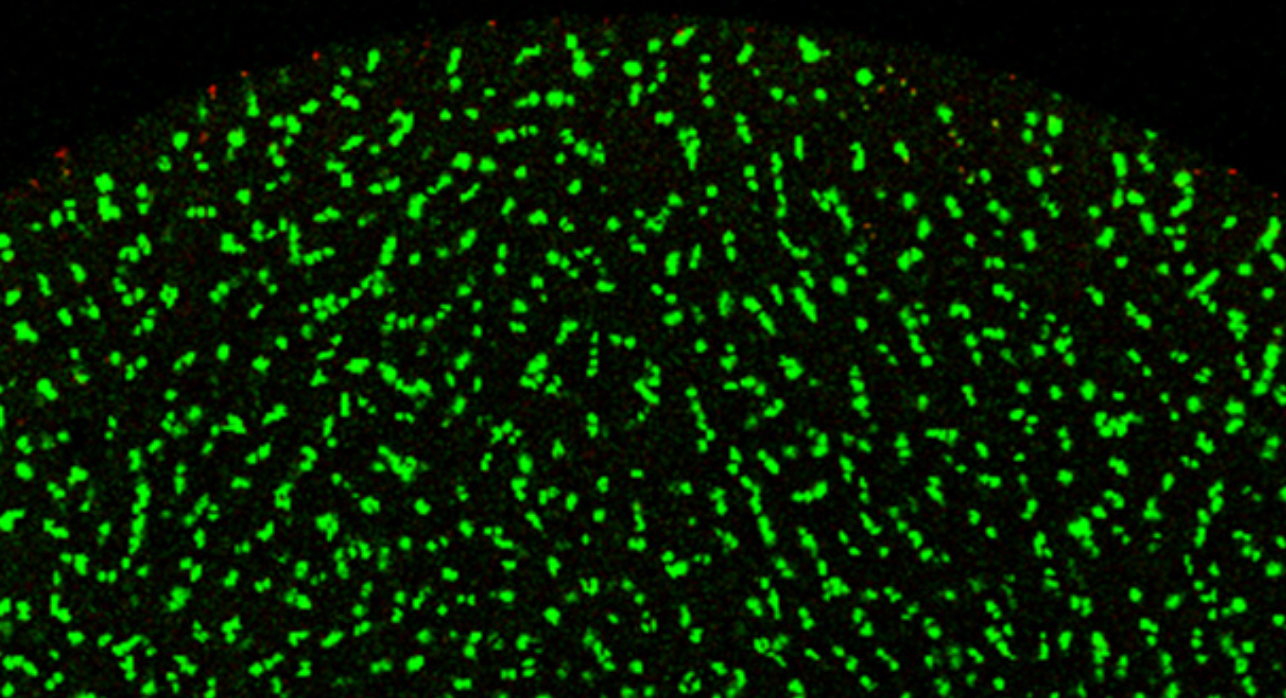
Repair not Replace:
Biologic Joint Preservation

Mario Hevesi MD



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“Repair not Replace: Biologic Joint Preservation”

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Chapter I:

General Introduction and Aims:

Hip and Knee Osteoarthritis: A Global Burden

Hip and knee osteoarthritis remains a central challenge of orthopedics, affecting more than 300 million patients worldwide.[73, 117] Osteoarthritis (OA) is characterized by progressive cartilage loss, osteophyte formation, and synovial inflammation which clinically manifests as pain, stiffness, and variable swelling.[43] It has been estimated that the direct medical costs of hip osteoarthritis alone in the United States are above $100 billion annually[299] with up to an additional $150 billion in indirect costs[45, 253]. The scale of OA's effect on society reaches proportions such that the World Health Organization labelled 2000 to 2010 the "Bone and Joint Decade" and continues to consider musculoskeletal conditions as the major burden on individuals, health, and social care systems.[423]

Currently recommended treatments for hip and knee OA focus on symptom relief and include activity modification, weight control, and intra-articular corticosteroid injections.[43] Unfortunately, many patients fail to achieve adequate symptom control and arthroplasty remains the only definitive treatment option for refractory, disabling OA. In 2009, over 900,000 knee and hip replacements were performed in the United States, amounting to over $42 billion in arthroplasty costs alone.[291] These impacts continue to grow, with a projected 174% increase in hip and 673% increase in total knee arthroplasty between 2005 and 2030.[225, 226, 260, 417] Consequently, the rate and burden of revision hip and knee arthroplasty continues to rise. [11, 225] Of note, in contrast to primary arthroplasty which is often considered highly efficacious, revision arthroplasty has generally experienced more guarded outcomes.[258]

Given the unacceptably high global societal burdens of osteoarthritis, we have made it the goals of this thesis to provide tools for clinical cartilage assessment and decision making, to optimize and expand available allografts for osteochondral defects, and to assess the efficacy of modern and evolving interventions in hip and knee preservation.

