axis. This puts more load on the less affected compartment (LAC), and has shown good long-term survival.[12,13] Further, HTO treatment has shown an increase in radiographic joint space width (JSW) and, in some cases, even cartilage restoration.[14–16] Yet, comparison of JSW before and after HTO may be unreliable, as pseudo-widening of the unloaded compartment may occur due to the induced change in leg axis. Therefore, a direct measurement of cartilage structure is required to evaluate whether HTO has indeed a positive effect on maintenance of cartilage tissue.

KJD has been used for uni- and bicompartmental knee OA. KJD aims to promote cartilage restoration by temporarily unloading both compartments, using an external fixation frame. Also KJD has shown good long-term survival and both radiographic JSW increase and cartilage thickness restoration by MRI.[14,17–24]

In a previous randomized controlled trial (RCT) that compared HTO with KJD, the clinical effects (based on patient-reported outcomes) and structural effects (based on radiographic measurements) of KJD and HTO were shown to be similar in patients indicated for HTO with an leg axis deviation of <10°.[14,21,22] However, for the reasons provided above, direct cartilage thickness measurements need to be compared between KJD and HTO in order to accurately evaluate the efficacy of both treatment options on cartilage structure. The main goal of this study therefore was to compare 2-year changes in MRI cartilage thickness and denuded joint surface areas during treatment with KJD *versus* HTO. We hypothesized that KJD is more effective in restoring cartilage in the MAC, while avoiding negative effects (more cartilage thinning) on the LAC. The secondary goal was to identify (baseline) factors that can predict cartilage restoration activity as measured on MRI, in order to help select the appropriate patients for that type of therapy.

Methods

Patients

Patients were included from 2 different RCTs, 1 comparing KJD with HTO, and 1 comparing KJD with TKA. In the KJD *versus* HTO trial, patients with medial compartmental knee OA considered for HTO according to regular clinical practice were included to be treated with either KJD (n=23; KJD_{HTO}) or HTO (n=46; HTO).[22] In the KJD *versus* TKA trial, knee OA patients considered for TKA according to regular clinical practice were included for treatment with KJD (n=20; KJD_{TKA}) or TKA (n=40; TKA). The TKA patients were not included in this study, because they no longer had their native knee after surgery and no structural parameters could be analyzed.[21] Inclusion and exclusion criteria for both trials have been previously published, including the following inclusion criteria: radiological joint damage (Kellgren-Lawrence grade >2 as judged by the orthopedic surgeon), age <65 years (a TKA placed <65 years brings an increased revision risk[6]), ability to undergo MRI examination, <10° knee malalignment (is preferably treated by realignment surgery), BMI <35 (mechanical limitations of the distraction frame), and no joint prosthesis elsewhere in the body (because risk of infection in case of pin tract infection occurs).[25] As part of the inclusion process, in the KJD *versus* HTO trial standing whole-leg radiographs were performed to measure the preoperative leg axis, while in the KJD *versus* TKA trial these radiographs were performed only in around half of the patients.

Both trials were granted ethical approval by the medical ethical review committee of the University Medical Center Utrecht (protocol numbers 10/359/E and 11/072), registered in the Netherlands Trial Register (trial numbers NL2761 and NL2680) and were performed in accordance with the ethical principles from the Declaration of Helsinki. All patients gave written informed consent. All actions described in this manuscript were part of the original research protocol and ethical approval as well as patient informed consent; no additional actions were performed in the included patients for these post-hoc analyses.

Treatment

Distraction surgery (KJD) was performed using an external fixation frame (Stryker) consisting of 2 dynamic monotubes, bridging the knee medially and laterally and fixated to the tibia and femur using 8 half-pins.[25] During surgery the knee was distracted 2 mm, extended for an additional 1 mm per day during a short hospitalization until 5 mm distraction was reached, confirmed radiographically. Subsequently, patients were discharged with prophylactic anticoagulant prescribed for use during treatment and were allowed full weight-bearing of the distracted knee, supported by crutches if needed. After 6 weeks, the frame and pins were surgically removed during day treatment.

For HTO patients, bi-plane medial-based opening-wedge osteotomy was performed. The method of Miniaci was used to preoperatively define the amount of correction needed and TomoFix medial high tibial plates and screws (DePuy Synthes, Switzerland) or Synthes locking compression plate (LCP) system (DePuy Synthes, Switzerland) were used for fixation.[26] After surgery, partial weight-bearing (maximum 20 kg) was allowed for 6 weeks, after which full weight-bearing was started gradually. Prophylactic anticoagulant was used for 6 weeks. At 18 months after surgery, the metal plate and screws were removed, to allow imaging at 2 years.

Image acquisition and analysis

1.5T or 3T MRIs with 3D spoiled gradient recalled imaging sequence with fat suppression (SPGR-fs) were acquired at baseline (before treatment) and 2 years after treatment. While the MRI field strength differed as some patients were included in an extended imaging study, the protocols used were the same for both 1.5T and 3T MRI scans. To prevent bias, only patients who underwent MRI scans of sufficient quality to allow analysis and were scanned with the same hardware (1.5 or 3T) at both baseline and 2 years follow-up were included in the analyses. Reasons for insufficient quality to allow analysis were severe motion artifacts or insufficient positioning (e.g. relevant parts of the joint cut-off). There were no constraints regarding concomitant treatment during the 2 years of follow-up. Cartilage structure in the knee was measured using Chondrometrics Works 3.0 software.[27] The primary and secondary outcome parameters for the present study were the 2-year change in mean cartilage thickness over the total subchondral bone area (ThCtAB) of the MAC and the percentage of denuded subchondral bone area (dABp) of the MAC, respectively.[28] On an exploratory basis, longitudinal changes were determined for 16 femorotibial subregions: the central, internal, external, anterior, and posterior tibia and the central, internal, and external femur for both the MAC and the LAC.[27] Further, location-independent analysis was used to determine the total (summed) thinning and thickening scores across all subregions.[29]

Standardized semi-flexed weight-bearing radiographs were performed at the same time points, according to the Buckland-Wright protocol, using an aluminum step wedge as a reference standard for image analysis.[30,31] Using knee images digital analysis (KIDA) software, the mean JSW of the MAC was determined.[32]

Both MRI and radiograph analyses were performed by experienced observers blinded to the type of intervention and acquisition order. For the radiograph analyses, 1 observer analyzed all images. For the MRI analyses, 2 different observers analyzed the images, where each of the observers processed pairs of baseline and follow-up of each patient in the same session. Also, the number of patients from each treatment was equally divided between the 2 observers. The reproducibility of both types of analysis have been reported before in detail.[27,32–34]

Statistical analysis

This study is a post-hoc analysis on the data of the original RCTs. Potential differences in baseline characteristics between the 3 groups (KJD_{TKA}, KJD_{HTO}, and HTO) were analyzed using 1-way ANOVA with, in case of statistically significant differences, post-hoc Tukey HSD tests. In case of not normally distributed continuous variables, Kruskal-Wallis tests with post-hoc Dunn tests in case of statistically significant differences were used. For categorical variables, chi-square tests were used.

Changes between pre- and 2 years post-treatment values for all cartilage thickness and JSW parameters were calculated using paired *t*-tests. Linear regression was used for comparisons in cartilage thickness and JSW changes over 2 years between groups, correcting for any significantly different baseline patient characteristics. Consistency was tested by in- and excluding baseline cartilage thickness and JSW as confounder. The influence of baseline characteristics on the change in MAC cartilage thickness was tested using linear regression. As leg axis measurements were only available around half of the KJD_{TKA} patients, this parameter was not used in linear regression models (except when specifically mentioned when testing the effect of leg axis). KJD and HTO patients were divided in subgroups based on the strongest predictor of MAC cartilage thickness change; the same statistical tests for changes over time and differences between groups were applied on these subgroups. Sensitivity analyses were performed by adding the trial in which patients were originally included as potential confounder. Absolute values are presented with mean and standard deviation (SD) while changes over time are presented as mean change and 95% confidence interval (95%CI). A p-value of <0.05 was considered statistically significant. As a measure for effect size of the primary and secondary outcome, Cohen's d was used when comparing changes between different groups. Values of 0.20, 0.50 and 0.80 indicate small, moderate and large effect sizes, respectively.[35]

Results

Patients

A flowchart of the final patient selection is shown in Figure 1. In the KJD_{HTO} group, 1 patient was excluded before surgery due to inoperability, 2 patients received other surgery and 2 patients had MRI scans of insufficient quality, leaving 18 patients for analysis. In the HTO group, 1 patient was excluded before treatment due to anxiety, 4 patients were lost to follow-up because of comorbidities interfering with follow-up, 2 patients did not undergo MRI at 2 years, 2 patients had MRI scans with different hardware at baseline and 2 years, and 4 patients had MRI scans of insufficient quality, leaving 33 patients for analysis. In the KJD_{TKA} group, 1 patient received a different surgery within 2 years of follow-up and 1 patient refused imaging at 2 years, leaving 18 patients for analysis.

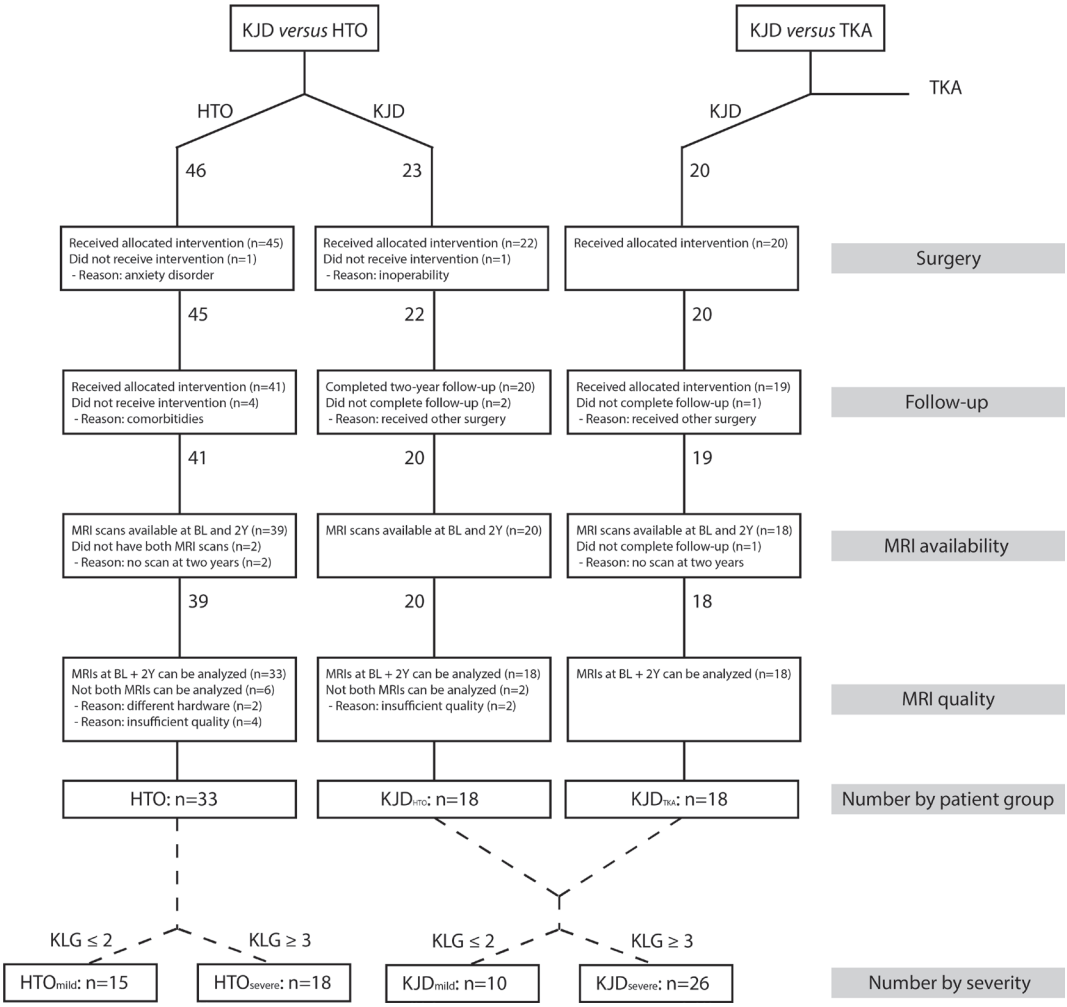


Figure 1: Flowchart of final patient selection

The baseline characteristics of the 3 patient groups are displayed in Table 1. The KJD_{TKA} group had a higher age and Kellgren-Lawrence grade than the HTO and KJD_{HTO} groups. It also had a higher MAC denuded bone area and lower MAC cartilage thickness, pointing towards more severe structural pathology, and a lower leg axis deviation than the other 2 groups. Between KJD_{HTO} and HTO there were no statistically significant differences in the baseline characteristics.

Table 1: Baseline characteristics of the 3 patient groups

	KJD_{HTO} (n=18)	HTO (n=33)	KJD_{TKA} (n=18)	*P*-value
Age (years)	50.6 (5.3)	49.6 (5.5)	56.6 (6.5)	**<0.001**
Male sex, n (%)	13 (72)	19 (58)	8 (44)	0.240*
BMI (kg/m^2)	27.6 (3.4)	27.3 (3.4)	26.9 (3.8)	0.825
Leg axis (degrees)	5.7 (2.6)	6.1 (2.4)	2.1 (7.0)#	**0.013**
Kellgren-Lawrence grade, n (%)				**0.001***
- Grade 0	0 (0)	1 (3)	0 (0)	
- Grade 1	5 (28)	4 (12)	0 (0)	
- Grade 2	4 (22)	10 (30)	1 (6)	
- Grade 3	9 (50)	14 (42)	7 (39)	
- Grade 4	0 (0)	4 (12)	10 (56)	
Baseline cartilage				
MAC ThCtAB (mm)	2.5 (1.0)	2.4 (0.8)	1.8 (0.8)	**0.044**
LAC ThCtAB (mm)	4.1 (0.8)	4.0 (0.5)	4.0 (1.1)	0.881
MAC dABp (%)	16 (15)	14 (14)	34 (16)	**<0.001**
LAC dABp (%)	5.6 (6.6)	3.3 (3.9)	8.4 (12)	0.075
Mean MAC JSW (mm)	2.4 (1.4)	2.2 (1.3)	2.1 (2.2)	0.786

Mean and standard deviation or n (%) are given. *P*-values were calculated with 1-way ANOVA, with post-hoc Tukey HSD tests in case of statistical significance (bold *p*-values), or chi-square (indicated with *). All statistically significant differences were between knee joint distraction patients indicated for total arthroplasty (KJD_{TKA}) and the other 2 groups; there were no statistically significant differences between KJD patients indicated for high tibial osteotomy (KJD_{HTO}) and HTO. #Leg axis measurements in the KJD_{TKA} group were available in only 8 of 18 patients. dABp: percentage of denuded subchondral bone area; JSW: joint space width; LAC: less affected compartment; MAC: more affected compartment; ThCtAB: mean cartilage thickness over the total subchondral bone area.

For around half of the included patients (46%) 3T MRIs were performed at baseline and 2 years (KJD_{HTO} 33%, HTO 52%, KJD_{TKA} 50%); the other patients received 1.5T MRI scans at baseline and 2 years. This number was not statistically significantly different between groups (p=0.432), so comparisons between groups were not corrected for field strength.

Longitudinal changes by patient group

MRI MAC cartilage thickness and denuded bone area (Figure 2A/B) in the KJD_{HTO} group showed no significant changes over time; neither did the radiographic MAC JSW (Table 2). The HTO group, in contrast, displayed a significant decrease in MAC cartilage thickness and an increase in MAC denuded bone area. Yet, the HTO group showed a significant increase in radiographic mean MAC JSW. The KJD_{TKA} group displayed a substantial increase in the MAC cartilage thickness and in mean MAC JSW, and a decrease in MAC denuded bone area.

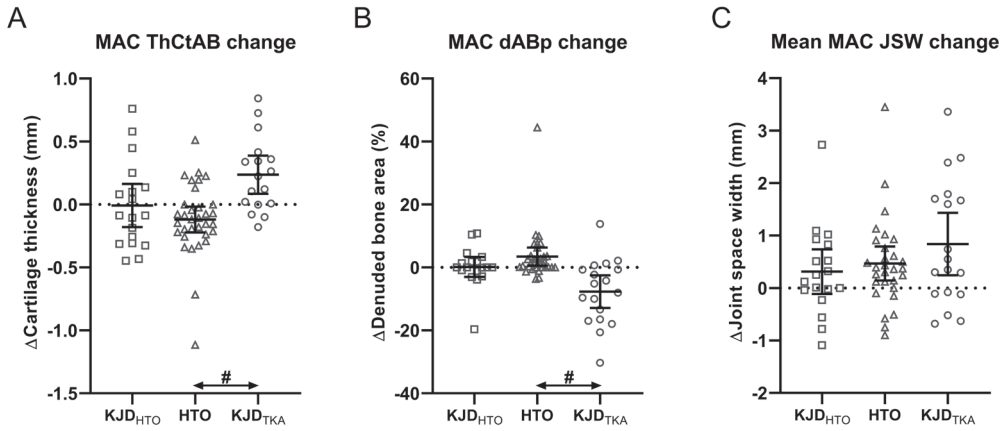


Figure 2: Two-year change in radiographic and MRI cartilage parameters. (A) Change in MRI mean cartilage thickness over the total subchondral bone area (ThCtAB) of the more affected compartment (MAC), for the 3 groups: KJD_{HTO}: KJD patients with indication high tibial osteotomy (HTO); KJD_{TKA}: knee joint distraction (KJD) patients with indication total knee arthroplasty. (B) Change in MRI percentage of denuded subchondral bone area (dABp) of the MAC for the 3 groups. (C) Change in mean radiographic joint space width (JSW) of the MAC for the 3 groups. Markers represent individual patients, dashes represent the group mean and 95% confidence interval. Hashes (#) between groups indicate statistically significant differences between each 2 groups (p<0.05), corrected for baseline patient characteristics statistically significantly different between each 2 groups.

Differences in cartilage structural change over time between KJD_{HTO} and HTO and between KJD_{HTO} and KJD_{TKA} did not reach statistical significance for any of the 3 MAC parameters (Table 2). Between KJD_{TKA} and HTO, both the cartilage thickness and denuded bone area showed large, statistically significant differences, while the radiographic JSW did not.

Correcting the between-group comparisons for baseline cartilage thickness, denuded bone area, or JSW values did not change significance for any of the comparisons in all 3 parameters. The MRI field strength (1.5T or 3T) did not have a significant influence on the change in MAC cartilage thickness or denuded bone area in any of the 3 patient groups (all p>0.3).

In the LAC, most groups did not show a significant change in any of the 3 parameters (cartilage thickness, denuded bone area, and JSW), except for the KJD_{HTO} group that showed a significant (but small) increase in LAC denude bone area (Table 2).

Subregional cartilage thickness changes and location-independent cartilage thinning and thickening scores are shown in the supplementary data.

Table 2: Two-year changes in the 3 patient groups

	KJD_{HTO}	HTO	KJD_{TKA}	KJD_{HTO} *vs* HTO			KJD_{HTO} *vs* KJD_{TKA}			KJD_{TKA} *vs* HTO		
	Change	**Change**	**Change**	**Difference**	***P***	***d***	**Difference**	***P***	***d***	**Difference**	***P***	***d***
MAC ThCtAB (mm)	-0.01 (-0.18 to 0.16)	-0.12 (-0.22 to -0.02)	0.24 (0.08 to 0.39)	0.11 (-0.07 to 0.29)	0.225	0.36	-0.01 (-0.29 to 0.28)	0.954	0.76	-0.35 (-0.58 to -0.12)	**0.004**	1.22
LAC ThCtAB (mm)	-0.07 (-0.15 to 0.00)	-0.02 (-0.09 to 0.05)	-0.01 (-0.12 to 0.10)	-0.05 (-0.16 to 0.06)	0.351	0.28	-0.07 -0.25 to 0.11)	0.416	0.34	-0.02 (-0.18 to 0.14)	0.814	0.06
MAC dABp (%)	0.1 (-3.0 to 3.3)	3.4 (0.5 to 6.3)	-7.7 (-12.9 to -2.5)	-3.3 (-7.7 to 1.1)	0.142	0.44	3.6 (-4.3 to 11.5)	0.366	0.91	11.1 (4.2 to 18.0)	**0.002**	1.44
LAC dABp (%)	0.5 (0.2 to 0.8)	0.1 (-0.1 to 0.3)	0.1 (-1.2 to 1.4)	0.4 (0.1 to 0.8)	**0.026**	0.67	0.1 (-1.7 to 1.9)	0.903	0.23	-0.3 (-1.5 to 1.0)	0.678	0.02
Mean MAC JSW (mm)	0.31 (-0.11 to 0.74)	0.47 (0.14 to 0.79)	0.84 (0.24 to 1.43)	-0.15 (-0.67 to -0.36)	0.547	0.18	-0.02 (-0.97 to 0.94)	0.969	0.51	-0.36 (-1.16 to 0.44)	0.374	0.37
Mean LAC JSW (mm)	0.22 (-0.63 to 1.06)	-0.47 (-1.08 to 0.13)	0.15 (-0.36 to 0.66)	0.69 (-0.30 to 1.68)	0.167	0.42	0.08 (-1.26 to 1.41)	0.904	0.05	-0.62 (-1.75 to -0.50)	0.271	0.44

Changes and differences are shown with mean and 95% confidence interval. Bold *p*-values indicate statistical significance (p<0.05), for changes over time calculated with paired *t*-tests. Differences between groups and corresponding *p*-values were calculated with linear regression, correcting for statistically significantly different baseline characteristics. *d*: Cohen's *d*; dABp: percentage of denuded subchondral bone area; HTO: high tibial osteotomy; JSW: joint space width; KJD_{HTO}: knee joint distraction (KJD) patients with indication HTO; KJD_{TKA}: KJD patients with indication total knee arthroplasty; LAC: least affected compartment; MAC: most affected compartment; ThCtAB: mean cartilage thickness over the total subchondral bone area.

Prediction of cartilage thickness changes

Kellgren-Lawrence grade and treatment were the strongest statistically significant predictors of MAC cartilage thickness change. A higher Kellgren-Lawrence grade was associated with in a greater increase in cartilage thickness during treatment (B=0.174; R^2=0.255; p=0.002). Detailed results can be found in the supplementary data.

A Kruskal-Wallis test confirmed that, for KJD patients, the distribution of the MAC cartilage thickness change was not the same across the different Kellgren-Lawrence grades (p=0.009). Post-hoc tests identified statistically significant differences between grade 1–3, grade 1–4, grade 2–3 and grade 2–4. Separating KJD patients in those with mild OA (Kellgren-Lawrence grade ≤2; KJD_{mild}) and with severe knee OA (Kellgren-Lawrence grade ≥3; KJD_{severe}) resulted in the best fit of the univariable regression model (B=0.209; R^2=0.317; p<0.001): KJD patients with severe OA showed a significantly greater increase in cartilage thickness than those with mild OA.

Longitudinal changes by baseline severity

Since baseline OA severity was the strongest predictor for cartilage tissue changes over time, and had a stronger influence than the trial in which patients were included, the main MRI and JSW outcome parameters are presented here comparing mild and severe OA groups irrespective of the trial the patients originated from. Additionally, severe KJD patients are compared with severe HTO patients, and mild KJD patients with mild HTO patients. The changes over time for the different groups are shown in Table 3; the differences between the groups are shown in Table 4.

Table 3: Two-year changes for mild and severe knee joint distraction and high tibial osteotomy patients

	KJD_{mild}	KJD_{severe}	HTO_{mild}	HTO_{severe}
MAC ThCtAB (mm)	-0.19	0.23	-0.10	-0.13
	(-0.36 to -0.02)	(0.10 to 0.35)	(-0.20 to -0.01)	(-0.31 to -0.05)
MAC dABp (%)	2.3	-6.1	1.2	5.3
	(-1.1 to 5.6)	(-10.1 to -2.2)	(-0.2 to 2.6)	(0.0 to 10.5)
Mean MAC JSW (mm)	0.04	0.78	0.46	0.47
	(-0.38 to 0.47)	(0.32 to 1.24)	(0.14 to 0.79)	(-0.09 to 1.03)

Mean changes and 95% confidence interval are shown. dABp: percentage of denuded subchondral bone area; HTO_{mild}: high tibial osteotomy patients with mild osteoarthritis (OA); HTO_{severe}: HTO patients with severe OA; JSW: joint space width; KJD_{mild}: knee joint distraction (KJD) patients with mild OA; KJD_{severe}: KJD patients with severe OA; MAC: most affected compartment; ThCtAB: mean cartilage thickness over the total subchondral bone area.

Table 4: Differences in 2-year changes between groups based on osteoarthritis severity and treatment

	KJD_{mild} *vs* KJD_{severe}			HTO_{mild} *vs* HTO_{severe}			KJD_{mild} *vs* HTO_{mild}			KJD_{severe} *vs* HTO_{severe}		
	Difference	***P***	***d***	**Difference**	***P***	***d***	**Difference**	***P***	***d***	**Difference**	***P***	***d***
MAC ThCtAB (mm)	0.46 (0.22 to 0.70)	**<0.001**	1.47	-0.02 (-0.23 to 0.19)	0.828	0.08	0.08 (-0.09 to 0.25)	0.332	0.40	-0.33 (-0.55 to -0.11)	**0.005**	1.09
MAC dABp (%)	-8.7 (-16.0 to -1.4)	**0.020**	0.97	4.1 (-1.6 to 9.8)	0.154	0.52	-1.1 (-4.0 to 1.9)	0.459	0.31	10.5 (3.7 to 17.2)	**0.003**	1.13
Mean MAC JSW (mm)	0.75 (-0.11 to 1.60)	0.084	0.72	0.01 (-0.66 to 0.67)	0.985	0.01	0.42 (-0.07 to 0.91)	0.089	0.75	-0.25 (-1.02 to 0.52)	0.521	0.28

Differences are shown with mean and 95% confidence interval. Differences between groups and corresponding *p*-values were calculated with linear regression, correcting for statistically significantly different baseline characteristics; bold *p*-values indicate statistical significance ($p<0.05$). *d*: Cohen's *d*; dABp: percentage of denuded subchondral bone area; HTO: high tibial osteotomy; JSW: joint space width; KJD_{HTO}: knee joint distraction (KJD) patients with indication HTO; KJD_{TKA}: KJD patients with indication total knee arthroplasty; LAC: least affected compartment; MAC: most affected compartment; ThCtAB: mean cartilage thickness over the total subchondral bone area.

The only patient characteristic significantly different between KJD_{mild} and KJD_{severe} was sex (p=0.017). Corrected for sex, there was a large and statistically significant difference in MAC cartilage thickness change between KJD patients with mild compared to more severe OA: KJD_{mild} patients showed a significant decrease and KJD_{severe} patients showed a significant increase in cartilage thickness (Figure 3A; Table 3 and 4). Similarly, the change in MAC denuded bone area showed a large significant difference between both groups, with only KJD_{severe} patients displaying a significant decrease in denuded bone area over time (Figure 3B; Table 3 and 4). The difference in cartilage structure changes between groups was not as clearly observed by MAC JSW change (Figure 3C; Table 4). Lastly, only KJD_{mild} showed a significant negative change with the LAC denuded bone area increasing over time (+0.64; 0.08–1.18; p=0.028). Not correcting for sex did not change significance for any comparison between KJD_{mild} and KJD_{severe}.

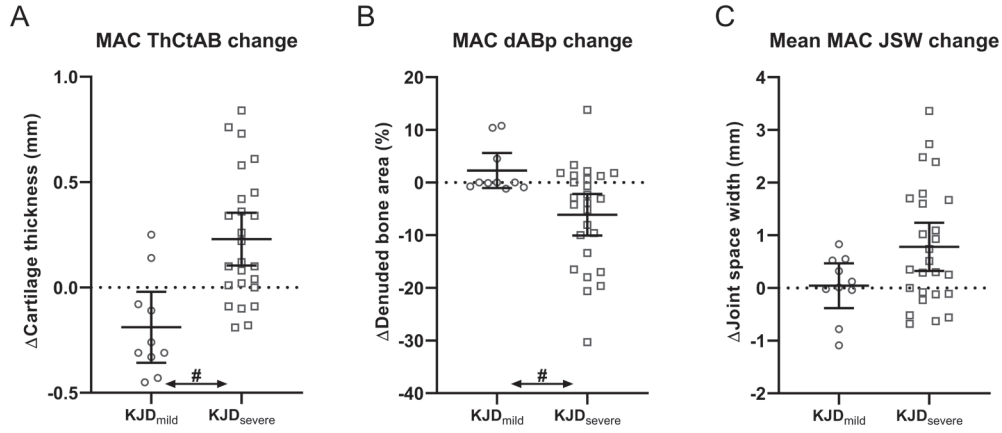


Figure 3: Two-year change in radiographic and MRI cartilage thickness parameters for knee joint distraction (KJD) patients with mild (KJD_{mild}) and severe (KJD_{severe}) osteoarthritis. (A) Change in MRI mean cartilage thickness over the total subchondral bone area (ThCtAB) of the more affected compartment (MAC). (B) Change in MRI percentage of denuded subchondral bone area (dABp) of the MAC. (C) Change in mean radiographic joint space width (JSW) of the MAC. Markers represent individual patients, dashes represent the group mean and 95% confidence interval. Hashes (#) between groups indicate statistically significant differences between each 2 groups (p<0.05), corrected for statistically significantly different baseline characteristics.

When dividing HTO patients into HTO_{mild} and HTO_{severe}, there were no statistically significant differences in baseline characteristics or in 2-year changes between these 2 groups for any of the MAC MRI or JSW parameter (Table 4).

KJD_{severe} showed a significantly greater cartilage restoration response in the MAC than HTO_{severe}, with large effect sizes for both MAC cartilage thickness and denuded bone area (Table 3). This was not observed with MAC JSW change. These comparisons were corrected for age, which was significantly different between the 2 groups (p=0.009). The changes in all 3 parameters did not differ significantly between KJD_{mild} and HTO_{mild} (Table 4); there were no statistically significant differences between the 2 groups (all p>0.05).

Sensitivity analyses, correcting for the fact that patients in almost all comparisons were included in different trials, are shown in Supplementary Table S1. Correcting for the trial did not change significance for the primary outcome (change in MAC cartilage thickness) or for MAC JSW change. For the change in denuded bone area the difference was no longer statistically significantly different for any comparison when correcting for the original trial patients were included in.

Discussion

The main goal of this study was to compare 2-year quantitative cartilage changes during treatment with KJD *versus* HTO, hypothesizing that KJD is more effective in restoring cartilage in the MAC, while avoiding negative effects on the LAC. The secondary goal was to identify factors that can predict cartilage restoration activity. Baseline OA severity was the strongest indicator of cartilage restoration response after treatment, independent of treatment and only severe knee OA patients showed statistically significant cartilage restoration after treatment in both cartilage thickness and denuded bone area, in accordance with radiographic JSW results used as reference. Contrarily, HTO treated patients showed statistically significant cartilage loss on MRI, while the radiographic JSW of the MAC increased. Patients that received KJD in case of HTO indication, with relatively mild OA as compared to KJD in case of TKA indication, demonstrated no differences in cartilage restoration when compared to HTO treated patients. Effect sizes were moderate to large and the changes, although seemingly small in mm and percentage of area, seem to be clinically significant as compared to natural progression of loss in cartilage thickness and increase in denuded bone area in comparable untreated knee OA patients.[19] Discussion of the subregional results can be found in the supplementary data.[36,37]

The leg axis deviation, the main reason to indicate a knee OA patient for treatment with HTO, did not have a significant influence on the amount of cartilage restoration (supplementary data). Instead, along with the Kellgren-Lawrence grade, a higher patient age and lower baseline cartilage thickness were the strongest indicators for greater cartilage restoration, likely because both these parameters are significantly associated with a higher Kellgren-Lawrence grade (1-way ANOVA: both $p<0.045$; data not shown). A Kellgren-Lawrence grading providing compartment-specific instead of knee-specific scores was applied and there was only 1 KJD patient whose LAC was scored with a Kellgren-Lawrence grade >2. This patient displayed a relatively large increase in cartilage thickness in the LAC that was comparable to that in the MAC (MAC +0.22m; LAC +0.24 mm).

Treatment with HTO demonstrated both cartilage thickness loss and increase in denuded bone area by MRI of the MAC whereas radiographic MAC JSW increased. It is therefore likely that the MAC JSW increase is predominantly a result of pseudo-widening, due to a mechanical

axis shift that is induced with HTO treatment and not due to actual cartilage thickness gain. Despite the increased loading on the LAC, it did not show significant changes in cartilage thickness. Any changes in cartilage thickness after HTO may therefore be solely natural progression, which means HTO treatment does not (quantitatively) affect the tibiofemoral cartilage 2 years after treatment. The axis shift appeared to offer enough relieve in itself, as these same HTO patients have previously shown a significant increase in clinical patient-reported outcomes over the 2-year period after treatment.[14,21,22]

The results for HTO patients contradict those found in literature, where quantitative cartilage restoration was seen, although most studies used second-look arthroscopy to visually score cartilage restoration after HTO and discrepancies may be expected between such different scoring/measurement methods.[38] Two studies have suggested cartilage gain to occur after HTO using the same MRI measurement method as used in the current study, although in both cases the increases were not statistically significant.[39,40] Also, those studies measured the cartilage thickness 1 year after treatment instead of after 2 years. In the current study, MRI measurements were not performed at 1 year after treatment for HTO patients as the metal plate and screws were still present in the knee. A previous study demonstrated that while 2-year values were significantly improved compared to baseline, even better results were seen 1 year after treatment.[18,19] This observation suggests that the cartilage restoration in the current study could be an underestimation of the true initial restorative effect caused by KJD treatment. Similarly, it might be that the HTO patients would have shown a slight increase in cartilage thickness after 1 year, but subsequent loss of cartilage (natural progression) in the second year causes an overall negative 2-year effect. This also brings forward a limitation of our study in that it did not include a natural progression group with similar baseline characteristics as the HTO- and TKA-indicated patients. The question is whether such a population exists for TKA-indicated patients, because indication for TKA needs a past of ineffective conservative treatment. This may make it unethical to keep these patients on conservative treatment for an additional 2 years to serve as a control group.

Despite severe *versus* mild OA being the strongest predictor of cartilage thickness changes after KJD, it should be noted that the R^2 value of this model was only 0.32, so only 32% of the group variance could be explained by the baseline OA severity. This might be the result of the small number of patients included in the analysis, so it would be worthwhile to perform these analyses in more KJD patients in the future. However, despite the small patient number, the between-group effect sizes for almost all comparisons were moderate to large when dividing groups by severity. This could mean that there are other important factors involved that determine the amount of cartilage restoration that were not included in this study, such as baseline cartilage quality measurements or metabolic joint condition reflected in e.g. synovial fluid marker levels. The fact that the significance of difference in denuded

bone area changes between groups changed when correcting for the trial in which patients were treated, indicates there are indeed parameters of importance that were not considered in this trial. These are likely to be structural parameters, since the influence of baseline clinical outcome on cartilage thickness change was found not to be significant (baseline VAS pain, EQ5D, ICOAP, WOMAC and KOOS, including all subscales, all $p>0.1$). Future studies including more parameters, using for example qualitative MRI scans, could provide a better insight into which factors determine cartilage restoration response and with that might improve the patient selection process.

In conclusion, for patients included in the same trial (KJD *versus* HTO), the 2 treatments showed similar results in MAC cartilage restoration. It was expected that HTO would show worse results in the LAC, but this was not the case. Based on subgroup analyses, it was shown that in patients with severe knee OA, KJD may be more efficient in restoring cartilage thickness than HTO is. In patients with mild knee OA, neither HTO nor KJD treatment results in significant cartilage restoration over 2 years and both treatments show a slight deterioration that is likely the result of natural OA progression. There were no differences between the treatments for changes in the LAC. Based on these results, this research suggests that knee joint distraction as joint-preserving surgery could be a good option in case of knee OA patients with more severe structural damage. This should be confirmed in a larger trial specifically designed for this purpose.

References

1. Bijlsma JW, Berenbaum F, Lafeber FP. Osteoarthritis: an update with relevance for clinical practice. The Lancet. 2011 Jun 18;377(9783):2115–26.
2. Woolf AD, Pfleger B. Burden of major musculoskeletal conditions. Bulletin of the World Health Organization. 2003;81(9):646–56.
3. Cross M, Smith E, Hoy D, *et al*. The global burden of hip and knee osteoarthritis: Estimates from the Global Burden of Disease 2010 study. Annals of the Rheumatic Diseases. 2014 Jul;73(7):1323–30.
4. Carr AJ, Robertsson O, Graves S, *et al*. Knee replacement. The Lancet. 2012;379(9823):1331–40.
5. Lützner J, Kasten P, Günther K-P, *et al*. Surgical options for patients with osteoarthritis of the knee. Nature Reviews Rheumatology. 2009 Jun;5(6):309–16.
6. Bayliss LE, Culliford D, Monk AP, *et al*. The effect of patient age at intervention on risk of implant revision after total replacement of the hip or knee: A population-based cohort study. The Lancet. 2017 Apr 8;389(10077):1424–30.
7. Johal S, Nakano N, Baxter M, *et al*. Unicompartmental knee arthroplasty: The past, current controversies, and future perspectives. Journal of Knee Surgery. 2018;31(10):992–8.
8. Liddle AD, Pandit H, Judge A, *et al*. Patient-reported outcomes after total and unicompartmental knee arthroplasty: A study of 14 076 matched patients from the national joint registry for EngLand and Wales. Bone and Joint Journal. 2015 Jun 1;97-B(6):793–801.
9. Amendola A, Bonasia DE. Results of high tibial osteotomy: Review of the literature. International orthopaedics. 2010 Feb;34(2):155–60.
10. Dean CS, Liechti DJ, Chahla J, *et al*. Clinical outcomes of high tibial osteotomy for knee instability: A systematic review. Orthopaedic Journal of Sports Medicine. 2016 Mar;4(3):2325967116633419.
11. Takahashi T, Baboolal TG, Lamb J, *et al*. Is knee joint distraction a viable treatment option for knee oa? – A literature review and meta-analysis. Journal of Knee Surgery. 2019 Aug;32(08):788–95.
12. Efe T, Ahmed G, Heyse TJ, *et al*. Closing-wedge high tibial osteotomy: Survival and risk factor analysis at long-term follow up. BMC Musculoskeletal Disorders. 2011;12.
13. Niinimäki TT, Eskelinen A, Mann BS, *et al*. Survivorship of high tibial osteotomy in the treatment of osteoarthritis of the knee: Finnish registry-based study of 3195 knees. Journal of Bone and Joint Surgery British Volume. 2012 Nov;94(11):1517–21.
14. Jansen MP, Besselink NJ, van Heerwaarden RJ, *et al*. Knee joint distraction compared with high tibial osteotomy and total knee arthroplasty: Two-year clinical, radiographic, and biochemical marker outcomes of two randomized controlled trials. Cartilage. 2019 Feb 13;194760351982843.
15. Jung WH, Takeuchi R, Chun CW, *et al*. Comparison of results of medial opening-wedge high tibial osteotomy with and without subchondral drilling. Arthroscopy – Journal of Arthroscopic and Related Surgery. 2015 Apr 1;31(4):673–9.
16. Jung WH, Takeuchi R, Chun CW, *et al*. Second-look arthroscopic assessment of cartilage regeneration after medial opening-wedge high tibial osteotomy. Arthroscopy – Journal of Arthroscopic and Related Surgery. 2014 Jan;30(1):72–9.
17. Intema F, van Roermund PM, Marijnissen ACA, *et al*. Tissue structure modification in knee osteoarthritis by use of joint distraction: An open 1-year pilot study. Annals of the Rheumatic Diseases. 2011 Aug 1;70(8):1441–6.
18. Wiegant K, van Roermund PM, Intema F, *et al*. Sustained clinical and structural benefit after joint distraction in the treatment of severe knee osteoarthritis. Osteoarthritis and Cartilage. 2013 Nov;21(11):1660–7.

19. van der Woude JAD, Wiegant K, van Roermund PM, *et al*. Five-year follow-up of knee joint distraction: Clinical benefit and cartilaginous tissue repair in an open uncontrolled prospective study. Cartilage. 2017;8(3):263–71.

20. Jansen MP, van der Weiden GS, van Roermund PM, *et al*. Initial tissue repair predicts long-term clinical success of knee joint distraction as treatment for knee osteoarthritis. Osteoarthritis and Cartilage. 2018;26(12):1604–8.

21. van der Woude JAD, Wiegant K, van Heerwaarden RJ, *et al*. Knee joint distraction compared with total knee arthroplasty: A randomised controlled trial. Bone and Joint Journal. 2017;99-B(1):51–8.

22. van der Woude JAD, Wiegant K, van Heerwaarden RJ, *et al*. Knee joint distraction compared with high tibial osteotomy: A randomized controlled trial. Knee Surgery, Sports Traumatology, Arthroscopy. 2017;25(3):876–86.

23. Jansen MP, Mastbergen SC, van Heerwaarden RJ, *et al*. Knee joint distraction in regular care for treatment of knee osteoarthritis: A comparison with clinical trial data. PLOS ONE. 2020 Jan 22;15(1).

24. Jansen MP, Boymans TAEJ, Custers RJH, *et al*. Knee joint distraction as treatment for osteoarthritis results in clinical and structural benefit: A systematic review and meta-analysis of the limited number of studies and patients available. Cartilage. 2020 Jul 22;194760352094294.

25. Wiegant K, van Heerwaarden R, van der Woude JAD, *et al*. Knee joint distraction as an alternative surgical treatment for osteoarthritis: Rationale and design of two randomized controlled trials (*vs* high tibial osteotomy and total knee prosthesis). International Journal of Orthopaedics. 2015 Aug 23;2(4):353–60.

26. Martineau PA, Fening SD, Miniaci A. Anterior opening wedge high tibial osteotomy: the effect of increasing posterior tibial slope on ligament strain. Journal Canadien de Chirurgie. 2010 Aug;53(4):261–7.

27. Wirth W, Eckstein F. A technique for regional analysis of femorotibial cartilage thickness based on quantitative magnetic resonance imaging. IEEE Transactions on Medical Imaging. 2008 Jun;27(6):737–44.

28. Buck RJ, Wyman BT, Graverand MPH Le, *et al*. An efficient subset of morphological measures for articular cartilage in the healthy and diseased human knee. Magnetic Resonance in Medicine. 2010 Mar;63(3):680–90.

29. Eckstein F, Buck R, Wirth W. Location-independent analysis of structural progression of osteoarthritis – Taking it all apart, and putting the puzzle back together makes the difference. Seminars in Arthritis and Rheumatism. 2017 Feb;46(4):404–10.

30. Buckland-Wright JC, Wolfe F, Ward RJ, *et al*. Substantial superiority of semiflexed (MTP) views in knee osteoarthritis: a comparative radiographic study, without fluoroscopy, of standing extended, semiflexed (MTP), and schuss views. Journal of Rheumatology. 1999 Dec;26(12):2664–74.

31. Buckland-Wright JC, Ward RJ, Peterfy C, *et al*. Reproducibility of the semiflexed (metatarsophalangeal) radiographic knee position and automated measurements of medial tibiofemoral joint space width in a multicenter clinical trial of knee osteoarthritis. Journal of Rheumatology. 2004 Aug;31(8):1588–97.

32. Marijnissen ACA, Vincken KL, Vos PAJM, *et al*. Knee Images Digital Analysis (KIDA): A novel method to quantify individual radiographic features of knee osteoarthritis in detail. Osteoarthritis and Cartilage. 2008 Feb 1;16(2):234–43.

33. Eckstein F, Buck RJ, Burstein D, *et al*. Precision of 3.0 Tesla quantitative magnetic resonance imaging of cartilage morphology in a multicentre clinical trial. Annals of the Rheumatic Diseases. 2008 Dec;67(12):1683–8.

34. Graichen H, Eisenhart-Rothe R V., Vogl T, *et al*. Quantitative assessment of cartilage status in osteoarthritis by quantitative magnetic resonance imaging: Technical validation for use in analysis of cartilage volume and further morphologic parameters. Arthritis and Rheumatism. 2004 Mar;50(3):811–6.