Biologic Preservation

A preservative and restorative approach to hip and knee cartilage defects is attractive, especially given that [structural] articular cartilage restoration has demonstrated effectiveness in reducing pain and functional disability [285]. A variety of surgical options are available to treat

cartilage lesions and these include microfracture, osteochondral allograft transplantation (OCA), and cell therapies.

Following the introduction of microfracture by Steadman in the 1990s, large increases in knee microfracture volume were observed, with this technique becoming one of the most common reparative orthopedic procedures performed in the United States.[99, 277, 380] Although this technique remains popular to date, its structural utility and durability has been limited, given the form of its regenerate which manifests as a fibrocartilage scar.

Osteochondral Allograft Transplantation

First described as early as 1908, OCA has become the gold standard for the treatment of cartilage defects greater than 2 cm^2, with well-established safety, efficacy, and durability.[244, 273, 300, 334] The use of osteochondral tissue allows for the simultaneous transplantation of cartilage and underlying bone, enabling clinicians to address pathology extending beyond the subchondral plate and providing true, structural repair.

With the emergence of uniform cartilage banking and testing protocols embodied in part by the 2004 adoption of United States Pharmacopeia (USP) <71>, OCA tissues were stored at 4°C for a minimum of 14 days and up to 28 - 35 days prior to implantation.[399] Subsequently, it has been well-demonstrated that cellular demise, driven by apoptosis and cellular-stress at sub-physiologic temperature, significantly deteriorates allograft viability and quality, even within the first 14 days of storage.[248, 284, 382] Alternative storage methods at room temperature (22 – 25° C) and 37° C have subsequently been proposed and demonstrated to be superior to refrigerated storage, as is current clinical practice.[146, 381]

The central limitations of increasing clinical implementation of OCA are two-fold: 1) cartilage viability, which has been linked to outcome, has been shown to decrease in storage over time and 2) allografts are currently obtained from young deceased donors, leading to a lack of scalability of this efficacious resource. In addition to the inherent limitations of allografts obtained from deceased donors, the unexpected passing of donors adds an additional layer of logistical complexity for scheduling OCA transplantation. Due to the critical role that OCA transplantation plays in the structural treatment of osteochondral defects, research that can

both optimize and expand this precious resource is needed to assist in articular surface restoration and joint preservation for patients with deep-seated defects.

Emerging Cell-Based Interventions

In addition to established therapeutics such as OCA, the technovolution of the cartilage surgeon's toolkit have opened the door to single-stage procedures as well as the implementation / combination of mesenchymal stem/stromal cell (MSC)-based interventions for structural cartilage defects.[95, 103, 112, 113, 136, 206, 269, 327, 350, 419, 427]

Adipose-Derived Mesenchymal Stem Cell Therapy

In recent years, multiple investigations have demonstrated the potential therapeutic effects of MSCs due to their anti-inflammatory, immunomodulatory, and anti-apoptotic effects, as well as their potential to regenerate cartilage.[95, 103, 136, 206, 269, 327, 350, 419, 427] Preliminary investigations from other countries have reported on the safety and efficacy of single applications of AMSCs for joint disorders including arthritis.[95, 200, 327, 430] However, no currently published United States study has documented the safety of a single, culture expanded AMSC injection to treat hip OA. Given the anti-inflammatory and potential regenerative effects of MSCs, we believe that injection treatment with autologous, culture expanded AMSCs are feasible in patients with symptomatic hip OA, and would offer a potential therapeutic option for patients with refractory OA symptoms. Furthermore, this option would provide a substantially larger dose of MSCs, as compared to point-of-care based solutions such as that provided by bone marrow aspirate, in which approximately stem cells make up approximately 1 in 10,000 – 15,000 cells.[293]

Therefore, we have proposed, submitted, and begun enrollment for a Phase I clinical trial of culture-expanded AMSCs to be delivered in an intraarticular fashion into the hip, as outlined in *Part IV* of the presented thesis. In addition to this trial, the processes involved in stem cell acquiry, expansion, and banking have made it possible to source allogeneic AMSCs for combination therapeutics, such as that employed in subsequent ongoing single-stage focal cartilage defect regeneration efforts.

Single-Stage Cartilage Repair

ACI has demonstrated superior clinical outcomes and better structural repair compared to scar formation after microfracture. However, there are disadvantages of ACI, including the need for two-stage surgery with *ex vivo* expansion of chondrocytes. Successful cartilage repair requires an abundance of cells, growth factors, and intricate modulation of cellular processes. The combination of chondrocytes with other cell types has recently gained attention as others showed that cells respond to their environment and can be positively influenced by the presence of other cell types.

Based on previous data from the IMPACT trial[112, 113], a combined AMSC and chondron product has the potential to provide single-stage treatment of focal cartilage defects which is safe, efficacious, and furthermore, can be accomplished using expandable, characterized, and banked allogeneic AMSCs. Therefore, we have also proposed, submitted, and begun treatment for a Phase I clinical trial of human, autologous chondrocytes with their pericellular matrix (chondrons) combined with allogeneic AMSCs in a fibrin glue carrier, as presented in *Part IV* of this thesis. Using this combination of cells, the created investigational new drug has the potential to provide both the orchestrators of structural cartilage regeneration (AMSCs) as well as the chondrons necessary to regenerate the area left by focal defects.

Thesis Aims

The aim of this thesis is to 1) illustrate the critical need for hip and knee preservation, 2) provide prognostic tools for cartilage assessment to help clinical decision making, 3) optimize and expand available allografts for articular osteochondral defects, and 4) to assess the clinical efficacy of current modern interventions in hip and knee preservation and establish novel therapeutics with Phase I clinical trials in articular preservation of the hip and knee.

The following specific aims were defined in the structure of this thesis:

Part I:	Cost Modelling of Hip and Knee Preservation Durability and Efficacy
Part II:	Pre-Operative Assessment of Cartilage Damage
Part III:	Optimization of Osteochondral Tissues for Transplantation
Part IV:	Modernizing Interventions & Outcomes of Hip and Knee Preservation

These aims have been chosen given the substantial global burden represented by intra-articular hip and knee pathology as well as resultant osteoarthritis. In addressing these aims, we hope to achieve better patient care, in order to promote health, mobility, and quality of life. The thesis presented represents the culmination of years of direct laboratory and clinical research, with translational effects from bench-side to the clinic and operating room. The works presented are based upon the tireless work of countless previous researchers and ongoing collaborators, including the IMPACT team in the Netherlands and the unique standing of the Mayo Clinic as a high-volume hip and knee center, with the final remaining public bone bank [and source of osteochondral tissues] in North America. We have truly stood on the shoulders of giants.

Chapter II:

Why Pursue Biologic Preservation? Cost Modeling of Hip and Knee Preservation Durability and Efficacy

Reoperation, Revision, and Repeat Revision Rates and the Potential Cost-Utility of Knee Preservation in Young Total Knee Arthroplasty Patients

Hevesi M, Wyles CC, Sierra RJ, Trousdale RT, Habermann EB, Maradit-Kremers H, Krych AJ, Saris DBF.

Introduction:

Osteoarthritis remains a central challenge of orthopedics, affecting more than 1 in 4 American adults and more than 300 million patients worldwide.[73, 117] Osteoarthritis (OA) is characterized by progressive cartilage loss, osteophyte formation, subchondral bone remodeling, and synovial inflammation which clinically manifests as pain, stiffness, motion restriction, and variable swelling.[43] In the United States, OA has been estimated to affect an estimated 27 million individuals.[43, 123, 239]

Currently recommended treatments for knee OA focus extensively on symptom relief and include activity modification, therapeutic exercise, weight control, analgesic and/or anti-inflammatory medications, and intra-articular corticosteroid injections.[43] Unfortunately, many patients fail to achieve adequate symptom control with currently available treatments and total joint replacement remains the only definitive treatment option for refractory, disabling OA. In 2009, over 900,000 knee and hip replacements were performed in the United States, amounting to over $42 billion in arthroplasty costs alone.[291] These impacts continue to grow, with the rate of joint replacement rising by an estimated 11% annually and a projected 673% increase in total knee arthroplasty between 2005 and 2030.[225, 226, 260, 417] Consequently, the rate and burden of revision knee arthroplasty continues to rise, with revision knee arthroplasty growth rates projected to be 601% during the same time frame. [11, 225] Considering the vast financial costs and morbidity of arthroplasty and revision arthroplasty, other preservative interventions for OA are continuously being evaluated for both subjective and societal cost efficacy.

In parallel, while it has been proposed that modern implants will outlast primary total knee arthroplasties (TKAs) from previous generations, there is growing concern that TKA in young patients may lead to early failure, revision, subsequent repeat revisions, and increased medical costs. This is an increasing challenge given that the average age of TKA patients

continues to decrease while biomechanical risk factors for failure such as BMI continue to increase.[370, 407]

Therefore, the purpose of this study was to 1) describe the natural history of primary TKAs by patient age including reoperation and serial revision rates, and 2) explore the potential cost-utility of knee preservation interventions.

Methods:

Study Population:

An institutional total joint registry was reviewed for all primary TKAs performed between 1985 and 2015 for degenerative joint disease, excluding post-traumatic, neoplastic, and inflammatory indications. A total of 24,094 patient records were reviewed, and 23,173 (96.2%) met inclusion criteria. All included patients had ≥2 years follow-up, with a mean follow-up of 8.9 years (range: 2.0 – 32.2 years). One patient <30 (age 27), 36 patients aged 30 – 39, and 468 patients aged 40 – 49 years underwent TKA (Figure 1). At final follow-up, 9,418 (40.6%) patients were deceased.