35. Husted JA, Cook RJ, Farewell VT, *et al*. Methods for assessing responsiveness: A critical review and recommendations. Journal of Clinical Epidemiology. 2000;53(5):459–68.

36. Buck RJ, Wyman BT, Hellio Le Graverand MP, *et al*. Osteoarthritis may not be a one-way-road of cartilage loss – Comparison of spatial patterns of cartilage change between osteoarthritic and healthy knees. Osteoarthritis and Cartilage. 2010 Mar;18(3):329–35.

37. Wirth W, Hellio Le Graverand MP, Wyman BT, *et al*. Regional analysis of femorotibial cartilage loss in a subsample from the Osteoarthritis Initiative progression subcohort. Osteoarthritis and Cartilage. 2009;

38. Thambiah M, Tan M, Hui J. Role of high tibial osteotomy in cartilage regeneration – Is correction of malalignment mandatory for success? Indian Journal of Orthopaedics. 2017 Oct;51(5):588–99.

39. Moyer R, Birmingham T, Lorbergs A, *et al*. Decreased medial compartment loading and increased medial femorotibial articular cartilage thickness 12 months after limb realignment surgery. Osteoarthritis and Cartilage. 2018 Apr;26:S279–80.

40. Moyer R, Birmingham T, Eckstein F, *et al*. Validation of a novel blinding method for measuring postoperative knee articular cartilage using magnetic resonance imaging. Magnetic Resonance Materials in Physics, Biology and Medicine. 2019 Dec;32(6):693–702.

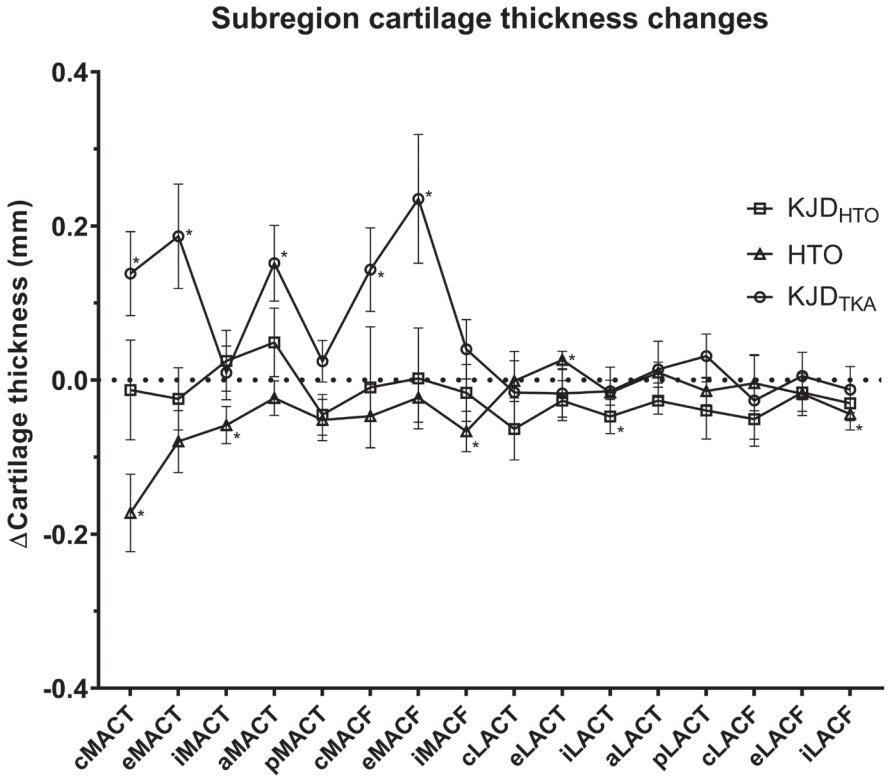
SUPPLEMENTARY DATA

Supplementary results

Longitudinal changes by patient group

Subregions

Cartilage thickness changes in the 16 subregions are shown in Supplementary Figure 1 for each of the 3 groups. The KJD_{HTO} group did not show statistically significant thickness changes in any of the regions, except for a small but statistically significant decrease in the internal LAC tibia. The HTO group showed a statistically significant cartilage thickness decrease in the central tibia, internal tibia, and internal femoral areas of the MAC and internal femoral area of the LAC, while the external tibial LAC area showed a statistically significant increase. The KJD_{TKA} group showed a significant increase in cartilage thickness in the central, anterior, and external areas of the tibia and femur of the MAC, while the internal and posterior areas of the MAC and all areas in the LAC showed no statistically significant change over time.



Supplementary Figure S1: Two-year cartilage thickness changes in each of the 16 subregions. Subregions are the central (c), external (e), internal (i), anterior (a) and posterior (p) parts of the tibia (T) and the central, external and internal parts of the femur (F) for both the most (MAC) and least (LAC) affected compartment. HTO: high tibial osteotomy; KJD_{HTO}: knee joint distraction (KJD) patients from the HTO trial; KJD_{TKA}: KJD patients from the total knee arthroplasty trial. Significant 2-year changes are indicated with *. Means and standard errors are shown.

Location-independent results

The location-independent cartilage thickening scores were 0.81mm (SD 0.93) for KJD_{HTO}, 0.55 (0.48) for HTO, and 1.62 (0.95) for KJD_{TKA}. The thinning scores were -1.14 (0.95) for KJD_{HTO}, -1.14 (1.48) for HTO, and -0.72 (0.69) for KJD_{TKA}. Kruskal-Wallis tests showed no statistically significant difference between the 3 groups in thinning scores (p=0.23) but the thickening score was significantly greater for KJD_{TKA} than for the other 2 groups as confirmed by post-hoc Dunn tests (KJD_{HTO} p=0.016; HTO p=0.001). Yet, this was no longer true for the comparison KJD_{TKA} *versus* KJD_{HTO} when correcting for significantly different baseline characteristics using linear regression (p=0.505).

Prediction of cartilage thickness changes

A multivariable linear regression model, using patient baseline characteristics and baseline MAC cartilage thickness as independent variables, revealed that only the Kellgren-Lawrence grade was a significant predictor (B=0.105; p=0.01) of MAC cartilage thickness change in all KJD and HTO patients together: a higher Kellgren-Lawrence grade was associated with in a greater increase in cartilage thickness during treatment.

Using treatment as independent variable resulted in a better fit of the univariable model (R^2=0.120 with p=0.004 compared to R^2=0.095 with p=0.01), therefore KJD and HTO treated patients were evaluated in separate models as well. For HTO patients, none of the parameters, including leg axis deviation, significantly predicted the MAC cartilage thickness or JSW change. In contrast, in KJD patients a multivariable linear regression model left only Kellgren-Lawrence grade as a significant predictor for MAC cartilage thickness change.

Univariable models showed that patient age (B=0.018; R^2=0.128; p=0.04), baseline MAC cartilage thickness (B=-0.165; R^2=0.207; p=0.006) and patient group KJD_{TKA}/KJD_{HTO} (B=-0.245; R^2=0.133; p=0.03) significantly predicted cartilage change as well, but Kellgren-Lawrence grade (B=0.174; R^2=0.255; p=0.002) remained the strongest predictor.

Longitudinal changes by baseline severity

Sensitivity analyses

Supplementary Table S1: Sensitivity analyses for comparisons where patients were included in different trials

	KJD_{mild} *vs* KJD_{severe}		KJD_{mild} *vs* HTO_{mild}		KJD_{severe} *vs* HTO_{severe}	
	Difference	***P***	**Difference**	***P***	**Difference**	***P***
MAC ThCtAB (mm)	0.42 (0.15 to 0.68)	**0.003**	0.09 (-0.08 to 0.27)	0.289	-0.31 (-0.59 to 0.03)	**0.031**
MAC dABp (%)	-5.9 (-13.8 to 2.0)	0.139	-1.4 (-4.5 to 1.7)	0.351	7.5 (-0.8 to 15.9)	0.075
Mean MAC JSW (mm)	0.61 (-0.35 to -1.57)	0.204	0.48 (-0.03 to 1.00)	0.064	-0.16 (-1.11 to 0.80)	0.742

Differences are shown with mean and 95% confidence interval. Differences between groups and corresponding *p*-values were calculated with linear regression, correcting for statistically significantly different baseline characteristics and the trial in which patients were included; bold *p*-values indicate statistical significance ($p<0.05$). dABp: percentage of denuded subchondral bone area; HTO: high tibial osteotomy; JSW: joint space width; KJD_{HTO}: knee joint distraction (KJD) patients with indication HTO; KJD_{TKA}: KJD patients with indication total knee arthroplasty; LAC: least affected compartment; MAC: most affected compartment; ThCtAB: mean cartilage thickness over the total subchondral bone area.

Supplementary discussion

In KJD patients, the anterior region of the MAC tibia and the central and external regions of the MAC tibia and femur clearly showed the most substantial cartilage restoration. The baseline cartilage thickness in the central femur and external tibia and femur was much smaller than that of the other regions (≥40%; data not shown). This could explain the greater restoration in these 3 areas. In another MRI cartilage study, the anterior tibial region has been shown to be frequently involved in both thickening and thinning of cartilage.[36] Similarly, in another study, the central tibial and femoral regions showed a greater loss of cartilage than the other regions.[37] As such, the higher rate of cartilage restoration at the central, anterior, and external parts of the MAC may be the result of natural sensitivity to change.

CHAPTER 15

Cartilage collagen structure upon knee joint distraction and high tibial osteotomy as measured with T2-mapping MRI

M.P. Jansen
S.C. Mastbergen
W. Wirth
S. Spruijt
R.J.H. Custers
R.J. van Heerwaarden
F.P.J.G. Lafeber

Submitted for publication

Abstract

Background: High tibial osteotomy (HTO) and knee joint distraction (KJD) are joint-preserving knee osteoarthritis (OA) treatments that have previously shown good clinical results and cartilage thickness increase. The objective of this exploratory study was to evaluate the change in cartilage T2 relaxation times, as a measure of collagen structure, after treatment with HTO or KJD, and compare this to natural OA progression.

Methods: Ten patients indicated for total knee arthroplasty (TKA) were treated with KJD (KJD_{TKA}). Thirty patients indicated for HTO were treated with KJD (KJD_{HTO}; n=10) or HTO (n=20). 3T T2-mapping MRI scans were performed before and 1 (KJD groups only) and 2 years after treatment, from which cartilage was segmented and the volume and T2 relaxation times were calculated. Patients were matched with untreated patients from the Osteoarthritis Initiative (OAI) to compare the change in T2 values over time.

Results: KJD_{HTO} (n=8) and HTO (n=17) patients both showed statistically significant increases in T2 values but no volume changes. KJD_{TKA} patients (n=8) only showed a tendency for (first-year) T2 value increase, and a significant volume increase in the most affected compartment (MAC). There were no significant differences between the 3 groups. All treated patients combined showed a significantly higher increase in T2 times than untreated patients from the OAI for both femur and tibia.

Conclusion: KJD and HTO treatment result in a significant T2 value increase. In TKA-indicated KJD patients, this goes paired with volume increase, indicating it may be the result of maturation of newly formed cartilage.

Introduction

Cartilage degeneration and substance loss are hallmark features of knee osteoarthritis (OA). Cartilage thinning is an important parameter in the diagnosis of knee OA, in staging its severity and as outcome measure for monitoring disease progression and treatment effect.[1,2] Traditionally, cartilage thickness changes have been evaluated indirectly from radiographic joint space narrowing. Nowadays, MRI is frequently used for semi-quantitative scoring of OA-related parameters, but also to quantitatively measure cartilage thickness.[3,4] Quantitative analyses typically rely on 3D spoiled gradient recalled imaging sequences with fat suppression, which have been validated for measuring cartilage thickness and volume, but do not provide much information about cartilage quality.[5] In order to measure quality, sequences that can visualize cartilage composition are required, such as delayed gadolinium-enhanced MRI of cartilage (dGEMRIC) and T2-mapping.[6,7] dGEMRIC MRI allows to depict the distribution of glycosaminoglycans, whereas T2-mapping is sensitive to changes in water content and the collagen fiber network, reflecting collagen content and orientation.[8,9] Compared to healthy cartilage, OA cartilage shows higher T2 relaxation times, as a result of loss of collagen content and matrix anisotropy (structure) and subsequent increase in permeability and water content.[8,10–12] T2-mapping is frequently used in observational studies[5], but has also been applied to investigate cartilage quality after cartilage defect treatment, where quality of the repair tissue can be compared to that of the surrounding native cartilage.[7,10,13] Cartilage T2-mapping is, however, not typically applied to evaluate the effect of joint-preserving surgical treatments for severe OA in whole (tibiofemoral) cartilage plates.

Two such treatments are high tibial osteotomy (HTO) and knee joint distraction (KJD), both used in younger knee OA patients to postpone a knee arthroplasty (KA). In KJD, the tibia and femur are temporarily placed at a distance with an external fixation frame, unloading the tibiofemoral compartments. In HTO, the mechanical leg axis is (over)corrected by wedging the bone, unloading the most affected compartment (MAC) permanently.[14,15] Both treatments have shown not only good and comparable clinical results, but also cartilage restoration activity, demonstrated by radiographs, MRI-based cartilage thickness, and second-look arthroscopy as well as biochemical marker analyses.[16–23] Cartilage quality was previously evaluated with dGEMRIC, which showed that values after KJD and HTO treatment were on average not different from pre-treatment.[24] T2-mapping, however, has not yet been assessed and compared. The objective of this exploratory study was to evaluate cartilage T2 relaxation times as a measure of collagen structure before and after treatment with KJD and with HTO, and compare results between the 2 treatments. To compare these results to natural progression that might be expected in comparable, untreated OA patients, retrospective data from the Osteoarthritis Initiative (OAI) was used.

Methods

Patients

Patients were included from 2 randomized controlled trials (RCTs). In 1 RCT, patients below the age of 65 years with indication total knee arthroplasty (TKA) were randomized to KJD (n=20) or TKA (n=40) treatment. In a separate RCT, patients with medial compartmental knee OA who in regular care were considered for HTO for medial compartmental knee OA were randomized to KJD (n=23) or HTO (n=46) treatment. Inclusion and exclusion criteria for both trials were primarily based on the indication TKA or HTO have been described previously; they included age <65 years old, Kellgren-Lawrence grade (KLG) >2 (judged by orthopedic surgeon), no history of inflammatory disease, no surgical treatment of the involved knee <6 months ago, and no primary patellofemoral OA.[17,25]

After inclusion in 1 of the 2 RCTs, patients randomized to treatment with KJD or HTO were asked to participate in an extended imaging protocol, extending the standard MRI scans performed in all patients with additional modalities, including T2-mapping. The first 20 HTO patients and the first 20 KJD patients (irrespective of the trial from which they originated) who gave written informed consent for the extended imaging protocol were included. From the KJD *versus* TKA trial, 10 KJD patients were included (KJD_{TKA}); from the KJD *versus* HTO trial 10 KJD patients (KJD_{HTO}) and 20 HTO patients were included. It was previously shown that patient demographics of these subgroups of KJD and HTO patients participating in the extended imaging protocol did not significantly differ from the original KJD and HTO groups, except for the proportion of male patients that was significantly higher in the whole HTO group, which was considered coincidental.[24]

The original RCTs and the extended imaging protocol were granted ethical approval by the medical ethical review committee of the University Medical Center Utrecht (protocol numbers 10/359/E, 11/072 and 11/482/E). All patients gave written informed consent.

Treatment

The KJD treatment protocol has been extensively described previously.[15,25] In short, at surgery an external fixation device consisting of 2 dynamic monotubes was fixed medially and laterally of the knee joint, using bone pins. Over 3 days, the joint was gradually distracted to a total of 5 mm, confirmed radiographically, after which patients were discharged and allowed full weight-bearing, supported by crutches if needed. After 6 weeks of distraction, the frame was removed at day treatment, without further imposed rehabilitation protocol.

For HTO treatment, biplane medial-based opening-wedge osteotomy was performed. Patients were discharged after 3 days, followed by 6 weeks of limited weight-bearing. At 18 months, the plate was removed to allow imaging at 2 years.

Image acquisition

Multi-slice multi-echo spin-echo (MSME) T2-mapping scans were performed on a clinical 3T MRI scanner (Achieva 3T; Philips Medical Systems) using a 16-channel knee coil. T2 relaxation times were obtained from T2 maps reconstructed using sagittal SE acquisition, with 8 echo times (TE) of 10, 20, 30, 40, 50, 60, 70, and 80 ms. The slice thickness was 3 mm, with a pixel matrix of 640x640 and a pixel size of 0.25x0.25 mm. In the same session, a sagittal proton-density weighted (PDW) scan with fat suppression was performed, with an echo time of 40 ms, slice thickness of 2.7 mm, pixel matrix of 528x528 mm and pixel size of 0.30x0.30 mm.

Scans were performed before treatment (baseline) and at 1 years and 2 years after treatment. HTO patients did not undergo MRI scans at 1 year due to the metal-plate *in situ*. Only patients with scans available for analysis at baseline and 2-year follow-up were included in this study.

Image analysis

Segmentation was performed thrice for all images, by 3 independent observers (MJ, NB, CN). Based on initial experimental segmentation, a consensus was reached between the 3 observers on how to perform the segmentations. The knee joint was divided in 4 regions: lateral femur, medial femur, lateral tibia, and medial tibia. Segmentation began from the center of the joint and was performed on 7 slices, counting outwards from the first slice without cruciate ligaments. As was done for the dGEMRIC analyses in this same group of patients, regions reached until the most anterior part of the tibia plateau; the posterior tibial region reached until the most posterior part of the tibia plateau; and the posterior femoral regions encompassed all visible cartilage.[24] Regions of interests (ROI) were drawn on the PDW images using in-house developed software (Experimental Analysis, Image Sciences Institute) and automatically applied on the T2-mapping images, where manual corrections could be performed if necessary.

From all scans, the volume (mm^3) and T2 relaxation times (ms) were calculated for each of the 4 segmented regions. Pixels with T2 relaxation times >100 ms were excluded, as these were not realistic for cartilage, but instead likely represented the bone edge included in the ROI. An example image with the included ROI is shown in Figure 1.

Untreated control group

The OAI used a comparable protocol with somewhat lower resolution for the acquisition of MSME MRIs.[26] Cartilage T2 times from the OAI were based on a quality-controlled manual segmentation of femorotibial cartilages and were used as an untreated group of OA patients. Cartilage T2 times were available at baseline, 1 year, and 4 years from previous analyses.[27,28] From the available subset of OAI knees with T2-mapping results, control patients were selected

with case-control matching, attempting to find a matched control patient for all treated (KJD and HTO) patients pre-treatment. Case-control matching was performed separately for the tibia (average of medial and lateral tibia) and femur (average of weight-bearing part of medial and lateral femur) and based on baseline T2 relaxation times as well as patient characteristics that had a significant influence on changes in T2 values in either group (treated or untreated). Tolerances were chosen as small as possible, while still ensuring the majority of treated patients could be matched with untreated OAI patients.

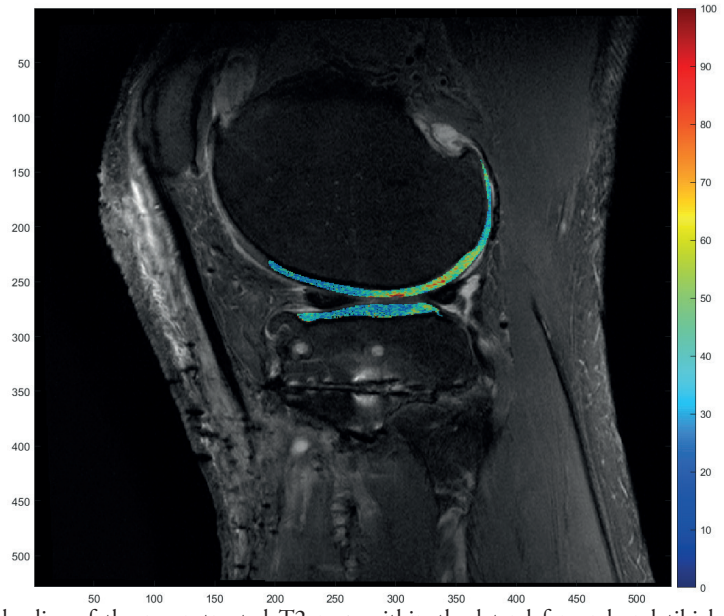


Figure 1: Example slice of the reconstructed T2 map within the lateral femoral and tibial region of interest, superimposed on a proton density weighted scan.

Statistical analysis

Baseline differences between the 3 groups (2 KJD groups because of the different indication) were calculated with 1-way ANOVA and, in case of statistically significant differences, post-hoc Tukey HSD tests.

The intraclass correlation coefficient (ICC) between the 3 observers was calculated for all T2 relaxation times and cartilage volumes, for each of the regions separately and combining all time points, using a 2-way random model with absolute agreement. Assuming a good ICC for average measures, the results of the 3 observers were averaged to obtain the final T2 relaxation times and cartilage volumes. ICCs were interpreted according to the definitions of Koo and Li: an ICC <0.50 was considered poor, 0.50< ICC >0.75 was moderate, 0.75< ICC >0.90 was good, and ICC >0.90 was excellent.[29]

Since previous research has shown that structural results are often significantly different between

the most affected compartment (MAC) and least affected compartment (LAC) of the joint, which were determined at patient inclusion, results were separated in the MAC and LAC femur and tibia (instead of medial and lateral femur and tibia). For both KJD groups (for KJD_{TKA} and for KJD_{HTO}), the changes over time were calculated using repeated measures ANOVA. For differences in changes between these groups, mixed ANOVA was used, correcting for significantly different baseline characteristics. For the HTO group, the changes over time were calculated using paired *t*-tests, since only 2 time points were available. For differences in 2-year changes between HTO and KJD_{HTO}, linear regression was used, correcting for baseline values and significantly different baseline characteristics.

Pearson correlations were calculated between 1- and 2-year changes in T2 values and volumes, for each compartment and group separately.

Since different time points were available for KJD patients, HTO patients and OAI patients, regression coefficients were calculated for the average tibia and average femur T2 relaxation times for each patient separately, including all available time points, to represent changes over time (ms/year). These coefficients were used to calculate the influence of baseline characteristics on the change in tibia and femur T2 relaxation times for each of the 3 treated patient groups and the untreated OAI patients separately, using linear regression. Each characteristic and baseline value was evaluated in separate models.

To compare treated patients with the matched OAI untreated patients, regression coefficients were compared using linear regression, correcting for statistically significant differences in baseline characteristics between the groups.

Continuous variables are given with mean and standard deviation, categorical variables with n and %; changes over time are given with mean change and 95% confidence interval (CI). For all tests, $p<0.05$ was considered statistically significant.

Results

Patients

For the KJD patients, 4 patients did not have complete T2-mapping datasets because of either motion artifacts, refusal for follow-up or conversion to another treatment (HTO or TKA), resulting in 8 KJD_{TKA} and 8 KJD_{HTO} patients. For the HTO patients, 3 patients did not receive the extended imaging at 2 years: 1 was MRSA positive and no imaging was performed, 1 did not want the metal plate removed at 18 months, and 1 converted to another treatment. As such, 17 HTO patients could be analyzed.

The baseline characteristics of the 3 patient groups are shown in Table 1. KJD_{TKA} patients had a higher age than HTO patients, and a higher KLG than KJD_{HTO} and HTO patients. There were no statistically significant differences between KJD_{HTO} and HTO.

Table 1: Baseline parameters of the 3 patient groups

	KJD_{TKA} (n=8)	KJD_{HTO} (n=8)	HTO (n=17)	*P*-value
Age (years)	57.8 (6.3)	50.9 (7.7)	48.9 (6.3)	**0.014**
BMI (kg/m^2)	26.9 (3.7)	27.7 (3.9)	26.7 (2.8)	0.785
Male sex, n (%)	4 (50)	6 (75)	12 (71)	0.530*
Medial MAC, n (%)	6 (75)	8 (100)	8 (100)	**0.034***
Kellgren-Lawrence, n (%)				**0.002***
- Grade 0	0 (0)	0 (0)	0 (0)	
- Grade 1	0 (0)	1 (13)	2 (12)	
- Grade 2	0 (0)	1 (13)	7 (41)	
- Grade 3	3 (38)	6 (75)	7 (41)	
- Grade 4	5 (63)	0 (0)	1 (4)	
Baseline T2 relaxation times (ms)				
MAC tibia	48.1 (2.8)	47.4 (4.1)	47.9 (4.8)	0.932
MAC femur	55.0 (2.4)	53.7 (1.9)	54.9 (3.3)	0.571
LAC tibia	43.1 (2.3)	40.3 (3.2)	41.4 (3.5)	0.231
LAC femur	52.8 (2.4)	52.0 (3.0)	53.4 (4.9)	0.778
Baseline volumes (mm^3)				
MAC tibia	876 (285)	1496 (502)	1432 (466)	**0.011**
MAC femur	2074 (289)	2967 (712)	2802 (636)	**0.010**
LAC tibia	1962 (632)	2074 (523)	2022 (282)	0.882
LAC femur	3776 (1352)	3745 (774)	3463 (700)	0.646

Mean and standard deviation or n (%) are shown. *P*-values are calculated with 1-way ANOVA, with post-hoc Tukey HSD tests in case of statistical significance (bold *p*-values; $p<0.05$), or chi-square tests (indicated with *). All statistically significant differences were between KJD_{TKA} and HTO (age and medial MAC) or KJD_{TKA} and both other groups. There were no statistically significant differences between KJD_{HTO} and HTO. HTO: high tibial osteotomy; KJD_{HTO}: knee joint distraction (KJD) patients with indication HTO; KJD_{TKA}: KJD patients with indication total knee arthroplasty; LAC: least affected compartment; MAC: most affected compartment.

T2-mapping results after treatment

For both T2 relaxation times and volumes, ICC values showed good (all femur ICCs) or excellent (all tibia ICCs) agreement between the observers (Supplementary Table S1).

Baseline T2 times and volumes are shown in Table 1. There were no statistically significant differences between the groups in T2 times. The KJD_{TKA} group showed significantly lower volumes for the MAC tibia and femur than the KJD_{HTO} and HTO groups.

Changes in T2 relaxation time in the 3 separate groups are shown in Figure 2 (baseline is set to 0). The KJD_{TKA} group did not show statistically significant changes over time (all $p>0.1$), but

did show a trend of a 1-year increase followed by a slight decrease (for the MAC) or plateau (for the LAC) between 1 and 2 years. The KJD_{HTO} group showed an increase in T2 times, which was statistically significant for all regions (all $p<0.025$) except the LAC femur ($p=0.054$). HTO patients showed a significant T2 time increase in all regions (all $p<0.006$). There were no significant differences between groups (all $p>0.08$).

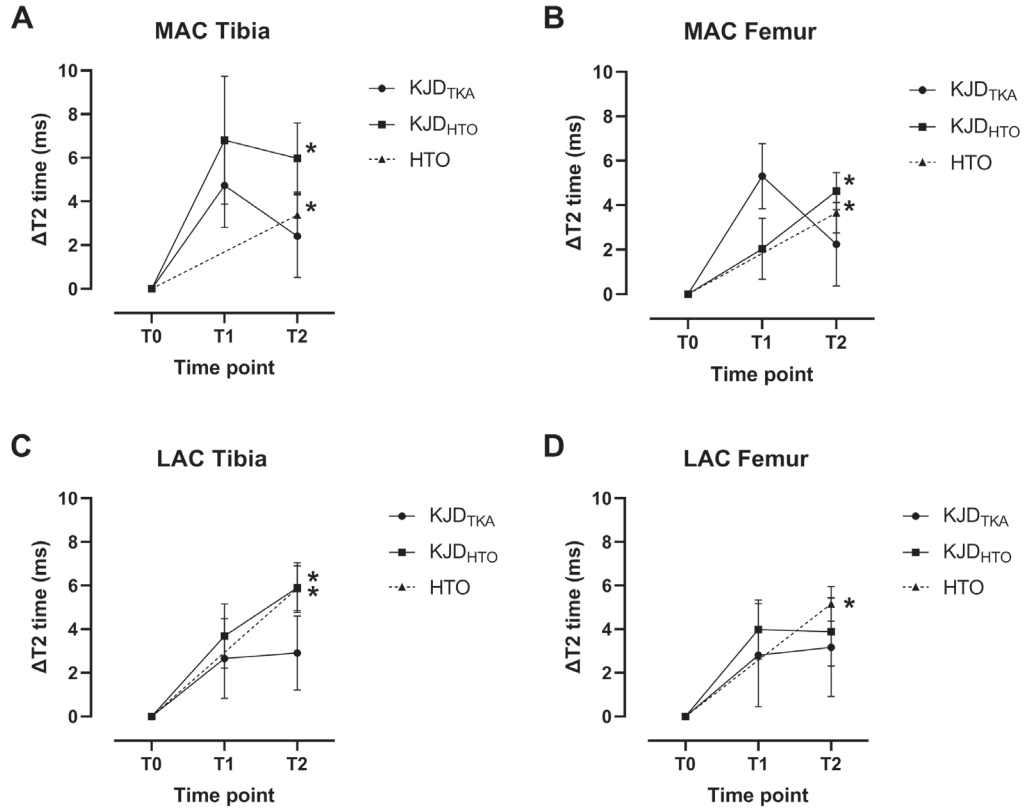


Figure 2: Baseline-corrected T2 relaxation times for the 3 patient groups: patients indicated for total knee arthroplasty (TKA) and treated with knee joint distraction (KJD), patients indicated for high tibial osteotomy (HTO) and treated with KJD, and patients indicated for and treated with HTO. Changes are split per compartment: (A) the tibia of the most affected compartment (MAC), (B) the femur of the MAC, (C) the tibia of the least affected compartment (LAC), (D) the femur of the LAC. * indicates statistically significant changes ($p<0.05$), for the KJD groups calculated with repeated measures ANOVA and for the HTO group calculated with paired *t*-tests.

Changes in segmented cartilage volumes in the 3 groups are shown in Figure 2 (baseline is set to 0). Only the KJD_{TKA} group showed significant volume increases in the MAC, statistically significant for the tibia ($p=0.004$) but not the femur ($p=0.052$). The other groups did not show clear volume changes (all $p\geq0.1$). The changes in MAC tibia volume were significantly different between KJD_{TKA} and KJD_{HTO} ($p=0.029$), but not when corrected for KLG ($p=0.457$), which was significantly different between the two.

Pearson correlations between 1- or 2-year changes in T2 values and volumes were not statistically significant for any of the compartments or groups (all p>0.09), except for the 2-year LAC femur changes in the HTO group (R=-0.660; p=0.004).

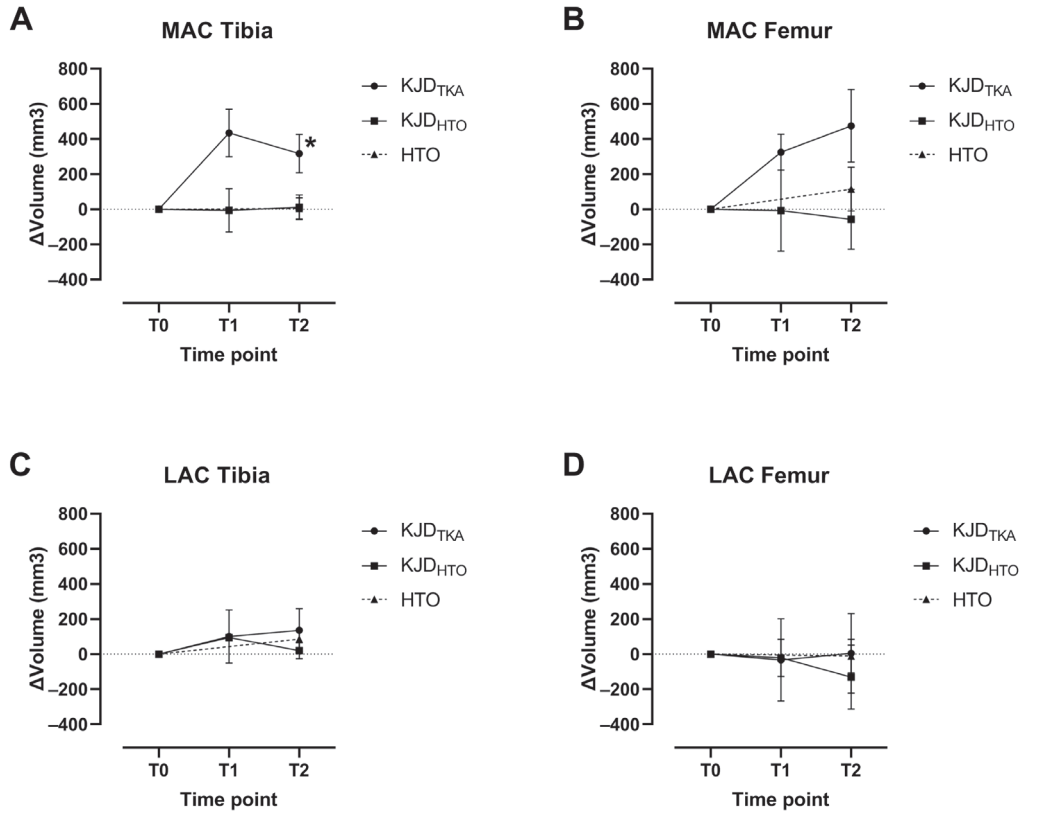


Figure 3: Baseline-corrected segmented volumes for the 3 patient groups: patients indicated for total knee arthroplasty (TKA) and treated with knee joint distraction (KJD), patients indicated for high tibial osteotomy (HTO) and treated with KJD, and patients indicated for and treated with HTO. Changes are split per compartment: (A) the tibia of the most affected compartment (MAC); (B) the femur of the MAC; (C) the tibia of the least affected compartment (LAC); (D) the femur of the LAC. * indicates statistically significant changes (p<0.05), for the KJD groups calculated with repeated measures ANOVA and for the HTO group calculated with paired t-tests.

Influence of baseline characteristics

Combining the MAC and LAC, in the KJD_{TKA} group, only age had a significant positive effect on the change in T2 relaxation times in the tibia (B=0.310, p=0.023) and baseline T2 time had a significant negative effect on the change in the femur (B=-0.629, p=0.019). In the KJD_{HTO} group, none of the baseline characteristics or T2 values had a statistically significant influence. In the HTO group, BMI (B=-0.365, p=0.002) and baseline T2 time (B=-0.234, p=0.015) had a significant negative effect on the change in the femur.

Comparison with Osteoarthritis Initiative

Regression analysis investigating the influence of baseline measures on cartilage T2 change were calculated from the (combined medial and lateral) femur and tibia using T2 times of 421 OAI participants that had at least 2 time points available. None of the patient characteristics had a significant influence on these changes over time, but baseline T2 times were negatively associated with the change in T2 times in the tibia (B=-0.070, p=0.001) and femur (B=-0.079, p<0.001), respectively. In all treated (KJD and HTO) patients together, only BMI (B=-0.209, p=0.029) and baseline femur T2 times (B=-0.330, p<0.001) had a significant influence on the change in femur T2 relaxation times. As such, case control matching between treated and untreated patients was based on baseline T2 values and BMI. For both the tibia and femur, tolerances of 4 ms and 5 kg/m^2 resulted in a match for all but 1 treated patient for tibia and femur.

Changes over time as represented by regression coefficients are shown for all treated (KJD and HTO) patients together and the matched OAI patients in Figure 4. Treated patients showed an increase of 2.2 (95%CI 1.5–3.0) ms/year in the tibia and 2.1 (1.4–2.7) ms/year in the femur; Cartilage T2 in untreated OAI patients showed no change with 0.1 (-0.2 to 0.4) ms/year in the tibia and -0.1 (-0.8 to 0.7) ms/year in the femur.

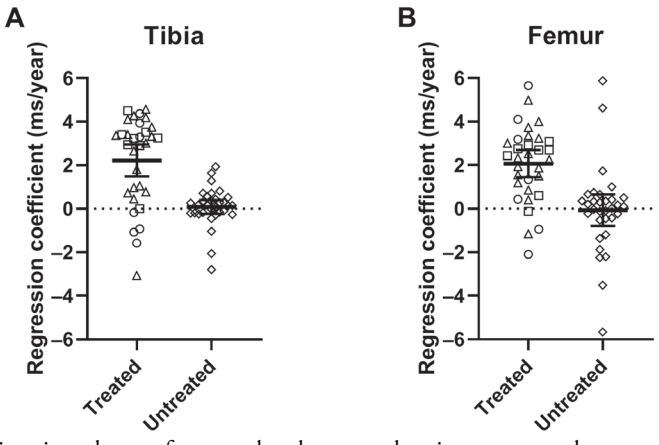


Figure 4: T2 relaxation time changes for treated and untreated patients, expressed as regression coefficients (ms/year), for (A) the tibia and (B) the femur. Treated patients consisted of 32 patients treated with knee joint distraction (indicated for total knee arthroplasty (circles) or high tibial osteotomy (squares) or high tibial osteotomy (triangles); untreated patients consisted of 32 patients from the Osteoarthritis Initiative matched separately for the tibia and femur (diamonds), based on baseline T2 values and BMI.

For both the tibia and femur matched patients, patient age, baseline T2 relaxation time, sex, and KLG were statistically significantly different between the 2 groups (all p<0.03). Corrected for these parameters, differences in T2 relaxation time changes were statistically significantly different between treated and untreated patients for the tibia (p=0.003) and femur (p<0.001).

Discussion

After treatment with KJD or HTO, an increase in cartilage T2 relaxation times was observed throughout the entire joint, similar between the 2 treatments and larger than could be expected as a result of natural OA progression alone. In TKA-indicated KJD patients the T2 value increase was not statistically significant.

An increase in T2 relaxation times can be the result of higher water content, lower collagen concentration, loss of collagen framework integrity, or a combination.[9] Remarkably, patients treated with KJD showed an initial T2 value increase in the first year after treatment, but a stabilization or even a decrease between 1 and 2 years post-treatment, especially in TKA-indicated patients. This might be a delayed effect of the 6-week unloading in KJD treatment: articular cartilage may need loading for normal structuring of the collagen framework. A previous study applying T2-mapping of knee cartilage showed that 45 minutes of unloading (lying down) resulted in a T2 relaxation time increase (+0.9 ms), an effect that was even more pronounced in cartilage repair tissue (+4.3 ms) and the authors speculated it was the result of hydration and/or reorganization of the collagen organization.[30] As such, it is not unthinkable that 6-week unloading may still show its effects on the collagen structure 1 year after treatment.

Systemic collagen type II markers have previously been evaluated in multiple KJD cohorts, including the RCTs from which patients in the current study were included. Interestingly, all cohorts showed an initial decrease in net collagen type II synthesis (i.e. more breakdown than synthesis), which gradually increased and at 2 years after treatment showed a significant increase in net collagen type II synthesis.[17,31] This corresponds largely with the T2 relaxation times initially increasing and after 1 year decreasing, and suggests a short-term decrease in cartilage collagen content followed by a normalization after 1 year.

Only in TKA-indicated KJD patients, the increase in T2 relaxation times goes paired with a volume increase in the MAC. In a previous study optimized for cartilage thickness changes in patients from these RCTs, it was shown that KJD_{TKA} patients showed a significant increase in MAC cartilage thickness and decrease in denuded bone areas, indicating there is indeed new cartilage tissue formation.[18,32] The increase in T2 relaxation time could be the result of newly formed cartilage that needs time to mature. A T2-mapping study in children and adolescents showed that skeletal maturation in children caused a decrease in T2 relaxation times, potentially caused by increasing collagen content as a result of maturation.[33] Furthermore, T2-mapping studies in patients with a cartilage defect showed higher initial T2-values for repair cartilage compared to normal cartilage that decreased over time, and histological studies in dogs treated with KJD suggested a somewhat delayed normalization based on proteoglycan turnover.[7,30,34,35] Newly formed, young, repair cartilage that needs time to mature could explain the 1-year T2 value increase and subsequent normalization that, at least in the MAC of TKA-indicated

KJD patients, goes paired with an increase in cartilage volume. Alternatively, the collagen orientation of newly formed cartilage could be simply be similar to the more superficial tissue that had been lost before, as T2 values are short in the deep layer, where the collagen is oriented perpendicular to the subchondral bone, and longer in the superficial layer, where the collagen fibers are oriented more parallel to the cartilage surface.[9] Either way, while it is tempting to draw direct conclusion on paired T2 value and volume increases, it is important to realize that the T2 values represent the entire cartilage and not just newly formed tissue.

In HTO-indicated KJD patients and HTO patients a significant increase in T2 values is seen, but no significant changes in cartilage volume, which corresponds with previous cartilage thickness results.[18] Although the increase in T2 values was significantly larger than in matched OAI patients, case-control matching between a late OA cohort (patients who need surgical treatment) and an early OA cohort (OAI) is not perfect, and the T2 value increase might still be the result of natural progression. The fact that a higher age and BMI had a positive influence on the T2 value increase is consistent with other studies showing natural progression.[10,36,37] Also, in patients treated with an autologous chondrocyte transplantation for a cartilage defect, an increase in T2 values of 2.8 ms in a 1–2 year period was seen in the healthy (control) cartilage.[7] It might be that any surgical intervention, or a change in weight-bearing as a result, already affects cartilage content or structure, regardless of what intervention is performed.

The difference between the KJD groups is somewhat surprising. In the larger MRI cartilage thickness study in the original RCT, it was shown that mild OA patients (KLG ≤2) did not show significant changes in cartilage thickness or denuded bone areas, while severe OA patients (KLG ≥3) showed significant regeneration. In the current study, mild and severe OA could not be compared, since by this definition only 2 KJD patients in the current study had mild OA. The original indication of TKA or HTO might still reflect a difference in somewhat more or less severe OA, as indicated by the significant baseline difference in MAC cartilage volume as well. As such, the different responses in the 2 groups might be because more severely affected patients show a better response to KJD. Anecdotally, the 2 KJD patients with a KLG of 1 and 2 showed a higher than average T2 value increase combined with a much higher than average decrease in cartilage volume.

A clear limitation of this study was sample size. While it provides interesting exploratory results that despite the small sample size could reach statistical significance, and correspond well previous results, a larger sample size would likely allow for stronger conclusions. It would be worthwhile to perform imaging studies in a larger group of patients, either 3T T2-mapping or more advanced sequences on a 7T scanner, and add more time points, including a scan immediately post-treatment. HTO patients could be included as well, although that may require changes to the treatment protocol. Imaging studies could be combined with synovial biomarker analyses to better interpret imaging analysis results.

Another limitation of this study was that we could not separate deep and artificial cartilage, as is done often in T2-mapping studies. Many patients showed severely degenerated joints, especially in the MAC, that at times barely had cartilage left and as such did not allow for segmentation of different layers.

In conclusion, treatment with KJD or HTO results in an increase in T2 relaxation times, which could indicate a progressive loss or a reorganization of collagen structure integrity. In the most severe KJD patients with indication TKA, this increase seems limited to the first year after treatment, after which the relative collagen content and structure improves. This may partly be the result of maturation of newly formed cartilage, since part of the KJD patients show a significant cartilage volume increase as well, which fits previous biochemical markers studies and animal studies on KJD.

References

1. Buckwalter JA, Martin JA. Osteoarthritis. Advanced Drug Delivery Reviews. 2006 May 20;58(2):150–67.
2. Kellgren JH, Lawrence JS. Radiological assessment of osteo-arthrosis. Annals of the Rheumatic Diseases. 1957 Dec 1;16(4):494–502.
3. Hunter DJ, Guermazi A, Lo GH, *et al*. Evolution of semi-quantitative whole joint assessment of knee OA: MOAKS (MRI Osteoarthritis Knee Score). Osteoarthritis and Cartilage. 2011 Aug;19(8):990–1002.
4. Eckstein F, Wirth W. Quantitative cartilage imaging in knee osteoarthritis. Arthritis. 2011 Dec 8;2011:1–19.
5. Gold GE, Chen CA, Koo S, *et al*. Recent advances in MRI of articular cartilage. American Journal of Roentgenology. 2009 Sep;193(3):628–38.
6. Trattnig S, Mamisch TC, Pinker K, *et al*. Differentiating normal hyaline cartilage from post-surgical repair tissue using fast gradient echo imaging in delayed gadolinium-enhanced MRI (dGEMRIC) at 3 Tesla. European Radiology. 2008 Jun;18(6):1251–9.
7. Welsch GH, Trattnig S, Hughes T, *et al*. T2 and T2*mapping in patients after matrix-associated autologous chondrocyte transplantation: Initial results on clinical use with 3.0-Tesla MRI. European Radiology. 2010 Nov 25;20(6):1515–23.
8. Choi JA, Gold GE. MR imaging of articular cartilage physiology. Magnetic Resonance Imaging Clinics of North America. 2011 May;19(2):249–82.
9. Mosher TJ, Dardzinski BJ. Cartilage MRI T2 relaxation time mapping: Overview and applications. Seminars in Musculoskeletal Radiology. 2004;8(4):355–68.
10. Baum T, Joseph GB, Karampinos DC, *et al*. Cartilage and meniscal T2 relaxation time as non-invasive biomarker for knee osteoarthritis and cartilage repair procedures. Osteoarthritis and Cartilage. 2013;21(10):1474–84.
11. Kester BS, Carpenter PM, Yu HJ, *et al*. T1ρ/T2-mapping and histopathology of degenerative cartilage in advanced knee osteoarthritis. World Journal of Orthopaedics. 2017 Apr 18;8(4):350–6.
12. Stahl R, Blumenkrantz G, Carballido-Gamio J, *et al*. MRI-derived T2 relaxation times and cartilage morphometry of the tibio-femoral joint in subjects with and without osteoarthritis during a 1-year follow-up. Osteoarthritis and Cartilage. 2007 Nov;15(11):1225–34.
13. David-Vaudey E, Ghosh S, Ries M, *et al*. T2 relaxation time measurements in osteoarthritis. Magnetic Resonance Imaging. 2004 Jun;22(5):673–82.
14. Amendola A, Bonasia DE. Results of high tibial osteotomy: Review of the literature. International orthopaedics. 2010 Feb;34(2):155–60.
15. Intema F, vdan Roermund PM, Marijnissen ACA, *et al*. Tissue structure modification in knee osteoarthritis by use of joint distraction: An open 1-year pilot study. Annals of the Rheumatic Diseases. 2011 Aug 1;70(8):1441–6.
16. van der Woude JAD, Wiegant K, van Heerwaarden RJ, *et al*. Knee joint distraction compared with high tibial osteotomy: A randomized controlled trial. Knee Surgery, Sports Traumatology, Arthroscopy. 2017;25(3):876–86.
17. Jansen MP, Besselink NJ, van Heerwaarden RJ, *et al*. Knee joint distraction compared with high tibial osteotomy and total knee arthroplasty: Two-year clinical, radiographic, and biochemical marker outcomes of two randomized controlled trials. Cartilage. 2019 Feb 13;1947603519828843.
18. Jansen MP, Maschek S, van Heerwaarden RJ, *et al*. Changes in cartilage thickness and denuded bone area after knee joint distraction and high tibial osteotomy – Post-hoc analyses of two randomized controlled trials. Journal of Clinical Medicine. 2021 Jan 19;10(2):368.
19. Hoorntje A, Kuijer PPFM, Koenraadt KLM, *et al*. Return to sport and work after randomization for knee

distraction *versus* high tibial osteotomy: Is there a difference? The Journal of Knee Surgery. 2020 Nov 23;

20. Jansen MP, Boymans TAEJ, Custers RJH, *et al*. Knee joint distraction as treatment for osteoarthritis results in clinical and structural benefit: A systematic review and meta-analysis of the limited number of studies and patients available. Cartilage. 2020 Jul 22;194760352094294.
21. Jung WH, Takeuchi R, Chun CW, *et al*. Second-look arthroscopic assessment of cartilage regeneration after medial opening-wedge high tibial osteotomy. Arthroscopy – Journal of Arthroscopic and Related Surgery. 2014 Jan;30(1):72–9.
22. Jung WH, Takeuchi R, Chun CW, *et al*. Comparison of results of medial opening-wedge high tibial osteotomy with and without subchondral drilling. Arthroscopy – Journal of Arthroscopic and Related Surgery. 2015 Apr 1;31(4):673–9.
23. Jansen MP, Mastbergen SC, Turmezei TD, *et al*. Knee joint distraction results in MRI cartilage thickness increase up to ten years after treatment. Submitted.
24. Besselink NJ, Vincken KL, Bartels LW, *et al*. Cartilage quality (dGEMRIC index) following knee joint distraction or high tibial osteotomy. Cartilage. 2018;1947603518777578.
25. Jansen MP, Mastbergen SC, van Heerwaarden RJ, *et al*. Knee joint distraction in regular care for treatment of knee osteoarthritis: A comparison with clinical trial data. PLOS ONE. 2020 Jan 22;15(1).
26. Peterfy CG, Schneider E, Nevitt M. The osteoarthritis initiative: report on the design rationale for the magnetic resonance imaging protocol for the knee. Osteoarthritis and Cartilage. 2008 Dec;16(12):1433–41.
27. Wirth W, Maschek S, Beringer P, *et al*. Subregional laminar cartilage MR spin–spin relaxation times (T2) in osteoarthritic knees with and without medial femorotibial cartilage loss – Data from the Osteoarthritis Initiative (OAI). Osteoarthritis and Cartilage. 2017 Aug 1;25(8):1313–23.
28. Wirth W, Maschek S, Roemer FW, *et al*. Radiographically normal knees with contralateral joint space narrowing display greater change in cartilage transverse relaxation time than those with normal contralateral knees: a model of early OA? – Data from the Osteoarthritis Initiative (OAI). Osteoarthritis and Cartilage. 2019 Nov 1;27(11):1663–8.
29. Koo TK, Li MY. A guideline of selecting and reporting intraclass correlation coefficients for reliability research. Journal of Chiropractic Medicine. 2016 Jun;15(2):155.
30. Mamisch TC, Trattnig S, Quirbach S, *et al*. Quantitative T2-mapping of knee cartilage: Differentiation of healthy control cartilage and cartilage repair tissue in the knee with unloading – Initial results. Radiology. 2010 Mar 8;254(3):818–26.
31. Wiegant K, van Roermund PM, Intema F, *et al*. Sustained clinical and structural benefit after joint distraction in the treatment of severe knee osteoarthritis. Osteoarthritis and Cartilage. 2013 Nov;21(11):1660–7.
32. Jansen MP, Maschek S, van Heerwaarden RJ, *et al*. Knee joint distraction is more efficient in rebuilding cartilage thickness in the more affected compartment than high tibial osteotomy in patients with knee osteoarthritis. Osteoarthritis and Cartilage. 2019 Apr;27(1):S330–1.
33. Kim HK, Shiraj S, Anton CG, *et al*. Age and sex dependency of cartilage t2 relaxation time mapping in mri of children and adolescents. American Journal of Roentgenology. 2014 Mar 20;202(3):626–32.
34. van Valburg AA, van Roermund PM, Marijnissen ACA, *et al*. Joint distraction in treatment of osteoarthritis (II): Effects on cartilage in a canine model. Osteoarthritis and Cartilage. 2000 Jan 1;8(1):1–8.
35. Wiegant K, Intema F, van Roermund PM, *et al*. Evidence of cartilage repair by joint distraction in a canine model of osteoarthritis. Arthritis and Rheumatology. 2015 Feb 28;67(2):465–74.
36. Baum T, Joseph GB, Nardo L, *et al*. Correlation of magnetic resonance imaging-based knee cartilage T2 measurements and focal knee lesions with body mass index: Thirty-six-month followup data from a longitudinal, observational multicenter study. Arthritis Care and Research. 2013 Jan 1;65(1):23–33.

37. Mosher TJ, Liu Y, Yang QX, *et al*. Age dependency of cartilage magnetic resonance imaging T2 relaxation times in asymptomatic women. Arthritis and Rheumatism. 2004 Sep;50(9):2820–8.

SUPPLEMENTARY DATA

Supplementary Table S1: Intraclass correlation coefficients for the 3 observers

	T2 relaxation times	Volumes
MAC tibia	0.973	0.950
MAC femur	0.828	0.841
LAC tibia	0.973	0.923
LAC femur	0.895	0.827

LAC: least affected compartment; MAC: most affected compartment. Coefficients were calculated for average measures with a 2-way random model.

CHAPTER 16

The molecular profile of synovial fluid changes upon joint distraction and is associated with clinical response in knee osteoarthritis

F.E. Watt
B. Hamid
C. Garriga
A. Judge
R. Hrusecka
R.J.H. Custers
M.P. Jansen
F.P.J.G. Lafeber
S.C. Mastbergen & T.L. Vincent

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Abstract

Background: Surgical knee joint distraction (KJD) leads to clinical improvement in knee osteoarthritis (OA) and also apparent cartilage regeneration by magnetic resonance imaging. We investigated if alteration of the joint's mechanical environment during the 6 week period of KJD was associated with a molecular response in synovial fluid, and if any change was associated with clinical response.

Methods: 20 individuals undergoing KJD for symptomatic radiographic knee OA had SF sampled at baseline, midpoint and endpoint of distraction (6 weeks). SF supernatants were measured by immunoassay for 10 predefined mechanosensitive molecules identified in our previous preclinical studies. The composite Knee injury and OA Outcome Score-4 ($KOOS_4$) was collected at baseline, 3, 6 and 12 months.

Results: 13/20 (65%) were male with mean age 54° yrs (SD 5°). All had Kellgren-Lawrence grade ≥2 knee OA. 6/10 analytes showed statistically significant change in SF over the 6 weeks distraction (activin A; TGFβ-1; MCP-1; IL-6; FGF-2; LTBP2), $p<0.05$. Of these, all but activin A increased. Those achieving the minimum clinically important difference of 10 points for KOOS4 over 6 months showed greater increases in FGF-2 and TGFβ-1 than non-responders. An increase in IL-8 during the 6 weeks of KJD was associated with significantly greater improvement in $KOOS_4$ over 12 months.

Conclusion: Detectable, significant molecular changes are observed in SF following KJD, that are remarkably consistent between individuals. Preliminary findings appear to suggest that increases in some molecules are associated with clinically meaningful responses. Joint distraction may provide a potential opportunity in the future to define regenerative biomarker(s) and identify pathways that drive intrinsic cartilage repair.

Introduction

Osteoarthritis (OA) affects all joint tissues, with articular cartilage loss being 1 of the hallmarks of progressive disease[1]. It is likely that excessive mechanical load or loss of mechanoprotective mechanisms in the joint is an underlying process in many cases of disease, but that there are other superimposed factors such as inflammation that modify its course.[2–6] Longitudinal cohorts such as the Osteoarthritis Initiative and Clinical Assessment of the Knee (CAS-K) show that in ~40% of individuals with early knee OA, pain may stabilize or improve over time, suggesting that the disease may remit and is not inevitably progressive.[7] Interventions that mechanically off-load the joint, such as strengthening exercises, weight loss, orthotics such as bracing or surgical interventions such as osteotomy or unloading devices all reduce knee symptoms.[1,8]

It is often stated that adult articular cartilage is unable to repair but a body of literature is emerging that challenges this concept. This is best exemplified by traumatic focal cartilage defects that can repair spontaneously in young joints (reviewed in[9]), but in individuals undergoing high tibial or distal femoral osteotomy for OA, structural modification has also been observed.[10] The other evidence comes from studies of surgical knee joint distraction (KJD). The primary goal of this treatment is to improve symptoms sufficiently to delay knee arthroplasty. This is especially the case in younger patients, since these individuals have an increased risk of revision arthroplasty.[11] KJD is a technique where, under anesthesia, an external fixation frame is placed on both sides of the joint, allowing distraction (gradual pulling apart of the joint's bony ends by ~5 mm for 6 weeks). During distraction, the patient is encouraged to weight-bear on the extended knee. Such weight-bearing creates intermittent joint fluid pressure changes, due to built-in springs in the frame enabling a maximal 3 mm axial displacement under full body weight.[12] Studies of joint distraction have shown sustained and clinically significant improvement at a number of joint sites.[13,14] For knee OA, joint distraction improved knee symptoms for 5–9 years in individuals with established OA.[15,16] Remarkably, the 6 week intervention also led to apparent cartilage regeneration in the subsequent months and years, with increase in joint space width on X-ray, and increased articular cartilage thickness on magnetic resonance imaging (MRI).[14,16–18] These studies suggest that, by temporarily off-loading the joint, KJD might somehow be responsible for 'priming' the joint to enable intrinsic cartilaginous repair. The biological mechanisms which underlie such a response are not understood but may include changes in the periarticular bone and enhanced mesenchymal stem cell attachment to the damaged joint surface.[19,20] KJD is therefore an attractive mechanistic model in which to investigate potential reparative pathways and identify novel associated markers of clinical response.

Synovial fluid (SF) represents an accessible fluid that contains molecules reflecting biological processes within the joint. These molecules are joint tissue-agnostic; likely being derived from all the tissues interfacing the joint cavity and can be sampled repeatedly to monitor change

over time within an individual. SF may represent joint tissue changes more accurately than measurements from blood or urine.[21,22] We have previously investigated 7 candidate proteins in the SF of individuals after acute knee injury. These molecules were originally shown to be induced in murine knee OA in a highly mechanosensitive manner.[3] 6 out of 7 proteins were found to be substantially up-regulated in those with acutely injured knees compared with controls.[23] These molecules included interleukin (IL)-6, matrix metalloproteinase (MMP)3 and monocyte chemoattractant protein (MCP)-1, associated with inflammatory activation but also others such as activin A, tumor necrosis factor-stimulated gene (TSG)-6 or tissue inhibitor of metalloproteinases (TIMP)-1, which have purported anticatabolic/anabolic roles.[24] Our preclinical work has also identified candidate chondroprotective molecules that are released by damaged cartilage including FGF-2 and TGFβ.[25–27] Both of these are present in SF and have roles in chondrogenesis.[28,29]

We hypothesized that over the course of KJD, changes in the joint's mechanical environment modulate these candidate SF markers. We further hypothesized that changes in these mechanosensitive molecules either alone or in combination would be associated with clinical outcome. We set out to test these hypotheses in a proof-of-concept study in a group of individuals undergoing planned surgical KJD.

Method

Ethics

Approval for this study was given by a research ethics committee (#15-160/D; NL51539.041.15). Usual care clinical data was also accessed (#17-005). All participants gave written informed consent to participate prior to screening, according to the Declaration of Helsinki.

Participants

Potential participants were identified by the orthopedic surgeon (RC) from a population with knee OA attending for consideration of KJD as part of their usual clinical care at a single site in Netherlands (University Medical Center Utrecht). Inclusion criteria were: age<65 years; knee OA fulfilling ACR clinical criteria[30]; Kellgren and Lawrence (KL) grade ≥2 on radiograph[31]; knee ligaments intact; preserved range-of-motion (flexion>120°; no loss of full extension); SF sample available at baseline. Exclusion criteria were: history of inflammatory arthritis affecting the index knee including rheumatoid arthritis; recent infection or systemic inflammatory disease; post-traumatic fibrosis; tibial plateau fracture; extensive bone-on-bone contact on X-ray; previous or planned knee arthroplasty during study period; surgery to the index knee within last 6 months; primary (isolated) patellofemoral OA; contralateral knee requiring surgical treatment; inability/contraindication/not consenting to provide SF; BMI ≥35 kg/m^2; pregnancy.

Clinical outcomes

Knee injury and Osteoarthritis Outcome Score (KOOS) was collected as part of usual hospital care electronically at baseline, 3, 6 and 12 months (Figure 1A). From this, $KOOS_4$, a single composite score which has been validated as a single outcome in other clinical studies was calculated (the mean of 4 of 5 KOOS subscales: Pain, Symptoms, Sports/Recreation and Quality of Life).[32,33]

Usual care intervention

A non-hinged, external proof-of-concept fixation joint distraction frame (Monotube Triax with pin clamps, Stryker) (Figure 1B) was fitted to the index knee by an orthopedic surgeon (RC) whilst the patient was under spinal or general anesthesia (GA) and the joint surfaces distracted by 5 mm. The frame was then worn for 6–7 weeks.

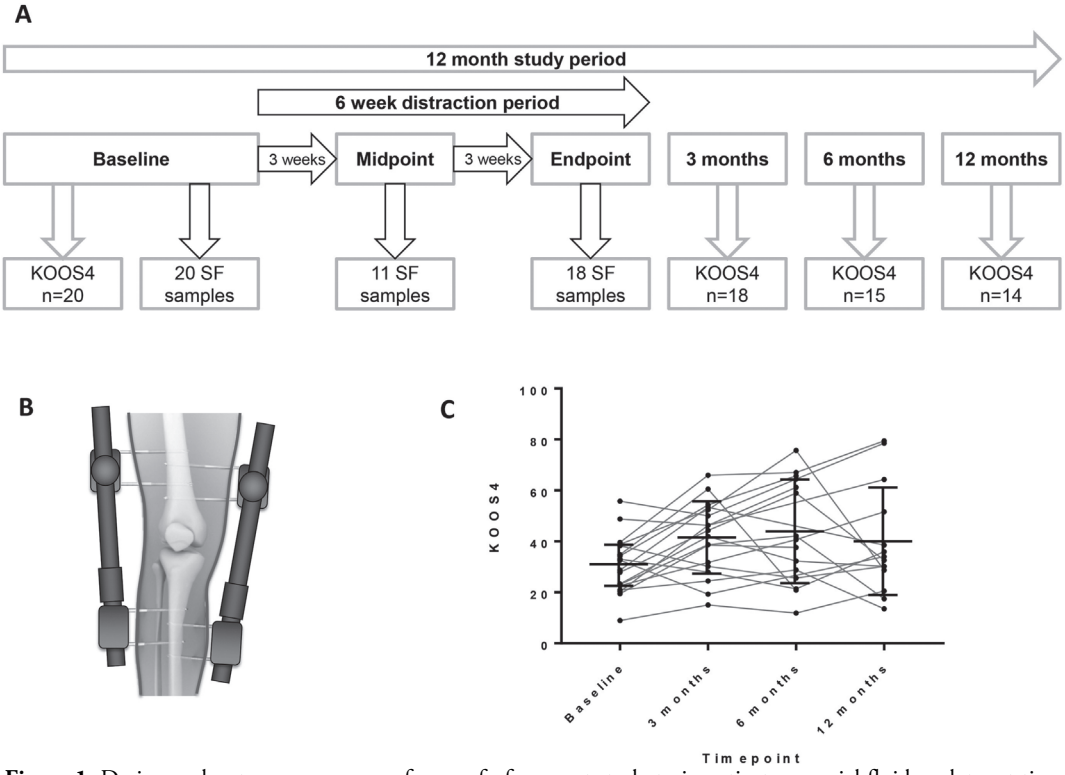


Figure 1: Design and outcome measures of a proof-of-concept study to investigate synovial fluid analytes at time of knee joint distraction. (A) Flow chart indicating timings of study visits, collection of synovial fluid samples and collection of KOOS from 20 participants, including completeness of sampling/data over the 12 month study period. A further 2 participants gave consent but no baseline SF could be aspirated so they were excluded from further analysis as per protocol. (B) Illustration of distraction frame which is surgically placed on the knee joint for a 6 week period. (C) $KOOS_4$ measurements in participants at baseline (predistraction), 3 months, 6 months and 12 months after surgical knee joint distraction. Medians and inter-quartile ranges are shown (bar and line). KOOS: Knee Injury and Osteoarthritis Outcome Score ($KOOS_4$ is composite measure of 4 domains); SF: synovial fluid.

Participant biological samples

A maximum of 2 ml of SF was aspirated by needle from the index knee at baseline visit (whilst participant under anesthesia and prior to the distraction frame being fitted), subsequently at midpoint of distraction (3–4 weeks, under local anesthesia) and at endpoint of distraction (at 6–7 weeks, immediately after the distraction frame was removed under anesthesia; Figure 1A). Within 2 h, all samples were centrifuged for 20 min at 3000G. Supernatants were stored in 200 µl aliquots in cryovials at -80°C in monitored freezers.

Comparator ranges

Normal: These were calculated in previously collected SF from patients undergoing amputation for treatment of lower limb tumor, at Royal National Orthopaedic Hospital (Stanmore), London, UK, or transplant donation, at Charing Cross Hospital, London, UK (REC 09/H0710/60), who had macroscopically normal knee articular cartilage at the time of surgery and no evidence of arthritis or tumor invasion into the joint.[23] *OA*: These were calculated from measurements in SF from research tissue bank samples of patients with a confirmed diagnosis of OA undergoing partial or total joint replacement surgery at the Nuffield Orthopaedic Centre, Oxford, UK (REC 09/H0606/11 + 5). SF had been processed and stored as above.

Reagents

General laboratory reagents were the best available grade from either Sigma–Aldrich (Dorset, UK) or BDH (Dorset, UK) unless otherwise stated. MesoScale Discovery (MSD) plates and MSD SULFO-TAG labeled Streptavidin (#R32AD-5) were from MSD (Rockville, MD, USA). Enzyme-linked immunosorbent assays (ELISAs) were from commercial providers (Table 1).

Assays

Assays were conducted for 10 predefined candidate molecules listed in Table I. All assays were carried out as per manufacturers' instructions unless stated otherwise. Each assay had either previously undergone validation by us[23] or else underwent structured performance assessment and optimization for SF for this project, and all also passed quality performance requirements during sample reads (Table I). ELISA plates were read using Berthold Mithras LB940 reader and MSD plates by MSD QuickPlex SQ120 reader (analyzed with MSD Discovery Workbench software v4.0.12). For TSG-6, each plate well (MSD, Rockville, USA, L15XA) was custom-coated with 30 µl 10 µg/ml TSG-6 capture antibody (Merck, MABT108) in phosphate-buffered saline (PBS) overnight at 4°C. Methods were then as described[23]. Mean concentrations of analytes were calculated from duplicate assay reads for each participant for each time point. Inter- and intra-assay coefficients of variation (CVs) were calculated for all assays. The lower limit of quantitation (LLOQ) was calculated for all assays. Where a measurement was below LLOQ, 50% of this value was used.[22,23] Lower and upper limits were also calculated for all assays for normal ranges using the geometric mean ± 2 standard deviations (SDs).

Table 1: Assay characteristics of panel of 10 candidate markers

Analyte	Assay	Manufacturer (Catalog No.)	Intra-Assay CV (%)	Inter-Assay CV (%)	Lower Limit of Normal (SF) (pg/ml)	Upper Limit of Normal (SF) (pg/ml)	Dil_n Factor (SF)
Activin A	Human/Mouse/Rat Activin A Quantikine ELISA	R&D (DAC00B)	3.9	11.7	1028	5253	50
MCP-1	V-PLEX Human MCP-1	MSD (K151NND-1)	3.1	5.1	60	493	5
FGF-2	V-PLEX Human (basic) FGF-2	MSD (K151MDD-1)	4.0	6.1	2	411	4
IL-6	V-PLEX Custom Human Cytokine	MSD (K151A0H-1)	4.1	9.7	1	20	5
IL-8	V-PLEX Custom Human Cytokine	MSD (K151A0H-1)	3.5	8.9	2	39	5
LTBP2	Human LTBP2 ELISA	Abbexa (abx 152242)	6.6	17.3	1887	13630	4
MMP3	Human MMP3 Ultra-Sensitive	MSD (K151FZC-1)	4.7	13.6	3742	231000	50
TGFβ-1	Human TGFβ-1 Quantikine ELISA	R&D (DB100B)	3.7	13.0	257.3	1545	4
TIMP-1	Human TIMP-1 Ultra-sensitive	MSD (K151JFC-1)	9.1	10.3	143000	744700	200
TSG-6	In-house, self-coated MSD	MSD (L15XA-1)	4.5	7.1	6479	19060	6

Inter- and intra-assay coefficients of variation (CVs) were calculated for all assays. Lower and upper limits were also calculated for all assays for normal ranges using the geometric mean ± 2 standard deviations. CV: coefficient of variation; Dil_n: Dilution; MSD: Mesoscale Discovery.

Statistical analysis

All available data were analyzed on all participants with sufficient SF at each of the 3 time points (and 1 patient with samples at baseline and 3 weeks). All SF analytes were above LLOQ (allowing attribution of endpoint measurements) except for 1 sample each for TGFβ1 at baseline, FGF-2 at midpoint and activin A at endpoint. These values were considered as 50% of the LLOQ. Sample and KOOS completeness are shown in Figure 1A. Missing data were not imputed.

Change in $KOOS_4$ over time

Median differences between paired observations of $KOOS_4$ at baseline and either 3, 6 or 12 months were compared by Wilcoxon Signed Rank test.

Change in analyte levels over time

Median differences between paired observations (baseline *versus* 3 or 6 weeks) of analyte levels were compared by Wilcoxon signed rank test. Effect size (ES) was reported as the difference

between medians. Correlations between the changes over 6 weeks for each analyte were assessed by Spearman's *R* coefficient (range -1 to 1; where ±1 = strongest positive (or negative) correlation, 0 = no correlation).

Association of change in analytes with $KOOS_4$

The clinical outcome variable was change in $KOOS_4$ over time ($KOOS_4$ at either 3, 6 or 12 months respectively - $KOOS_4$ at baseline). Linear regression was employed to model the relationship between continuous change in analyte levels (concentrations at 6 or 3 weeks - baseline concentrations) and change in $KOOS_4$.

In a planned secondary analysis, linear regression also assessed change in $KOOS_4$ by categories of change in analytes. Concentrations of analytes (at baseline and 6 weeks) were classified into normal (≥25th and <75th percentiles), high (≥75th percentile) and low (<25th percentile) categories. The 25th and 75th centiles were calculated from measurements of these molecules in SF from 40 individuals with OA who had undergone either partial or total knee joint replacement (see Comparator ranges). These data were generated at same time as participant data, using the same assay batches. 'Relevant change' was defined as a movement between at least 1 category from baseline to 6 weeks (relevant increase, or relevant decrease), or as no relevant change.

Change in analytes by responders and non-responders in $KOOS_4$

Responders (those whose change in $KOOS_4$ over 6 months (the latest point at which there was clinical change from baseline), (Figure 1C) was ≥10 points, i.e., the minimal clinically important difference (MICD) for $KOOS_4$)[32]; and non-responders (those whose $KOOS_4$ change over 6 months was <10 points) were categorized. Differences between molecular changes in these 2 groups were compared by Mann-Whitney *U* test.

Data were stored on a secure database (OpenClinica). Analysis was performed in STATA IC 13.1 and Graphpad Prism 6.03.

Results

13/20 (65%) participants were male with mean age 55 ± 5 years (Table II). All had KL grade≥2; 18 (90%) grade 3/4, with substantial knee pain at baseline (KOOS pain 38.6 (SD 16.0); where 100 is no pain, normal function). As expected from previously published studies, there was an improvement in $KOOS_4$ in the subsequent months following the intervention (Figure 1C).

Table 2: Baseline characteristics of study participants

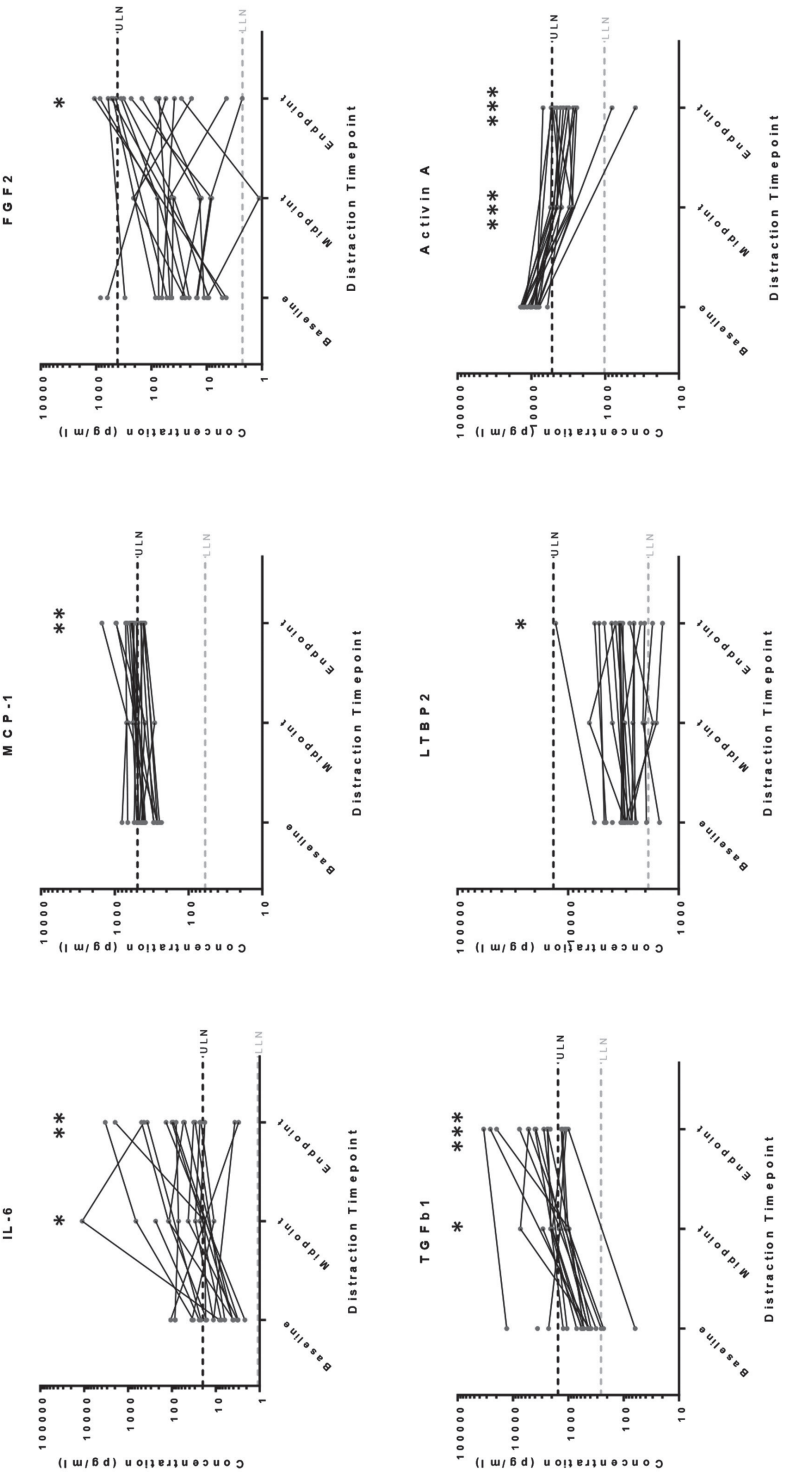
	KJD patients (n=20)
Male sex, n (%)	13 (65)
Age (years)	55.5
BMI (kg/m^2)	29.3
Kellgren and Lawrence, n (%)	
- Grade 2	2 (10)
- Grade 3	10 (50)
- Grade 4	8 (40)
$KOOS_4$ (0–100)	30.11

Mean or n (%) is given. BMI: body mass index; $KOOS_4$: Knee injury and osteoarthritis outcome score-4.

6/10 SF analytes showed changes between baseline and 6 weeks (IL-6: ES 56.6, p=0.0043; MCP-1: ES 155.1, p=0.0016; FGF-2: ES 164.7, p=0.0123; TGFβ-1: ES 2.1, p=0.0003; LTBP2: ES 0.4, p=0.0475; activin A: ES -6.8, p=0.0002) (Figure 2A and Supplementary Table 1). Of these, IL-6, MCP-1, FGF-2 and TGFβ-1 showed a predominant increase in levels, while activin A mainly decreased (to within normal range for most individuals). There was variation in response between individuals, exemplified by LTBP-2. For several analytes, change was detectable within 3 weeks of distraction (activin A, TGFβ-1 and IL-6) (Supplementary Table 1). 2 further molecules, IL-8 and TIMP-1 were different at 3 weeks (ES 73.5 and 389, respectively), but not at 6 weeks (ES 10.5 and 115.2, respectively) (Figure 2B, upper panels). The remaining 2 analytes (MMP3, TSG-6) did not change over the distraction period (ES -75.3, p=0.53 and 41508, p=0.21 respectively) (Figure 2B, lower panels).

Several analytes correlated with each other in their change over the 6 week distraction period (Figure 3). Associations between changes in markers could also be seen over the initial 3 weeks of knee joint distraction (Supplementary Figure 1). Higher correlations were found for TGFβ-1 and FGF-2 (R=0.68); IL-6, TIMP-1 and either MMP3 or TSG-6; (all pairs R>0.5). LTBP2 and activin A had low correlation with other analytes over time. TGFβ-1 and IL-6 were negatively correlated (R=-0.43).

The association of change in candidate molecules over the distraction period with subsequent change in $KOOS_4$ was examined. Change in 4 molecules was associated with change in $KOOS_4$ over the first 3 months: activin A, TGFβ-1, FGF-2 and MCP-1 (Figure 4A). For all except activin A, an increase in the analyte was associated with greater improvement in $KOOS_4$, but the effects were weak (Supplementary Table 2). The low effect sizes were primarily because the unit of change of a marker within the regression model was per 1 pg/ml, whereas often much larger changes in markers than 1 pg/ml were seen. Similar associations persisted at 6 months for all 4 molecules.


A
IL-6
MCP-1
FGF2
TGFb1
LTBP2
Activin A
Concentration (pg/ml)
Distraction Timepoint
Baseline
Midpoint
Endpoint
ULN
LLN

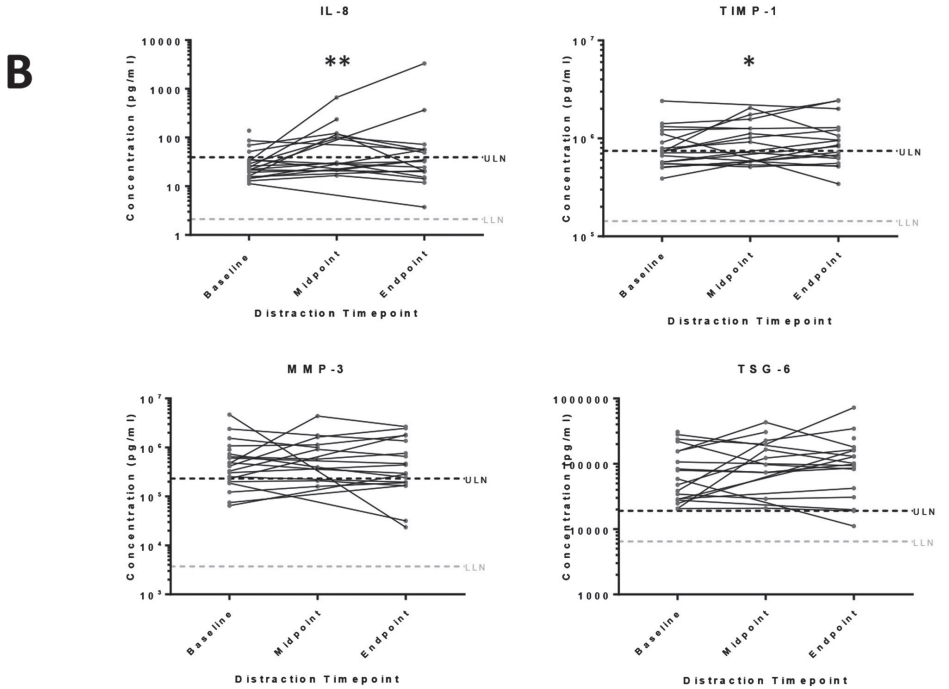


Figure 2: Measurement of synovial fluid analytes during knee joint distraction. Synovial fluid from study participants immediately prior to distraction ('baseline'), after 3 weeks of knee joint distraction ('midpoint') and at 6 weeks after knee joint distraction ('endpoint') were assayed for pre-defined markers of interest by electrochemiluminescence or ELISA (see Table I). Measurements for each of 10 analytes are shown, with mean concentrations for each analyte plotted on a log 10 y axis. *p<0.05,**p<0.01,***p<0.001 by Wilcoxon Signed Rank test, comparing paired levels at end point or midpoint *versus* baseline (individual p-values are given in Supplementary Table 1). (A) 6 analytes with change at endpoint *versus* baseline, (B) 4 analytes without change at endpoint (although upper 2 showed change at midpoint). ULN (dark dashed line) and LLN (light dashed line) of normal ranges were calculated for each analyte as described in methods and Table I. FGF-2: basic fibroblast growth factor; IL-6: interleukin 6; IL-8: interleukin 8; LLN: lower limit of normal; LLOQ: lower limit of quantification; LTBP2: latent-transforming growth factor beta-binding protein 2; MCP-1: monocyte chemoattractant protein 1; MMP3: matrix metalloproteinase-3; TGFβ-1: transforming growth factor beta 1; TIMP-1: tissue inhibitor of metalloproteinases 1; TSG-6: tumour necrosis factor-inducible gene 6 protein; ULN: upper limit of normal.

For example, for the effect of change in FGF-2 over 6-weeks, on change in $KOOS_4$ over 6-months, for a 1-unit increase in FGF-2 change per pg/ml, the change in $KOOS_4$ is 0.03 points. To interpret the 95%CI, the underlying effect in the population could lie between 0.004 and 0.057. To aid interpretation, the median increase of FGF-2 over 6 weeks is 165 pg/ml. Hence for a 165 pg/ml unit increase in FGF-2, the change in KOOS4 is 4.95 points (95%CI 0.66–9.41). IL-8 had the largest and increasing effect size (0.28 by 12 months), but the confidence intervals at all time points were wide.

	Activin A	LTBP2	TGFβ-1	FGF-2	TIMP-1	TSG-6	IL-6	MCP-1	IL-8	MMP3
Activin A	–									
LTBP2	0.09	–								
TGFβ-1	-0.04	0.17	–							
FGF-2	-0.20	0.08	0.68**	–						
TIMP-1	-0.03	-0.13	-0.23	-0.12	–					
TSG-6	0.02	-0.17	-0.43*	-0.20	0.55**	–				
IL-6	0.31*	-0.24	-0.02	0.05	0.42*	0.28	–			
MCP-1	0.08	-0.20	-0.13	0.23	0.40*	0.44*	0.40*	–		
IL-8	-0.02	-0.11	-0.25	-0.21	0.60**	0.58**	<0.01	-0.04	–	
MMP3	0.04	-0.23	-0.19	-0.29	0.64**	0.61**	0.39*	0.44*	0.25	–

Figure 3: Correlation between change of analytes in the synovial fluid of participants over period of knee joint distraction. Spearman rank tests were performed to determine correlations between the change in levels of synovial fluid analytes over the 6 week distraction period (concentration at 6 weeks - baseline concentrations). Correlation coefficients were calculated using all available participant data and the mean of 2 repeated (duplicate) measures for each synovial fluid sample. Strength of correlation by Spearman *R* coefficient is shown: * (Mid gray shading): Low positive (negative) correlation, 0.30–0.49 (-0.30 to -0.49). ** (Dark gray shading): Moderate positive (negative) correlation, 0.50–0.69 (-0.50 to -0.69). FGF-2: basic fibroblast growth factor; IL-6: interleukin 6; IL-8: interleukin 8; LTBP2: latent-transforming growth factor beta-binding protein 2; MCP-1: monocyte chemoattractant protein 1; MMP3: matrix metalloproteinase 3; TGFβ-1: transforming growth factor beta 1; TIMP-1: tissue inhibitor of metalloproteinases 1; TSG-6: tumor necrosis factor-inducible gene 6 protein.

To test the relevance of these findings, we categorized participants' molecular measurements as having no relevant change, a relevant increase or a relevant decrease over the 6 week distraction period (see methods) and examined the association of these categories with change in $KOOS_4$. Those with a relevant increase in SF IL-8 during the distraction period had a greater improvement in $KOOS_4$ over 12 months than those with no change (regression coefficient 17.6 (1.2–34.0); p=0.04). However, no other molecular changes were associated with clinical outcome when categorized in this way (Supplementary Table 3). Furthermore, the confidence intervals for this observation are wide and given that the other findings for IL-8 did not reach significance (Figure 4A), this could be a chance finding).

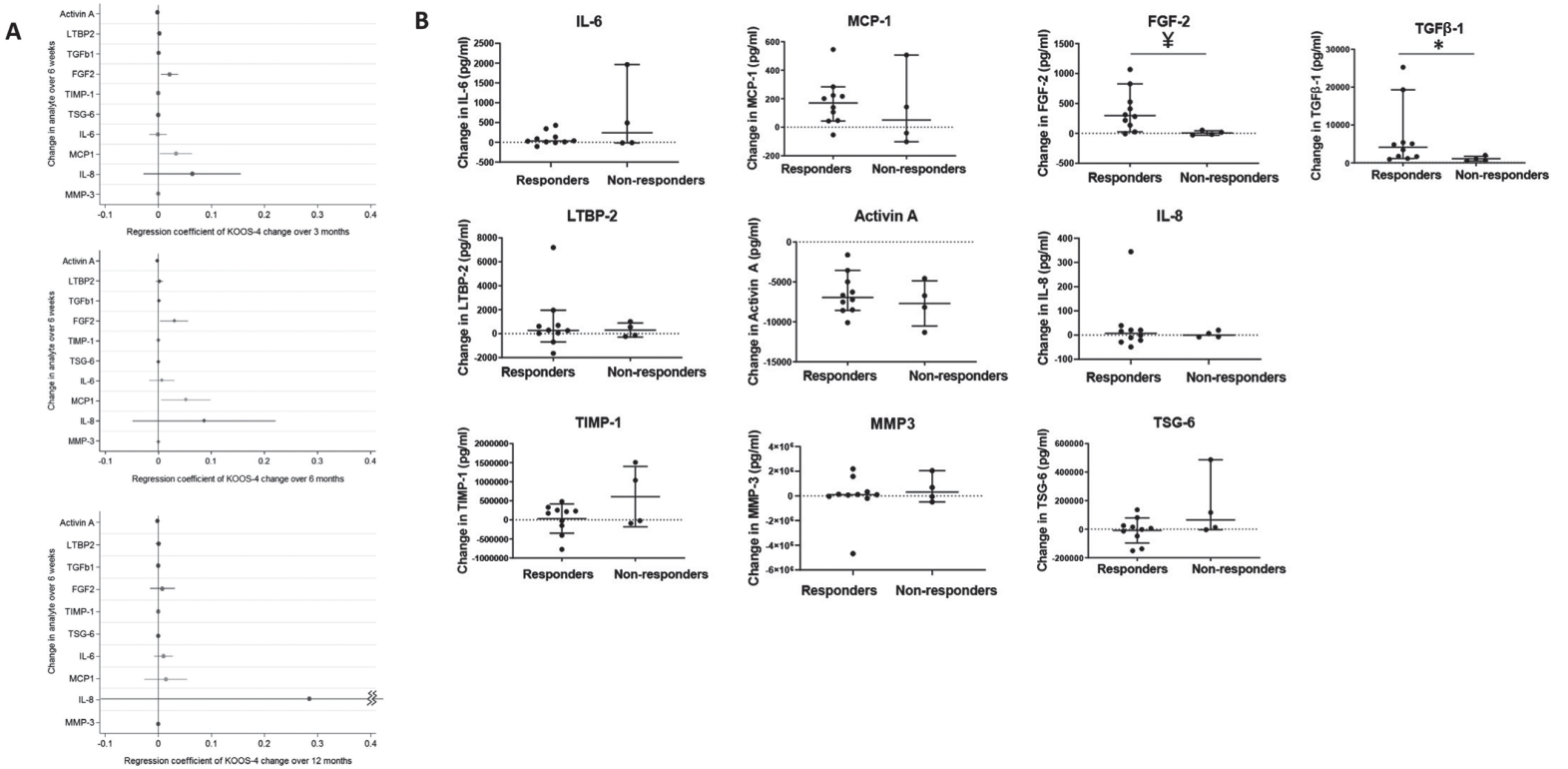


Figure 4: Association of change in synovial fluid analytes with the clinical outcome $KOOS_4$. (A) Linear regression models for the association of the change over the distraction period for each of 10 synovial fluid analytes (measured in pg/ml) with participants' change in $KOOS_4$ over varying periods are shown: upper panel, change in $KOOS_4$ over 3 months; middle panel, change in $KOOS_4$ over 6 months and lower panel, change in $KOOS_4$ over 12 months. Forest Plots of unadjusted (crude) results, including the regression coefficient for the effect on KOOS4 change over the specified period and 95% confidence intervals are shown. (B) The change of concentration in each analyte over the 6 week distraction period is shown, for clinical responders and non-responders. The bars represent the median and 95% confidence intervals for each group. Between group comparisons were by Mann-Whitney *U* test, * p=0.04; ¥ p=0.01. LTBP2, latent-transforming growth factor beta-binding protein 2; TGFβ-1, transforming growth factor beta 1; FGF-2, basic fibroblast growth factor; TIMP-1, tissue inhibitor of metalloproteinases 1; TSG-6, tumour necrosis factor-inducible gene 6 protein; IL-6: interleukin 6; MCP-1, monocyte chemoattractant protein 1; IL-8, interleukin 8; MMP3, matrix metalloproteinase-3; KOOS, Knee injury and Osteoarthritis Outcome Score ($KOOS_4$ is composite measure of 4 domains).