Cost Calculations:

Cost is an increasingly important factor in patient care, reimbursement, and sustainable healthcare access. To analyze modern revision costs, line-itemized costs for all first-time revisions performed at our institution from 2009 to 2015 were obtained and categorized by indication to calculate the costs incurred due to TKA failure over time and the potential cost-utility of interventions delaying primary TKA in young patients. Cost data was obtained from the Mayo Clinic Cost Data Warehouse using line-item details for every service or procedure billed to patients undergoing revision at our institution in the modern era between 2009 and 2015[404]. In total, we analyzed the line-item costs for 1,542 rTKAs including 266 two-stage revisions, 74 rTKA for fracture, 586 for wear/loosening, and 366 for instability. Recognizing discrepancies between billed charges and true resource use, bottom-up microcosting valuation techniques were employed to generate standardized inflation-adjusted cost estimates[189, 241, 262].

Statistical Methods:

Descriptive statistics were used to present demographic data with means, standard deviations, and percentages, as appropriate. Fisher's exact test was employed for proportions

and Mann-Whitney-U testing was used for nominal values. Survivorship was investigated using Kaplan-Meier analysis for survival free of PJI. Statistical analyses were performed using SAS Version 9.4 (SAS Institute, Inc, Cary, NC, USA) and R Version 3.4.3 (R Core Team, Vienna, Austria).

Results:

Reoperation occurred in 2,417 (10.4%) patients and differed significantly by patient age, with younger patients having higher reoperation rates as compared to older patients. The 5-, 10- and 20-year survival free of reoperation for patients aged 30 – 39 was 86.5%, 77.8%, and 38.4% compared to 84.3%, 74.5%, and 53.2% for patients aged 40 – 49 and 94.6%, 92.4%, and 88.3% for patients aged 70 – 79, respectively ($p < 0.01$).
First- and second-time revision rates were significantly higher in younger patients (Figure 2, $p < 0.01$). 1,357 (5.9%) patients underwent one revision (13.6% septic; 86.3% aseptic [15.3% fracture, 15.5% instability, 59.3% wear/loosening, 9.9% other]), 63 patients (0.3%) underwent a second revision (10.0% septic; 90.0% aseptic [22.2% fracture, 13.3% instability, 55.6% wear/loosening, 8.9% other]), and one patient underwent a third revision (septic).

Revision two-stage exchange TKA for septic indications averaged $52,608 per patient and aseptic revision TKA averaged $32,214 for fracture, $24,807 for wear/loosening, and $21,995 for instability. Based on the observed cost and revision rates, the average direct costs incurred in the first 20 years of follow-up for any given patient aged <39 years at the time of primary TKA was $14,469, in addition to the cost of primary arthroplasty. A potential for large first- and second-time revision cost savings was observed within a 20-year management window for interventions delaying primary TKA by 5-, 10- or 20 years in patients aged under 39 years ($5,454, $9,467, and $14,469 saved, respectively) and patients aged 40 – 49 ($3,165, $6,258, and $9,969, respectively) (Figure 3, $p < 0.01$).

Discussion:

This study demonstrates that even when analyzing only direct in-hospital costs, patients under 39 years of age undergoing primary TKA generate substantial costs within the first 20-years of post-operative management, not including the initial cost of arthroplasty. Furthermore, societal costs of early TKA are likely even greater when accounting for indirect

costs and subsequent revisions occurring outside of the analyzed timeframe. Given the growing availability of knee preservation interventions, cost, quality of life, and function analyses are necessary to evaluate the utility of knee preservation procedures in comparison to TKA for young patients. This paper provides one of the first analyses of the natural history of patients undergoing TKA below the age of 50, a growing population which are likely to play an increasing role the societal cost of knee arthritis.[359, 370]

There are documented and increased efforts to expand the efficacy of knee preservation, especially in young and active patients. Such therapies range from biologic interventions such as platelet rich plasma (PRP), stem cell injections, to surgical interventions such as proximal tibial osteotomy, osteochondral allograft transplantation, and implanted compartmental unloading devices.[75, 181, 215, 254] Given the significant costs associated with these interventions, and the evolving understanding of the role of biologics in knee preservation efficacy and safety, benchmarks must exist in determining the societal value and acceptable cost for these modalities.

The average direct revision costs of $14,000 associated with primary TKA in patients under 39 years of age is clinically significant, as is the low survival free of repeat surgery, observed to be only 38% in this cohort at 20 years. These values highlight the need for non-arthroplasty interventions for young patients with knee osteoarthritis. However, biologic interventions such as stem cell therapy and PRP have come under increasing scrutiny as their often high costs are evaluated in light of mixed results in terms of efficacy.[279, 400] As such, there is significant value in creating benchmarks for acceptable costs on an efficacy basis in terms of years during which patients reach an acceptable symptom states prior to TKA. Small improvements may be justified in the setting of small costs, however, for therapies to warrant significant financial investment, patients must gain either significant or lasting improvements, ideally both. Therefore, cost over time analyses, such as those presented in this manuscript, provide substantial potential benefit in evaluating knee preservation therapies.