We also compared the change in analyte levels over the 6 weeks of distraction in those making the MCID of 10 points or more by $KOOS_4$ (responders) with those who did not improve by this amount (non-responders). The clinical response to joint distraction was most pronounced at 6 months, with 11/15 (73%) of individuals with available data reaching a MCID on $KOOS_4$. Responders at 6 months had a greater increase in TGFβ-1 and FGF-2 during the distraction period than non-responders (Figure 4B, Supplementary Table 4 and Supplementary Figure 2). Similar analyte changes were also seen in responders and non-responders at 3 months, when TIMP-1 levels were also different between the 2 groups (ES 497 ng/ml, p=0.02, Supplementary Figure 3).

Discussion

Easily detectable, substantial changes in levels of 8 putative mechanosensitive molecules of the inflammatory response (activin A, LTBP2, TGFβ-1, FGF-2, TIMP-1, IL-6, MCP-1, and IL-8) were seen in SF over the period of KJD. There were also associations between several of these molecules over time. These changes would not appear to be due to SF volume change because whilst some analytes increase, others stay the same or even decrease. Of the regulated molecules, whilst IL-6 and MCP-1 (also known as CCL-2) have been associated with degeneration or pain in the osteoarthritic joint[34,35], FGF-2 and TGFβ-1 are more typically associated with repair.[27,36] It is perhaps not surprising that a mechanically-induced inflammatory response should include both catabolic and reparative processes. But that an intervention which apparently leads to net articular cartilage repair involves the activation of traditionally inflammatory pathways would go against current convention. Overall there was substantial variation between individuals for certain molecules in the extent and sometimes direction of this response. This supports the notion that an individual's biological response to the intervention could vary and be related to their clinical response. On the other hand, some molecules like TGFβ-1 and activin A showed very consistent directional changes following KJD.

Our proof-of-concept study appears to suggest an association between this measurable biological response to joint distraction and subsequent clinical outcome. The clinical response to joint distraction was most pronounced at 6 months. Several of the associations between change in analytes and $KOOS_4$ at 6 months were also apparent at 3 and 12 months, and when individuals were stratified, either by their molecular response or their clinical response. This supports that elements of this biological response to distraction appeared to be associated with a clinically meaningful response: for example, FGF-2 and TGFβ-1, typically associated with cartilage anabolism/anticatabolism, were raised in responders.[37,38]

One molecule, activin A, strikingly fell in all individuals to what we estimate are normal levels in human SF. Activin A is produced by osteoarthritic and injured articular cartilage and

promotes skin wound healing.[39,40] Its direction of change (opposite to that of FGF-2/TGFβ-1) is perhaps surprising: activin A is a TGFβ superfamily member[24] and is strongly FGF-2-dependent in the joint in our preclinical studies.[38,39] It may be that these apparent paradoxes are because different joint tissues are involved: FGF-2 and TGFβ-1 may derive from the capsule, say, whereas joint-offloading may reduce the cartilage injury response, reducing activin A. Whilst activin A appears to be a highly sensitive read-out of the intervention, it does not show association with benefit, perhaps because its change is so consistent.

There are some limitations of this study. It is important to avoid over-interpretation of what was a small experimental study, and we have reported confidence intervals of association of change in molecules with change in $KOOS_4$, to reflect the level of certainty. No correction was made for multiple testing: some apparent associations could have been found by chance.

Identification of truly 'normal' individuals or those with OA who are of exactly the same demographic and stage of disease and who are willing to undergo sampling of SF is challenging. Our 'Normal comparator' group included those individuals undergoing surgery for musculoskeletal tumors, which could potentially have influenced circulating levels of analytes. The OA comparator group was selected from a bank of samples collected at the time of arthroplasty to be as similar as possible in terms of sex and age. However, it is possible by the nature of the intervention that some would have had more advanced stage of disease or slight differences in other factors to those in the Joint Distraction group, meaning they were not directly comparable. However, the validity of our findings do not rely solely on such Comparator data (with most comparisons made within the cohort of those undergoing distraction).

These results need to be validated in a larger, independent study, where potentially relevant additional covariates (such as age, BMI) and structural imaging outcomes are incorporated[13] (correlation of marker change with imaging-based measures of cartilage thickness or volume in this current small study was not included as there would have been lack of power to detect an effect). As this intervention was part of usual care and not a clinical trial, this may have led to increased missing data and somewhat less striking improvement in clinical outcomes. This contrasts with previously published data in KJD suggesting a clinically significant long-term response.[14,16–18] A comparison between patients treated in clinical practice and those in (randomized) clinical trials revealed no clear differences in clinical outcomes between these 2 settings at 12 months (data to be published elsewhere). This study was not designed to detect a difference in clinical outcome and likely lacked power to detect differences at 12 months.

In summary, we have shown a measurable molecular response in SF to joint distraction, which appears to be associated with patient-reported outcomes. This observation supports the accurate

measurement of this response in SF as both possible and informative.[22,41] Ways of finding associations with a positive outcome to distraction are currently limited.[13] These observations show the potential to define biomarker(s) associated with positive clinical responses to this and similar interventions aiming to off-load the joint surfaces.[42,43] Biomarker stratification, identifying individuals most likely to respond in clinical trials or usual care would increase the utility of this already apparently cost-effective intervention.[44] Experimental studies of joint distraction represent a novel way of identifying potential regenerative pathways that drive intrinsic connective tissue repair; these pathways might be amenable to augmentation, by pharmacological or other means to treat symptomatic OA.

References

1. Bijlsma JW, Berenbaum F, Lafeber FP. Osteoarthritis: An update with relevance for clinical practice. The Lancet. 2011 Jun 18;377(9783):2115–26.
2. Brandt KD, Dieppe P, Radin EL. Commentary: Is it useful to subset "primary" osteoarthritis? A critique based on evidence regarding the etiopathogenesis of osteoarthritis. Seminars in Arthritis and Rheumatism. 2009 Oct;39(2):81–95.
3. Burleigh A, Chanalaris A, Gardiner MD, *et al*. Joint immobilization prevents murine osteoarthritis and reveals the highly mechanosensitive nature of protease expression in vivo. Arthritis and Rheumatism. 2012 Jul;64(7):2278–88.
4. Vincent TL, Wann AKT. Mechanoadaptation: Articular cartilage through thick and thin. Journal of Physiology. 2019 Mar;597(5):1271–81.
5. Benichou C, Wirotius JM. Articular cartilage atrophy in lower limb amputees. Arthritis and Rheumatism. 1982;25(1):80–2.
6. O'Neill TW, McCabe PS, McBeth J. Update on the epidemiology, risk factors and disease outcomes of osteoarthritis. Best Practice and Research: Clinical Rheumatology. 2018 Apr;32(2):312–26.
7. Nicholls E, Thomas E, van der Windt DA, *et al*. Pain trajectory groups in persons with, or at high risk of, knee osteoarthritis: Findings from the Knee clinical assessment study and the osteoarthritis initiative. Osteoarthritis and Cartilage. 2014;22(12):2041–50.
8. Callaghan MJ, Parkes MJ, Hutchinson CE, *et al*. A randomised trial of a brace for patellofemoral osteoarthritis targeting knee pain and bone marrow lesions. Annals of the Rheumatic Diseases. 2015 Jun 1;74(6):1164–70.
9. Dell'accio F, Vincent TL. Joint surface defects: Clinical course and cellular response in spontaneous and experimental lesions. European cells and Materials. 2010 Sep;20:210–7.
10. Parker DA, Beatty KT, Giuffre B, *et al*. Articular cartilage changes in patients with osteoarthritis after osteotomy. American Journal of Sports Medicine. 2011 May;39(5):1039–45.
11. Schreurs BW, Hannink G. Total joint arthroplasty in younger patients: Heading for trouble? The Lancet. 2017 Apr;389(10077):1374–5.
12. Struik T, Jaspers JEN, Besselink NJ, *et al*. Technical feasibility of personalized articulating knee joint distraction for treatment of tibiofemoral osteoarthritis. Clinical Biomechanics. 2017 Nov 1;49:40–7.
13. Marijnissen ACA, Hoekstra MCL, Pré BCD, *et al*. Patient characteristics as predictors of clinical outcome of distraction in treatment of severe ankle osteoarthritis. Journal of Orthopaedic Research. 2014 Jan;32(1):96–101.
14. Wiegant K, van Roermund PM, Intema F, *et al*. Sustained clinical and structural benefit after joint distraction in the treatment of severe knee osteoarthritis. Osteoarthritis and Cartilage. 2013 Nov;21(11):1660–7.
15. van der Woude JAD, Wiegant K, van Roermund PM, *et al*. Five-year follow-up of knee joint distraction: Clinical benefit and cartilaginous tissue repair in an open uncontrolled prospective study. Cartilage. 2017;8(3):263–71.
16. Jansen MP, van der Weiden GS, van Roermund PM, *et al*. Initial tissue repair predicts long-term clinical success of knee joint distraction as treatment for knee osteoarthritis. Osteoarthritis and Cartilage. 2018;26(12):1604–8.
17. van der Woude JAD, van Heerwaarden RJ, Spruijt S, *et al*. Six weeks of continuous joint distraction appears sufficient for clinical benefit and cartilaginous tissue repair in the treatment of knee osteoarthritis. Knee. 2016 Oct 1;23(5):785–91.
18. Jansen MP, Besselink NJ, van Heerwaarden RJ, *et al*. Knee joint distraction compared with high tibial osteotomy and total knee arthroplasty: Two-year clinical, radiographic, and biochemical marker outcomes of

two randomized controlled trials. Cartilage. 2019 Feb 13;194760351982843.

19. Intema F, Thomas TP, Anderson DD, *et al*. Subchondral bone remodeling is related to clinical improvement after joint distraction in the treatment of ankle osteoarthritis. Osteoarthritis and Cartilage. 2011 Jun 1;19(6):668–75.
20. Baboolal TG, Mastbergen SC, Jones E, *et al*. Synovial fluid hyaluronan mediates MSC attachment to cartilage, a potential novel mechanism contributing to cartilage repair in osteoarthritis using knee joint distraction. Annals of the Rheumatic Diseases. 2016;75(5):908–15.
21. Lafeber FPJG, van Spil WE. Osteoarthritis year 2013 in review: Biomarkers; reflecting before moving forward, one step at a time. Osteoarthritis and Cartilage. 2013 Oct;21(10):1452–64.
22. Struglics A, Larsson S, Kumahashi N, *et al*. Changes in cytokines and aggrecan ARGS neoepitope in synovial fluid and serum and in C-terminal crosslinking telopeptide of type II collagen and N-terminal crosslinking telopeptide of type I collagen in urine over five years after anterior cruciate ligament rupture: An exploratory analysis in the knee anterior cruciate ligament, nonsurgical *versus* surgical treatment trial. Arthritis and Rheumatology. 2015 Jul 1;67(7):1816–25.
23. Watt FE, Paterson E, Freidin A, *et al*. Acute molecular changes in synovial fluid following human knee injury: association with early clinical outcomes. Arthritis and Rheumatology. 2016 Sep 1;68(9):2129–40.
24. Munz B, Hübner G, Tretter Y, *et al*. A novel role of activin in inflammation and repair. Journal of Endocrinology. 1999 May;161(2):187–93.
25. Tang X, Muhammad H, McLean C, *et al*. Connective tissue growth factor contributes to joint homeostasis and osteoarthritis severity by controlling the matrix sequestration and activation of latent TGFβ. Annals of the Rheumatic Diseases. 2018 Sep 1;77(9):1372–80.
26. Vincent T, Hermansson M, Bolton M, *et al*. Basic FGF mediates an immediate response of articular cartilage to mechanical injury. Proceedings of the National Academy of Sciences of the United States of America. 2002 Jun 11;99(12):8259–64.
27. Chia SL, Sawaji Y, Burleigh A, *et al*. Fibroblast growth factor 2 is an intrinsic chondroprotective agent that suppresses ADAMTS-5 and delays cartilage degradation in murine osteoarthritis. Arthritis and Rheumatism. 2009 Jul;60(7):2019–27.
28. Solchaga LA, Penick K, Goldberg VM, *et al*. Fibroblast growth factor-2 enhances proliferation and delays loss of chondrogenic potential in human adult bone-marrow-derived mesenchymal stem cells. Tissue Engineering – Part A. 2010 Mar 1;16(3):1009–19.
29. Yang X, Chen L, Xu X, *et al*. TGF-β/Smad3 signals repress chondrocyte hypertrophic differentiation and are required for maintaining articular cartilage. Journal of Cell Biology. 2001 Apr 2;153(1):35–46.
30. Altman RD, Block DA, Brandt KD, *et al*. Osteoarthritis: Definitions and criteria. Annals of the Rheumatic Diseases. 1990 Mar;49(3):201.
31. Kellgren JH, Lawrence JS. Radiological assessment of osteo-arthrosis. Annals of the rheumatic diseases. 1957 Dec 1;16(4):494–502.
32. Roos EM, Lohmander LS. The Knee injury and Osteoarthritis Outcome Score (KOOS): From joint injury to osteoarthritis. Health and Quality of Life Outcomes. 2003 Nov 3;1:64.
33. Frobell RB, Roos EM, Roos HP, *et al*. A randomized trial of treatment for acute anterior cruciate ligament tears. New England Journal of Medicine. 2010 Jul 22;363(4):331–42.
34. Latourte A, Cherifi C, Maillet J, *et al*. Systemic inhibition of IL-6/Stat3 signalling protects against experimental osteoarthritis. Annals of the Rheumatic Diseases. 2017 Apr 1;76(4):748–55.
35. Miotla Zarebska J, Chanalaris A, Driscoll C, *et al*. CCL2 and CCR2 regulate pain-related behaviour and early gene expression in post-traumatic murine osteoarthritis but contribute little to chondropathy. Osteoarthritis

and Cartilage. 2017 Mar;25(3):406–12.

36. Blaney Davidson EN, van der Kraan PM, van den Berg WB. TGF-β and osteoarthritis. Osteoarthritis and Cartilage. 2007 Jun;15(6):597–604.
37. Sawaji Y, Hynes J, Vincent T, *et al*. Fibroblast growth factor 2 inhibits induction of aggrecanase activity in human articular cartilage. Arthritis and Rheumatism. 2008 Nov;58(11):3498–509.
38. Chong KW, Chanalaris A, Burleigh A, *et al*. Fibroblast growth factor 2 drives changes in gene expression following injury to murine cartilage in vitro and in vivo. Arthritis and Rheumatism. 2013 Aug;65(9):2346–55.
39. Alexander S, Watt F, Sawaji Y, *et al*. Activin a is an anticatabolic autocrine cytokine in articular cartilage whose production is controlled by fibroblast growth factor 2 and NF-κB. Arthritis and Rheumatism. 2007 Nov;56(11):3715–25.
40. Munz B, Smola H, Engelhardt F, *et al*. Overexpression of activin A in the skin of transgenic mice reveals new activities of activin in epidermal morphogenesis, dermal fibrosis and wound repair. EMBO Journal. 1999 Oct 1;18(19):5205–15.
41. Catterall JB, Stabler T V., Flannery CR, *et al*. Changes in serum and synovial fluid biomarkers after acute injury (NCT00332254). Arthritis Research and Therapy. 2010 Dec 31;12(6).
42. van der Woude JAD, Wiegant K, van Heerwaarden RJ, *et al*. Knee joint distraction compared with high tibial osteotomy: a randomized controlled trial. Knee Surgery, Sports Traumatology, Arthroscopy. 2017;25(3):876–86.
43. van Outeren M V., Waarsing JH, Brouwer RW, *et al*. Is a high tibial osteotomy (HTO) superior to non-surgical treatment in patients with varus malaligned medial knee osteoarthritis (OA)? A propensity matched study using 2 randomized controlled trial (RCT) datasets. Osteoarthritis and Cartilage. 2017 Dec 1;25(12):1988–93.
44. van der Woude JAD, Nair SC, Custers RJH, *et al*. Knee joint distraction compared to total knee arthroplasty for treatment of end stage osteoarthritis: Simulating long-term outcomes and cost-effectiveness. PLOS ONE. 2016 May 12;11(5):e0155524.

SUPPLEMENTARY DATA

Supplementary Table 1: Biomarker levels at baseline, 3 weeks and 6 weeks post knee joint distraction

Analyte	Baseline	3 weeks	Effect size	*P*-value	6 weeks	Effect size	*P*-value
Activin A (ng/ml)	10.5 (8.1–12.9)	4.0 (3.0–5.0)	-6.5	**0.003**	3.7 (2.0–5.4)	-6.8	**0.0002**
LTBP2 (ng/ml)	3.0 (2.7–3.3)	3.1 (2.0–3.2)	0.1	0.37	3.4 (2.5–4.0)	0.4	**0.05**
TGFβ-1 (ng/ml)	0.5 (0.4–1.1)	2.0 (1.1–2.1)	1.5	**0.01**	2.6 (1.3–5.3)	2.1	**0.0003**
FGF-2 (pg/ml)	26.6 (13.0–69.3)	39.3 (8.6–77.4)	12.7	0.42	191.3 (38.4–496.1)	164.7	**0.01**
TIMP-1 (ng/ml)	729.0 (563.1–1163.5)	1118.0 (717.5–1568.0)	389	**0.02**	844.2 (624.3–1225.0)	115.2	0.11
TSG-6 (ng/ml)	58.5 (28.5–156.9)	122.4 (73.7–227.4)	63.9	0.29	100.0 (42.4–164.3)	41.5	0.21
IL-6 (pg/ml)	11.3 (4.2–28.4)	70.9 (23.2–236.7)	59.6	**0.02**	67.9 (23.2–366.2)	56.6	**0.004**
MCP-1 (pg/ml)	410.0 (282.9–482.6)	524.8 (485.5–658.1)	114.8	0.25	565.1 (440.1–681.4)	155.1	**0.002**
IL-8 (pg/ml)	23.1 (16.0–35.3)	96.6 (28.7–122.6)	73.5	**0.01**	33.6 (19.8–56.4)	10.5	0.31
MMP3 (ng/ml)	444.3 (215.7–815.0)	912.2 (358.2–1623.3)	467.9	0.86	369.0 (190.9–1361.8)	-75.3	0.53

Median and interquartile range are given. Comparison was by Wilcoxon signed rank test, comparing mean of duplicate measures at 3 weeks or 6 weeks to measures at baseline. Data are also shown graphically in Figure 2 (some units are shown in ng/ml rather than pg/ml in this table). Effect size is calculated as the difference of medians. FGF-2: basic fibroblast growth factor; IL-6: interleukin 6; IL-8: interleukin 8; LTBP2: latent-transforming growth factor beta-binding protein 2; MCP-1: monocyte chemoattractant protein 1; MMP3, matrix metalloproteinase-3; TGFβ-1: transforming growth factor beta 1; TIMP-1: tissue inhibitor of metalloproteinases 1; TSG-6: TNF stimulated protein-6.

Supplementary Table 2: Regression coefficients and confidence intervals of the association of change in markers over distraction period with change in $KOOS_4$ over 3 months, 6 months and 12 months (data are also shown by forest plot in Figure 4A)

Period	Analyte	Coefficient	95%CI	R^2	*P*-value
3 months	Activin A	-0.001	-0.002 to <0.001	0.39	0.01
	LTBP2	0.002	-0.002 to 0.006	0.07	0.29
	TGFβ-1	0.001	<0.001 to 0.002	0.37	0.01
	FGF-2	0.021	0.005 to 0.038	0.34	0.01
	TIMP-1	<0.001	<0.001 to <0.001	<0.01	0.96
	TSG-6	<0.001	<0.001 to <0.001	<0.01	0.89
	IL-6	<0.001	-0.017 to 0.016	<0.01	0.96
	MCP-1	0.034	0.003 to 0.064	0.27	0.03
	IL-8	0.064	-0.028 to 0.156	0.13	0.16
	MMP3	<0.001	<0.001 to <0.001	0.05	0.41
6 months	Activin A	-0.002	-0.003 to <0.001	0.36	0.02
	LTBP2	0.002	-0.004 to 0.009	0.05	0.42
	TGFβ-1	0.002	<0.001 to 0.003	0.35	0.02
	FGF-2	0.030	0.004 to 0.057	0.32	0.03
	TIMP-1	<0.001	<0.001 to <0.001	<0.01	0.92
	TSG-6	<0.001	<0.001 to <0.001	0.03	0.55
	IL-6	0.007	-0.017 to 0.031	0.03	0.55
	MCP-1	0.052	-0.005 to 0.098	0.31	0.03
	IL-8	0.087	-0.048 to 0.221	0.13	0.19
	MMP3	<0.001	<0.001 to <0.001	<0.01	0.81
12 months	Activin A	-0.002	-0.006 to 0.002	0.08	0.34
	LTBP2	-0.002	-0.007 to 0.003	0.05	0.45
	TGFβ-1	-0.001	-0.002 to 0.001	0.05	0.48
	FGF-2	-0.001	-0.025 to 0.024	<0.01	0.95
	TIMP-1	<0.001	<0.001 to <0.001	0.02	0.62
	TSG-6	<0.001	<0.001 to <0.001	0.05	0.45
	IL-6	0.005	-0.014 to 0.023	0.03	0.59
	MCP-1	-0.013	-0.062 to 0.036	0.03	0.58
	IL-8	0.277	-0.096 to 0.651	0.20	0.13
	MMP3	<0.001	<0.001 to <0.001	0.02	0.61

FGF-2: basic fibroblast growth factor; IL-6: interleukin 6; IL-8: interleukin 8; $KOOS_4$: Knee injury and osteoarthritis outcome score-4; LTBP2: latent-transforming growth factor beta-binding protein 2; MCP-1: monocyte chemoattractant protein 1; MMP3, matrix metalloproteinase-3; TGFβ-1: transforming growth factor beta 1; TIMP-1: tissue inhibitor of metalloproteinases 1; TSG-6: TNF stimulated protein-6.

Supplementary Table 3: Change of $KOOS_4$ over 12 months according to the response of biomarkers to knee joint distraction by categories of relevant change (decrease, no change, or increase) over 6 weeks (see Methods)

Analyte (reference category)	Coefficient	95%CI	*P*-value
Activin A (no change)			
decrease	9.99	(-6.03 to 26.02)	0.20
LTBP2 (no change)			
increase	8.16	(-18.57 to 34.89)	0.52
TGFβ-1 (no change)			
increase	6.62	(-5.72 to 18.96)	0.26
FGF-2 (no change)			
increase	5.52	(-10.26 to 21.30)	0.46
decrease	9.24	(-18.08 to 36.57)	0.47
TIMP-1 (no-change)			
increase	11.38	(-5.05 to 27.81)	0.16
decrease	-5.68	(-42.42 to 31.06)	0.74
IL-6 (no change)			
increase	7.76	(-4.73 to 20.24)	0.20
decrease	2.95	(-23.53 to 29.44)	0.81
MCP-1 (no change)			
increase	10.41	(-4.55 to 25.36)	0.15
decrease	6.90	(-29.73 to 43.54)	0.69
IL-8 (no change)			
increase	17.63	(1.22 to 34.04)	0.04
decrease	-4.32	(-23.27 to 14.63)	0.63
MMP3 (no-change)			
increase	5.14	(-18.06 to 28.33)	0.64
decrease	0.61	(-27.80 to 29.02)	0.96

N=15. *P*-values were calculated with Wald tests. CI: confidence interval; FGF-2: basic fibroblast growth factor; IL-6: interleukin 6; IL-8: interleukin 8; KOOS4: Knee injury and osteoarthritis outcome score-4; LTBP2: latent-transforming growth factor beta-binding protein 2; MCP-1: monocyte chemoattractant protein 1; MMP3, matrix metalloproteinase-3; TGFβ-1: transforming growth factor beta 1; TIMP-1: tissue inhibitor of metalloproteinases 1; TSG-6: TNF stimulated protein-6.

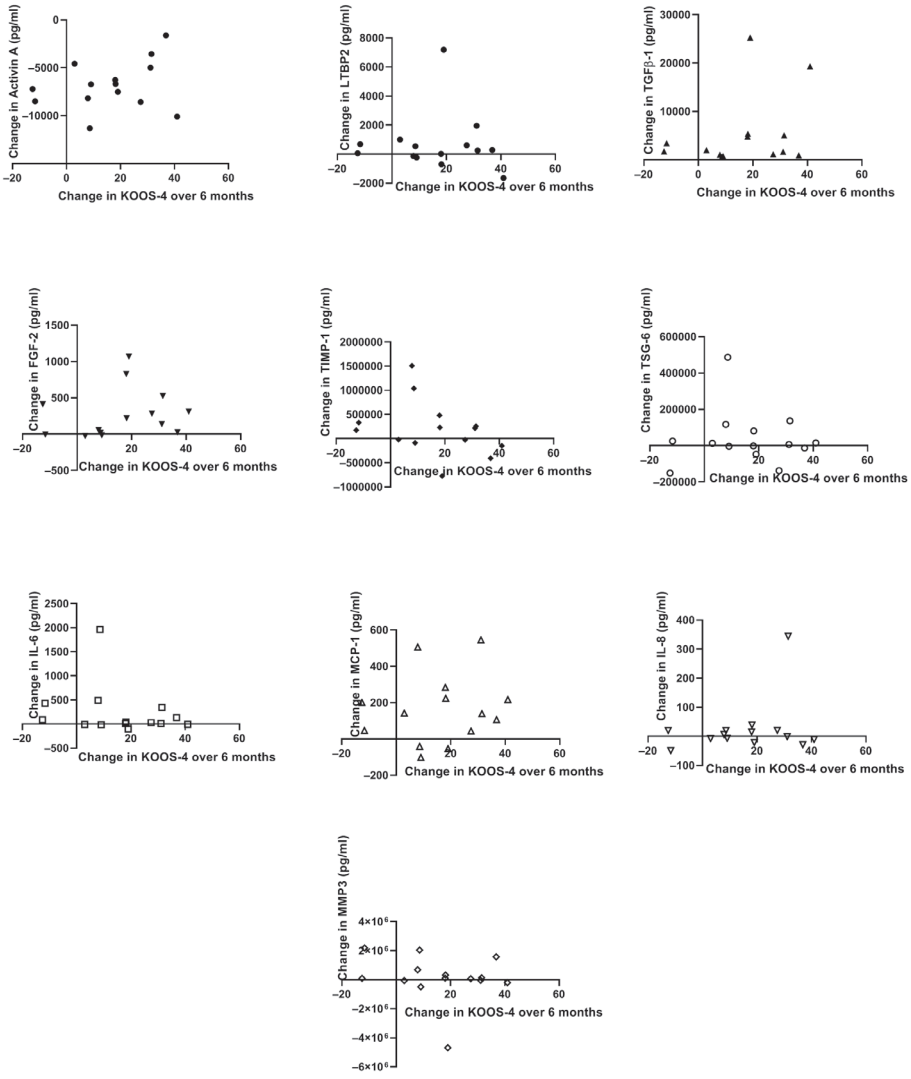
Supplementary Table 4: The median change in concentration of each analyte over the 6 week distraction period for clinical responders and non-responders

Analyte	Change in responders	Change in non-responders	Effect size	*P*-value
Activin A (ng/ml)	-6940	-7443	-503.2	0.64
LTBP2 (ng/ml)	270.0	207.4	-62.7	0.84
TGFβ-1 (ng/ml)	4128	918	-3210	0.036
FGF-2 (pg/ml)	297.1	1.23	-295.9	0.014
TIMP-1 (ng/ml)	194.5	508.7	314.2	0.37
TSG-6 (ng/ml)	2.5	65.0	62.5	0.24
IL-6 (pg/ml)	33.87	241.7	207.9	0.84
MCP-1 (pg/ml)	170.1	50.78	-119.3	0.54
IL-8 (pg/ml)	7.105	-0.19	-7.3	0.99
MMP3 (ng/ml)	102.3	315.8	213.5	0.99

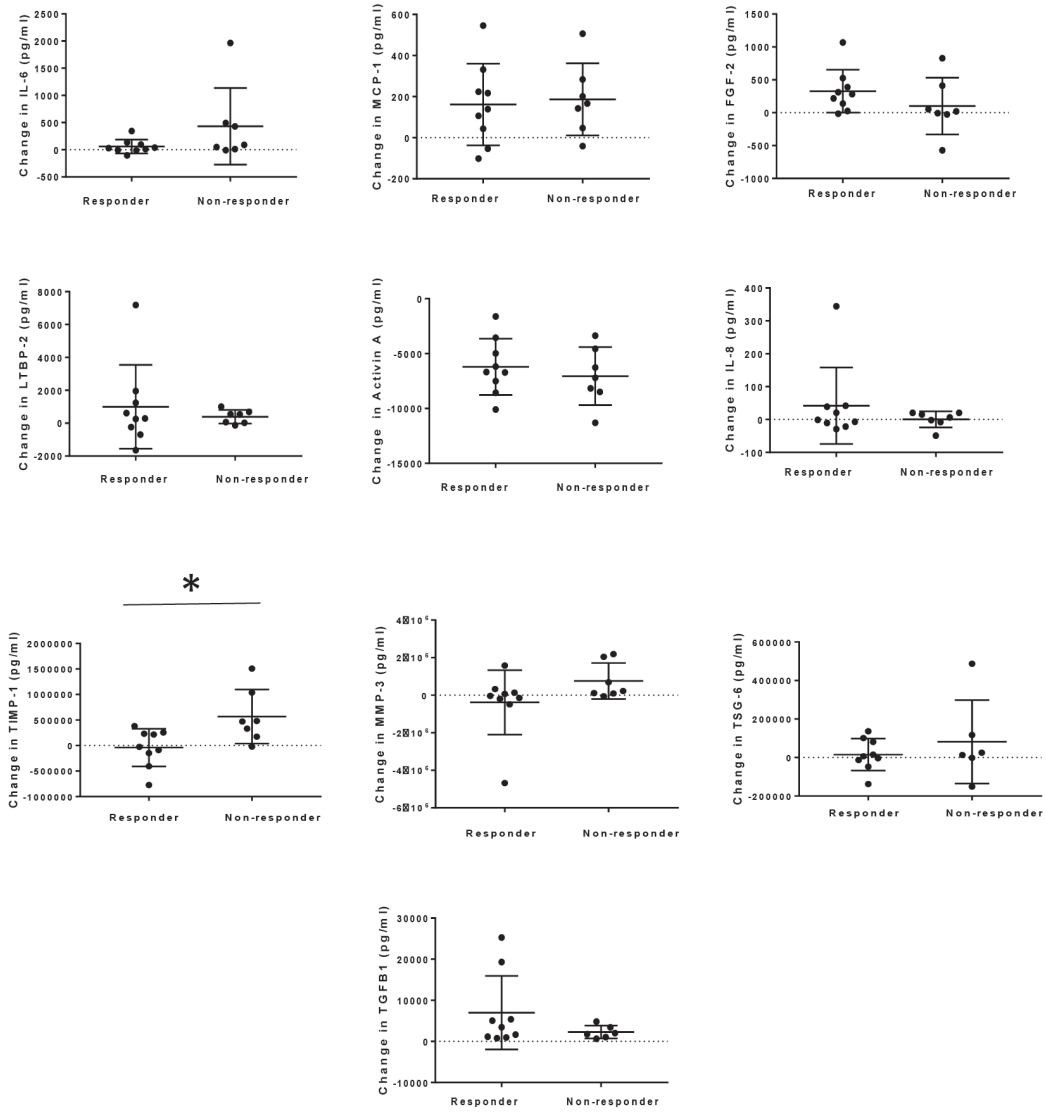
Medians are shown. The calculated effect size is the difference between the medians. Figure 4B also includes the 95% confidence intervals. Between group comparisons were by Mann-Whitney *U* test. FGF-2: basic fibroblast growth factor; IL-6: interleukin 6; IL-8: interleukin 8; LTBP2: latent-transforming growth factor beta-binding protein 2; MCP-1: monocyte chemoattractant protein 1; MMP3, matrix metalloproteinase-3; TGFβ-1: transforming growth factor beta 1; TIMP-1: tissue inhibitor of metalloproteinases 1; TSG-6: TNF stimulated protein-6.

	Activin A	LTBP2	TGFβ-1	FGF-2	TIMP-1	TSG-6	IL-6	MCP-1	IL-8
Activin A									
LTBP2	0.25								
TGFβ-1	-0.35*	0.35*							
FGF-2	<0.01	-0.02	0.27						
TIMP-1	0.07	0.15	0.07	0.05					
TSG-6	0.41*	0.20	0.01	0.01	0.35*				
IL-6	0.16	0.23	0.01	-0.15	0.24	0.79***			
MCP-1	0.35*	-0.45*	-0.45*	0.35*	-0.06	0.20	0.07		
IL-8	0.15	0.49*	-0.02	-0.42*	-0.25	0.47*	0.55**	-0.16	
MMP3	<0.01	0.45*	0.04	-0.03	0.69**	-0.10	0.11	-0.32*	-0.07

Supplementary Figure 1: Correlation between change of analytes in the synovial fluid of participants over 3 weeks of knee joint distraction. Spearman rank tests were performed to determine correlations between the change in levels of synovial fluid analytes over 3 weeks of distraction period (concentration at 3 weeks-baseline concentrations). Correlation coefficients were calculated using all available participant data and the mean of 2 repeated (duplicate) measures for each synovial fluid sample. Strength of correlation by Spearman *R* coefficient is shown: * (Light gray shading): Low positive (negative) correlation, 0.30 to 0.49 (–0.30 to –0.49); ** (Mid gray shading): Moderate positive (negative) correlation, 0.50 to 0.69 (–0.50 to –0.69); *** (Dark gray shading): High positive (negative) correlation, 0.70 to 0.89 (–0.70 to –0.89). FGF-2: basic fibroblast growth factor; IL-6: interleukin 6; IL-8: interleukin 8; LTBP2: latent-transforming growth factor beta-binding protein 2; MCP-1: monocyte chemoattractant protein 1; MMP3, matrix metalloproteinase-3; TGFβ-1: transforming growth factor beta 1; TIMP-1: tissue inhibitor of metalloproteinases 1; TSG-6: TNF stimulated protein-6.



Supplementary Figure 2: Scatter plots showing the association between the change in synovial fluid analyte for each individual over the distraction period with the change in clinical outcome $KOOS_4$ over 6 months, for each of the 10 analytes (regression statistics for these data are shown in middle panel of Figure 4A and Supplementary Table 2). FGF-2: basic fibroblast growth factor; IL-6: interleukin 6; IL-8: interleukin 8; $KOOS_4$: Knee injury and osteoarthritis outcome score-4; LTBP2: latent-transforming growth factor beta-binding protein 2; MCP-1: monocyte chemoattractant protein 1; MMP3, matrix metalloproteinase-3; TGFβ-1: transforming growth factor beta 1; TIMP-1: tissue inhibitor of metalloproteinases 1; TSG-6: TNF stimulated protein-6.



Supplementary Figure 3: The change of concentration in each analyte over the 6 week distraction period is shown (6 week level - baseline level), for 2 subgroups: responders (those whose change in $KOOS_4$ over 3 months was ≥ 10 points, i.e. those achieving the MCID for $KOOS_4$); and non-responders (those whose change in $KOOS_4$ over 3 months was <10 points, i.e. those not achieving the MCID for $KOOS_4$). The bars represent the median and 95% Confidence Intervals for each group. Between group comparisons were by Mann-Whitney *U* test, **p*=0.02. Abbreviations: MCID, minimal clinically important difference; LTBP2, latent-transforming growth factor beta-binding protein 2; TGFβ-1, transforming growth factor beta 1; FGF-2, basic fibroblast growth factor; TIMP-1, tissue inhibitor of metalloproteinases 1; TSG-6, tumor necrosis factor-inducible gene 6 protein; IL-6, interleukin 6; MCP-1, monocyte chemoattractant protein 1; IL-8, interleukin 8; MMP3, matrix metalloproteinase-3; KOOS: Knee injury and Osteoarthritis Outcome Score ($KOOS_4$ is composite measure of 4 domains).

CHAPTER 17

Cartilage repair activity during joint-preserving treatment may be accompanied by osteophyte formation

M.P. Jansen
S.C. Mastbergen
F.E. Watt
E.J. Willemse
T.L. Vincent
S. Spruijt
P.J. Emans
R.J.H. Custers
R.J. van Heerwaarden
F.P.J.G. Lafeber

Submitted for publication

Abstract

Background: Knee joint distraction (KJD) treatment has shown cartilage repair and clinical improvement in patients with osteoarthritis, as has high tibial osteotomy (HTO). Following KJD, in synovial fluid (SF) an increase was shown in transforming growth factor-β1 (TGFβ-1) and interleukin-6 (IL-6), factors related to cartilage regeneration, but also to osteophyte formation. As such, osteophyte formation resulting of both joint-preserving treatments was studied.

Methods: Radiographic osteophyte size was measured before treatment and 1 and 2 years after treatment. Changes were compared with natural progression in patients from the CHECK cohort just before undergoing total knee arthroplasty. An additional KJD cohort underwent SF aspiration, and 1-year Altman osteophyte score changes were compared to SF-marker changes during treatment.

Results: After 2 years, both KJD (n=58) and HTO (n=38) patients showed a significant increase in osteophyte size (+6.2 mm^2 and +7.0 mm^2 respectively; both $p<0.004$), with no significant differences between the treatments ($p=0.592$). Untreated CHECK patients (n=44) did not show significant 2-year changes (+2.1 mm^2; $p=0.207$) and showed significant differences with KJD and HTO (both $p<0.044$). In SF aspiration patients (n=17), there were significant differences in TGFβ-1 changes ($p=0.044$), but not IL-6 ($p=0.898$), between patients with a decrease, no change, or increase in osteophyte Altman score.

Conclusion: After KJD treatment, joint space widening and clinical improvement are accompanied by osteophyte formation, observed similarly after HTO. Increased osteophytosis after joint-preserving treatments may be a bystander effect of cartilage repair activity related to intra-articular factors like TGFβ-1 and questions osteophyte formation as solely characteristic of the joint degenerative process.

Introduction

Osteoarthritis (OA) is characterized by articular cartilage loss, intra-articular inflammation, and osteophyte formation.[1] Osteophytes are often formed at the joint margins, first as cartilage outgrowth and subsequently undergoing ossification.[2] While the exact purpose of osteophytes remains unknown, their presence and size in the knee are associated with joint space width (JSW) decrease and they are an important radiographic feature used to define the severity of knee OA in classifications like the Altman score and Kellgren-Lawrence grade.[3–7] Osteophytes are frequently present in patients with end-stage knee OA receiving surgical treatment such as total knee arthroplasty (TKA).[8]

TKA is widely used because of its clinical effectiveness, but in younger patients (<65 years) it has a significantly higher risk of failure and revision surgery later in life.[9,10] Therefore, there is a demand for joint-preserving treatments for (severe) knee OA at a younger age. A joint-preserving alternative for patients with unicompartmental knee OA as a result of malalignment is high tibial osteotomy (HTO), which shows good long-term results and clinical improvement and a certain degree of cartilage repair.[11–13] Knee joint distraction (KJD) is a relatively new joint-preserving treatment for patients with unicompartmental or generalized severe knee OA, where the tibia and femur are temporarily separated using an external fixation frame.[14] An open prospective study (OPS) has shown good long-term treatment results and 2 randomized controlled trials (RCTs), 1 comparing KJD with HTO and 1 with TKA, showed that clinical outcome after KJD is comparable to that after HTO or TKA.[15–20] Furthermore, cartilage repair has been shown on radiographs and on MRI scans, and systemic biomarker analyses suggest beneficial cartilage and bone turnover after KJD treatment.[18,21–23]

Cartilage repair activity as a result of treatment could be related to an increase in transforming growth factor-β1 (TGFβ-1), which is generally appreciated to stimulate cartilage repair.[24] During KJD treatment, an increase in synovial fluid TGFβ-1 level was observed.[25] While TGFβ-1 is associated with joint repair, it has also been shown to induce osteophyte formation, predominantly in experimental animal studies, but in *ex vivo* human studies as well.[26–31] Interleukin-6 (IL-6) was also observed to increase intra-articularly as a result of KJD treatment and could be positively associated with osteophyte presence as well, showing increased mRNA expression and protein production in *in vitro* studies with human osteophyte tissue.[25,30,32]

As such, we studied osteophyte formation during KJD and compared this to HTO and natural OA progression, hypothesizing that joint-preserving regenerative treatments demonstrating cartilage repair activity lead to tissue (re)generation in general, including osteophyte formation.

Methods

Knee joint distraction patients

63 Patients were included for KJD treatment in 3 different trials. Of these 63 patients, 20 patients with an indication for TKA and age <60 years old were included in the OPS. Secondly, 20 TKA-indicated patients <65 years old were treated with KJD in an RCT comparing KJD with TKA. The third and last group of 23 patients with medial compartmental knee OA, an indication for HTO and age <65 years were treated with KJD in an RCT comparing KJD with HTO. In- and exclusion criteria have been described before and included radiographic signs of tibiofemoral OA (Kellgren-Lawrence grade >2, judged by orthopedic surgeon), <10° knee malalignment, BMI <35, and no presence or history of inflammatory or septic arthritis.[33,34] All trials complied with the Declaration of Helsinki, were granted ethical approval by the medical ethical review committee of the University Medical Center Utrecht (protocol numbers 04/086, 10/359/E, and 11/072) and were registered in the Netherlands Trial Register (trial numbers NL419, NL2761 and NL2680). All patients gave written informed consent.

Distraction surgery was performed using an external fixation frame. The knee was distracted 2 mm during surgery and 1 mm every day during a short hospitalization until 5 mm distraction was reached, confirmed on radiographs. Patients were discharged with prophylactic anticoagulant to use during treatment and were allowed full weight-bearing of the treated knee, supported by crutches if necessary. After 6 to 8 weeks the distraction frame and pins were surgically removed.

Follow-up

Patients visited the hospital multiple times, including at baseline and 1 and 2 years after treatment, during which standardized weight-bearing, semi-flexed posterior-anterior radiographs were performed according to the Buckland-Wright protocol, using an aluminum step wedge as a reference standard for image analysis using 'knee images digital analysis' (KIDA) software (described below).[35,36] Patients completed the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC, version 3.1) questionnaire as well. Only patients with standardized radiographs at both baseline and 2 years were included.

High tibial osteotomy patients

HTO patients from the KJD *versus* HTO trial were used to study generalizability of the concept of osteophyte formation during regenerative treatments demonstrating endogenous cartilage repair activity. The 46 HTO patients were included in the trial to be treated with biplane medial-based opening-wedge osteotomy and had the same follow-up as described above for KJD patients. Only patients with standardized baseline and 2-year radiographs were included in the analyses. The HTO patients were compared to the 23 KJD patients (KJD_{HTO}) from the RCT comparing KJD and HTO.

Control group of untreated osteoarthritis patients

The only relevant OA cohort using the same standardized radiographic analyses, with quantification of osteophyte area, is CHECK (Cohort Hip & Cohort Knee), a cohort of 1002 participants with early symptomatic knee or hip OA who were followed for 10 years and had radiographs of both knees at baseline, 2, 5, 8 and 10 years follow-up.[37] From this cohort, patients that received a TKA during the follow-up period were selected to be compared with KJD patients, since most KJD patients were indicated for TKA but received KJD. For each knee that was treated with TKA in CHECK, all pre-TKA radiographic osteophyte measurements were analyzed to evaluate linearity of osteophyte formation using a linear regression model, with osteophyte size as dependent variable and the 'years before TKA' and 'years before TKA squared' as independent variables. The change in osteophyte area during the last 2 measurements before TKA, corrected to represent a 2-year period, was used as control osteophyte progression rate. WOMAC questionnaires from the last time point before TKA and 2 years prior were used to evaluate 2-year clinical changes.