This study is not without important limitations. First, the costs analyzed represent the average revision costs sustained in the first 20 years following primary TKA. Young patients undergoing TKA, such as those 39 years of age or under, are likely to have patient and implant lifetimes which far exceed the first two decades following arthroplasty and therefore, the lifetime costs of TKA are likely even higher than presented. Furthermore, while it is a distinct

strength of this analysis that we analyzed line-item costs at the individual level using our costing warehouse, the indirect costs sustained by patients represent further factors to be included in additional analyses. Finally, our study also contains biases inherent to a retrospective review, namely reliance of accurate and complete recordkeeping.

Conclusion:

Young primary TKA patients demonstrate significantly higher rates of reoperation and serial revision, with reoperation rates of up to 62% at 20 years following primary TKA and an average of over $14,000 in associated costs. These findings underscore the potential value and cost savings of arthroplasty-delaying interventions and serves as a baseline comparison for evaluating the societal utility of knee preservation interventions and procedures.

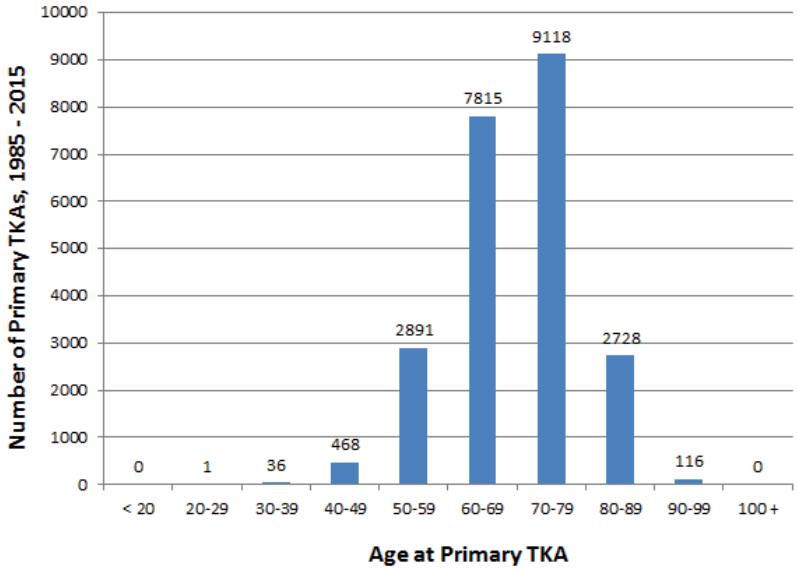

Figure 1: Institutional age distribution of primary TKA, 1985 – 2015.

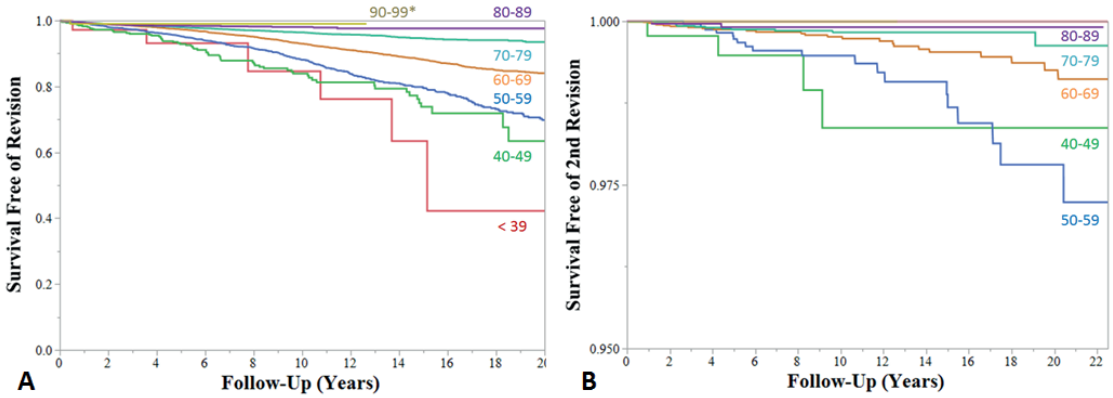

Figure 2: Index revision (A) and first re-revision (B) rates over time following primary TKA grouped by patient age in years.

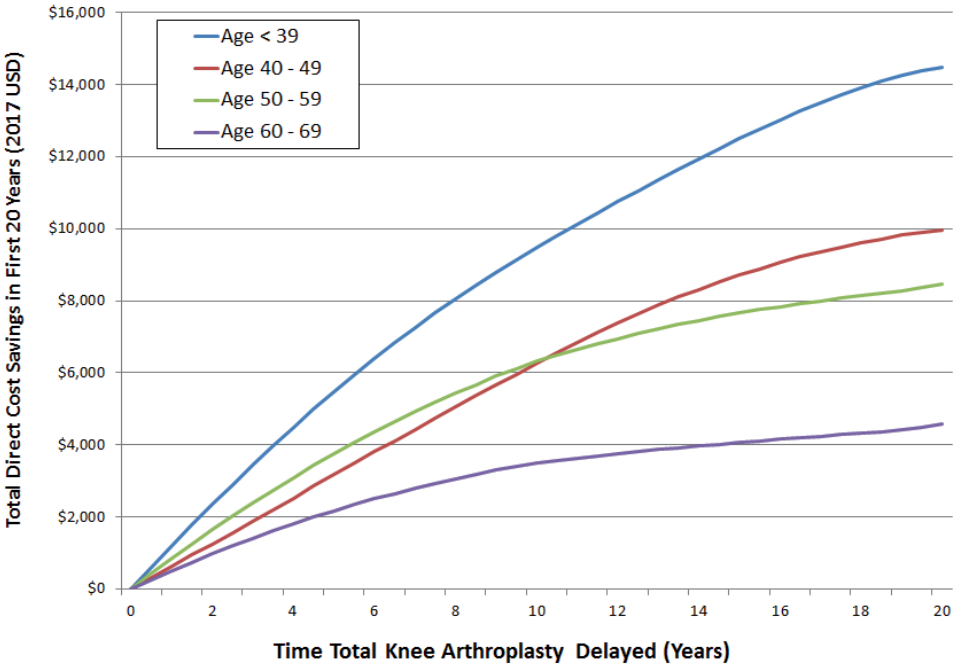

Figure 3: Direct in-hospital cost savings from first and second revision surgery prevention over the first 20 years based on age and years primary total knee arthroplasty is delayed.

Long-Term Mortality Trends after Revision Total Knee Arthroplasty

Yao JJ, **Hevesi M**, O'Byrne MM, Berry DJ, Maradit-Kremers H.

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Introduction

While the beneficial effects of total knee arthroplasty (TKA) on patients' symptoms and function are well recognized, long-term mortality trends remain unclear. Primary TKA patients have a survival advantage relative to the general population, particularly during the first decade following surgery [191-193, 261, 283, 287, 310, 341, 405]. This finding has been attributed to a "healthy-patient" selection bias, i.e., patients with severe comorbidities and the highest operative risk do not undergo TKA [193, 250, 287, 405]. Furthermore, better access to healthcare and other factors may also contribute to a higher overall health [50, 126, 405]. Despite the early survival advantage from selection bias, mortality following primary TKA consistently converges towards the general population mortality rates over time [193, 261, 341, 405]. In fact, while the survival advantage for TKA patients during the first decade is quite robust; there is evidence to suggest that the mortality risk is increased in later decades compared to the general population [261, 341, 405]. The reasons for this mortality shift are unclear; however comorbidities, decreased functional status, and/or increased proportion of younger patients at later follow-up may all contribute [250, 261, 341, 405].

Over time, some patients require revision TKA, and revision surgeries may potentially contribute to the mortality shift in TKA patients. Yet, there are no long-term mortality studies following revision TKA. Short- and mid-term mortality studies have found that revision TKA patients may be at an elevated risk of mortality, especially those with septic indications [83, 255]. For instance, over a median 4 years follow-up of 88 septic and 88 aseptic revision TKA patients, mortality after septic revision was six-fold higher than that of aseptic revision (18% versus 3%) [83]. It is unknown whether other surgical indications for revision TKA also affect long-term mortality risk. Therefore, the aims of this study were (a) to characterize long-term mortality risk according to surgical indications, (b) to characterize long-term mortality trends by age at surgery, years since surgery, and calendar year of surgery, and (c) compare long-term mortality risk following primary versus revision TKA. Our hypothesis was that mortality rates would differ by surgical indications with highest rates among patients with infections and fractures.

Methods

Following institutional review board approval, we performed a retrospective cohort study of patients who underwent revision TKA between January 1985 and December 2015 at a large tertiary care center in the United States. A total of 280 (5%) patients who had declined research authorization for use of their medical records in research were excluded from the study. The final study cohort comprised 4907 patients (Table 1). The revision TKAs included both first time and subsequent revisions. Of the 4907 patients, 3938 (80%) had only one revision TKA at our institution. The remaining 969 patients had two or more revision TKA, irrespective of laterality (i.e., 739 had two, 152 had three, 48 had four, 14 had five and 16 had six or more revision TKAs).