Radiographic analysis

The standardized radiographs were analyzed by 1 experienced observer, blinded to patient characteristics, using KIDA software.[38] The osteophyte size (area on the 2D image) was measured in mm^2 for 4 regions: the lateral and medial femur and tibia. The sum of these regions gives the whole-joint osteophyte size in mm^2. The JSW of the most affected compartment (MAC; determined pre-treatment) in mm provided by the KIDA measurement was evaluated as a representative of the cartilage regenerative activity of the treatment. In CHECK the compartment with the smallest JSW was chosen as MAC.

Synovial fluid aspirations

Between 2014 and 2015, 20 patients treated with KJD in regular care were included for synovial fluid (SF) aspirations in an ethically approved study (protocol number 15/160). The treatment protocol and in- and exclusion criteria in regular care were similar as explained above and have been described elsewhere[39], with the addition that patients in this study needed to have a successful baseline SF aspiration. At baseline (during frame placement surgery) and after treatment (during frame removal surgery) an SF sample of maximum 2 mL was aspirated from the treated knee. Biomarker levels were measured according to protocols described previously.[25] In short, samples were centrifuged for 20 min at 3000G and stored in 200 µl aliquots at -80°C. The supernatants were measured by immunoassay for 10 predefined mechanosensitive molecules; mean analyte concentrations were calculated from duplicate assay reads for each participant and time point. For the present evaluation, only TGFβ-1 and IL-6 were used as predefined potential candidates for association with osteophyte formation as only those have been related to osteophyte formation in literature.

As no standardized (KIDA) radiographs were available in these SF patients, radiographs taken in regular care at baseline and around 1 year after treatment (range 276–433 days) were used to score osteophytes using the revised Altman score.[6] The correlation between Altman and KIDA in KJD RCT patients was tested and showed to be moderately good (R=0.669; p<0.001; Supplementary Table S1). All images were scored for osteophytes in each of the 4 regions twice by 1 observer (SM), giving each compartment a grade from 0 (normal) to 3 (severe). The average of both scores was used and due to the wide follow-up range, the follow-up radiograph was linearly corrected (extrapolated) to 365 days with respect to the baseline radiograph. The separate compartment scores were summarized to obtain a 0–12 whole-joint scoring. Only patients with baseline and 1-year follow-up radiographs were included in the analyses.

Statistical analyses

For all continuous parameters, changes over time for separate patient groups were analyzed using paired *t*-tests or where more than 2 time points were available, repeated measures ANOVA. The influence of available predefined patient characteristics (age, sex, BMI and Kellgren-Lawrence grade) on osteophyte formation was tested with linear regression. For comparisons where in both groups more than 2 time points were available, mixed ANOVA was used instead.

In SF patients, for the categorical Altman score per region, the Wilcoxon Signed Rank test was used to test changes over time. The changes in whole-joint osteophyte Altman score and in synovial fluid biomarkers were analyzed with paired *t*-tests, and the Pearson correlations between total joint osteophyte Altman and biomarker baseline values and changes over time were calculated. Finally, SF patients were divided in 3 groups (trichotomized) based on an increase, no change or decrease in total osteophyte Altman score over time. The change in TGFβ-1 and in IL-6 during the distraction period was compared between these 3 groups using a Kruskal-Wallis test, because of the resulting limited number of patients per group.

Normal distribution was verified for all outcome parameters; in case outcomes were not normally distributed, log transformation was performed. For all tests, a p-value <0.05 was considered statistically significant. Absolute values are presented with mean ± standard deviation (SD) while changes over time are presented as mean change and 95% confidence interval (95%CI).

Results

Patients

Of all KJD patients, 1 was excluded before surgery due to inoperability, 3 KJD patients were lost to follow-up after receiving a different surgical treatment during follow-up and 1 patient

did not have a standardized baseline radiograph, leaving 58 KJD patients for analysis, of whom 20 in the KJD_{HTO} group.

Of the HTO patients, 1 was excluded before treatment due to anxiety while 4 patients were lost to follow-up due to comorbidities. Five did not have standardized radiographs at both baseline and 2 years follow-up, leaving 36 HTO patients.

In CHECK, 30 patients received a TKA during the 10-year follow-up, 14 of whom had a TKA in both knees, giving a total of 44 knees to be compared to the KJD patients.

Three of the 20 patients with SF aspirations did not have both a baseline and follow-up radiograph available, leaving 17 SF patients.

The baseline characteristics of all groups are shown in Table 1.

Table 1: Baseline characteristics of the different patient groups

	KJD (n=58)	KJD_{HTO} (n=20)	HTO (n=36)	CHECK (n=44)	SF (n=17)
Age (years)	51.4 (8.0)	51.2 (5.8)	49.1 (6.5)	64.0 (4.3)	53.8 (4.7)
Male sex, n (%)	34 (59)	15 (75)	23 (64)	5 (11)	10 (59)
BMI (kg/m^2)	28.0 (3.4)	27.4 (3.3)	27.0 (3.5)	29.4 (4.6)	29.0 (3.3)
Kellgren-Lawrence grade, n (%)					
- Grade 0	0 (0)	0 (0)	1 (3)	2 (5)	0 (0)
- Grade 1	8 (14)	5 (25)	4 (11)	18 (41)	0 (0)
- Grade 2	9 (16)	4 (20)	10 (28)	16 (36)	2 (12)
- Grade 3	28 (48)	10 (50)	18 (50)	8 (18)	7 (41)
- Grade 4	13 (22)	1 (5)	3 (8)	0 (0)	8 (47)

Mean and standard deviation or n (%) are given. BMI: body mass index; KJD: all knee joint distraction patients with available osteophyte measurements; KJD_{HTO}: subgroup of KJD patients who were included in the KJD *versus* HTO clinical trial; HTO: high tibial osteotomy patients from the KJD *versus* HTO clinical trial; CHECK: untreated knee osteoarthritis patients from the Cohort Hip & Cohort Knee trial who received a total knee arthroplasty during follow-up; SF: KJD patients from a separate clinical study who underwent synovial fluid aspirations.

Changes after knee joint distraction

As shown in Table 2, the total WOMAC showed significant improvement 2 years after KJD (+28.1; 95%CI 22.7–33.4; p<0.001), as did its subscales. The mean MAC radiographic JSW was significantly increased at 2 years as well (+0.66; 0.36–0.97; p<001).

Table 2: Baseline and 2-year WOMAC and JSW for the different patient groups

	KJD			HTO			CHECK		
	Baseline	**2 Years**	***P*-value**	**Baseline**	**2 Years**	***P*-value**	**Baseline**	**2 Years**	***P*-value**
Total WOMAC (0–100)	50.6 (15.7)	78.8 (19.3)	**<0.001**	50.7 (14.6)	81.5 (14.5)	**<0.001**	58.6 (15.9)	51.8 (20.3)	**0.035**
JSW (mm)	2.36 (1.73)	3.03 (1.57)	**<0.001**	2.24 (1.28)	2.56 (1.37)	**0.034**	3.18 (1.76)	2.52 (1.72)	**<0.001**

Mean and standard deviation are given. *P*-values are calculated for 2-year changes with paired *t*-tests; bold *p*-values indicate statistical significance. CHECK: Cohort Hip & Cohort Knee; HTO: high tibial osteotomy; JSW: joint space width (mean JSW of the most affected compartment is shown); KJD: knee joint distraction; WOMAC: Western Ontario and McMaster Universities Osteoarthritis Index (scale 0–100).

The total osteophyte size showed a statistically significant increase after treatment (p=0.003), from 40.9 (SD 28.0) mm^2 at baseline to 47.1 (28.1) mm^2 at 2 years, as shown in Figure 1A. Only the lateral femur showed a significant increase (from 9.1 (9.4) mm^2 to 11.9 (9.8) mm^2; p<0.001), the other compartments did not (all p≥0.19; Figure 1B). A representative radiograph of a patient before and 2 years after KJD treatment is shown in Figure 2.

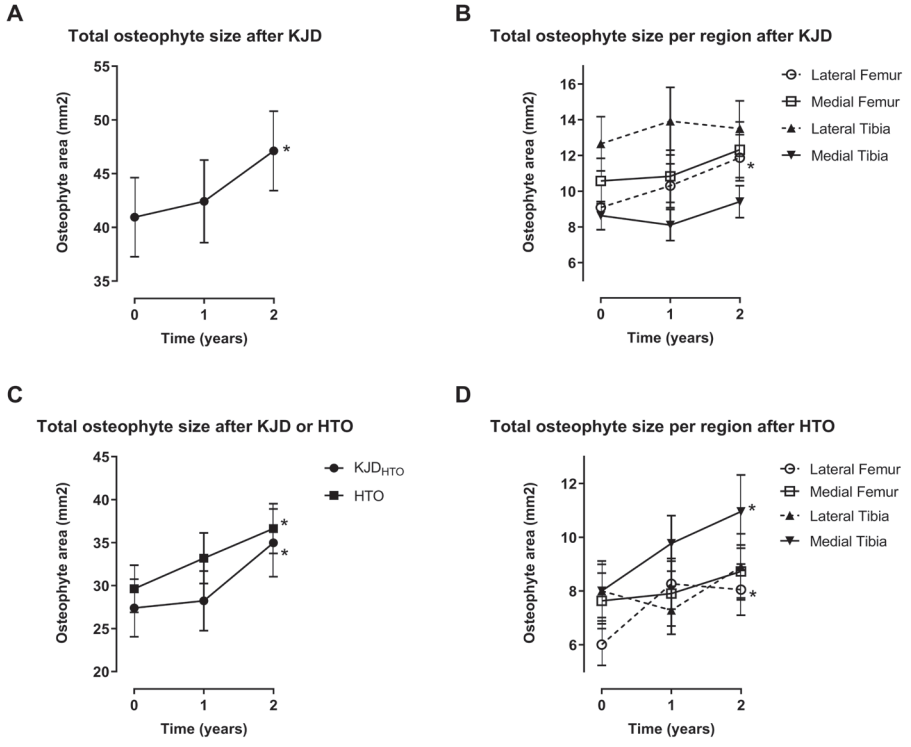


Figure 1: Change in osteophyte size in mm^2 before and 1 and 2 years after treatment with knee joint distraction (KJD) or high tibial osteotomy (HTO). (A) The total joint osteophyte area and (B) the osteophyte area per compartment after KJD. (C) Total joint osteophyte area after KJD or HTO and (D) osteophyte area per compartment after HTO. Mean and standard error of the mean (SEM) are shown, * indicates significant changes compared to baseline using repeated measures ANOVA (p<0.05).

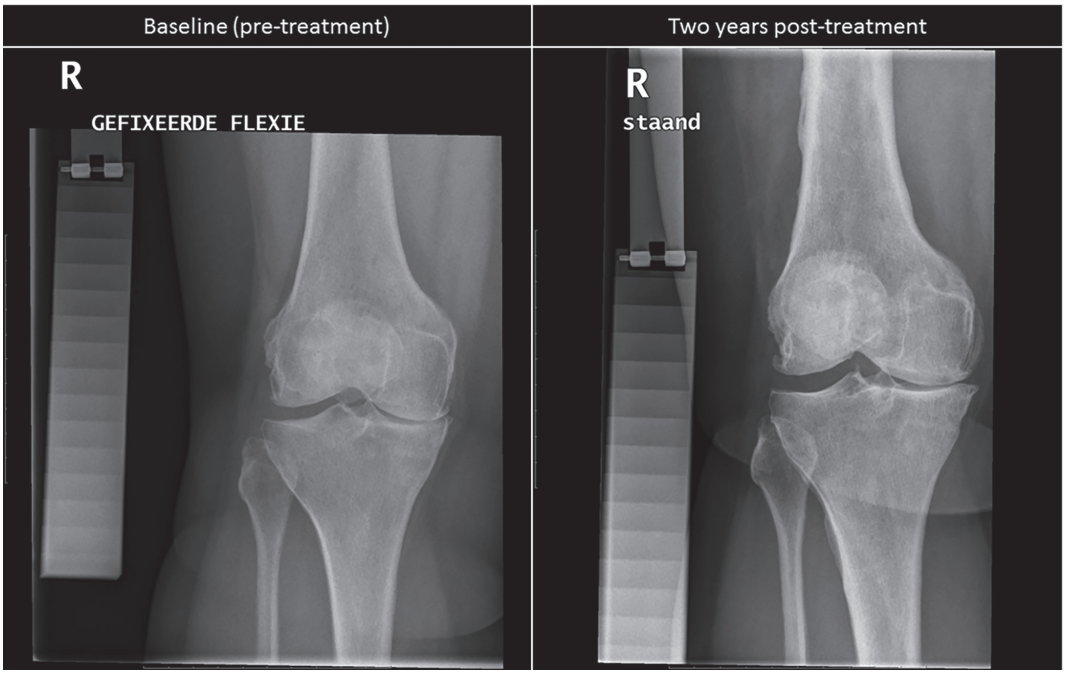


Figure 2: Representative radiograph of a patient before and 2 years after knee joint distraction treatment.

None of the baseline characteristics in Table 1 had a significant influence on the 2-year change in osteophyte size (all $p>0.32$; Supplementary Table S2).

Comparison with high tibial osteotomy

HTO patients showed a significant increase in total WOMAC (+30.8; 95%CI 25.5–36.1; $p<0.001$) and in MAC JSW (+0.32; 0.03–0.61; $p=0.034$) as shown in Table 2. The WOMAC subscales showed a similar increase.

HTO patients showed a significant osteophyte change after treatment ($p<0.001$), increasing from 29.6 (SD 16.5) mm^2 at baseline to 36.6 (17.4) mm^2 at 2 years (Figure 1C). The changes in the lateral femur (6.0 (4.6) mm^2 to 8.1 (5.7) mm^2; $p<0.001$) and medial tibia (8.0 (6.7) mm^2 to 11.0 (8.2) mm^2; $p=0.006$) were statistically significant (Figure 1D). Like the entire KJD cohort, the KJD_{HTO} patients showed a significant increase after treatment (from 27.4 (15.0) mm^2 to 35.0 (17.6) mm^2; $p<0.001$), and only the lateral femur showed a significant increase (from 4.6 (3.8) mm^2 to 8.1 (4.5) mm^2; $p=0.006$; Supplementary Figure S1). There was no significant difference between KJD_{HTO} and the other KJD patients for the total osteophyte changes over 2 years ($p=0.566$). There was no significant difference in the osteophyte changes between HTO and KJD_{HTO} ($p=0.592$; Figure 1C).

Comparison with untreated osteoarthritis patients

In the 44 knees that received a TKA in CHECK, 124 KIDA measurements were available in the years before the TKA, which were used to confirm a linear approach to osteophyte change over time could be assumed, as the variable 'years to TKA squared' did not contribute significantly to the linear regression model predicting osteophyte size (p=0.759). CHECK patients showed a significant decrease in total WOMAC (-6.3; 95%CI -12.1 to -0.5; p=0.04) and MAC JSW (-0.67; 95%CI -0.86 to -0.47; p<0.001) before undergoing TKA, as shown in Table 2.

Before TKA, CHECK knees showed a small non-significant increase in osteophyte size (+2.1mm^2; 95%CI -1.2 to 5.5; p=0.207; Figure 3A). Correcting for baseline osteophyte size, all KJD patients together (p=0.027), KJD$_{HTO}$ patients (p=0.043) and HTO patients (p=0.027) showed a significantly greater osteophyte increase than CHECK patients prior to TKA. Taking the average of both knees in patients with a TKA in both knees, instead of using the knees separately, did not change significance. Figure 3B displays the 2-year changes in total osteophyte size for the different groups.

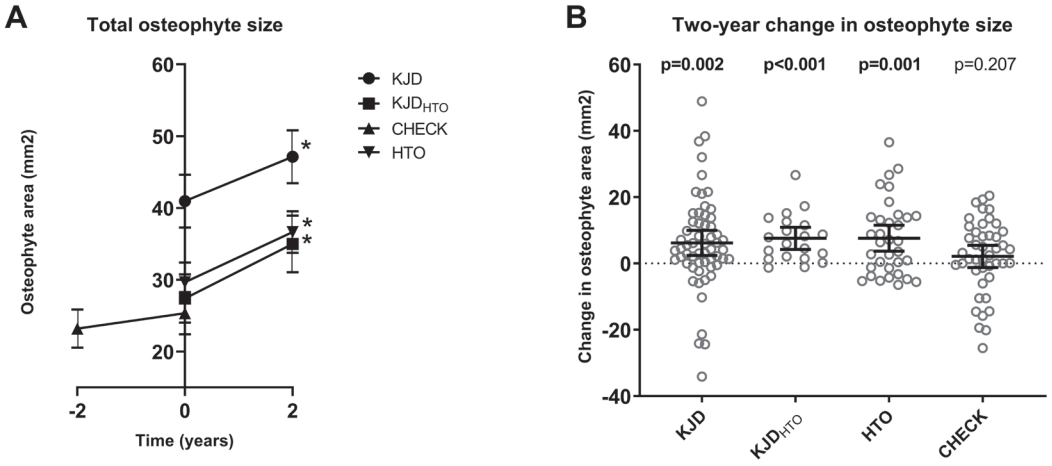


Figure 3: Two-year changes in total joint osteophyte size in mm^2. (A) Osteophyte size after treatment for all patients treated with knee joint distraction (KJD), high tibial osteotomy (HTO), HTO-indicated KJD patients (KJD$_{HTO}$), and for untreated knee osteoarthritis patients before receiving a total knee arthroplasty (CHECK). Mean and standard error of the mean (SEM) are shown, * indicates significant changes (p<0.05) compared to baseline using paired t-tests. (B) Two-year osteophyte size changes for individual KJD, HTO, KJD$_{HTO}$ and CHECK patients. Mean and 95% confidence interval are shown, p-values above groups indicate significance of 2-year changes.

Relation with synovial fluid markers

None of the 4 osteophyte locations showed statistically significant 1-year changes in Altman score compared to baseline in the SF patients (all p>0.074; Supplementary Table S3). The total Altman osteophyte score summarized for the entire joint was at 1 year not different from

baseline, increasing with 0.2 points (95%CI -0.6 to 0.9; p=0.653). As the biomarkers were not normally distributed, they were log transformed. In case of negative change values, the log transformation of the absolute change was subtracted from zero. Two patients did not have biomarker results after treatment, and 1 patient did not have a baseline value for TGFβ-1 only, leaving 14 patients for TGFβ-1 analysis and 15 patients for IL-6 analysis. Both biomarkers showed statistically significant changes during the distraction period, as shown previously[24]: TGFβ-1 (1527.9 (SD 3346.8) to 8027.9 (10534.8) pg/mL; p<0.001); IL-6 (24.4 (31.3) to 466.3 (936.4) pg/mL; p=0.011). There was no apparent association between baseline values of these biomarkers and the baseline total Altman osteophyte score, or between the changes in these parameters (all p≥0.28; Supplementary Table S4). Trichotomization of patients in groups with a decrease (n=5), no change (n=3) or increase (n=6 for TGFβ-1; n=7 for IL-6) in total Altman osteophyte score showed there was a statistically significant difference in changes in analyte levels during treatment between the 3 groups for TGFβ-1 (p=0.044), but not for IL-6 (p=0.898), as shown in Figure 4.

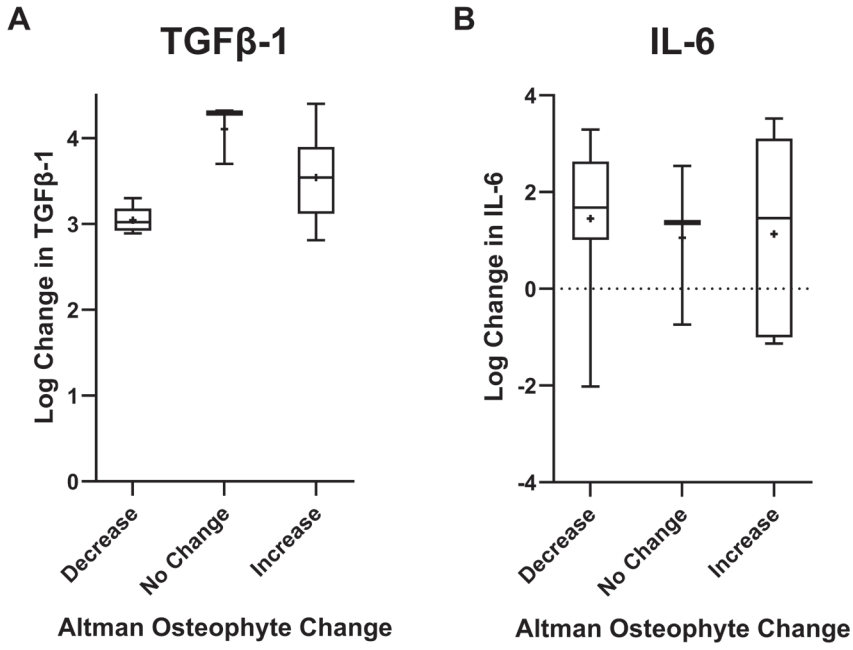


Figure 4: Box plots for the changes in synovial fluid concentrations over the course of 6 weeks of knee joint distraction, of (A) transforming growth factor-β1 (TGF-β1) and (B) interleukin-6 (IL-6), categorized into groups of patients with a decrease (n=5), no change (n=3) or increase (n=6 for TGFβ-1; n=7 for IL-6) in total Altman osteophyte score. The bar represents the median, whiskers represent the minimum and maximum value, the + represents the mean.

Discussion

Based on radiographic measurement, using sensitive image analyses like KIDA, KJD seems to induce increased osteophyte formation in the first 2 years following treatment. This argues against the general assumption that osteophytosis is solely a hallmark of OA worsening or joint degeneration, since this osteophytosis during KJD is combined with a significant increase in clinical benefit and joint space widening (supported in previous studies by MRI cartilage volume measurements[21,22,32]). Increased osteophyte presence has often been associated with increased pain knee OA patients[39–41], but in KJD patients improvement in clinical outcome, including a significant decrease in pain, goes parallel with an increase in osteophyte size. No correlation could be found between (changes in) osteophyte size and WOMAC scores or JSW (except between baseline JSW and osteophyte size, see supplementary Tables S5 and S6), expectedly due to limited numbers.

Treatment-related osteophyte formation is not limited to KJD, but is demonstrated after HTO as well. HTO patients were compared with KJD_{HTO} patients, since those groups were randomized as such in the original RCT, and showed similar osteophyte formation. While KJD_{HTO} patients showed similar results as the entire KJD group, their baseline osteophyte size was smaller and more comparable with the HTO group. This is likely because while KJD_{HTO} patients were in regular care indicated for a HTO, all other KJD patients were in regular care indicated for TKA and thus likely had further progressed OA. Nevertheless, both treatments showed changes predominantly in the lateral compartment. While in HTO patients this might be explained by an increased load on the lateral side as a result of the medial unloading, such a shift is not necessarily expected in KJD. Since HTO shows an osteophyte increase on the medial side as well, loading may not be directly involved in osteophyte formation after these treatments. Like in KJD, osteophyte formation in HTO accompanies clinical improvement and JSW increase, further questioning the role of osteophytes in OA. Other studies have shown similar findings, showing that lateral osteophyte presence is not associated with lateral cartilage degeneration or with medial knee OA severity.[42–44] Our findings suggest that the presence, size and localization of osteophytes may not be such a clear indication of joint degeneration and accompanying symptoms as is generally assumed.

With the analysis of untreated patients from the CHECK cohort it was shown that the increase in osteophytes after KJD was greater than the natural progression that can be expected in knee OA patients. It should be noted however that, despite making a selection of patients that received TKA during follow-up, the CHECK patients differed in baseline characteristics and seemed to have less severe OA at the moment of treatment (TKA) than the KJD patients, as shown by Kellgren-Lawrence grade and osteophyte size. This might be related to the specific characteristics of this CHECK cohort where pain was an essential inclusion criterion, and might be irrelevant for comparison with KJD or HTO, as in none of the groups the baseline

osteophyte size or Kellgren-Lawrence grade had a significant influence on the change in osteophyte size (CHECK: p=0.391 and p=0.457, respectively).

For patients who had SF aspirations, the osteophyte formation after KJD seems to be associated with the increase in TGFβ-1 during the 6 weeks of treatment, based on dividing patients into groups showing an increase, no change or a decrease in Altman osteophyte score after KJD. However, there were no associations between the (changes in) actual Altman scores and TGFβ-1 values. These results are as such indicative and not conclusive, corroborating the reported role of TGFβ-1 in osteophyte formation. While both TGFβ-1 and IL-6 significantly increased during treatment, the change in IL-6 was not associated with osteophyte formation.

This study has several limitations. First, the different cohorts were not initiated and powered for the presented statistical evaluations and should therefore be considered exploratory. Second, retrospectively comparing patient cohorts that have not been randomized or carefully matched, as was done when comparing KJD patients with CHECK, provides a risk for coincidental findings. Despite selecting the most relevant subgroup from CHECK, there was a clear difference in OA severity with KJD patients. Also, although the comparison between KJD and CHECK was corrected for baseline osteophyte size and the Kellgren-Lawrence grade was shown to not be on influence on the change in osteophyte size, it could still be that the results in CHECK patients underestimate the natural progression in more severe knee OA patients. CHECK was used since it was a well-established cohort of untreated knee OA patients of which radiographs were evaluated with KIDA, but patients generally had mild OA. Patients with a more comparable severity would make a better comparison, although purposefully not treating severe knee OA patients for multiple years would be ethically unsound.

Another limitation was the fact that no KIDA evaluations were available for the SF patient group. The Altman osteophyte score may not have been sensitive enough to show 1-year changes in osteophyte size after KJD, especially in this small group of patients. As TGFβ-1 has previously been associated with both cartilage repair and osteophyte formation, morphometric MRI scans in sufficient numbers of patients could be of added value in future studies. The present study provides an indication that a rise in TGFβ-1 might be a mediator in tissue repair activity upon KJD leading to osteophyte formation in addition to cartilage repair, but future studies would have to proof this concept.

Lastly, osteophyte formation was measured on 2D images. In a future study, it would be interesting to measure osteophyte formation after regenerative treatments like KJD and HTO in 3-dimensional CT images as well, to improve sensitivity (to change) and to add to pathobiological mechanisms regarding osteophytosis during natural progression compared to these joint regenerative treatments.

In conclusion, KJD is accompanied by osteophytosis occurring in parallel with radiographic joint space widening and clinical improvement including significant pain relief. Similarly, HTO is accompanied by osteophytosis as well. The osteophyte formation during joint-preserving treatments with observed endogenous cartilage repair activity seems to be a bystander effect and may be related to a change in intra-articular anabolic factors such as TGFβ-1. This observation argues against osteophytosis as solely a key parameter in the joint degenerative process.

References

1. Woolf AD, Pfleger B. Burden of major musculoskeletal conditions. Bulletin of the World Health Organization. 2003;81(9):646–56.
2. van der Kraan PM, van den Berg WB. Osteophytes: Relevance and biology. Osteoarthritis and Cartilage. 2007 Mar 1;15(3):237–44.
3. Felson DT, Gale DR, Elon Gale M, *et al*. Osteophytes and progression of knee osteoarthritis. Rheumatology. 2005 Jan 1;44(1):100–4.
4. Dieppe PA, Cushnaghan J, Shepstone L. The Bristol "OA500" study: Progression of osteoarthritis (OA) over 3 years and the relationship between clinical and radiographic changes at the knee joint. Osteoarthritis and Cartilage. 1997 Mar 1;5(2):87–97.
5. Braun HJ, Gold GE. Diagnosis of osteoarthritis: Imaging. Bone. 2012 Aug;51(2):278–88.
6. Altman RD, Gold GE. Atlas of individual radiographic features in osteoarthritis, revised. Osteoarthritis and Cartilage. 2007 Jan 1;15(SUPPL. 1):1–56.
7. Kellgren JH, Lawrence JS. Radiological assessment of osteo-arthrosis. Annals of the Rheumatic Diseases. 1957 Dec 1;16(4):494–502.
8. Nevalainen MT, Kauppinen K, Pylväläinen J, *et al*. Ultrasonography of the late-stage knee osteoarthritis prior to total knee arthroplasty: Comparison of the ultrasonographic, radiographic and intra-operative findings. Scientific Reports. 2018 Dec 10;8(1):17742.
9. Lützner J, Kasten P, Günther K-P, *et al*. Surgical options for patients with osteoarthritis of the knee. Nature Reviews Rheumatology. 2009 Jun;5(6):309–16.
10. Bayliss LE, Culliford D, Monk AP, *et al*. The effect of patient age at intervention on risk of implant revision after total replacement of the hip or knee: A population-based cohort study. The Lancet. 2017 Apr 8;389(10077):1424–30.
11. Dean CS, Liechti DJ, Chahla J, *et al*. Clinical outcomes of high tibial osteotomy for knee instability: A systematic review. Orthopaedic Journal of Sports Medicine. 2016 Mar;4(3):2325967116633419.
12. Kim C-W, Seo S-S, Lee C-R, *et al*. Factors affecting articular cartilage repair after open-wedge high tibial osteotomy. The Knee. 2017 Oct;24(5):1099–107.
13. Kim J-H, Kim H-J, Lee D-H. Survival of opening *versus* closing wedge high tibial osteotomy: A meta-analysis. Scientific Reports. 2017 Dec 4;7(1):7296.
14. Lafeber FP, Intema F, van Roermund PM, *et al*. Unloading joints to treat osteoarthritis, including joint distraction. Current Opinion in Rheumatology. 2006 Sep;18(5):519–25.
15. Jansen MP, van der Weiden GS, van Roermund PM, *et al*. Initial tissue repair predicts long-term clinical success of knee joint distraction as treatment for knee osteoarthritis. Osteoarthritis and Cartilage. 2018;26(12):1604–8.
16. van der Woude JAD, Wiegant K, van Heerwaarden RJ, *et al*. Knee joint distraction compared with total knee arthroplasty: A randomised controlled trial. Bone and Joint Journal. 2017;99-B(1):51–8.
17. van der Woude JAD, Wiegant K, van Heerwaarden RJ, *et al*. Knee joint distraction compared with high tibial osteotomy: A randomized controlled trial. Knee Surgery, Sports Traumatology, Arthroscopy. 2017;25(3):876–86.
18. Jansen MP, Besselink NJ, van Heerwaarden RJ, *et al*. Knee joint distraction compared with high tibial osteotomy and total knee arthroplasty: Two-year clinical, radiographic, and biochemical marker outcomes of two randomized controlled trials. Cartilage. 2019 Feb 13;1947603519828843.
19. Jansen MP, Boymans TAEJ, Custers RJH, *et al*. Knee joint distraction as treatment for osteoarthritis results

in clinical and structural benefit: A systematic review and meta-analysis of the limited number of studies and patients available. Cartilage. 2020 Jul 22;194760352094294.

20. Hoorntje A, Kuijer PPFM, Koenraadt KLM, *et al*. Return to sport and work after randomization for knee distraction *versus* high tibial osteotomy: Is there a difference? The Journal of Knee Surgery. 2020 Nov 23.
21. Wiegant K, van Roermund PM, Intema F, *et al*. Sustained clinical and structural benefit after joint distraction in the treatment of severe knee osteoarthritis. Osteoarthritis and Cartilage. 2013 Nov;21(11):1660–7.
22. van der Woude JAD, Wiegant K, van Roermund PM, *et al*. Five-year follow-up of knee joint distraction: Clinical benefit and cartilaginous tissue repair in an open uncontrolled prospective study. Cartilage. 2017;8(3):263–71.
23. Tuan RS, Chen AF, Klatt BA. Cartilage regeneration. Journal of the American Academy of Orthopaedic Surgeons. 2013 May;21(5):303–11.
24. Watt FE, Hamid B, Garriga C, *et al*. The molecular profile of synovial fluid changes upon joint distraction and is associated with clinical response in knee osteoarthritis. Osteoarthritis and Cartilage. 2020 Jan;28(3):324–33.
25. Blaney Davidson EN, van der Kraan PM, van den Berg WB. TGF-β and osteoarthritis. Osteoarthritis and Cartilage. 2007 Jun;15(6):597–604.
26. Bakker AC, van de Loo FAJ, van Beuningen HM, *et al*. Overexpression of active TGF-beta-1 in the murine knee joint: evidence for synovial-layer-dependent chondro-osteophyte formation. Osteoarthritis and Cartilage. 2001 Feb 1;9(2):128–36.
27. Scharstuhl A, Glansbeek HL, van Beuningen HM, *et al*. Inhibition of endogenous TGF-β during experimental osteoarthritis prevents osteophyte formation and impairs cartilage repair. Journal of Immunology. 2002 Jul 1;169(1):507–14.
28. van Beuningen HM, van der Kraan PM, Arntz OJ, *et al*. Transforming growth factor-beta 1 stimulates articular chondrocyte proteoglycan synthesis and induces osteophyte formation in the murine knee joint. Laboratory investigation; a journal of technical methods and pathology. 1994 Aug;71(2):279–90.
29. Dodds RA, Merry K, Littlewood A, *et al*. Expression of mRNA for IL1 beta, IL6 and TGF beta 1 in developing human bone and cartilage. Journal of Histochemistry and Cytochemistry. 1994 Jun 5;42(6):733–44.
30. Horner A, Kemp P, Summers C, *et al*. Expression and distribution of transforming growth factor-β isoforms and their signaling receptors in growing human bone. Bone. 1998 Aug 1;23(2):95–102.
31. Sakao K, Takahashi KA, Arai Y, *et al*. Osteoblasts derived from osteophytes produce interleukin-6, interleukin-8, and matrix metalloproteinase-13 in osteoarthritis. Journal of Bone and Mineral Metabolism. 2009 Jul 1;27(4):412–23.
32. Intema F, van Roermund PM, Marijnissen ACA, *et al*. Tissue structure modification in knee osteoarthritis by use of joint distraction: An open 1-year pilot study. Annals of the Rheumatic Diseases. 2011 Aug 1;70(8):1441–6.
33. Wiegant K, van Heerwaarden R, van der Woude JAD, *et al*. Knee joint distraction as an alternative surgical treatment for osteoarthritis: Rationale and design of two randomized controlled trials (*vs* high tibial osteotomy and total knee prosthesis). International Journal of Orthopaedics. 2015 Aug 23;2(4):353–60.
34. Buckland-Wright JC, Ward RJ, Peterfy C, *et al*. Reproducibility of the semiflexed (metatarsophalangeal) radiographic knee position and automated measurements of medial tibiofemoral joint space width in a multicenter clinical trial of knee osteoarthritis. Journal of Rheumatology. 2004 Aug;31(8):1588–97.
35. Buckland-Wright JC, Wolfe F, Ward RJ, *et al*. Substantial superiority of semiflexed (MTP) views in knee osteoarthritis: a comparative radiographic study, without fluoroscopy, of standing extended, semiflexed (MTP), and schuss views. Journal of Rheumatology. 1999 Dec;26(12):2664–74.
36. Wesseling J, Boers M, Viergever MA, *et al*. Cohort profile: Cohort Hip and Cohort Knee (CHECK) study.

International Journal of Epidemiology. 2016 Feb 1;45(1):36–44.

37. Marijnissen ACA, Vincken KL, Vos PAJM, *et al*. Knee Images Digital Analysis (KIDA): A novel method to quantify individual radiographic features of knee osteoarthritis in detail. Osteoarthritis and Cartilage. 2008 Feb 1;16(2):234–43.
38. Jansen MP, Mastbergen SC, Heerwaarden RJ van, *et al*. Knee joint distraction in regular care for treatment of knee osteoarthritis: A comparison with clinical trial data. PLOS ONE. 2020 Jan 22;15(1).
39. O'Reilly SC, Muir KR, Doherty M, *et al*. Screening for pain in knee osteoarthritis: which question? Annals of the Rheumatic Diseases. 1996;55:931–3.
40. Spector TD, Hart DJ, Byrne J, *et al*. Definition of osteoarthritis of the knee for epidemiological studies. Annals of the Rheumatic Diseases. 1993 Nov 1;52(11):790–4.
41. Lanyon P, O'Reilly S, Jones A, *et al*. Radiographic assessment of symptomatic knee osteoarthritis in the community: definitions and normal joint space. Annals of the Rheumatic Diseases. 1998 Oct 1;57(10):595–601.
42. Hamilton TW, Choudhary R, Jenkins C, *et al*. Lateral osteophytes do not represent a contraindication to medial unicompartmental knee arthroplasty: A 15-year follow-up. Knee Surgery, Sports Traumatology, Arthroscopy. 2017 Mar 1;25(3):652–9.
43. Waldstein W, Kasparek MF, Faschingbauer M, *et al*. Lateral-compartment osteophytes are not associated with lateral-compartment cartilage degeneration in arthritic varus knees. Clinical Orthopaedics and Related Research. 2017 May;475(5):1386–92.
44. Teitge RA. CORR Insights®: Lateral-compartment osteophytes are not associated with lateral-compartment cartilage degeneration in arthritic varus knees. Clinical Orthopaedics and Related Research. 2017 May 24;475(5):1393–4.

SUPPLEMENTARY DATA

Supplementary Table S1: Pearson correlation coefficients between the osteophyte Altman scores and the osteophyte size as measured by KIDA

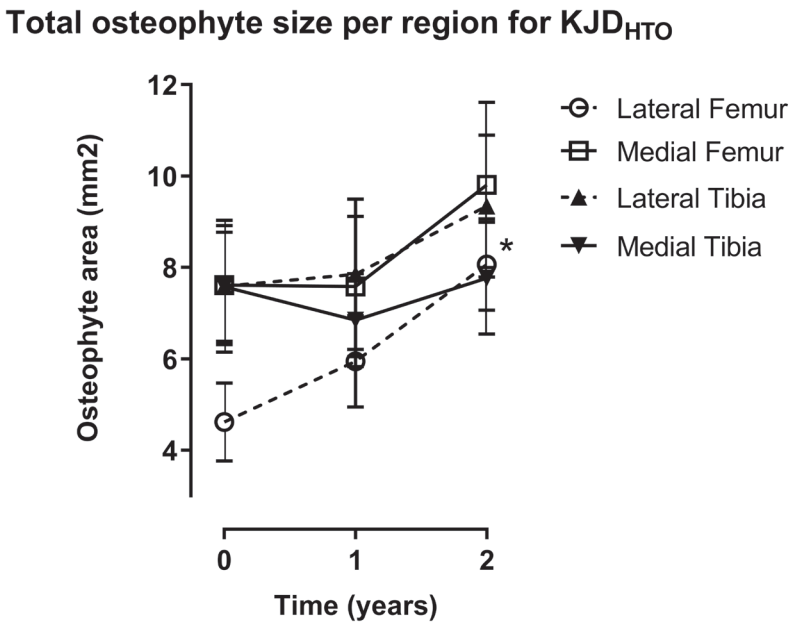
	Medial femur KIDA	Medial tibial KIDA	Medial total KIDA	Lateral femur KIDA	Lateral tibial KIDA	Lateral total KIDA	Total KIDA
Medial femur	*R*=0.560	*R*=0.489	*R*=0.633	*R*=0.382	*R*=0.347	*R*=0.404	*R*=0.569
Altman	*p*<0.001	*p*<0.001	*p*<0.001	*p*<0.001	*p*<0.001	*p*<0.001	*p*<0.001
Medial tibial	*R*=0.422	*R*=0.602	*R*=0.580	*R*=0.291	*R*=0.260	*R*=0.339	*R*=0.463
Altman	*p*<0.001	*p*<0.001	*p*<0.001	*p*<0.001	*p*<0.001	*p*<0.001	*p*<0.001
Medial total	*R*=0.545	*R*=0.586	*R*=0.664	*R*=0.373	*R*=0.337	*R*=0.410	*R*=0.570
Altman	*p*<0.001	*p*<0.001	*p*<0.001	*p*<0.001	*p*<0.001	*p*<0.001	*p*<0.001
Lateral femur	*R*=0.390	*R*=0.403	*R*=0.469	*R*=0.623	*R*=0.622	*R*=0.600	*R*=0.671
Altman	*p*<0.001	*p*<0.001	*p*<0.001	*p*<0.001	*p*<0.001	*p*<0.001	*p*<0.001
Lateral tibial	*R*=0.357	*R*=0.325	*R*=0.410	*R*=0.473	*R*=0.739	*R*=0.646	*R*=0.629
Altman	*p*<0.001	*p*<0.001	*p*<0.001	*p*<0.001	*p*<0.001	*p*<0.001	*p*<0.001
Lateral total	*R*=0.414	*R*=0.406	*R*=0.488	*R*=0.614	*R*=0.741	*R*=0.683	*R*=0.719
Altman	*p*<0.001	*p*<0.001	*p*<0.001	*p*<0.001	*p*<0.001	*p*<0.001	*p*<0.001
Total Altman	*R*=0.495	*R*=0.587	*R*=0.628	*R*=0.497	*R*=0.528	*R*=0.697	*R*=0.669
	p<0.001	*p*<0.001	*p*<0.001	*p*<0.001	*p*<0.001	*p*<0.001	*p*<0.001

Cells with thicker borders indicate the correlations between KIDA and Altman for the same part of the joint. All correlations were statistically significant ($p<0.001$).

Supplementary Table S2: Influence of baseline characteristics on 2-year osteophyte change after knee joint distraction treatment

	Unstandardized coefficient (*B*)	Standardized coefficient (β)	*P*-value
Age	0.166	0.092	0.495
Sex	-2.158	-0.075	0.570
BMI	-0.071	-0.018	0.890
Kellgren-Lawrence grade	2.423	0.160	0.330

Analyses performed using linear regression; the influence of baseline characteristics (age, sex, BMI, Kellgren-Lawrence grade) was corrected for baseline osteophyte size. Not correcting for baseline values did not change significance. BMI: body mass index.



Supplementary Figure S1: Change in osteophyte size in mm^2 per region before and 1 and 2 years after treatment with knee joint distraction, for patients indicated for high tibial osteotomy (KJD_{HTO}). Mean and standard error of the mean (SEM) are shown, * indicates significant changes compared to baseline using repeated measures ANOVA ($p<0.05$).

Supplementary Table S3: Baseline and 1-year Altman scores for patients with synovial fluid aspirations

	Baseline	1 year	*P*-value
Medial femur (0–3)	2.0 (0.5)	2.1 (1.1)	0.075
Lateral femur (0–3)	2.0 (1.0)	2.0 (1.5)	0.500
Medial tibia (0–3)	2.0 (0.8)	2.0 (0.8)	0.401
Lateral tibia (0–3)	1.0 (1.3)	1.0 (1.7)	0.260
Total (0–12)*	6.7 (2.0)	6.9 (1.8)	0.653

Median and interquartile ranges are given and *p*-values are calculated with Wilcoxon Signed Rank tests. *For the total Altman score, the mean and standard deviation are given and the *p*-value is calculated with a paired *t*-tests.

Supplementary Table S4: Pearson correlations between baseline total Altman score and TGFβ-1 and IL-6, and between 1-year changes

Baseline values

	Total Altman	TGFβ-1	IL-6
Total Altman	1	*R*=-0.380 *p*=0.147	*R*=0.209 *p*=0.422
TGFβ-1	*R*=-0.380 *p*=0.147	1	*R*=0.130 *p*=0.632
IL-6	*R*=0.209 *p*=0.422	*R*=0.130 *p*=0.632	1

One-year changes

	ΔTotal Altman	ΔTGFβ-1	ΔIL-6
ΔTotal Altman	1	*R*=0.305 *p*=0.289	*R*=0.299 *p*=0.280
ΔTGFβ-1	*R*=0.305 *p*=0.289	1	*R*=-0.438 *p*=0.118
ΔIL-6	*R*=0.299 *p*=0.280	*R*=-0.438 *p*=0.118	1

The row and column with thicker borders indicate the relevant correlations. IL-6: interleukin-6; TGFβ-1: transforming growth factor-β1.