Clinical, demographic, and surgical indication data were obtained from the institutional total joint registry and the medical records. Comorbidities were ascertained for each patient at the time of revision surgery using an electronic adaptation of the comorbidity index developed by Charlson et al [80], similar to that used by Deyo et al [116]. Although the Charlson comorbidity index was not in use in earlier portions of our study, our institution has a long history of coding diagnoses starting with in-house Berkson codes between 1966-1975 and Hospital Adaptation of the International Classification of Diseases codes between 1976-2010. Between 1966 and 2010, codes were assigned manually by trained nosologists through manual review of medical records. Billing data based ICD-9 coding started in 1995. Therefore, existing institutional research infrastructure allowed us to classify comorbidities according to the Charlson comorbidity index.

As the outcome of interest was mortality, patients with multiple revised TKA (irrespective of laterality) were counted only once. This was done in an effort to avoid immortal time bias, i.e., the time between the first and second revision TKA is called immortal time because the patient must remain alive after the first revision TKA in order to subsequently receive a second revision TKA. Excluding or misclassifying the time between first and second revision surgeries will result in immortal time bias. Therefore, patients with multiple revisions and/or multiple surgical indications were assigned to a hierarchical single category. Patients with prosthetic joint infections were classified as such, regardless of other revision TKA procedures for other surgical indications. Patients with fractures were classified as fracture

patients unless they had a revision for prosthetic joint infections. Patients with instability were classified as instability patients unless they had a revision for prosthetic joint infections or fracture. Patients with aseptic loosening and/or bearing wear were classified as such unless they had a revision for prosthetic joint infections, fracture, or instability. Patients were classified as "other" if they did not fit any of the above surgical indication categories. This classification resulted in a cohort of 4907 revision TKA patients grouped by surgical indication into 5 categories: 1370 (28%) for prosthetic joint infections, 399 (8%) for fracture, 1740 (35%) for aseptic loosening and/or bearing wear, 990 (20%) for instability, and 408 (9%) for other indications. The mean age in the entire cohort was 68.0 ± 11.2 years and 47% were males (Table 1). The mean severity-weighted sum of Charlson score at the time of surgery was highest (mean 1.4) in the infection group followed by fracture group (mean 1.1). Patients with periprosthetic joint infections had significantly higher prevalence of myocardial infarction, congestive heart failure, peripheral vascular disease, cerebrovascular disease, chronic pulmonary disease, ulcer, liver disease, diabetes without organ damage, moderate/severe renal disease, and non-metastatic cancer.

All patients were followed at regular intervals at least twice in the first postoperative year, at two, five, seven and ten years, and at five-year intervals thereafter until death or October 2, 2017. Deaths were recorded irrespective of joint-specific registry follow-up. Mean follow-up of the entire cohort was 9.5 years (range, 1 day-31 years). At the time of the study, 1994 (41%) individuals were known to have been deceased and 2913 (59%) were still alive at last follow-up.

Statistical Analyses and Standardized Mortality Ratios

Statistical analyses were performed both for the revision TKA cohort as a whole and also for each separate surgical indication category. Mortality rates were evaluated using a person-years approach, in which the observed number of deaths in the revision TKA cohort was compared with the expected number of deaths over the follow-up period. This approach was similarly applied within the surgical indication categories. The life tables for the US total population were used to generate expected survival rates [17]. Results are reported as standardized mortality ratios (SMR) with 95% confidence intervals calculated assuming expected mortality rates were fixed and that observed deaths followed a Poisson distribution. In the calculations of the standardized mortality ratios (SMR) for temporal trends, only events and

person-years of exposure during the follow-up time window of interest were considered. Poisson regression models were used to model relative mortality by age, time since surgery and calendar year of surgery. Multivariable Cox proportional hazards regression was used to evaluate the association of survival and potential risk factors, including the number of revision surgeries. Another set of analyses involved comparison of mortality rates in this cohort with 2259 primary TKA patients, as included in our previous study[261]. We used age-, sex- and calendar-year adjusted regression models to compare mortality rates following primary and revision TKA. All analyses were performed using SAS version 9.4 (SAS Institute, Inc., Cary, NC) and R version 3.2.0 (R Core Team, R Foundation for Statistical Computing, Vienna, Austria, 2015).

Results

The 10-year mortality rate was 47% (95% CI: 43%, 51%) in the prosthetic joint infection group, 46% (95% CI: 40%, 52%) in the fracture group, 34% (95% CI: 32%, 37%) in the aseptic loosening and/or wear group and 31% (95% CI: 27%, 35%) in the instability group (Table 2). In age, sex, and calendar year adjusted models, the overall mortality rate of revision TKA patients was worse than that of comparable individuals in the general population (SMR 1.08, 95% CI: 1.03, 1.13, p <0.001; Table 3).There were notable differences across the 5 surgical indication subcategories. Consequently, the relative mortality rate was significantly higher than the general population among patients undergoing revision TKA for prosthetic joint infection (SMR: 1.45, 95% CI: 1.33, 1.57, p<0.001) and fracture (SMR: 1.16, 95% CI: 1.00, 1.34, p=0.04). The relative mortality for patients undergoing revision TKA for aseptic loosening and/or wear (SMR: 0.95, 95% CI: 0.89, 1.02, p=0.16), instability (SMR: 1.00, 95% CI: 0.89, 1.13, p=0.95) or other indications (SMR: 0.93, 95% CI: 0.77, 1.12, p=0.50) was comparable to that of the general population.