Supplementary Table S5: Pearson correlations between baseline osteophyte size and baseline WOMAC and JSW

	Osteophyte size	**WOMAC total**	**WOMAC pain**	**WOMAC stiffness**	**WOMAC function**	**JSW**
Osteophyte size	1	*R*=-0.063	*R*=-0.086	*R*=-0.070	*R*=-0.048	***R*=-0.315**
		p=0.641	*p*=0.521	*p*=0.604	*p*=0.720	***p*=0.016**
WOMAC total	*R*=-0.063	1	***R*=0.923**	***R*=0.824**	***R*=0.989**	*R*=-0.210
	p=0.641		***p*<0.001**	***p*<0.001**	***p*<0.001**	*p*=0.113
WOMAC pain	*R*=-0.086	***R*=0.923**	1	***R*=0.757**	***R*=0.870**	*R*=-0.114
	p=0.521	***p*<0.001**		***p*<0.001**	***p*<0.001**	*p*=0.393
WOMAC stiffness	*R*=-0.070	***R*=0.824**	***R*=0.757**	1	***R*=0.779**	*R*=-0.188
	p=0.604	***p*<0.001**	***p*<0.001**		***p*<0.001**	*p*=0.158
WOMAC function	*R*=-0.048	***R*=0.989**	***R*=0.870**	***R*=0.779**	1	*R*=-0.227
	p=0.720	***p*<0.001**	***p*<0.001**	***p*<0.001**		*p*=0.087
JSW	***R*=-0.315**	*R*=-0.210	*R*=-0.114	*R*=-0.188	*R*=-0.227	1
	***p*=0.016**	*p*=0.113	*p*=0.393	*p*=0.158	*p*=0.087	

The row and column with thicker borders indicate the relevant correlations. Cells with bold text indicate statistically significant correlations ($p<0.001$). JSW: joint space width; WOMAC: Western Ontario and McMaster Universities Osteoarthritis Index.

Supplementary Table S6: Pearson correlations between 1- and 2-year changes in osteophyte size and WOMAC and JSW

One-year changes

	ΔOsteophyte size	**ΔWOMAC total**	**ΔWOMAC pain**	**ΔWOMAC stiffness**	**ΔWOMAC function**	**ΔJSW**
ΔOsteophyte size	1	*R*=0.031 *p*=0.818	*R*=0.121 *p*=0.372	*R*=0.139 *p*=0.302	*R*=0.113 *p*=0.404	*R*=-0.062 *p*=0.646
ΔWOMAC total	*R*=0.031 *p*=0.818	1	***R*=0.639** ***p*<0.001**	***R*=0.897** ***p*<0.001**	***R*=0.924** ***p*<0.001**	*R*=0.100 *p*=0.459
ΔWOMAC pain	*R*=0.121 *p*=0.372	***R*=0.639** ***p*<0.001**	1	***R*=0.666** ***p*<0.001**	***R*=0.750** ***p*<0.001**	*R*=-0.071 *p*=0.601
ΔWOMAC stiffness	*R*=0.139 *p*=0.302	***R*=0.897** ***p*<0.001**	***R*=0.666** ***p*<0.001**	1	***R*=0.985** ***p*<0.001**	*R*=0.159 *p*=0.239
ΔWOMAC function	*R*=0.113 *p*=0.404	***R*=0.924** ***p*<0.001**	***R*=0.750** ***p*<0.001**	***R*=0.985** ***p*<0.001**	1	*R*=0.122 *p*=0.366
ΔJSW	*R*=-0.062 *p*=0.646	*R*=0.100 *p*=0.459	*R*=-0.071 *p*=0.601	*R*=0.159 *p*=0.239	*R*=0.122 *p*=0.366	1

Two-year changes

	ΔOsteophyte size	**ΔWOMAC total**	**ΔWOMAC pain**	**ΔWOMAC stiffness**	**ΔWOMAC function**	**ΔJSW**
ΔOsteophyte size	1	*R*=0.080 *p*=0.557	*R*=0.146 *p*=0.283	*R*=0.165 *p*=0.224	*R*=0.158 *p*=0.244	*R*=-0.106 *p*=0.438
ΔWOMAC total	*R*=0.080 *p*=0.557	1	*R*=0.584 *p*<0.001	*R*=0.861 *p*<0.001	*R*=0.910 *p*<0.001	*R*=0.162 *p*=0.234
ΔWOMAC pain	*R*=0.146 *p*=0.283	***R*=0.584** ***p*<0.001**	1	***R*=0.639** ***p*<0.001**	***R*=0.692** ***p*<0.001**	*R*=-0.162 *p*=0.234
ΔWOMAC stiffness	*R*=0.165 *p*=0.224	***R*=0.861** ***p*<0.001**	***R*=0.639** ***p*<0.001**	1	***R*=0.989** ***p*<0.001**	*R*=0.193 *p*=0.153
ΔWOMAC function	*R*=0.158 *p*=0.244	***R*=0.910** ***p*<0.001**	***R*=0.692** ***p*<0.001**	***R*=0.989** ***p*<0.001**	1	*R*=0.158 *p*=0.246
ΔJSW	*R*=-0.106 *p*=0.438	*R*=0.162 *p*=0.234	*R*=-0.162 *p*=0.234	*R*=0.193 *p*=0.153	*R*=0.158 *p*=0.246	1

The row and column with thicker borders indicate the relevant correlations. Cells with bold text indicate statistically significant correlations ($p<0.001$). JSW: joint space width; WOMAC: Western Ontario and McMaster Universities Osteoarthritis Index.

CHAPTER 18

Exploring subchondral bone changes measured with CT after joint distraction treatment for end stage knee osteoarthritis

S.C. Mastbergen & A. Ooms
T.D. Turmezei
J.W. MacKay
R.J. van Heerwaarden
S. Spruijt
F.P.J.G. Lafeber
M.P. Jansen

Submitted for publication

Abstract

Background: Increased subchondral cortical bone plate thickness and trabecular bone density are characteristic of knee osteoarthritis (OA). Knee joint distraction (KJD) is a joint-preserving knee OA treatment where the joint is temporarily unloaded. It has previously shown clinical improvement and cartilage regeneration, indicating reversal of OA-related changes. The purpose of this research was to explore 3D subchondral bone changes after KJD treatment using computed tomography (CT) imaging.

Methods: Twenty patients were treated with KJD and included to undergo knee CT imaging before, 1, and 2 years after treatment. Tibia and femur segmentation and registration to canonical surfaces were performed semi-automatically. Cortical bone thickness and trabecular bone density were determined using an automated algorithm. Statistical parametric mapping (SPM) with 2-tailed *F*-tests was used to analyze whole-joint changes. Bone shape changes were explored visually.

Results: Data was available of 16 patients. Subchondral cortical bone plate thickness and trabecular bone density were higher in the weight-bearing region of the affected compartment (MAC; mostly medial). Especially the MAC showed a decrease in thickness and density in the first year after treatment, which was sustained towards the second year. Shape changes showed the femoral condyles became more convex while the tibial condyles became less concave, especially during the second year after treatment.

Conclusion: KJD treatment results in bone changes that include thinning of the subchondral cortical bone plate, decrease of subchondral trabecular bone density, and improved bone shape in the first 2 years after treatment, potentially indicating a partial normalization of subchondral bone.

Introduction

Knee osteoarthritis (OA) is characterized not only by cartilage degeneration, but by significant bone remodeling as well.[1] In end-stage knee OA, changes in the subchondral bone include subchondral (cortical) bone plate thickening and trabecular bone density decrease.[2,3] The overall bone shape changes as well, most notably by widening and flattening of femoral and tibial condyles and formation of osteophytes at the edges.[4] Bone changes after (joint-preserving) knee OA treatments are not evaluated often, as these studies generally focus on improving clinical patient-reported outcomes and, to a lesser degree, increasing cartilage thickness. Knee joint distraction (KJD) is 1 of the joint-preserving surgical treatments for relatively young (<65 years) knee OA patients. The treatment has been evaluated in several clinical trials, where it has shown significant short- and long-term clinical improvement.[5–8] Furthermore, KJD has demonstrated the ability to reverse OA cartilage degradation, as radiographic JSW and MRI cartilage thickness measurements showed significant short-term cartilage regeneration, which was sustained for up to 10 years after treatment.[6,9–11] Bone changes have been evaluated on plain radiographs, showing a decrease in overall subchondral bone density 1 year after treatment with increased osteophyte formation in the first 2 years after treatment.[9,12] However, bone changes after KJD have never been evaluated in 3-dimensions (3D), which enables measurement and visualization across the entire joint. As such, the purpose of this research was to explore subchondral cortical bone plate thickness, subchondral trabecular bone density, and overall bone shape from CT imaging before and up to 2 years after KJD treatment.

Methods

Patients

Patients were included from 2 randomized controlled trials (RCTs). In 1 RCT, relatively young (<65 years) OA patients considered for total knee arthroplasty (TKA) were randomized to either KJD (n=20) or TKA (n=40) treatment. In a separate RCT, relatively young (<65 years) OA patients considered for high tibial osteotomy (HTO) were randomized to either KJD (n=23) or HTO (n=46). Inclusion and exclusion criteria were similar between the 2 trials, and included Kellgren-Lawrence grade >2 (as judged by orthopedic surgeon), no history of inflammatory or rheumatoid arthritis, no primary patellofemoral OA, leg axis deviation less than 10 degrees, and no surgical treatment of the involved knee <6 months ago.[6,13,14]

In both RCTs, after randomization to KJD treatment, patients were asked to participate in an extended imaging protocol that included CT scans. The first 20 KJD patients (irrespective of the trial from which they were included) who gave written informed consent for the extended

imaging protocol were included (10 from each trial/original indication TKA or HTO, respectively).

KJD treatment was performed using an external fixation frame, fixed to the joint laterally and medially using 4 pairs of bone pins. During surgery the joint was distracted to a distance of 2 mm, which was gradually extended by 1 mm per day over the next 3 days, reaching 5 mm of total distraction. This was confirmed radiographically, after which patients were discharged. Full weight-bearing on the treated knee was allowed and encouraged, using crutches if necessary. After 6 weeks, patients returned to the hospital, where the frame and pins were removed, without further imposed rehabilitation protocol.

The original RCTs and the extended imaging protocol were granted ethical approval by the medical ethical review committee of the University Medical Center Utrecht (protocol numbers 10/359/E, 11/072 and 11/482/E). All patients gave written informed consent.

CT analyses

Patients underwent CT scanning with a reconstructed slice thickness of 0.45–0.5 mm, at baseline (pre-treatment) and 1 and 2 years after treatment. All CT scans were made at the UMC Utrecht using the same CT scanner and settings. All scans were performed with 120 kVp and exposure 87–232 mA. The field of view was 512x512 pixels and pixel spacing varied between 0.27x0.27 mm and 0.98x0.98 mm. The CT dose index ($CTDI_{vol}$) was 3.9–10 mGy and dose length product 174–495 mGy*cm.

Stradview v6.0 (University of Cambridge Department of Engineering, Cambridge, UK, in-house developed software freely available at https://mi.eng.cam.ac.uk/Main/StradView) was used for semi-automatic segmentation of the tibia and femur. Cortical bone thickness (mm, referring to the subchondral bone plate as well as cortical bone in non-articular regions) was determined using an automated optimized Gaussian model fit algorithm able to measure bone thickness in the sub-millimeter range, unconstrained by the point spread function limit of the CT imaging system.[15] Trabecular bone density (Hounsfield units, HU) was also measured as part of this optimized solution, from the inner cortical bone edge inwards to 12 mm beneath the mesh surface (outer bone surface). This is not the same as bone mineral density, as no dedicated phantom was scanned for calibration, but gives a reasonable approximation. A 3D isosurface was generated for the 2 bones separately through semi-automatic segmentation. This software and technique have been explained in detail previously.[16,17] Osteophytes were excluded from the segmentation (see example of segmentation in Figure 1).

Afterwards, wxRegSurf v18 (Cambridge University Engineering Department, Cambridge, UK, in-house developed software freely available at http://mi.eng.cam.ac.uk/~ahg/wxRegSurf/) was used for registration of all femur and tibia surfaces to a canonical femur and tibia respectively, to allow combining and comparing of surface objects from multiple scans. The vertex by vertex displacement data to the canonical surfaces of each individual scan was saved, and used to visually explore the bone shape changes between time points.

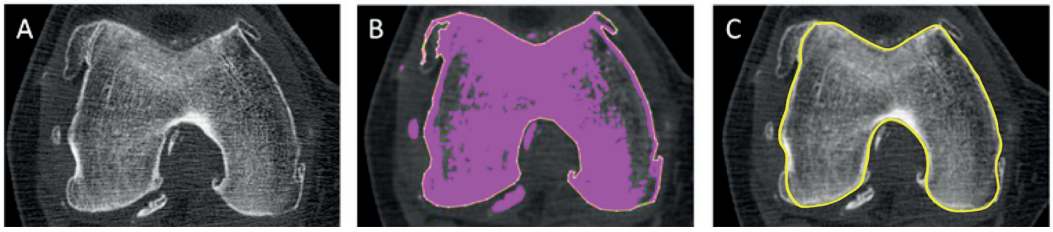


Figure 1: Example segmentation from 1 CT slice. (A) Axial CT slice; (B) thresholding of bone (pink); (C) final semi-automatic segmentation of this slice (yellow line), excluding osteophytes.

Only patients for whom baseline and at least 1 of the 2 follow-up time points available were included for analysis. Since KJD has previously shown significant results mostly in the patients' most affected compartment (MAC), patients were separated into 2 groups based predominantly medial compartmental OA and predominantly lateral compartmental OA, defining their most affected compartment for all analyses.

Statistical analyses

MATLAB R2020a and the SurfStat MATLAB package (https://www.math.mcgill.ca/keith/surfstat/, optimized for this specific application by Graham Treece of the University of Cambridge) were used for whole-bone, vertex-wise data analysis and visualization.

Average cortical bone thickness and trabecular density were displayed for each time point separately, by averaging data of all available patients at each time point. Statistical parametric mapping (SPM) was used for statistical analysis, which uses all subjects' values at each vertex for statistical testing and delivers vertex-wise *p*-value corrections for multiple comparisons at a set corrected *p*-value threshold.[16]

SPM with 2-tailed *F*-tests were used to calculate changes over time against a null hypothesis of no change.[18] In all cases, a p-value <0.05 was considered statistically significant. Although measurement and analysis of the bony parameters are performed for the whole bone surfaces, in this study we focus attention on the subchondral cortical bone plate and trabecular density.

Results

Patients

Three patients did not have appropriate CT imaging at baseline and at least 1 follow-up time point, 1 patient could not be analyzed because of metal artifact around the joint space area at baseline, and in 1 patient the imaged femur shaft at baseline was too short for final analysis. This left 16 patients for tibial analyses and 15 patients for femoral analyses at baseline. These patients were all available at 1-year follow-up as well, while 1 patient was lost to follow-up between 1 and 2 years because of additional surgery. Baseline characteristics for the 16 included patients are shown in Table 1. The MAC was predominantly the medial knee compartment (medial MAC n=14; lateral MAC n=2).

Table 1: Baseline parameters of included patients

	KJD patients (n=16)
Age (years)	53.8 (6.8)
BMI (kg/m^2)	26.7 (3.4)
Male sex, n (%)	11 (69)
Medial MAC, n (%)	14 (88)
Kellgren-Lawrence grade, n (%)	
- Grade 0	0 (0)
- Grade 1	2 (13)
- Grade 2	1 (6)
- Grade 3	9 (56)
- Grade 4	4 (25)

Mean and standard deviation or n (%) are given. BMI: body mass index; KJD: knee joint distraction; MAC: most affected compartment.

Cortical bone thickness

Cortical bone thickness results for patients with a predominantly medial compartmental knee OA are shown in Figure 2. On average a higher thickness was seen on the medial femur and tibia compared to the lateral side for these patients, as indicated by the green-blue color on the medial side as compared to the yellow-orange elsewhere. Similarly, the average of the 2 patients with predominantly lateral compartmental OA showed a higher subchondral cortical bone thickness at the lateral site as compared to the medial side (Supplementary Figure S1).

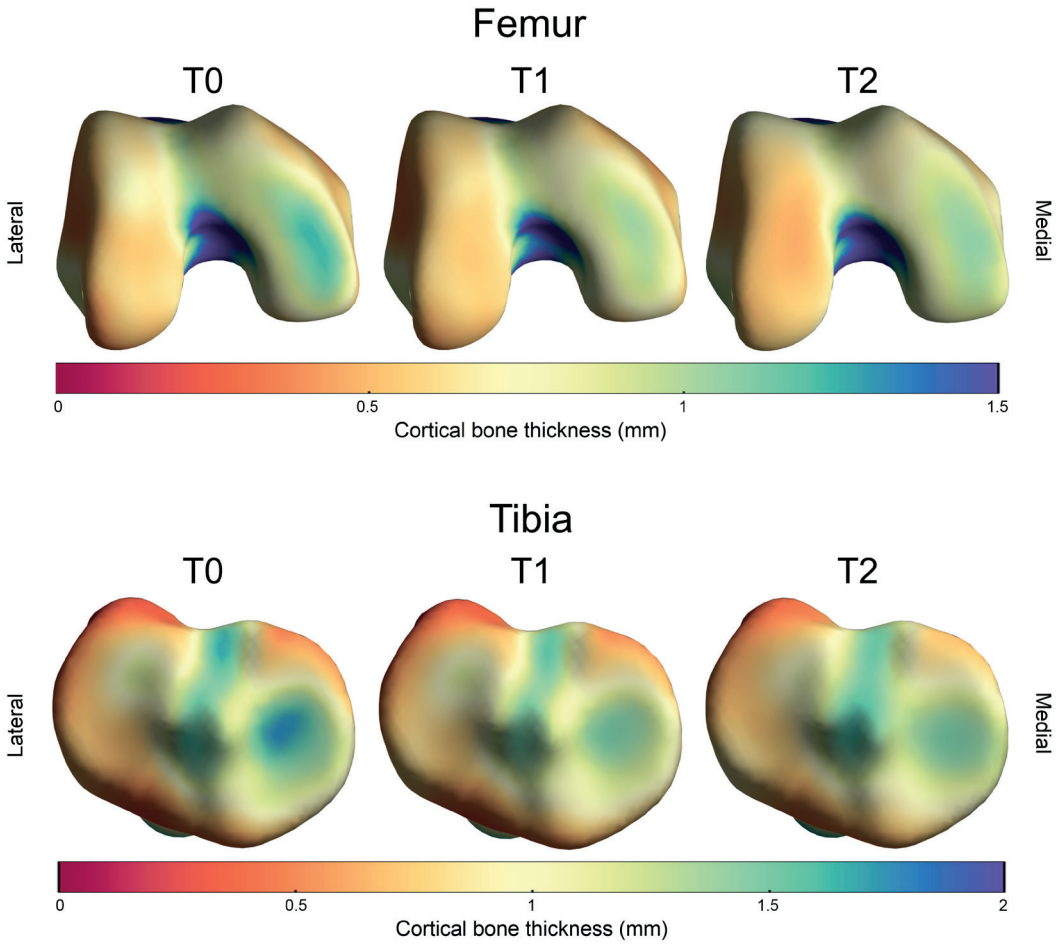


Figure 2: Average weight-bearing tibiofemoral subchondral cortical bone thickness of patients with predominantly medial compartmental osteoarthritis (n=14), before (T0), 1 (T1) and 2 years (T2) after treatment with knee joint distraction, looking at the femoral articular surface from below and the tibial articular surface from above.

One year after treatment, the cortical subchondral bone plate thickness at the medial weight-bearing femur and tibia of the predominantly medial compartmental OA patients decreased by up to 0.25 mm, as shown in Figure 3. Between 1 and 2 years after treatment, bone thinning was relatively small compared to that in the first year, showing a marginal bone thickness decrease on the lateral side as well. Cortical bone thickness around the joint margins seemed to increase between 1 and 2 years post-treatment. None of the changes reached statistical significance. Patients with a predominantly lateral compartmental OA showed a similar pattern, showing a decrease especially on the lateral side (Supplementary Figure S1).

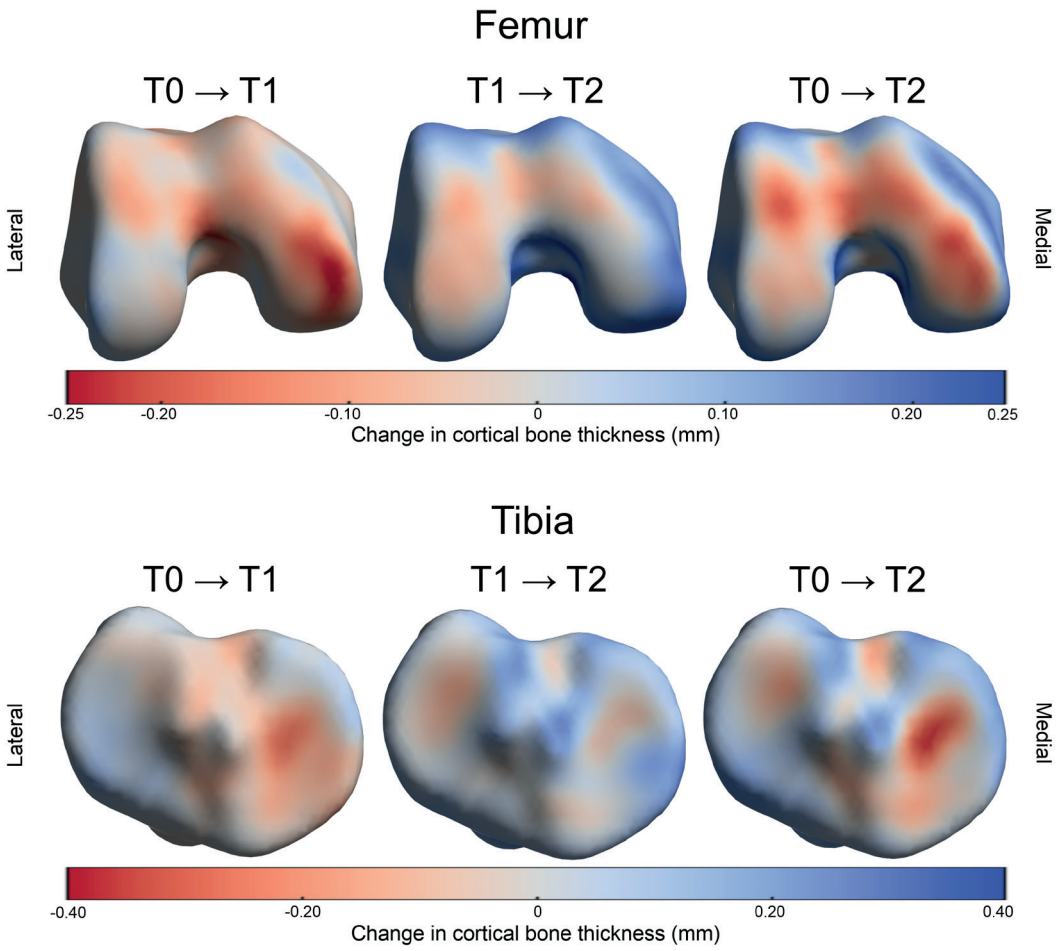


Figure 3: Cortical bone thickness changes 1 (left) and 2 (middle) years after treatment with knee joint distraction, and 2 years compared to 1 year post-treatment (right), for patients with predominantly medial compartmental osteoarthritis (n=14).

Trabecular bone density

The trabecular bone density was also higher before treatment on the medial (most affected) side as compared to the lateral side, for both the tibia and femur, for patients with predominantly medial compartmental OA as shown in Figure 4 with green-blue colors. Similarly, the 2 patients with predominantly lateral compartmental OA showed a higher subchondral trabecular bone density at the lateral site as compared to the medial site (Supplementary Figure S2).

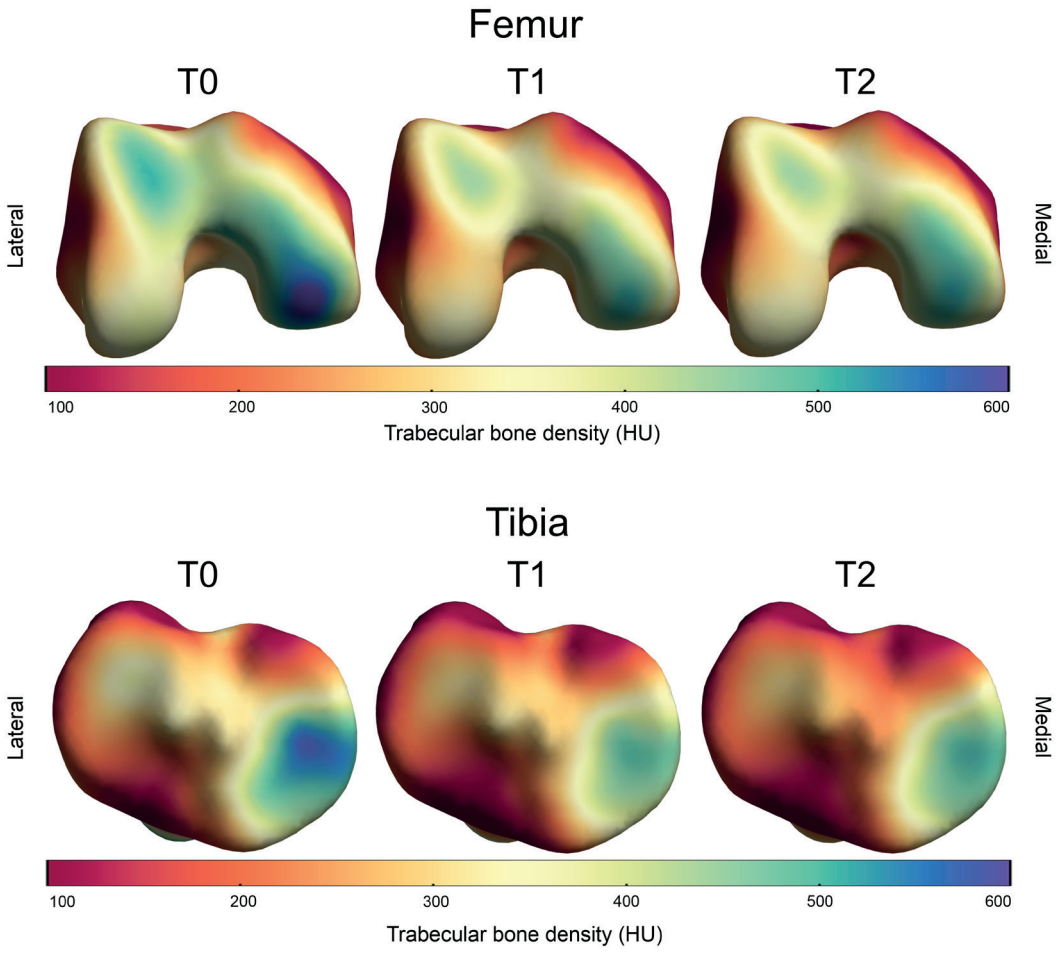


Figure 4: Trabecular bone density of patients with predominantly medial compartmental osteoarthritis (n=14), before and 1 and 2 years after treatment with knee joint distraction.

In the first year after treatment, a decrease in trabecular density was seen throughout the entire joint, although statistically significant only for small areas on mostly the medial side where this decrease was up to approximately 80 HU over the first year (Figure 5). Between 1 and 2 years after treatment, a (non-significant) increase throughout almost the entire joint was seen (~40 HU), except for a statistically significant decrease around the medial tibial eminence.

Although differences between the medial and lateral side were less pronounced than in patients with medial compartmental OA, also patients with predominantly lateral compartmental OA showed a general decrease in trabecular bone density throughout the joint (Supplementary Figure S2).

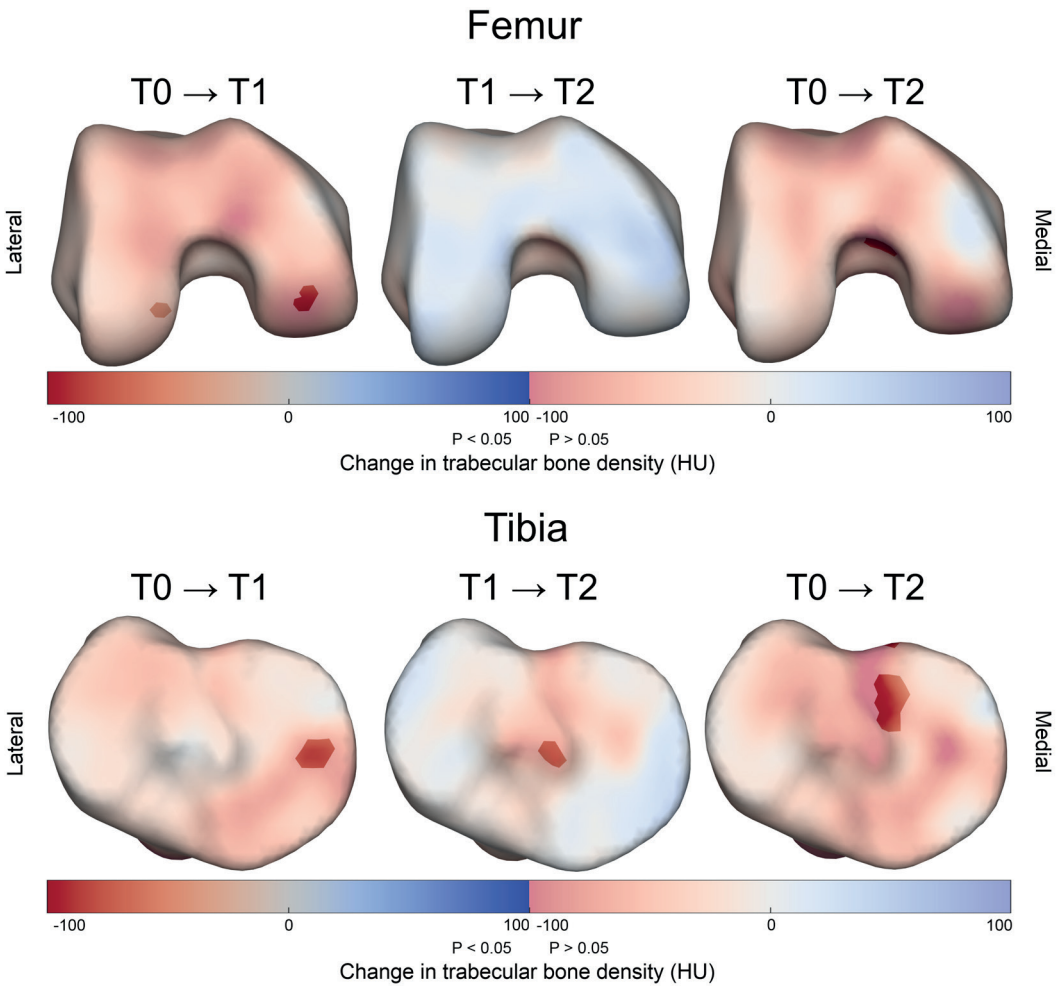


Figure 5: Trabecular bone density changes 1 (left) and 2 (middle) years after treatment with knee joint distraction, and 2 years compared to 1 year post-treatment (right), for patients with predominantly medial compartmental osteoarthritis (n=14). Statistically significant changes (p<0.05) are indicated by the unmasked regions.

Bone shape

Exploratory visual shape analyses showed similar general shape changes for both sides of the joint and both the femur and tibia, as seen in Figure 6: the central areas of both compartments showed an outward change (blue color), while the outer ring of both compartments showed inward changes (red color). This means the femoral condyles became more convex while the tibial condyles became less concave, which was the case between both time points, although the largest changes were seen between 1 and 2 years after treatment.

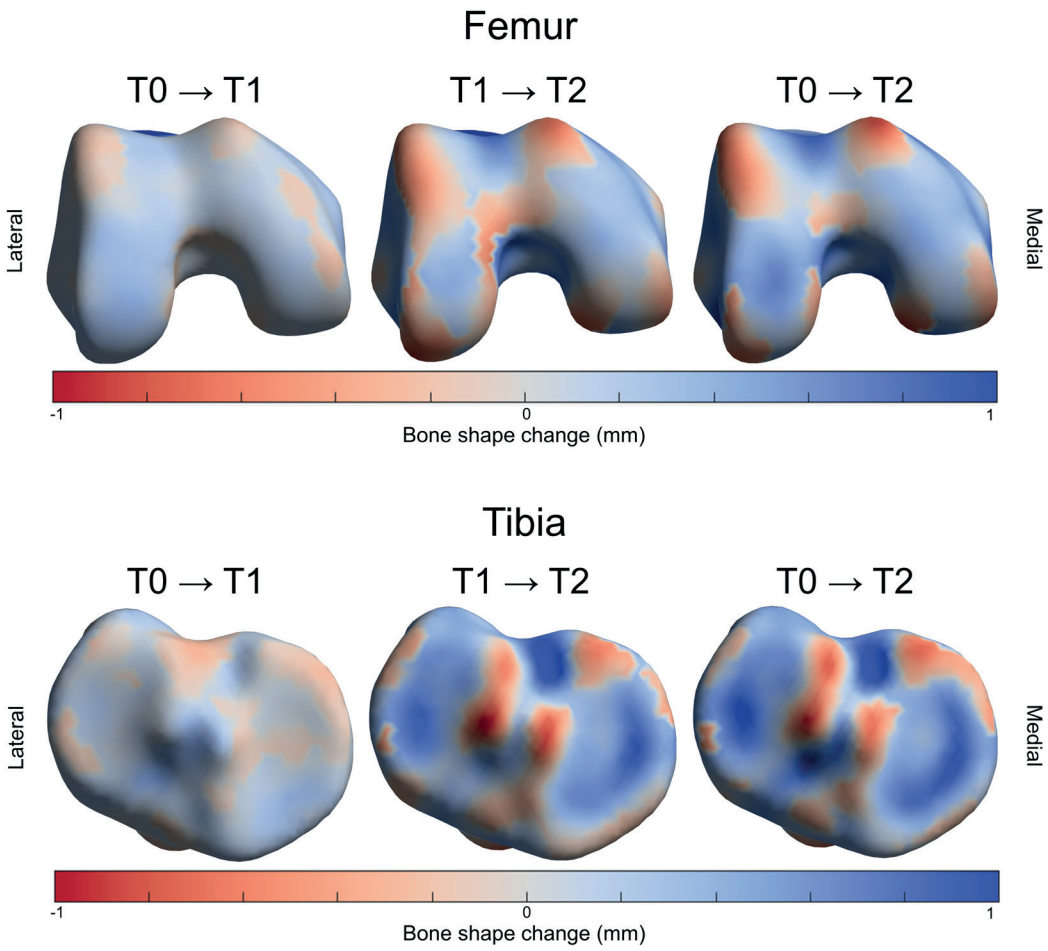


Figure 6: Bone shape changes 1 (left) and 2 (middle) years after treatment with knee joint distraction, and 2 years compared to 1-year post-treatment (right), for patients with predominantly medial compartmental osteoarthritis (n=14). Red colors indicate inward changes; blue colors indicate outward changes.

Discussion

This exploratory study demonstrates that in end-stage OA patients, KJD treatment causes remodeling of the subchondral bone plate especially in the first year after treatment and most notably in the most affected compartment, characterized by a decrease in subchondral cortical bone plate thickness, a decrease in subchondral trabecular thickness, and a rounding of the bone shape (more convex for the femur and less concave for the tibia). The first-year changes are largely sustained throughout the second year and go paired with overall bone shape alterations. In these same patients, significant clinical improvement and cartilage restoration have previously been reported in the same time period.[6,10,13,14,19] Apparently not only cartilage is repaired, but also bone shows alterations in architecture and shape that could be considered

a partial normalization. This, in combination with the fact that KJD has shown anabolic and catabolic changes in joint homeostasis as well (measured with synovial fluid biomarkers and mesenchymal stem cells), indicates KJD results in modification of the whole-joint including not only cartilage but also bone and synovial tissue activity that could lead to long-term joint repair.[20,21]

As the subchondral cortical bone plate is thicker in advanced OA, especially in the tibia, it was anticipated that at baseline the most affected compartment showed a higher cortical bone thickness compared to the less affected compartment (LAC) of the joint.[3,22] Throughout the entire subchondral bone, but most evidently in the most affected compartment, KJD appears to result in a decrease in thickness at the subchondral bone plate that is sustained at 2 years. Between 1 and 2 years after treatment, the cortical thickness around the joint margins seemed to increase, which might be related to formation of osteophytes in those regions, as previously shown using this same analysis technique in the hip.[16] This exploratory study is hampered by the absence of a matched healthy control group with CT images available. As such it is difficult to say what a normal subchondral cortical bone thickness is, particularly given the novelty of this analysis technique. The fact that the most affected compartment of the OA joint seems to become more similar to the less affected compartment, point towards (at least partial) normalization of subchondral cortical bone plate thickness. Effects appeared greater in patients with a higher age and Kellgren-Lawrence grade (data not shown), indicating more severe OA, which is consistent with previous bone-related results measured on radiographs and KJD treatment effects in general.[9,10,23]

The subchondral trabecular bone density showed higher values in the most affected compartment as well. The density decreased throughout the entire joint in the first year after treatment, likely the result of the 6-week unloading, and remained decreased at 2 years compared to baseline despite the small increase between 1 and 2 years after treatment. Also, values in the most affected compartment shifted towards values observed in the least affected compartment, with the largest and most significant changes occurring in the most affected compartment, again indicating a shift towards (partial) subchondral bone normalization.

CT analyses in patients treated with ankle distraction showed subchondral bone density normalization was well, as the overall density decreased while density in low-density (cystic) areas increased.[24] Previous radiographic evaluations showed a significant subchondral bone density decrease 1 year after KJD treatment as well, and this decrease was significantly larger in patients who 9 years after treatment still did not receive a TKA compared to patients who did.[9] In these studies, no differentiation between cortical plate thickness and trabecular density was made. In the present study for the first time we show that these observed density changes on ankle CTs and on plain knee radiographs could be the result of a combination of both a decrease in cortical plate thickness and a decrease in trabecular density. Also, as with cortical

bone thickness, male patients showed a smaller bone density decrease at the weight-bearing areas (data not shown), which may be associated with differences in response to KJD between male and female patients. It can only be speculated on this sex difference in response, but it is plausible that hormonal controlled bone density changes may be involved. For example, female (mild) OA patients have previously shown periarticular osteoporosis, while this was not seen in male patients.[25] In this respect bisphosphonate treatment in OA is subject of study.[26,27]

The observed bone shape changes, although very exploratory and analyzed only visually, may indicate a reversal of typical OA changes, since both compartments of the tibia and femur seem to become less wide and flat.[28] As opposed to subchondral bone results, the bone shape changed the most in the second year after treatment. Radiographically evaluated osteophytes also showed an increased growth especially in this second year.[12] The inward difference that was seen on the outer edges may therefore also be a result of osteophyte-related changes, since increasingly large osteophytes might have affected the bone segmentation at follow-up, and with that its influence cannot be excluded. Irrespectively, it makes sense that shape changes, including osteophyte formation, show a somewhat delayed response, as they are the result of internal processes and remodeling of subchondral bone.[2] Unfortunately the osteophyte size could not be measured automatically on CT with the current analysis method.

This study is clearly an explorative study regarding its sample size and the absence of a healthy control group as well as an untreated matched OA group. The sample size was small, which may be why there were only small areas with statistically significant changes, although they were largely in line with the general concept. KJD is still a relatively new treatment, and CT scans are not often included in studies and especially not in regular care. The observed changes agree with those found previously on radiographs. Furthermore, the 2 patients with a lateral MAC could be a mirrored control group, and the fact they showed opposite results (and as such both showed the same effect for the most affected compartment) is supportive to our conclusions. Notwithstanding, a healthy control group and a matched group of OA patients would have strengthened our conclusions significantly, although not treating patients with such severe OA for multiple years is (ethically) impossible. It also would have been worthwhile to include a calibration phantom during the CT scans, to enable measuring cortical bone mineral density, another useful parameter. Future studies should take these points into account to strengthen the concept of bone normalization upon distraction treatment as 1 of the underlying mechanisms of the observed clinical benefit.

In conclusion, we have shown that bone changes after KJD treatment include thinning of the subchondral cortical bone plate, decrease of subchondral trabecular bone density, and normalization of bone shape in the first year sustaining towards the second year.

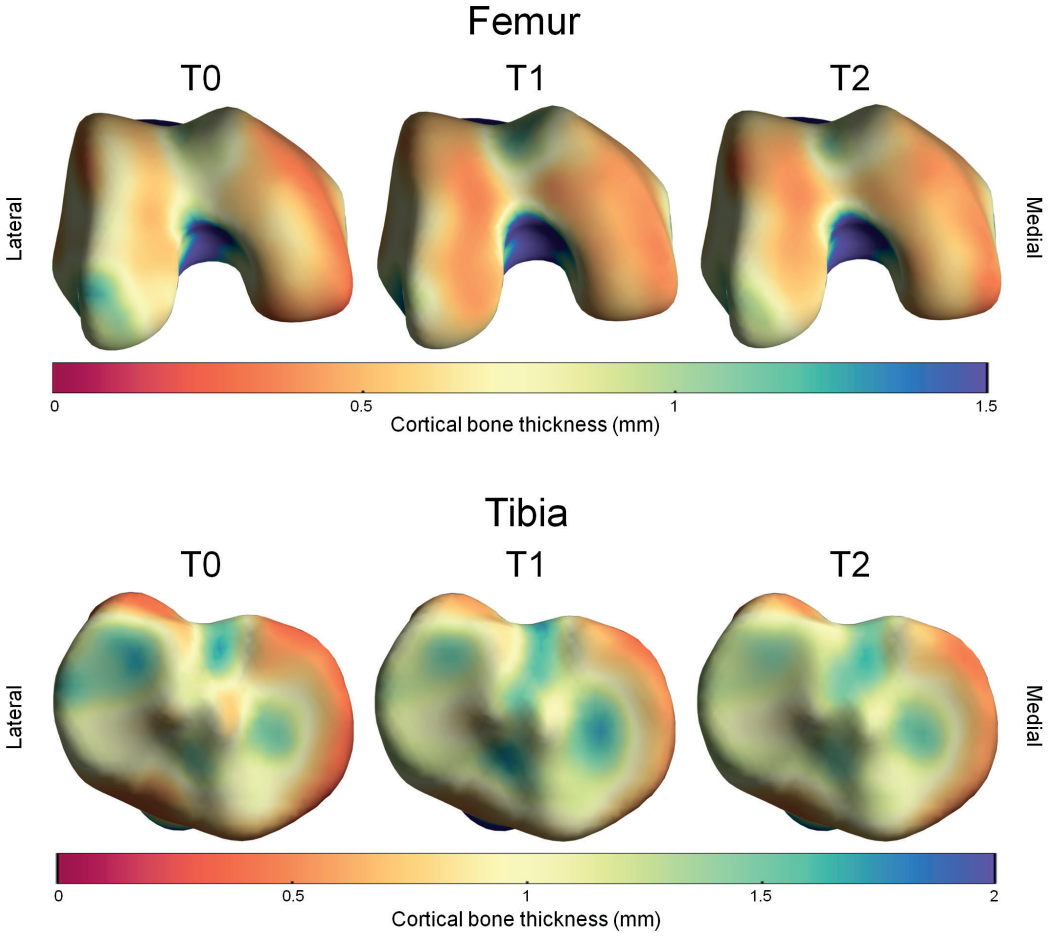
References

1. Burr DB, Gallant MA. Bone remodelling in osteoarthritis. Nature Reviews Rheumatology. 2012 Nov;8(11):665–73.
2. Donell S. Subchondral bone remodelling in osteoarthritis. EFORT Open Reviews. 2019 Jun 1;4(6):221–9.
3. Buckland-Wright C. Subchondral bone changes in hand and knee osteoarthritis detected by radiography. Osteoarthritis and Cartilage. 2004;12(SUPLL.):10–9.
4. Neogi T. Clinical significance of bone changes in osteoarthritis. Therapeutic Advances in Musculoskeletal Disease. 2012;4(4):259–67.
5. Jansen MP, Boymans TAEJ, Custers RJH, *et al*. Knee joint distraction as treatment for osteoarthritis results in clinical and structural benefit: A systematic review and meta-analysis of the limited number of studies and patients available. Cartilage. 2020 Jul 22;194760352094294.
6. Jansen MP, Besselink NJ, van Heerwaarden RJ, *et al*. Knee joint distraction compared with high tibial osteotomy and total knee arthroplasty: Two-year clinical, radiographic, and biochemical marker outcomes of two randomized controlled trials. Cartilage. 2019 Feb 13;194760351982843.
7. Hoorntje A, Kuijer PPFM, Koenraadt KLM, *et al*. Return to sport and work after randomization for knee distraction *versus* high tibial osteotomy: Is there a difference? The Journal of Knee Surgery. 2020 Nov.
8. Jansen MP, Mastbergen SC, Heerwaarden RJ van, *et al*. Knee joint distraction in regular care for treatment of knee osteoarthritis: A comparison with clinical trial data. PLOS ONE. 2020 Jan 22;15(1).
9. Jansen MP, van der Weiden GS, van Roermund PM, *et al*. Initial tissue repair predicts long-term clinical success of knee joint distraction as treatment for knee osteoarthritis. Osteoarthritis and Cartilage. 2018;26(12):1604–8.
10. Jansen MP, Maschek S, van Heerwaarden RJ, *et al*. Changes in cartilage thickness and denuded bone area after knee joint distraction and high tibial osteotomy – Post-hoc analyses of two randomized controlled trials. Journal of Clinical Medicine. 2021 Jan 19;10(2):368.
11. Jansen MP, Mastbergen SC, Turmezei TD, *et al*. Knee joint distraction results in MRI cartilage thickness increase up to ten years after treatment. Submitted.
12. Jansen MP, Mastbergen SC, Watt FE, *et al*. Cartilage repair activity during joint-preserving treatment may be accompanied by osteophyte formation. Submitted.
13. van der Woude JAD, Wiegant K, van Heerwaarden RJ, *et al*. Knee joint distraction compared with high tibial osteotomy: A randomized controlled trial. Knee Surgery, Sports Traumatology, Arthroscopy. 2017;25(3):876–86.
14. van der Woude JAD, Wiegant K, van Heerwaarden RJ, *et al*. Knee joint distraction compared with total knee arthroplasty: A randomised controlled trial. Bone and Joint Journal. 2017;99-B(1):51–8.
15. Treece GM, Gee AH, Mayhew PM, *et al*. High resolution cortical bone thickness measurement from clinical CT data. Medical Image Analysis. 2010 Jun 1;14(3):276–90.
16. Turmezei TD, Treece GM, Gee AH, *et al*. Quantitative 3D analysis of bone in hip osteoarthritis using clinical computed tomography. European Radiology. 2016 Jul 1;26(7):2047–54.
17. MacKay JW, Kaggie JD, Treece GM, *et al*. Three-dimensional surface-based analysis of cartilage MRI data in knee osteoarthritis: Validation and initial clinical application. Journal of Magnetic Resonance Imaging. 2020 Oct 24;52(4):1139–51.
18. Turmezei TD, Treece GM, Gee AH, *et al*. Quantitative 3D imaging parameters improve prediction of hip osteoarthritis outcome. Scientific Reports. 2020 Dec 1;10(1):1–11.
19. Jansen MP, Maschek S, van Heerwaarden RJ, *et al*. Knee joint distraction is more efficient in rebuilding

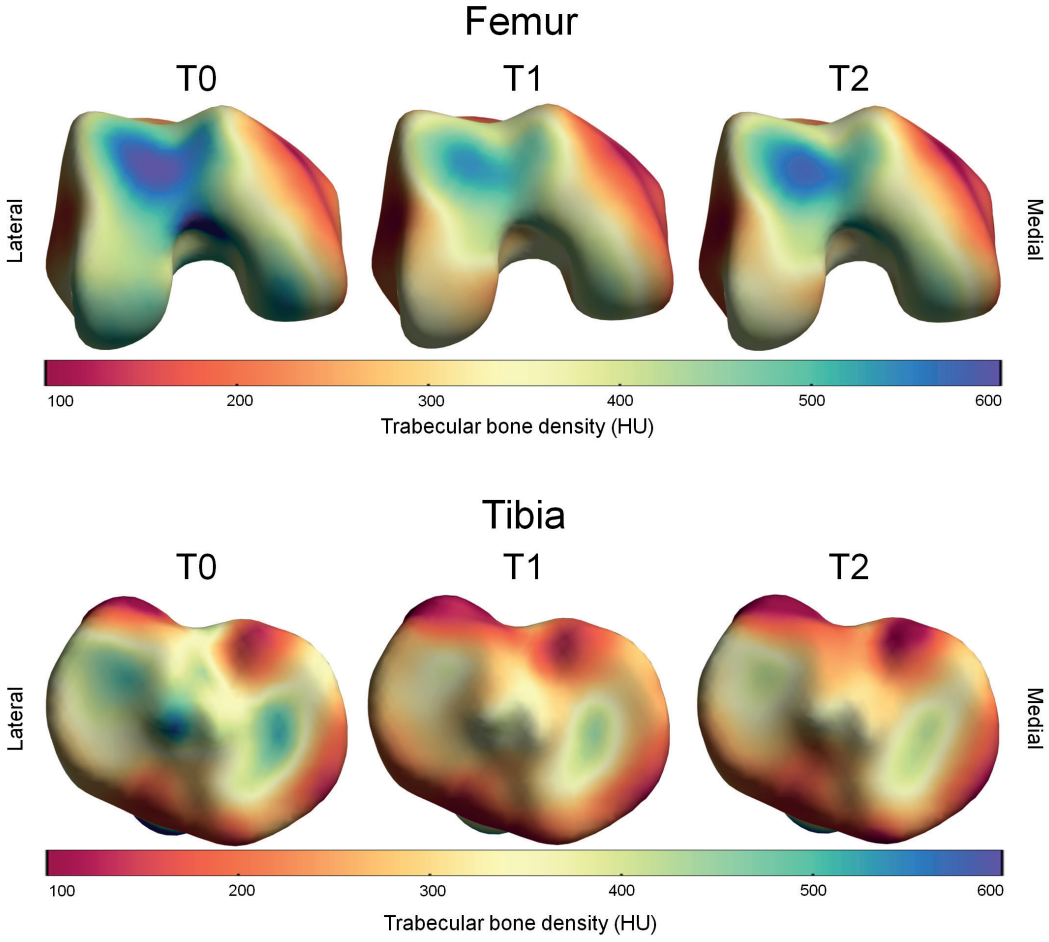
cartilage thickness in the more affected compartment than high tibial osteotomy in patients with knee osteoarthritis. Osteoarthritis and Cartilage. 2019 Apr;27(1):S330–1.

20. Watt FE, Hamid B, Garriga C, *et al*. The molecular profile of synovial fluid changes upon joint distraction and is associated with clinical response in knee osteoarthritis. Osteoarthritis and Cartilage. 2020 Jan;28(3):324–33.
21. Sanjurjo-Rodriguez C, Altaie A, Mastbergen S, *et al*. Gene expression signatures of synovial fluid multipotent stromal cells in advanced knee osteoarthritis and following knee joint distraction. Frontiers in Bioengineering and Biotechnology. 2020 Oct 14;8:1178.
22. Tomiyama Y, Koga H, Mochizuki T, *et al*. The relationship between knee osteoarthritis and femoral distal cortical bone thickness: Case control study from the matsudai knee osteoarthritis survey. Osteoarthritis and Cartilage. 2020 Apr 1;28:S208–9.
23. van der Woude JAD, Welsing PM, van Roermund PM, *et al*. Prediction of cartilaginous tissue repair after knee joint distraction. The Knee. 2016 Oct;23(5):792–5.
24. Intema F, Thomas TP, Anderson DD, *et al*. Subchondral bone remodeling is related to clinical improvement after joint distraction in the treatment of ankle osteoarthritis. Osteoarthritis and Cartilage. 2011 Jun 1;19(6):668–75.
25. Karvonen RL, Miller PR, Nelson DA, *et al*. Periarticular osteoporosis in osteoarthritis of the knee. Journal of Rheumatology. 1998 Nov 1;25(11):2187–94.
26. Vaysbrot EE, Osani MC, Musetti MC, *et al*. Are bisphosphonates efficacious in knee osteoarthritis? A meta-analysis of randomized controlled trials. Osteoarthritis and Cartilage. 2018 Feb 1;26(2):154–64.
27. Fu SH, Wang CY, Yang R Sen, *et al*. Bisphosphonate use and the risk of undergoing total knee arthroplasty in osteoporotic patients with osteoarthritis. Journal of Bone and Joint Surgery. 2017;99(11):938–46.
28. Bredbenner TL, Eliason TD, Potter RS, *et al*. Statistical shape modeling describes variation in tibia and femur surface geometry between control and incidence groups from the Osteoarthritis Initiative database. Journal of Biomechanics. 2010 Jun;43(9):1780–6.

SUPPLEMENTARY DATA



Supplementary Figure S1: Cortical bone thickness for patients with predominantly lateral compartmental osteoarthritis (n=2), before and 1 and 2 years after treatment with knee joint distraction.



Supplementary Figure S2: Trabecular bone density for patients with predominantly lateral compartmental osteoarthritis (n=2), before and 1 and 2 years after treatment with knee joint distraction.

CHAPTER 19

Summary and general discussion

Summary

In a population with a steadily increasing life expectancy that prefers to stay active at on older age, the ability to postpone a unilateral or total knee arthroplasty (UKA/TKA) in case of knee osteoarthritis (OA) as long as possible is becoming increasingly valuable.[1] Ideally, this is done with a joint-preserving treatment that not only improves patients' symptoms such as pain and stiffness, but is also able to actually modify tissue structure. As described in several previous PhD theses and many scientific publications, joint distraction in general and knee joint distraction (KJD) treatment more recently have the potential to provide clinical improvement as well as tissue structure modification.[2–9] The aim of the present thesis was to move forward with KJD as a treatment for relatively young knee osteoarthritis (OA) patients. These next steps are taken in 2 parts: I) evaluating newly available clinical outcome and improving treatment-related patient experience and II) elucidating the working mechanisms behind KJD and the joint processes that occur as a result of this treatment.

Part I: Clinical outcome and patient experience

Since the first scientific report on applying KJD to treat knee OA in 2007[10], several clinical studies have been performed in multiple medical centers world-wide. To collectively assess all relevant outcome data available, a systematic review of all clinical studies evaluating at least 1 of the predefined primary outcome parameters was performed and results were combined in a meta-analysis, as described in **chapter 2**. In total, 127 patients from 7 different studies were evaluated, and significant improvements in all primary parameters were found, comparable with control groups when used. However, this came along with frequently observed pin tract infections. While it was concluded that longer follow-up with more patients is necessary, the evidence showed KJD causes clear benefit, both short- and long-term. Attention for improving treatment indication was also considered important.

The first long-term results after KJD were highlighted in more detail in **chapter 3**, describing outcome and clinical success up to 9 years after treatment of 20 patients originally treated in the Netherlands. Half of the patients still had not undergone arthroplasty surgery after 9 years, despite being originally indicated for TKA. Interestingly, in male patients this was even more than 2 out of three. Patients who had not undergone additional surgery still showed significantly improved clinical and structural (radiographic joint space width; JSW) outcomes 9 years after treatment. Even in those who did receive TKA, clinical outcome was still significantly improved in the year prior. Interestingly, initial (first-year) cartilage repair activity appeared to be important for long-term (9-year) clinical success.

In order to compare KJD to alternative surgical treatments, **chapter 4** evaluated clinical and tissue structure benefit up to 2 years after KJD, TKA and high tibial osteotomy (HTO), in patients treated in 2 separate randomized controlled trials (RCTs). All treatments showed

significant benefit, comparable between KJD and HTO both clinically, as evaluated with questionnaires, and structurally, as measured with radiographic JSW change. TKA generally showed somewhat better clinical results than KJD, but at expense of the patients' native knee. Also, systemic (serum/urine) biomarkers in KJD patients showed a net increase of collagen type II synthesis over breakdown in the second year after treatment. Interestingly, shortly after treatment this was the opposite, as an initial negative net collagen type II synthesis was observed.

As an extension on the RCT comparing KJD and HTO, return to sport and work after the 2 treatments were described in **chapter 5**. The number of patients returning to sport and work was comparable between the treatments. After 6 months, 7 in 10 patients returned to sports and 9 in 10 patients returned to work. After 1 year, these rates were 16 and 19 in 20 patients for sports and work, respectively. While patients shifted towards less high-impact sports compared to pre-treatment, sports participation levels at 5 years were comparable to those at 1 year, indicating a sustained treatment effect, especially important in these younger, active OA patients independent of treatment HTO or KJD.

The positive results from the clinical trials resulted in implementation of KJD in regular care in a limited number of Dutch hospitals. Clinical data from registries of these patients were compared with clinical trial data in **chapter 6**. Patient characteristics were not different between regular care and trial patients, indicating application of similar selection criteria. Treatment complications, with pin tract infections occurring most often in both groups (2 in 3 patients), did not differ between regular care and trial patients either. Questionnaires showed significant clinical improvement in pain, stiffness, and function 1 year after treatment in regular care, similar to that in clinical trials, indicating that also in regular care KJD can be a viable treatment option.

Since patients thus far were being treated with a device not specifically designed for KJD, a dedicated KJD device was developed in collaboration with patients, clinicians, and engineers. The aim was to develop a more user-friendly device. Its user-friendliness was assessed and compared with the previously used concept device in **chapter 7**. The intervention duration when placing the dedicated device was significantly (~20%) shorter, and pin tract infections occurred less often than with the concept device (in 2 *versus* 3 out of 4 patients). Patient questionnaires showed the dedicated device was more user-friendly in several categories, including pin care. With that, the dedicated device contributes to further implementation of KJD treatment.

In addition to the steps already made to improve user-friendliness and patient experience of KJD treatment, **chapter 8** analyzes the use of cadexomer iodine ointment during KJD treatment to potentially reduce pin tract infections. Patients treated with KJD received a wound care

protocol, which for part of the patients included cadexomer iodine ointment. Patients who did not use this ointment experienced twice as many pin tract infections and 5 times as many serious infections (requiring more antibiotics than a single oral course). Using cadexomer iodine ointment during KJD treatment significantly reduced pin tract related complaints, decreasing treatment burden and further improving patient-friendliness, and should be considered as part of the standard treatment protocol.

A new multicenter prospective study was started to evaluate clinical outcomes after KJD treatment with the dedicated device, and **chapter 9** showed an interim analysis of 1-year follow-up results from this trial. Patient-reported clinical outcomes and radiographic JSW improved significantly after treatment and were comparable and largely non-inferior to results obtained with the previous concept device. Patient selection seemed to have shifted somewhat, as patients treated with the dedicated device had more complaints but less joint damage than patients from previous studies. Still, also with the dedicated device, KJD treatment results in significant clinical efficacy.

Part II: Joint processes and working mechanisms

Clinical studies initially focus on improving clinical outcome and increasing radiographic JSW (as this usually indicates cartilage restoration) but over the past years more research has been performed on the joint processes and mechanisms behind KJD. In **chapter 10**, an overall picture of KJD is given, providing an overview of the current clinical evidence underscoring part I of this thesis as well as discussing different concepts of potential underlying processes introducing part II of this thesis. Supported by recent literature, it is theorized that a combination of partial unloading, joint synovial fluid (SF) pressure oscillation, subchondral mechanical and biochemical bone changes, joint-derived stem cells, and a changed molecular joint milieu is causative to the observed tissue regeneration that occurs in KJD treatment.

When evaluating structural changes or processes inside the joint during or after treatment, imaging techniques are often used, as they allow non-invasive monitoring of tissue changes. Radiographically, characteristics such as JSW, osteophyte size and subchondral bone density can be assessed, using a standardized analysis method such as knee image digital analyses (KIDA). In **chapter 11**, the performance of this method was evaluated in patients with severe knee OA. Intra-observer parameters were good, especially when radiographs were reevaluated within 1 month (instead of years), and for most parameters the smallest detectable difference was comparable to that observed when analyzing radiographs of patients with mild OA. As such, the analysis method was proven useful for radiographic evaluation of severe OA as well. Importantly, radiographs should be analyzed in a limited time frame and ideally in randomized order.

Apart from bone-to-bone JSW measured on weight-bearing radiographs as an indirect measure for cartilage restoration, cartilage thickness can be measured directly on non-weight-bearing MRI scans. Strangely, these 2 techniques have always shown a poor correlation in longitudinal changes over time. In **chapter 12**, bone-to-bone JSW measured on non-weight-bearing CT is introduced to investigate whether the poor correlation is because of the difference in weight-bearing or because of measuring bone-to-bone distance *versus* cartilage thickness. Only CT 3D JSW and MRI cartilage thickness showed a significant longitudinal correlation, pointing towards the difference in weight-bearing as the cause of the weak correlation between changes in radiographic JSW and MRI cartilage thickness. Potentially this is because of the influence of cartilage resilience, although more research on this topic is warranted.

The MRI cartilage thickness up to 10 years after KJD treatment is reported in **chapter 13,** using a 3-dimensional whole-joint approach. At 1- and 2-years post-treatment, cartilage in the most affected weight-bearing region was significantly thicker than before treatment. Male patients and those with more severe OA showed somewhat enhanced benefit. From 5 years post-treatment the cartilage started gradually thinning again, likely the result of natural progression. Even 10 years after treatment an increase in cartilage thickness was still observed, especially in the less affected parts of the joint. Thus, an initial boost of cartilaginous tissue repair after KJD treatment provides long-term tissue structure benefit.

Subsequently, MRI cartilage thickness changes after KJD were compared with those after HTO treatment, as described in **chapter 14**. Two years after treatment, TKA-indicated KJD patients showed not only a significant increase in cartilage thickness, but also a decrease in denuded bone areas. HTO-indicated KJD patients showed no significant change, while patients treated with HTO even showed significant deterioration on MRI despite an increased radiographic JSW. OA severity most strongly predicted MRI cartilage restoration, and significant cartilage restoration was seen only after KJD in severe OA patients. It appeared that in patients with severe OA, KJD may be more effective in restoring cartilage thickness than HTO.

With the cartilage thickness changing after treatment, the next step was to evaluate the cartilage quality, which is presented in **chapter 15** using T2-mapping MRI, representing cartilage collagen structure. After treatment with KJD or HTO, cartilage T2 relaxation times increased more than might be expected in natural OA progression, which could indicate loss or reorganization of collagen structure integrity. In TKA-indicated KJD patients, this increase was limited to the first year after treatment, after which the collagen content or structure improved. As these same patients showed a significant cartilage volume increase as well, increasing T2 values may partly be the result of maturation of newly formed cartilage and reorganization of the matrix in the first period after treatment.

The exploration of KJD working mechanisms was not limited to only cartilage tissue. In **chapter 16**, SF biochemical marker levels were assessed before, during, and directly after treatment. KJD caused a measurable molecular response in SF with significant changes in markers associated both with degeneration and with repair, suggesting remodeling. Interestingly, for some markers such as transforming growth factor-β1 (TGFβ-1), their (biological) response even appeared to be associated with patient-reported clinical outcome in the year after treatment.

The in KJD upregulated SF markers like TGFβ-1 and interleukin-6 (IL-6) could be related to cartilage regeneration, but also to osteophyte formation, which is why osteophyte formation after KJD and HTO was studied radiographically in **chapter 17**. In the 2 years after treatment, a significant increase in osteophyte area was observed, higher than that in patients with natural OA progression in the years before undergoing TKA. The increased osteophyte formation in KJD patients tended to be associated with changes in TGFβ-1 but not IL-6. Osteophyte growth may therefore be a bystander effect of cartilage repair activity related to intra-articular factors such as TGFβ-1, and not just simply an indicator of joint degeneration as used in different OA grading systems.

Lastly, to further evaluate bone changes induced by KJD, the subchondral cortical bone thickness, subchondral trabecular bone density, and bone shape were explored on CT scans before and after treatment in **chapter 18**. Before treatment, the more affected weight-bearing part of the joint showed increased cortical thickness and trabecular density. Both parameters seemed to decrease in the first year after treatment, especially in the more affected parts, and this change was prolonged throughout the second year. Furthermore, the femoral condyles became more convex while the tibial condyles became less concave. These alterations suggest KJD treatment may induce a partial normalization of bone shape and structure affected by OA.

General discussion

For a disease with such a high socio-economic impact as OA, it is rather surprising that until not too long ago it was thought of as simply a disease of cartilage degeneration. Instead it is a whole-joint disease involving bone, cartilage, and synovial tissue that is not simply the result of wear and tear.[11] Proper cartilage regeneration was thought impossible, but it is now more and more accepted that cartilage can at least partly regenerate.[12–15] Still, development of disease-modifying osteoarthritis drugs (DMOADs) has thus far failed. This is partially because we increasingly appreciate that modification of multiple involved tissues and processes is required to have a lasting impact, whereas most drug development approaches thus far only target single molecules or pathways. New approaches such as a IL4-10 fusion protein, improving pain, inflammation and cartilage structure seem promising.[16–18] The research presented in this thesis

has moved the field on KJD forward, but additional steps forward could and should be made.

Moving forward with KJD as a successful treatment for severe knee OA means focusing on providing the clinical outcome that patients desire, not just on a group level but also on an individual patient level. It is clear from the research presented throughout part I that KJD is able to give patients relief of symptoms such as pain and stiffness, even for the long-term (**chapter 3**) and outside of trial conditions (**chapter 6**). KJD can even improve quality of life (**chapter 4** and **chapter 9**) especially with respect to physical problems. Despite many positive results, it is important to realize that KJD treatment is not the holy grail in treating knee OA. The ability to postpone TKA for at least 10 years in half of the patients that were originally indicated for it is impressive (**chapter 3** and **chapter 13**), but at the same time, there are also patients who within the first 2 years after treatment already choose additional surgical treatment (**chapter 4**). There is a contrast between individual patients in this regard that is not easily explained, probably partly because of the subjectivity involved in deciding to undergo additional surgery. Supporting this subjectivity is that KJD patients chose to have TKA surgery despite, on group level, still clearly experiencing the beneficial effects of KJD surgery (**chapter 3**). The decision-making in opting for TKA has been studied previously, showing that patients are heavily influenced by not only their own expectations and fears, but also by their close social environment and healthcare provider.[19,20] This results in an individual effect that is not easily measurable, and might influence any other surgical treatment as well including (follow-up) TKA surgery. Still, there are some indications that there are physiological differences between patients who do and do not respond well. Male patients show better response to distraction of not only the knee (**chapter 3** and **chapter 13**), but also the ankle and hip.[21,22] Patients with more severely affected joints show a better clinical (**chapter 3**) and cartilage restoration (**chapter 13** and **chapter 14**) response to KJD as well.[23] This suggests clinical treatment response is not solely subjective, but at least party dependent on underlying systemic and joint-specific characteristics.

It can also be debated whether patients choosing TKA surgery a few years after KJD should be interpreted as treatment failure. The goal of KJD is ultimately to postpone TKA surgery long enough that a revision surgery later in life can be prevented (see Figure 1).

The lifetime risk of revision is higher in younger patients, especially under the age of 65, and in these patients even postponing a TKA with 5 years could decrease the risk of revision with up to 20 percentage points.[24] Indeed, recent data from the Dutch Arthroplasty Register showed delaying TKA placement by 5 years in patients under the age of 75 could avoid 17% of revisions.[25] Furthermore, a first KJD treatment does not necessarily have to be followed by TKA or even a UKA. Treating patients with KJD for a second time years after the first treatment has never been tried. A successful second ankle distraction was anecdotally reported, so it is not unlikely that a second KJD could lead to additional years of positive outcome as well. There are also patients who have been treated with HTO years after KJD, or with

KJD years after HTO, and researching (long-term) outcomes in these patients could give interesting insights in the process of joint preservation. KJD could also be combined with other treatments, such as pharmacological or cell-based therapies, as has been speculated upon but never tried.[8] These possibilities all allow patients to retain their native knee for as long as possible and require minimal bone 'cutting or removal', which patients deem important when considering surgical interventions for knee OA.[26] It is also essential that, before choosing KJD as treatment to postpone TKA, patients have really exhausted conservative treatment options first, which is a criterion that should be considered before recommending KJD but, in general clinical practice, is not always followed.[27]

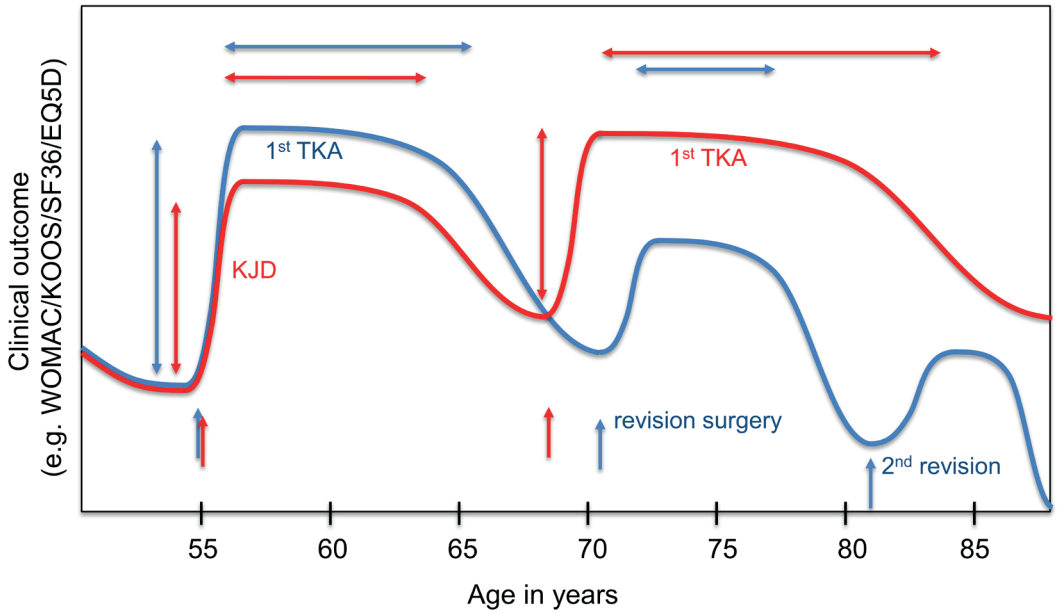


Figure 1: Envisioned treatment effect of knee joint distraction (KJD). In blue the conventional way of placing a total knee arthroplasty (TKA) at a young age because of lack of alternatives ending up with significant loss of quality of life later in life. In red the alternative using KJD as joint-preserving treatment, postponing a first TKA for years towards an age at which a first prosthesis preforms better and preferably lasts a lifetime with gain of quality of life.

Moving forward with KJD requires patients to have actually access to the treatment. In order to achieve this, it will have to be implemented in regular clinical practice, which means it should be reimbursed by patients' health insurance. In the past years, the first steps towards reimbursement by the Dutch Healthcare Authority (Nederlandse Zorgautoriteit; NZa) have been taken. The systematic review and meta-analysis (**chapter 2**) and the 2 year follow-up data of the RCTs (**chapter 4**) were used as part of the process to obtain reimbursement, in which the National healthcare institute (Zorginstituut Nederland; ZiN) performed an evaluation of the 'state of knowledge and clinical practice' (Stand van de Wetenschap en Praktijk; StWP) for KJD as treatment for relatively young (<65 years) knee OA patients indicated for TKA. It was concluded that while KJD was considered a promising treatment, the current evidence is

insufficient for KJD to be eligible for reimbursement.[28] Specifically, they could not conclude with enough certainty whether KJD is non-inferior to TKA with respect to clinical outcome because of limited number of treated patients, and whether KJD can sufficiently long postponement a TKA, because of insufficiently long follow-up data available. As the latter takes years to even decades to proof, it can only be addressed as more patients, including those from the previous prospective and RCT studies, reach longer follow-up. Additionally, it is important that more trials are performed, ideally comparing KJD to (T)KA, to increase numbers of treated patients. Further follow-up in the RCTs (**chapter 4**) and the currently ongoing prospective study evaluating results after treatment with the KneeReviver (**chapter 9**) will add long-term data of more than 100 additional patients. In the UK a new multicenter RCT comparing KJD with (T)KA, financed by the NHS, is currently recruiting patients, eventually treating 344 patients with KJD or (T)KA in a 1:1 ratio, providing direct comparison with (T)KA in a relatively large group of patients.[29] For the Netherlands, a funding request specifically meant to provide the data to enable reimbursement by the NZa was submitted. This involves a multicenter RCT in which 1200 patients are randomized (1:1) to treatment with either KJD or (TK)A. As such, it can be expected that in the forthcoming years (decade), more data will become available on whether KJD is indeed non-inferior with respect to clinical outcome after (T)KA and provides sufficiently long postponement of a first (T)KA. This will provide the required information to enable reimbursement and with that foundation for implementation in regular care.

An important point of discussion in both of these RCTs and the process of obtaining reimbursement, however, is whether KJD even has to be non-inferior in clinical outcome compared to (T)KA. KJD is not meant to be an alternative to TKA, but instead is meant to postpone it (see Figure 1). In fact, KJD should only be used in younger (<65 years) patients for whom TKA would bring an increased risk of revision surgery later in life.[24] KJD is in that perspective more comparable to UKA. KJD could even precede a UKA before undergoing TKA, worthwhile especially since receiving UKA at a younger age increases the chance for revision as well.[30] Evidently, defining when KJD treatment is successful (enough) is difficult, but important to evaluate soundly and robustly. In the end, KJD is an invasive treatment with a relative heavy burden for patients, even after efforts to reduce this burden (**chapter 7** and **chapter 8**). Ensuring the highest chance of treatment success is vital, and can perhaps only be done by improving patient selection. For this, not only larger number of treated patients with longer follow-up is needed, but also better understanding of the working mechanisms.

Moving forward with KJD can only happen by improving our understanding of the different processes taking place in the osteoarthritic joint before, during, and after treatment. KJD might be explained simply as unloading that stimulates regeneration of cartilage that, before treatment, had degenerated as a result of overloading. This is an oversimplification leaving out important aspects of the treatment (**chapter 10**), such as SF pressure oscillation purposefully induced by resilience in the frame, or even the possible effect of drilling pins in the femur

and tibia, which in dogs showed (some) repair even without distraction.[31] Furthermore, this thesis shows that KJD does not only induce regenerative processes over time, but also processes that could be categorized as degenerative or inflammatory during and shortly after treatment. It has previously been indicated that KJD results in a significant increase in SF-resident mesenchymal stem cell (MSC) promoting cartilage repair.[32] SF biochemical marker evaluation showed upregulation associated with repair, but at the same time markers associated with degeneration were upregulated as well, indicating activation of traditionally inflammatory pathways (**chapter 16**). KJD also causes increased osteophyte formation (**chapter 17** and **chapter 18**), a process that is generally considered a sign of OA progression. Systemic biomarkers showed an initial net collagen type II synthesis decrease, meaning more breakdown than regeneration of collagen type II, 1 of the most important molecules providing cartilage its mechanical integrity (**chapter 4**). Only from 1 year after treatment onward a net synthesis increase was observed, indicating an initial phase of breakdown (or turnover) is followed by regeneration in the long term. This was confirmed by T2-mapping, as in the first year after treatment cartilage T2 values significantly increased (deterioration of structure), but between 1 and 2 years a plateau or even a decrease was seen (improvement in structure), again indicating short-term breakdown followed by improvement (**chapter 15**). While there is clearly an initial boost in cartilaginous tissue regeneration in especially the first year after treatment (**chapter 3**, **chapter 4**, **chapter 9**, **chapter 13**, and **chapter 14**), it is plausible that it takes a bit more time for this tissue to become of similar quality as that of the native cartilage (**chapter 15**). It might well be, for example, that if aggrecan molecules are enzymatically truncated but not removed from the hyaluronic acid core in the process of OA and with that from the matrix, this aggrecan molecule cannot be replaced, leaving an impaired aggrecan complex. Only when further degradation is facilitated first, the truncated molecule can be fully replaced in the repair phase after the initial breakdown. Subchondral bone, in contrast to cartilage, showed early remodeling, which seemed to be a normalization, already in the first year after treatment (**chapter 3** and **chapter 18**), with shape improvement following shortly after (**chapter 18**). Interestingly, this was also followed by osteophyte growth (**chapter 17** and **chapter 18**). These bone changes are in line with previous results after ankle distraction, where especially the first year after treatment, a subchondral bone density normalization was seen, as the overall bone density decreased but the density in cystic areas increased.[33] Yet also bone goes through a breakdown phase by distraction, as clear osteopenia is caused during treatment because the load on the bone is taken over by the external distraction device.

Clearly, KJD significantly alters the joint homeostasis by inducing both anabolic and catabolic processes in the initial phase, resulting in changes in SF, bone, and cartilage, that manage to finally cause long-term repair. The research presented in this thesis moved our understanding of KJD treatment forward by evaluating these different components, and by partially identifying patient characteristics that are considered important for the effect. Male patients responded significantly better to KJD treatment (**chapter 3**), as is the case with ankle

and hip distraction[21,22], which could be related to hormonally controlled bone differences between men and (mostly post-menopausal) women.[34] Patients with more severe OA seemed to show a better response in cartilage regeneration and quality (**chapter 13**, **chapter 14**, and **chapter 15**), which in turn results in better long-term success (**chapter 3**), indicating that pre-treatment patient selection is crucial. Treating patients with severe complaints but only mild joint damage with KJD will likely not give the positive effect that the treatment can potentially bring. Still, there will be other characteristics, components or processes that are important in KJD treatment that we have not yet discovered or simply have not been studied yet. For example, the possible influence of muscles, ligaments and menisci has thus far not been investigated. The menisci, especially, could be of relevance, since they have an important role in load distribution during weight-bearing and in the structural progression of knee OA.[35] Also, including a well-matched, untreated control group as comparison when evaluating structural changes would be helpful in unraveling the mechanisms behind KJD and identifying important characteristics. Unfortunately, this is difficult, since a good control group would need to have similar, severely progressed, knee OA, and not treating such patients would be unethical. Performing advanced imaging of ideally larger groups of patients on more time points especially shorter after treatment, since that could allow linking SF biomarker and MSC response with structural bone and cartilage changes, would likely further improve understanding of the joint repair processes as well. Importantly, when further elucidating these processes they might be of direct help to development of other OA treatment modalities, where placement of a frame may be obsolete, in case the relevant process can be influenced without distraction (see Figure 2).

Moving forward with KJD also means looking beyond the original goal of using it to treat OA patients, and applying the knowledge gained from the repair processes that occur on the general field of OA. The regenerative processes upon KJD occur very fast compared with the slow rate degenerative processes in OA, as they show relatively large structural and clinical changes in a short amount of time. Having a treatment with clear regenerative capacity allows us to step off the old paradigm of trial and error of investigating targets and medication often aiming at a single molecule, pathway or tissue (such as cartilage) in the OA joint. Instead, we can learn of the integrated effects induced by distraction and use this knowledge, as summarized in Figure 2. Many researchers select (and rarely combine) components, mechanical, cellular and/or chemical, of supposed relevance to induce cartilage tissue repair. In this process, many components are discarded and several will be missed because they act only in synergy with others that have not been considered or are prematurely discarded. Moreover, researchers generally have either biochemical, cellular or mechanical expertise and seldom a combination of them. After decades, we still only have limited insight in the requirements needed for cartilage tissue repair, as they have to be found and combined by trial and error. Apparently KJD provides a joint homeostasis, both mechanically, cellular and chemically, with all required components,

combined in such a way that structural repair is possible. Using this integrated 'inside-out' concept can provide as new insight which might be of value to better understanding of the OA degenerative process as well.

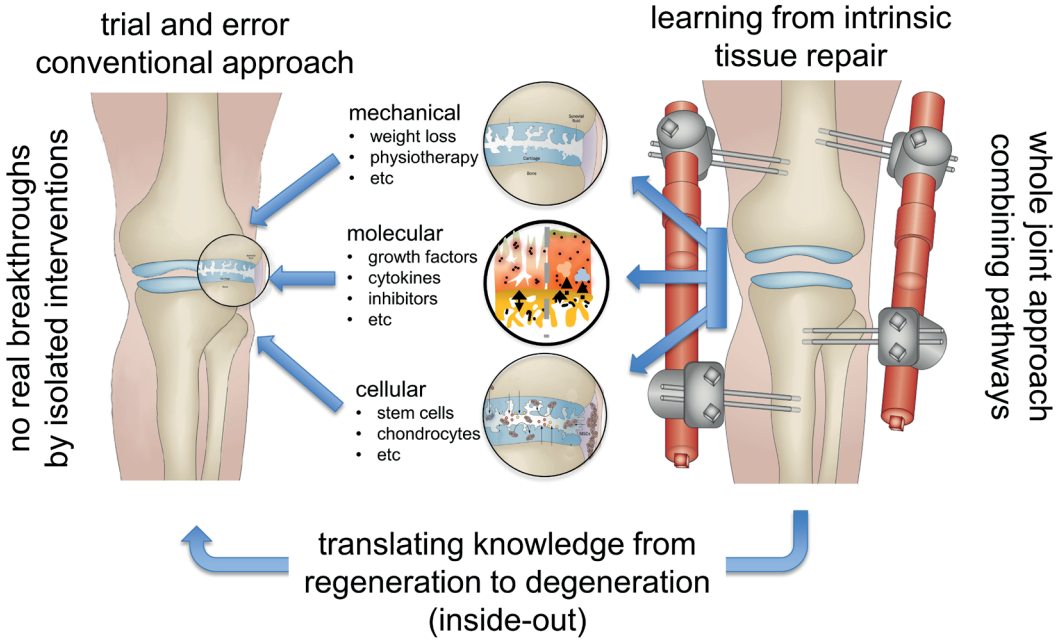


Figure 2: Instead of a conventional trial and error approach in a slowly progressing disease, we could learn from the relatively fast regenerative response with its integrated effects on all relevant tissues, pathways and molecules.

With that, it could provide clues for long-standing questions in the field of OA. One of these questions is the relation between structural damage and pain where, despite many attempts, it has not yet been possible to identify with certainty specific characteristics of tissue damage that are associated with pain.[36] Some suggestions have been made, such as presence of bone marrow lesions, but results are often contradictory.[36–38] Using high rate, within-patient, structural alterations as seen after KJD to find a relation with changes in clinical outcome, characteristics could be identified that are important in the relationship between structure and pain in OA. A larger number of patients with standardized imaging would be required, not only restricted to KJD, so other cohorts showing significant cartilage repair should be included as well, such as patients treated with distraction of the ankle or thumb-base, or even those with potential spontaneous repair.[9,39] Even the beneficial effects observed by, for example, weight loss or physiotherapy could be included in such approaches. Identifying the cause of pain in patients could help better choosing the appropriate therapy, improving patient selection and increasing treatment success. This also highlights the importance of looking at individual patients, or at least distinguishing different groups of patients. Phenotyping, defining subtypes that share distinct underlying pathways and pain mechanisms, is another important challenge in the OA field that high rate repair processes could help with.[40] Different strategies have

been used in the past, such as the currently ongoing APPROACH (Applied Public-Private Research enabling Osteoarthritis Clinical Headway) trial aiming for better identification of fast and slow progressors.[41] Repair-inducing treatments like KJD show a uniquely rapid response that provide a relatively large contrast between patients, which could be generalized to degenerative processes in OA. By analyzing and combining structural (imaging) markers and clinical outcome of a large number of these patients, concrete OA phenotypes might finally be identified. For example, those that do and do not respond to a certain treatment (such as distraction) might be related to a certain phenotype (for example, a bone phenotype that shows optimal regeneration in case of distraction). This would improve patient-specific prognosis and allow for more personalized medicine, but could also improve design of future studies, as it is believed that many therapeutic OA trials may have failed due to the unidentified phenotypic heterogeneity of included patients.[42,43] Ultimately, this might even lead to successful development of DMOADs.

In conclusion, work in this thesis has moved the field forward with clinical evaluation of KJD as a treatment for severe knee OA and improving understanding of the working mechanisms behind this treatment. KJD can bring long-lasting clinical efficacy and cartilage regeneration, and increasingly patient-friendly implementation in regular care is possible. KJD induces significant anabolic and catabolic changes in joint homeostasis, showing whole-joint modifications involving bone, cartilage, and synovial fluid, subsequently followed by overall repair. Future studies should focus on deepening comprehension of the mechanisms induced by KJD to improve patient selection, as well as using this unique population showing high rate structural and clinical response to improve understanding of different OA pathways in general.

References

1. Kontis V, Bennett JE, Mathers CD, *et al*. Future life expectancy in 35 industrialised countries: Projections with a Bayesian model ensemble. The Lancet. 2017 Apr 1;389(10076):1323–35.
2. van Valburg AA. Ilizarov joint distraction in treatment of osteoarthritis. Utrecht University; 1997.
3. Marijnissen ACA. Osteoarthritis and joint distraction: Models, mechanisms and long-term effects. Utrecht University; 2001.
4. Intema F. Loading and unloading in the development and treatment of osteoarthritis. Utrecht University; 2010.
5. Wiegant K. Knee joint distraction: Intrinsic cartilage repair and sustained clinical benefit. Utrecht University; 2015.
6. van der Woude JAD. Unloading the osteoarthritic knee: Osteotomy and joint distraction. Utrecht University; 2016.
7. Besselink NJ. Imaging tissue characteristics in osteoarthritis and rheumatoid arthritis. Utrecht University; 2018.
8. Mastbergen SC, Saris DBF, Lafeber FPJG. Functional articular cartilage repair: Here, near, or is the best approach not yet clear? Nature Reviews Rheumatology. 2013 May;9(5):277–90.
9. Spaans AJ, Minnen LP van, Braakenburg A, *et al*. Joint distraction for thumb carpometacarpal osteoarthritis: A feasibility study with 1-year follow-up. Journal of Plastic Surgery and Hand Surgery. 2017 Jul 4;51(4):254–8.
10. Deie M, Ochi M, Adachi N, *et al*. A new articulated distraction arthroplasty device for treatment of the osteoarthritic knee joint: A preliminary report. Arthroscopy. 2007;23(8):833–8.
11. Castañeda S, Vicente EF. Osteoarthritis: More than Cartilage degeneration. Clinical Reviews in Bone and Mineral Metabolism. 2017 Jun 1;15(2):69–81.
12. Hunziker EB. Articular cartilage repair: Basic science and clinical progress. A review of the current status and prospects. Osteoarthritis and Cartilage. 2002;10(6):432–63.
13. Marijnissen ACA, Lafeber FPJG, Hunziker EB. Re: E.B. Hunziker. Articular cartilage repair: Basic science and clinical progress. A review of the current status and prospects. Osteoarthritis and Cartilage. 2003 Apr 1;11(4):300–1.
14. Armiento AR, Alini M, Stoddart MJ. Articular fibrocartilage – Why does hyaline cartilage fail to repair? Advanced Drug Delivery Reviews. 2019 Jun 1;146:289–305.
15. Tiku ML, Sabaawy HE. Cartilage regeneration for treatment of osteoarthritis: A paradigm for nonsurgical intervention. Therapeutic Advances in Musculoskeletal Disease. 2015;7(3):76–87.
16. Karsdal MA, Michaelis M, Ladel C, *et al*. Disease-modifying treatments for osteoarthritis (DMOADs) of the knee and hip: Lessons learned from failures and opportunities for the future. Osteoarthritis and Cartilage. 2016 Dec 1;24(12):2013–21.
17. Steen-Louws C, Hartgring SAY, Popov-Celeketic J, *et al*. IL4-10 fusion protein: A novel immunoregulatory drug combining activities of interleukin 4 and interleukin 10. Clinical and Experimental Immunology. 2019 Jan 1;195(1):1–9.
18. Steen-Louws C, Boross P, Prado J, *et al*. Sialic acid-engineered IL4–10 Fusion protein is bioactive and rapidly cleared from the circulation. Pharmaceutical Research. 2020 Feb 1;37(2):1–10.
19. Suarez-Almazor ME, Richardson M, Kroll TL, *et al*. A qualitative analysis of decision-making for total knee replacement in patients with osteoarthritis. Journal of Clinical Rheumatology. 2010 Jun;16(4):158–63.
20. Selten EM, Vriezekolk JE, Geenen R, *et al*. Reasons for treatment choices in knee and hip osteoarthritis: A qualitative study. Arthritis Care and Research. 2016 Sep 1;68(9):1260–7.

21. Marijnissen ACA, Hoekstra MCL, Pré BCD, *et al*. Patient characteristics as predictors of clinical outcome of distraction in treatment of severe ankle osteoarthritis. Journal of Orthopaedic Research. 2014 Jan;32(1):96–101.
22. Gomez JA, Matsumoto H, Roye DP, *et al*. Articulated hip distraction: A treatment option for femoral head avascular necrosis in adolescence. Journal of Pediatric Orthopaedics. 2009 Mar;29(2):163–9.
23. van der Woude JAD, Welsing PM, van Roermund PM, *et al*. Prediction of cartilaginous tissue repair after knee joint distraction. The Knee. 2016 Oct;23(5):792–5.
24. Bayliss LE, Culliford D, Monk AP, *et al*. The effect of patient age at intervention on risk of implant revision after total replacement of the hip or knee: A population-based cohort study. The Lancet. 2017 Apr 8;389(10077):1424–30.
25. Gademan MGJ, van Steenbergen LN, Cannegieter SC, *et al*. Population-based 10-year cumulative revision risks after hip and knee arthroplasty for osteoarthritis to inform patients in clinical practice: A competing risk analysis from the Dutch arthroplasty register. Acta Orthopaedica. 2021 Jan 22;1–5.
26. Moorman CT, Kirwan T, Share J, *et al*. Patient preferences regarding surgical interventions for knee osteoarthritis. Clinical Medicine Insights: Arthritis and Musculoskeletal Disorders. 2017 Sep 19;10.
27. O'Brien P, Bunzli S, Ayton D, *et al*. What are the patient factors that impact on decisions to progress to total knee replacement? A qualitative study involving patients with knee osteoarthritis. BMJ Open. 2019 Sep 1;9(9):e031310.
28. Zorginstituut Nederland. Standpunt Kniedistractie bij volwassen patiënten jonger dan 65 jaar met end-stage knieartrose én een indicatie voor een totale knieprothese. https://www.zorginstituutnederland.nl/publicaties/standpunten/2020/10/28/standpunt-kniedistractie-bij-volwassen-patienten-jonger-dan-65-jaar-met-end-stage-knieartrose. 2020.
29. ISRCTN registry. ISRCTN14879004: A comparison of knee replacement surgery and knee joint distraction for treating osteoarthritis of the knee. https://www.isrctn.com/ISRCTN14879004.
30. W-Dahl A, Robertsson O, Lidgren L, *et al*. Unicompartmental knee arthroplasty in patients aged less than 65: Combined data from the Australian and Swedish knee registries. Acta Orthopaedica. 2010;81(1):90–4.
31. Wiegant K, Intema F, van Roermund PM, *et al*. Evidence of cartilage repair by joint distraction in a canine model of osteoarthritis. Arthritis and Rheumatology. 2015 Feb 28;67(2):465–74.
32. Sanjurjo-Rodriguez C, Altaie A, Mastbergen S, *et al*. Gene expression signatures of synovial fluid multipotent stromal cells in advanced knee osteoarthritis and following knee joint distraction. Frontiers in Bioengineering and Biotechnology. 2020 Oct 14;8:1178.
33. Intema F, Thomas TP, Anderson DD, *et al*. Subchondral bone remodeling is related to clinical improvement after joint distraction in the treatment of ankle osteoarthritis. Osteoarthritis and Cartilage. 2011 Jun 1;19(6):668–75.
34. Roman-Blas JA, Castañeda S, Largo R, *et al*. Osteoarthritis associated with estrogen deficiency. Arthritis Research and Therapy. 2009 Sep 21;11(5):1–14.
35. Englund M, Roemer FW, Hayashi D, *et al*. Meniscus pathology, osteoarthritis and the treatment controversy. Nature Reviews Rheumatology. 2012 Jul 22;8(7):412–9.
36. Hunter DJ, Guermazi A, Roemer F, *et al*. Structural correlates of pain in joints with osteoarthritis. Osteoarthritis and Cartilage. 2013 Sep 1;21(9):1170–8.
37. O'Neill TW, Felson DT. Mechanisms of osteoarthritis (OA) pain. Current Osteoporosis Reports. 2018 Oct 1;16(5):611–6.
38. Torres L, Dunlop DD, Peterfy C, *et al*. The relationship between specific tissue lesions and pain severity in persons with knee osteoarthritis. Osteoarthritis and Cartilage. 2006 Oct 1;14(10):1033–40.

39. Marijnissen ACA, van Roermund PM, van Melkebeek J, *et al*. Clinical benefit of joint distraction in the treatment of severe osteoarthritis of the ankle: Proof of concept in an open prospective study and in a randomized controlled study. Arthritis and Rheumatism. 2002 Nov;46(11):2893–902.

40. van Spil WE, Kubassova O, Boesen M, *et al*. Osteoarthritis phenotypes and novel therapeutic targets. Biochemical Pharmacology. 2019 Jul;165:41–8.

41. van Helvoort EM, van Spil WE, Jansen MP, *et al*. Cohort profile: The Applied Public-Private Research enabling OsteoArthritis Clinical Headway (IMI-APPROACH) study: A 2-year, European, cohort study to describe, validate and predict phenotypes of osteoarthritis using clinical, imaging and biochemical markers. BMJ Open. 2020 Jul 28;10(7):e035101.

42. Mobasheri A, Saarakkala S, Finnilä M, *et al*. Recent advances in understanding the phenotypes of osteoarthritis. F1000Research. 2019;8.

43. Berenbaum F. Deep phenotyping of osteoarthritis: A step forward. Annals of the Rheumatic Diseases. 2019 Jan 1;78(1):3–5.

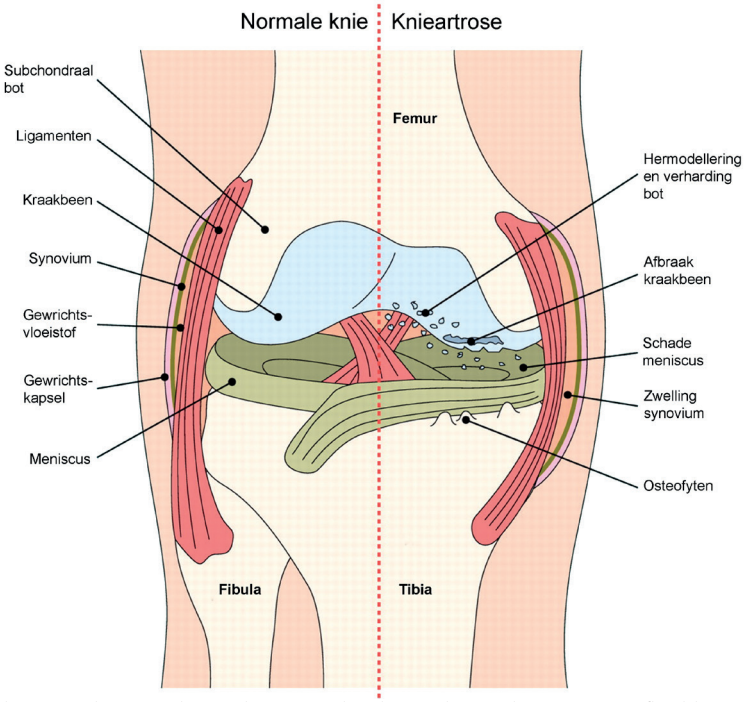
ADDENDUM

Nederlandse samenvatting

Introductie

Knieartrose

Artrose is de meest voorkomende chronische gewrichtsaandoening ter wereld en treft alleen in Nederland al bijna 1.5 miljoen mensen, waarvan ongeveer de helft gediagnosticeerd is met knieartrose. Artrose wordt vaak ook wel gewrichtsslijtage of kraakbeenslijtage genoemd, maar omvat veranderingen in het gehele gewricht en is meer dan simpelweg slijtage. De verschillende onderdelen van het kniegewricht en de belangrijkste veranderingen bij knieartrose zijn samengevat in Figuur 1. Een gezond kniegewricht bestaat uit twee botuiteinden, die bedekt zijn met een laag kraakbeen en bij elkaar worden gehouden door een gewrichtskapsel, met aan de binnenkant het gewrichtsvlies (synovium, of synoviaal membraan). Het bot heeft naast een mechanische functie ook een invloed op het kraakbeen als bron van mineralen en eiwitten. Het kraakbeen zorgt voor een glad oppervlak bij beweging, schokabsorptie en drukverdeling. Het synoviaal membraan produceert gewrichtsvloeistof (synoviaal vocht), belangrijk voor smering van het gewricht en voeding van het kraakbeen. De knieschijf is ook onderdeel van het kniegewricht en heeft aan de achterkant ook een laag kraakbeen. Hoewel er ook artrose van de knieschijf kan optreden, gaat het bij knieartrose meestal om veranderingen in het dijbeen (femur) en scheenbeen (tibia).



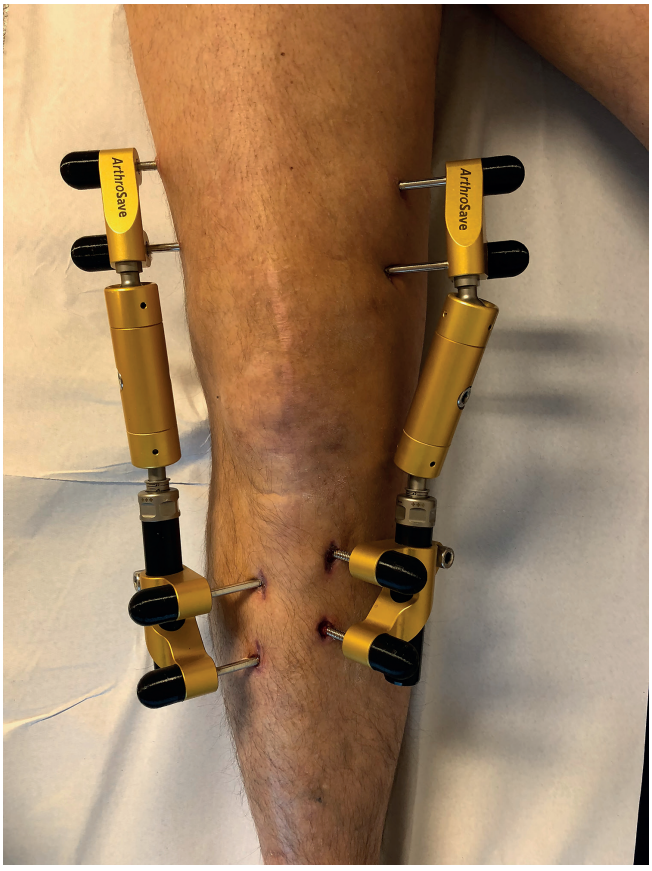
Figuur 1: Veranderingen die optreden in het gewricht als gevolg van knieartrose. Afbeelding overgenomen uit Osteoarthritis, David J Hunter en David T Felson, BMJ 2006;332:639-42.

Bij artrose vindt er veranderde opbouw (hermodellering) en verstijving plaats van het bot direct onder het kraakbeen (subchondraal bot). Ook verandert de algemene vorm van het bot en ontstaat er uitgroei in de vorm van bothaakjes (osteofyten). Het kraakbeen wordt afgebroken, waardoor de afstand tussen de botten (de gewrichtsspleetafstand) wordt verkleind. Niet alleen de hoeveelheid kraakbeen, maar ook de kwaliteit van het kraakbeen vermindert. Vaak is het synoviaal membraan ontstoken (synovitis), wat invloed heeft op de samenstelling van het membraan en het synoviaal vocht. Niet bij alle patiënten met knieartrose gebeuren al deze processen op dezelfde manier soms overheerst het een en soms het andere proces, soms de combinatie van processen en over de tijd kan er ook een wisselende invloed van de verschillende processen zijn.

Diagnose en behandeling

Patiënten komen vaak in eerste instantie bij een arts met klachten als pijn, verminderde functie en stijfheid van de knie. De diagnose knieartrose wordt gesteld op basis van deze klachten, in combinatie met lichamelijk onderzoek en indien nodig een röntgenfoto van de knie. Behandeling begint vaak met conservatieve opties zoals gewichtsverlies, het gebruik van een brace en medicatie zoals pijnstillers, ontstekingsremmers en eventueel een injectie in het gewricht. Uiteindelijk krijgen veel patiënten een kunstknie (knieprothese). Een groot deel van de patiënten is daar blij mee, maar 1 op de 5 patiënten behoudt klachten. Bovendien gaat een knieprothese niet levenslang mee, waardoor hij later soms vervangen moet worden (revisie), vooral als de knieprothese wordt geplaatst bij relatief jonge patiënten onder 65 jaar, omdat patiënten dan nog actiever zijn en de prothese nog langer mee moet. Deze revisie geeft vaak niet zulke goede resultaten. Het lijkt dus belangrijk dat het plaatsen van een knieprothese wordt uitgesteld in deze jongere patiënten, met behulp van gewrichtssparende behandelingen. Een van deze gewrichtssparende behandelingen is kniedistractie.

Bij kniedistractie worden de femur en de tibia tijdelijk ongeveer 5 mm van elkaar gehouden. Zo wordt er weer een grotere afstand tussen de botten gecreëerd, nadat deze afstand door de kraakbeenafbraak bij artrose een stuk kleiner was geworden en het gewricht als het ware in elkaar was gezakt. Dit uit elkaar houden van de botten wordt gedaan met een distractieframe, dat met pinnen aan de botten wordt vastgezet, zoals te zien in Figuur 2. Na 6-9 weken wordt het frame weer verwijderd. Kniedistractie is in verschillende klinische studies toegepast en zelfs toegepast in de reguliere zorg in een beperkt aantal ziekenhuizen in Nederland. Het doel van de behandeling is niet alleen verminderen van symptomen, maar ook het (deels) herstellen van de weefselveranderingen die door artrose optreden in de knie. De exacte werkingsmechanismen van kniedistractie zijn nog niet duidelijk, maar we weten inmiddels steeds meer over de processen die plaatsvinden in het gewricht tijdens en na de behandeling.



Figuur 2: Kniedistractie met een KneeReviver van ArthroSave, 1 van de mogelijke frames die voor distractie gebruikt kunnen worden.

Voorgaand onderzoek heeft reeds laten zien dat kniedistractie effectief is en dat er gewrichtsherstel kan plaatsvinden. Het werk in dit proefschrift borduurt daarop voort en is gericht op het nemen van de volgende *stappen voorwaarts met kniedistractie*, enerzijds wat betreft klinische resultaten en de ervaringen van patiënten en anderzijds wat betreft de kennis van de processen en mogelijke werkingsmechanismen in het gewricht als gevolg van kniedistractie.

Samenvatting hoofstukken

Deel I: Klinische resultaten en ervaringen van patiënten

Sinds de eerste wetenschappelijke publicatie over het gebruik van kniedistractie in 2007, zijn er meerdere klinische studies uitgevoerd in verschillende ziekenhuizen over de hele wereld. Om al die resultaten samen te kunnen analyseren, hebben we een systematische review en meta-analyse uitgevoerd van alle relevante publicaties over kniedistractie, zoals beschreven in **hoofdstuk 2**. In totaal zijn er 127 patiënten uit 7 verschillende studies geëvalueerd en hebben we significante verbetering gevonden in alle primaire uitkomstmaten, vergelijkbaar met controlegroepen die

gebruikt zijn. Veel patiënten hebben echter wel last van pengatinfecties. De conclusie was dat er langere follow-up nodig is met meer patiënten, maar dat het bewijs tot nu toe laat zien dat patiënten duidelijk baat hebben bij kniedistractie, zowel op korte (2 jaar) als lange (>7 jaar) termijn. Wel is het belangrijk dat er aandacht is voor het verbeteren van de indicatie voor behandeling met kniedistractie.

De eerste lange termijn resultaten van kniedistractie zijn weergegeven in **hoofdstuk 3**, waar de klinische resultaten tot negen jaar na behandeling worden beschreven van 20 patiënten in Nederland behandeld met kniedistractie. De helft van de patiënten had na negen jaar nog steeds geen knieprothese, ondanks het feit dat ze daar oorspronkelijk voor in aanmerking kwamen. In mannelijke patiënten was dit zelfs meer dan twee op de drie. Patiënten die nog geen vervolgoperatie ondergaan hadden, lieten na 9 jaar nog steeds een significante verbetering in klinische en structurele (gewrichtsspleetafstand) uitkomsten zien. Zelfs patiënten die wel een knieprothese kregen lieten het jaar ervoor nog steeds significant betere klinische resultaten zien dan vóór behandeling met distractie. De mate van kraakbeenherstel in het eerste jaar na behandeling lijkt een belangrijke factor te zijn voor klinisch succes op lange termijn (9 jaar).

Om kniedistractie te vergelijken met alternatieve chirurgische behandelingen, worden in **hoofdstuk 4** klinische uitkomsten en structureel weefselherstel geëvalueerd tot 2 jaar na kniedistractie, knieprothese, of (hoge tibiakop) osteotomie, bij patiënten die behandeld waren in 2 aparte gerandomiseerde gecontroleerde studies. Alle behandelingen lieten significante verbetering zien, vergelijkbaar tussen kniedistractie en osteotomie zowel voor klinische (vragenlijsten) en structurele (gewrichtsspleetafstand) resultaten. Patiënten met een knieprothese lieten wat betere klinische resultaten zien dan patiënten met kniedistractie, maar wel ten koste van hun eigen knie. Specifieke eiwitten (biomarkers) in bloed en urine van kniedistractie patiënten lieten in eerste instantie een netto afname, maar na 2 jaar een netto toename in collageen type II synthese zien. De toename van deze belangrijke bouwsteen van kraakbeen wijst op de aanmaak van een type kraakbeen (hyalien kraakbeen) dat belangrijk is voor het langdurige herstel van het gewricht.

Voortbordurend op de studie die kniedistractie en osteotomie vergelijkt, zijn in **hoofdstuk 5** terugkeer naar sport en werk na beide behandelingen vergeleken. Het aantal patiënten dat na behandeling weer kon sporten en werken was vergelijkbaar tussen de behandelingen. Na 6 maanden konden 7 op 10 patiënten weer sporten en 9 op 10 patiënten weer werken. Na een jaar was dit respectievelijk 8 en 9.5 op 10 patiënten voor sport en werk. Vergeleken met voor de behandeling beoefenden patiënten minder intensieve (high-impact) sporten, maar deelname aan sport was 5 jaar na behandeling vergelijkbaar met 1 jaar na behandeling. Dit duidt op een langdurend behandeleffect na zowel kniedistractie als osteotomie, wat belangrijk is voor deze relatief jonge en actieve artrosepatiënten.

De positieve resultaten uit klinische studies hebben ertoe geleid dat kniedistractie ook buiten studieverband werd toegepast, in een beperkt aantal Nederlandse ziekenhuizen. Klinische data van deze patiënten is vergeleken met de voorheen behandelde studiepatiënten in **hoofdstuk 6**. De patiënten waren vergelijkbaar tussen reguliere zorg en klinische studies wat betreft kenmerken zoals leeftijd en geslacht, wat betekent dat er vergelijkbare selectiecriteria voor de behandeling zijn gebruikt. Complicaties als gevolg van de behandeling verschilden ook niet tussen de groepen. Pengatinfecties kwamen het vaakst voor: ongeveer in 2 op de 3 patiënten. Vragenlijsten lieten ook in reguliere zorg significante en vergelijkbare verbeteringen in pijn, stijfheid en functie zien. Kniedistractie lijkt dus ook buiten studieverband een goede optie voor de behandeling van jongere patiënten met knieartrose.

Aangezien patiënten tot dusver werden behandeld met een apparaat (frame) dat niet specifiek was ontworpen voor kniedistractie, is er een specifiek distractieframe ontwikkeld in samenwerking met patiënten, clinici en ingenieurs. Het doel was om een meer gebruiksvriendelijk frame te ontwikkelen dat makkelijker door de orthopedisch chirurg is te plaatsen en minder belastend is voor de patiënt. De gebruiksvriendelijkheid van dit nieuwe frame is onderzocht en vergeleken met het eerder gebruikte frame in **hoofdstuk 7**. De operatietijd voor plaatsing van het frame was significant (~20%) korter met het specifieke distractieframe en pengatinfecties kwamen minder vaak voor dan bij het eerder gebruikte frame (bij 2 *versus* 3 op 4 patiënten). Vragenlijsten beantwoord door patiënten lieten zien dat het nieuwe frame minder belastend was (gebruiksvriendelijker) in een aantal categorieën, waaronder verzorging van de pennen. Daarmee draagt het nieuwe distractieframe bij aan het verder toepassen van kniedistractie als behandeling.

Om de ervaring van patiënten tijdens kniedistractie verder te verbeteren en de behandeling minder belastend te maken, is in **hoofdstuk 8** het gebruik van een speciale zalf (cadexomeer-jodium) om pengatinfecties te verminderen tijdens behandeling geëvalueerd. Alle patiënten die behandeld zijn met kniedistractie kregen een wondverzorgingsprotocol, en bij een deel van de patiënten hoorde hier het gebruik van cadexomeer-jodium zalf bij. Patiënten die deze zalf niet gebruikten, ervaarden 2 keer zoveel pengatinfecties en 5 keer zoveel ernstige infecties die moesten worden behandeld met meer dan één standaard kuur orale antibiotica. Het gebruik van cadexomeer-jodium zalf zorgde dus voor een significante vermindering in pengat-gerelateerde klachten, wat resulteert in verminderde behandelingslast en verdere verbetering van patiëntvriendelijkheid. Het zou daarom onderdeel moeten zijn van het standaard behandelprotocol.

Een nieuwe prospectieve studie is gestart in verschillende ziekenhuizen en Nederland en België om de resultaten na kniedistractie met het gebruiksvriendelijke distractieframe te onderzoeken. In **hoofdstuk 9** is een tussentijdse analyse van de resultaten na 1 jaar follow-up in deze studie

beschreven. Klinische resultaten gerapporteerd door patiënten en de gewrichtsspleetafstand gemeten op röntgenfoto's lieten significante verbetering zien na behandeling. Ook waren ze grotendeels vergelijkbaar en niet ondergeschikt ten opzichte van resultaten van het eerder gebruikte frame. De selectie van patiënten leek wel wat veranderd, aangezien patiënten behandeld met het gebruiksvriendelijke distractieframe meer klachten en minder gewrichtsschade hadden dan patiënten uit de vorige studies bij aanvang van de onderzoeken. Desalniettemin zorgt kniedistractie met het specifieke distractieframe ook voor significante klinische verbetering in deze groep patiënten.

Deel II: Processen en werkingsmechanismen in het gewricht
Klinische studies waren in eerste instantie gericht op het verbeteren van klinische uitkomsten en het vergroten van de gewrichtsspleetafstand, aangezien dit duidt op kraakbeenherstel. De afgelopen jaren is er echter ook meer onderzoek gedaan naar de processen en werkingsmechanismen achter kniedistractie. Een algemeen beeld van kniedistractie wordt gegeven in **hoofdstuk 10**, dat een overzicht geeft van het huidige klinische bewijs zoals onderstreept in deel I van dit proefschrift en tevens verschillende concepten van mogelijke onderliggende processen bespreekt die deel II van dit proefschrift introduceren. Ondersteund door recente literatuur wordt beredeneerd wat er ten grondslag ligt aan het weefselherstel dat we zien na kniedistractie: een combinatie van gedeeltelijke mechanische ontlasting van het gewricht, wisselingen in de druk van de gewrichtsvloeistof, mechanische en biochemische veranderingen van het onder het kraakbeen gelegen bot, stamcellen afkomstig uit het gewricht en een veranderd moleculair gewrichtsmilieu.

Bij het evalueren van weefselveranderingen of processen in het gewricht tijdens en na behandeling worden vaak beeldvormende technieken gebruikt. Deze geven namelijk de mogelijkheid om veranderingen te monitoren zonder daadwerkelijk het gewricht binnen te dringen. Op röntgenfoto's kunnen typische kenmerken zoals de gewrichtsspleetafstand, grootte van osteofyten en de subchondrale botdichtheid worden geëvalueerd met een gestandaardiseerde meetmethode, zoals 'knee images digital analysis' (KIDA). In **hoofdstuk 11** wordt het gebruik van deze methode bij patiënten met ernstige knieartrose, die in aanmerking komen voor een chirurgische behandeling, geanalyseerd. De 'intraobserver' parameters waren goed, wat betekent dat er goede overeenkomst was tussen resultaten wanneer dezelfde röntgenfoto's twee keer werden geanalyseerd door dezelfde persoon. Dit was vooral het geval wanneer de foto's binnen een maand opnieuw werden geanalyseerd (in plaats van met enkele jaren na de eerste analyses). Voor de meeste parameters was het kleinst meetbare verschil tussen foto's vergelijkbaar met die gemeten bij patiënten met milde knieartrose. KIDA is daarom ook een bruikbare meetmethode bij patiënten met ernstige knieartrose. Het is wel belangrijk dat röntgenfoto's in een beperkt tijdsbestek worden geanalyseerd en idealiter in een wisselende (random) volgorde.

De bot tot bot gewrichtsspleetafstand gemeten op staande röntgenfoto's is een indirecte maat voor kraakbeenherstel, maar kraakbeendikte kan ook direct worden gemeten op MRI-scans. Een verschil is dat MRI-scans in een liggende onbelaste positie gemaakt worden, terwijl röntgenfoto's staand in een belaste positie gemaakt worden. Deze twee technieken hebben altijd een slechte overeenkomst (correlatie) laten zien wanneer de veranderingen over de tijd worden vergeleken. In **hoofdstuk 12** wordt bot op bot gewrichtsspleetafstand gemeten op CT-scans, waarbij het gewricht net als bij de MRI-scans niet belast wordt. Dit is gedaan om te onderzoeken of de slechte correlatie komt door het verschil in het belast *versus* onbelast maken van de scan, of door het verschil in meten van bot tot bot afstand *versus* daadwerkelijke kraakbeendikte. De resultaten lieten zien dat alleen de gewrichtsspleetafstand gemeten op CT en de kraakbeendikte gemeten op MRI significant correleren. Aangezien CT en MRI-scans allebei onbelast zijn gemaakt, maar de röntgenfoto niet, wijst dit erop dat het verschil in het belaste *versus* onbelast maken van scans de reden is waarom de metingen op röntgenfoto's en MRI-scans niet goed correleren en niet zozeer het meten van de bot tot bot afstand of de daadwerkelijke kraakbeendikte. Dit zou kunnen komen door de invloed van veerkracht van het kraakbeen (in plaats van alleen de dikte), maar er is meer onderzoek nodig om hier meer inzicht in te krijgen.

Het beloop van de kraakbeendikte tot 10 jaar na kniedistractie gemeten met MRI wordt beschreven in **hoofdstuk 13**, waarbij een driedimensionale aanpak is gebruikt om de kraakbeendikte door het hele gewricht te kunnen zien. Na 1 en 2 jaar was het kraakbeen in de meest aangedane delen van het gewricht (waar het kraakbeen voor behandeling het dunst was) significant dikker geworden. Mannen en patiënten met meer ernstige knieartrose lieten enigszins betere resultaten zien. Vanaf 5 jaar na behandeling werd het kraakbeen weer langzaam dunner, waarschijnlijk als gevolg van natuurlijke proces (progressie) van artrose. Zelfs 10 jaar na behandeling was er echter nog een toename in kraakbeendikte te zien, vooral in de minder aangedane delen van het gewricht. Een eerste 'boost' van kraakbeenweefselherstel in de eerste jaren na kniedistractie levert dus langdurig voordeel op.

Hierop volgend is de verandering in kraakbeendikte gemeten met MRI 2 jaar na kniedistractie vergeleken met de verandering na osteotomie, zoals te lezen in **hoofdstuk 14**. Patiënten met meer ernstige knieartrose lieten na behandeling met kniedistractie niet alleen een significante toename in kraakbeendikte zien, maar ook een vermindering in gebieden met blootliggend subchondraal bot. Dat wil zeggen dat het kraakbeen niet alleen dikker werd, maar er ook weer opnieuw kraakbeen te zien was in gebieden waar het voor behandeling helemaal verdwenen was. Bij patiënten met minder ernstige knieartrose was er geen significante verandering in kraakbeendikte te zien na behandeling met kniedistractie. Patiënten die behandeld waren met osteotomie lieten een verslechtering zien op MRI, waarbij de kraakbeendikte afnam en de gebieden met blootliggend bot toenamen. Bij patiënten met ernstige knieartrose lijkt kniedistractie dus effectiever in het herstellen van kraakbeendikte dan osteotomie.

Aangezien de dikte van het kraakbeen na behandeling veranderde, was de volgende stap het evalueren van de kwaliteit van het kraakbeen. Dit wordt in **hoofdstuk 15** gedaan met behulp van een speciale MRI-techniek genaamd T2-mapping, waarmee de collageenstructuur in het kraakbeen kan worden bepaald. Deze collageenstructuur is belangrijk voor het goed functioneren van het kraakbeen. Kniedistractiepatiënten waren gescheiden in indicatie 'knieprothese' of 'osteotomie': patiënten die in normale zorg behandeld zouden zijn met respectievelijk knieprothese of osteotomie, maar in plaats daarvan in onderzoekverband zijn behandeld met kniedistractie. In de 2 jaar na behandeling met zowel kniedistractie als osteotomie gingen de T2 relaxatietijden in het kraakbeen omhoog, wat kan duiden op verlies van integriteit of reorganisatie van de collageenstructuur. Bij patiënten met indicatie 'knieprothese' was deze toename beperkt tot het eerste jaar na behandeling met kniedistractie, waarna er weer een afname van het MRI-signaal (verbetering) te zien was. Bovendien lieten alleen deze zelfde patiënten een toename in kraakbeenvolume zien. De toename in T2 relaxatietijden zou daarom deels het gevolg kunnen zijn van de ontwikkeling (rijping) van het nieuwgevormde kraakbeen en reorganisatie van de collageenmatrix in het eerste jaar na behandeling met kniedistractie.

Er is verder gekeken dan alleen kraakbeenweefsel bij het onderzoeken van de werkingsmechanismen van kniedistractie. In **hoofdstuk 16** zijn biochemische markers in de synoviale vloeistof geanalyseerd voor, tijdens en na behandeling met kniedistractie. Er waren meetbare veranderingen te zien zowel in markers die geassocieerd zijn met herstel als markers die geassocieerd zijn met degeneratie, wat duidt op hermodellering. De verandering in sommige markers, zoals 'transforming growth factor-β1' (TGFβ-1), leek zelfs geassocieerd te zijn met door de patiënt gerapporteerde klinische resultaten in het jaar na de behandeling.

De markers die toenemen in de synoviale vloeistof tijdens kniedistractie, zoals TGFβ-1 en interleukin-6 (IL-6), kunnen gerelateerd zijn aan kraakbeenregeneratie, maar ook aan de vorming van osteofyten. Daarom is osteofytvorming na kniedistractie en osteotomie geanalyseerd op röntgenfoto's in **hoofdstuk 17**. In de 2 jaar na beide behandelingen was een significante toename van osteofyten te zien en die toename was groter dan bij patiënten met knieartrose die niet behandeld waren. De verhoogde osteofytgroei bij patiënten behandeld met kniedistractie leek gerelateerd te zijn aan veranderingen in TGFβ-1 maar niet aan veranderingen in IL-6. De verhoogde toename in osteofyten zou daarom een bijeffect kunnen zijn van de herstelactiviteit gerelateerd aan intra-articulaire factoren zoals TGFβ-1 en niet slechts een kenmerk van degeneratie van het gewricht, zoals vorming van osteofyten meestal gezien wordt.

Tot slot zijn botveranderingen na kniedistractie verder onderzocht met behulp van CT-scans in **hoofdstuk 18**. Twee kenmerken van het subchondrale bot zijn geëvalueerd: de dikte van de harde en compacte buitenste laag van het bot (het corticale bot) en de dichtheid van het meer poreuze bot daar direct onder (het trabeculair bot). Voor de behandeling was te zien dat de corticale dikte en trabeculaire dichtheid hoger waren in het meer aangedane deel van het

gewricht. Beide parameters leken af te nemen in het eerste jaar na de behandeling, vooral in de meer aangetaste delen, en deze verandering hield aan gedurende het tweede jaar. De algehele vorm van het bot veranderde ook: de twee bolvormige condylen aan het uiteinde van de femur (Figuur 1) werden meer convex (meer bol), terwijl de twee holle condylen aan het uiteinde van de tibia minder concaaf (minder hol) werden. Bij patiënten met knieartrose wordt vaak een tegenovergestelde verandering gezien. Deze veranderingen na kniedistractie, in de structuur en vorm van het bot, kunnen daarom duiden op een gedeeltelijke normalisatie van het door artrose aangetaste bot.

Conclusie

In dit proefschrift is een *stap voorwaarts* gezet met de klinische evaluatie van kniedistractie als behandeling voor relatief jonge patiënten met ernstige knieartrose en het beter begrijpen van de werkingsmechanismen achter deze behandeling. Kniedistractie kan zorgen voor langdurend klinisch profijt en kraakbeenregeneratie en een steeds meer patiëntvriendelijke implementatie in de reguliere zorg is mogelijk. De behandeling brengt een hermodellering teweeg waarbij het hele gewricht betrokken is. Veranderingen in bot, kraakbeen en synoviaal vocht worden gevolgd door algeheel herstel van het gewricht. Vervolgstudies zouden zich moeten focussen op een verdieping van het begrip van de mechanismen die door kniedistractie worden geïnduceerd, enerzijds om de selectie van patiënten voor deze behandeling te verbeteren en anderzijds om met deze kennis nieuwe behandeltechnieken te ontwikkelen. Deze unieke populatie, die een sterke structurele en klinische respons laat zien, kan worden gebruikt om het begrip van verschillende karakteristieken en herstelprocessen bij artrose te begrijpen en te gebruiken voor verbetering van behandeling. Het zou tevens kunnen bijdragen aan een beter inzicht in verschillende groepen artrosepatiënten, waardoor er in de toekomst een betere patiëntselectie gemaakt zou kunnen worden voor diverse behandelingen, en klinische studies beter ontworpen zouden kunnen worden gericht op de juiste behandeling voor de juiste patiëntengroep. Uiteraard vergt ook dit eerst weer *nieuwe stappen voorwaarts.*

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List of publications

M.P. Jansen, G.S. van der Weiden, P.M. van Roermund, R.J.H. Custers, S.C. Mastbergen, F.P.J.G. Lafeber. Initial tissue repair predicts long-term clinical success of knee joint distraction as treatment for knee osteoarthritis. Osteoarthritis and Cartilage. 2018;26(12):1604–8.

M.P. Jansen, N.J. Besselink, R.J. van Heerwaarden, R.J.H. Custers, P.J. Emans, S. Spruijt, S.C. Mastbergen, F.P.J.G. Lafeber. Knee joint distraction compared with high tibial osteotomy and total knee arthroplasty: Two-year clinical, radiographic, and biochemical marker outcomes of two randomized controlled trials. Cartilage. 2019;1947603519828432.

F.E. Watt, B. Hamid, C. Garriga, A. Judge, R. Hrusecka, R.J.H. Custers, **M.P. Jansen**, F.P.J.G. Lafeber, S.C. Mastbergen, T.L. Vincent. The molecular profile of synovial fluid changes upon joint distraction and is associated with clinical response in knee osteoarthritis. Osteoarthritis and Cartilage 2020;28(3):324–33.

M.P. Jansen, S.C. Mastbergen, R.J. van Heerwaarden, S. Spruijt, M.D. van Empelen, E.C. Kester, F.P.J.G. Lafeber, R.J.H. Custers. Knee joint distraction in regular care for treatment of knee osteoarthritis: A comparison with clinical trial data. PLOS ONE. 2020;15(1):e0227975.

E.M. van Helvoort, W.E. van Spil, **M.P. Jansen**, P.M.J. Welsing, M. Kloppenburg, M. Loef, F.J. Blanco, I.K. Haugen, F. Berenbaum, J. Bacardit, C.H. Ladel, J. Loughlin, A.C. Bay-Jensen, A. Mobasheri, J. Larkin, J. Boere, H.H. Weinans, A. Lallande, A.C.A. Marijnissen, F.P.J.G. Lafeber. Cohort profile: The Applied Public-Private Research enabling OsteoArthritis Clinical Headway (IMI-APPROACH) study: A 2-year, European, cohort study to describe, validate and predict phenotypes of osteoarthritis using clinical, imaging and biochemical markers. BMJ Open. 2020;10(7):e035101.

M.P. Jansen, T.A.E.J. Boymans, R.J.H. Custers, R.C.I. van Geenen, R.J. van Heerwaarden, M.R. Huizinga, J.M. Nellensteijn, R. Sollie, S. Spruijt, S.C. Mastbergen. Knee joint distraction as treatment for osteoarthritis results in clinical and structural benefit: A systematic review and meta-analysis of the limited number of studies and patients available. Cartilage. 2020;1947603520942945.

M.P. Jansen, N. van Egmond, E.C. Kester, S.C. Mastbergen, F.P.J.G. Lafeber, R.J.H. Custers. Reduction of pin tract infections during external fixation using cadexomer iodine. Journal of Experimental Orthopaedics. 2020;7:88.

A. Hoortje, P.F.M. Kuijer, K.L.M. Koenraadt, S. Waterval-Witjes, G.M.M.J. Kerkhoffs, S.C. Mastbergen, A.C.A. Marijnissen, **M.P. Jansen**, R.C.I. van Geenen. Return to sport and work after randomization for knee distraction versus high tibial osteotomy: Is there a difference? Journal of Knee Surgery. 2020.

M.P. Jansen, F.P.J.G. Lafeber. Letter to the Editor. Cartilage. 2020;1947603520966856.

M.P. Jansen, S. Maschek, R.J. van Heerwaarden, S.C. Mastbergen, W. Wirth, F.P.J.G. Lafeber, F. Eckstein. Changes in cartilage thickness and denuded bone area after knee joint distraction and high tibial osteotomy – Post-hoc analyses of two randomized controlled trials. Journal of Clinical Medicine. 2020;10(2):368.

M.P. Jansen, T. Struik, J. Jaspers, S.C. Mastbergen, R.J.H. Custers. User-friendliness of a novel dedicated knee joint distraction device: Experiences from clinical practice. Journal of Cartilage and Joint Preservation. 2021;0(0):100007.

M.P. Jansen, S.C. Mastbergen. Joint distraction for osteoarthritis: Clinical evidence and molecular mechanisms. Accepted for publication, Nature Reviews Rheumatology.

M.P. Jansen, P.M.J. Welsing, K.L. Vincken, S.C. Mastbergen. Performance of Knee Images Digital Analysis in advanced knee osteoarthritis. Conditionally accepted for publication, Osteoarthritis and Cartilage.

M.P. Jansen, S.C. Mastbergen, F. Eckstein, R.J. van Heerwaarden, S. Spruijt, F.P.J.G. Lafeber. Comparison between 2D radiographic weight-bearing joint space width and 3D MRI non-weight-bearing cartilage thickness measures in the knee using non-weight-bearing 2D and 3D CT as an intermediary. Conditionally accepted for publication, Therapeutic Advances in Chronic Disease.

M.P. Jansen, S.C. Mastbergen, T.D. Turmezei, F.P.J.G. Lafeber. Knee joint distraction results in MRI cartilage thickness increase up to ten years after treatment. Conditionally accepted for publication, Rheumatology.

M.P. Jansen, S.C. Mastbergen, W. Wirth, S. Spruijt, R.J.H. Custers, R.J. van Heerwaarden, F.P.J.G. Lafeber. Cartilage collagen structure upon knee joint distraction and high tibial osteotomy as measured with T2-mapping MRI. Under review, Journal of Orthopaedic Research.

M.P. Jansen, S.C. Mastbergen, F.E. Watt, E.J. Willemse, T.L. Vincent, S. Spruijt, P.J. Emans, R.J.H. Custers, R.J. van Heerwaarden, F.P.J.G. Lafeber. Cartilage repair activity during joint-preserving treatment may be accompanied by osteophyte formation. Under review, Scandinavian Journal of Rheumatology.

S. C. Mastbergen, A. Ooms, T.D. Turmezei, J.W. MacKay, R.J. van Heerwaarden, S. Spruijt, F.P.J.G. Lafeber, **M.P. Jansen**. Exploring subchondral bone changes measured with CT after joint distraction treatment for end stage knee osteoarthritis. Submitted for publication.

List of conference abstracts

Initial tissue repair predicts long-term clinical success of knee joint distraction as treatment for knee osteoarthritis (chapter 3).
Poster tour presentation at the ORS congress 2019; poster presentation at the EULAR congress 2018, ICRS congress 2018, ICRS focus meeting 2018, IWOAI congress 2018, NVR congress 2018, and OARSI congress 2018.

Knee joint distraction compared with high tibial osteotomy and total knee arthroplasty: Two-year clinical, radiographic, and biochemical marker outcomes of two randomized controlled trials (chapter 4).
Oral presentation at the EULAR congress 2018 and NVR congress 2018; poster presentation at the ICRS focus meeting 2018 and IWOAI congress 2018.

Knee joint distraction in regular care for treatment of knee osteoarthritis: A comparison with clinical trial data (chapter 6).
Oral presentation at the NOV congress 2019; poster presentation at the EULAR congress 2019, ICRS congress 2019, and OARSI congress 2019.

User-friendliness of a novel dedicated knee joint distraction device: Experiences from clinical practice (chapter 7).
Poster presentation at the EULAR congress 2020, ICRS congress 2019, and OARSI congress 2020.

Reduction of pin tract infections during external fixation using cadexomer iodine (chapter 8).
Oral presentation at the NOV congress 2020.

Knee joint distraction results in MRI cartilage thickness increase up to ten years after treatment (chapter 13).
Poster presentation at the OARSI congress 2021 and EULAR congress 2021.

Changes in cartilage thickness and denuded bone area after knee joint distraction and high tibial osteotomy: Post-hoc analyses of two randomized controlled trials (chapter 14).
Oral presentation at the EULAR congress 2020; poster presentation at the OARSI congress 2020.

The molecular profile of synovial fluid changes upon joint distraction and is associated with clinical response in knee osteoarthritis (chapter 16).
Poster presentation at the ORS congress 2019.

Cartilage repair activity during joint-preserving treatment may be accompanied by osteophyte formation (chapter 17).
Poster presentation at the EULAR congress 2020 and OARSI congress 2020.

Exploring subchondral bone changes measured with CT after joint distraction treatment for end stage knee osteoarthritis (chapter 18).
Oral presentation at the OARSI congress 2021; poster presentation at the EULAR congress 2021.

Visualizing cartilage and joint homeostasis changes after knee joint distraction using 7T MRI and synovial fluid aspirations.
Poster presentation at the ICRS focus meeting 2019.

Curriculum vitae

Mylène Paulien Jansen was born on May 10th 1992 in Zevenaar, The Netherlands. After attending secondary school at the Liemers College, from which she graduated *cum laude* in 2010, she moved to Enschede to study Technical Medicine at the University of Twente. During her bachelor she followed the extracurricular Excellence Stream, a mathematics program for which the best students of a number of technical studies are invited. She obtained her bachelor degree *cum laude* in 2013, after which spent a year as full-time board member of European student association AEGEE-Enschede as Secretary, Officer Internal Affairs & Officer European Affairs. She then started the master Technical Medicine, choosing the master track Medical Imaging and Interventions because of her particular interest in imaging techniques. As part of this track she obtained her certification to work with ionizing radiation (radiation safety level 3). During the master's program she did internships at the Medical Spectrum Twente, University Medical Center Utrecht, Radboud University, and Massachusetts General Hospital in Boston (US), all of which involved using medical imaging techniques to improve patient care. She performed her graduation research at the department of Rheumatology & Clinical Immunology at the University Medical Center Utrecht, aiming to develop a 3D joint space width measurement technique using CT scans of osteoarthritis patients. After graduating in September 2017, she immediately continued as a PhD candidate at this same department, under supervision of prof. dr. F.P.J.G. Lafeber, dr. S.C. Mastbergen, and dr. R.J.H. Custers. In 3.5 years, she predominantly researched knee joint distraction as a joint-preserving treatment for knee osteoarthritis, using various imaging techniques and personally collaborating with external research groups and (imaging) experts in the field, such as the universities of Oxford, Cambridge, East Anglia, and Salzburg. To further deepen her knowledge, she recently took a course 'Deep Learning for Medical Applications' at the University of Twente. Her work during these years thus far led to 9 peer reviewed publications, a letter to the editor, and an additional 7 manuscript submissions (all except 2 as first or last author) described in this thesis. Additionally, she contributed to work of colleagues in the field of osteoarthritis, as represented by a co-authorship. She intends to stay on as a postdoctoral researcher, to use the knowledge she gained in the past years to apply medical imaging techniques and keep researching joint repair and its relation with pain.