Relative Mortality Trends

Observed and expected survival trends by surgical indications revealed that revision TKA patients with prosthetic joint infections experienced excess mortality soon after surgery which continued to worsen over the next 10-15 years (Figure 1A). Excess mortality among revision TKA patients with fractures exhibited beyond 6-7 years after surgery (Figure 1B). In contrast, revision TKA patients with aseptic loosening and/or wear (Figure 1C) and instability

(Figure 1D) had decreased mortality early on which eventually shifted to excess mortality during long-term follow-up. Among patients who underwent revision TKA for aseptic loosening and/or wear, there was a shift to excess mortality beyond 11-12 years as evidenced by the shaded confidence intervals separating from the dotted expected line (Figure 1C). The SMR was 0.41 (95% CI 0.27, 0.60) within the first year, 0.55 (95% CI 0.47, 0.63) by 5 years and 0.73 (95% CI 0.67, 0.80) by 10 years after surgery. Among patients who underwent revision TKA for instability, there was a shift to excess mortality beyond 5- 6 years (Figure 1D).

We further examined relative mortality trends for each of the indications by age at surgery (Figure 2) and calendar year of surgery (Figure 3). In all indications, the relative mortality rates were highest in younger age groups until approximately 60 years of age and declined with increasing age at surgery (Figure 2). The relative mortality rates according to calendar year of surgery also differed across the groups (Figure 3). Most notably, the relative mortality rate in the aseptic loosening revision group showed almost a linear decline with time, indicating steady mortality improvements over time since 1980's and 1990's. We did not observe a similar improvement in mortality for the other two groups. The relative mortality in the fracture and infection groups appear relatively flat ($p<0.05$) indicating no notable mortality improvements over time. In terms of comorbidities, we did not observe any significant temporal trends among patients undergoing surgery for loosening/wear but patients who underwent revisions for fractures and infections in the last decade had a higher comorbidity burden than the previous decades.

We also examined number of revisions as a potential predictor of mortality. We observed a significant 10% increased hazard for each additional surgery in an age, sex and calendar year adjusted Cox model ($p=0.004$). Yet, this finding was no longer significant (HR 1.04, 95% CI: 0.97, 1.11, $p=0.24$) upon further adjustment for surgical indications and comorbidities, suggesting that the indication is a more significant predictor of mortality than the number of revisions.

Mortality Rates in Revision TKA compared with Primary TKA

In comparison to primary TKA, the overall mortality risk of revision TKA patients was significantly worse than that of primary TKA patients (Risk ratio 1.42, 95% CI: 1.32, 1.53). The

mortality risk among patients who undergoing revision TKA for aseptic loosening and/or wear was similarly worse than that of primary TKA patients. (Risk ratio 1.24, 95% CI: 1.13, 1.36).

Discussion

We investigated long-term mortality trends in a cohort of 4907 revision TKA patients over a mean follow-up of 9.5 years. The only group of patients who experienced about a decade long survival advantage are patients who underwent revision TKA for aseptic loosening and/or wear. Secular trends in this group are also encouraging with steady declines in mortality in recent years. In contrast, the overall mortality risk was particularly high among those with prosthetic joint infections and fractures as the underlying surgical indications with no notable improvements over time.

The reasons for the excess mortality following revision TKA are unknown, but may potentially include comorbidities and other common risk factors. For instance, obesity, diabetes mellitus, cardiovascular disorders, depression, and substance abuse not only increase the risk of prosthetic joint infections [224], they may increase the mortality risk in these patients (i.e., shared risk factors). Similarly, periprosthetic and implant fracture in TKA patients are associated with conditions such as inflammatory arthritis or chronic steroid use which are both associated with excess mortality risk [428]. These previously described risk factors, in concordance with our comorbidity analyses, confirm a higher comorbidity burden in patients with fracture and periprosthetic joint infections. In contrast, aseptic loosening and/or wear patients had lower comorbidity scores and had an equivocal overall risk of mortality compared to the general population. Consequently, part of the excess mortality observed in revision TKA patients with periprosthetic joint infections and fractures is potentially attributable to the overall health rather than the surgery itself.

Further examination of secular trends revealed steady improvements in mortality among patients with aseptic indications. This has also been previously described in other mortality studies of primary TKA patients [341]. Patients receiving revision TKA for aseptic loosening and wear showed a survival advantage after revision TKA for the first ten years after surgery. However, after ten years, the mortality risk for aseptic loosening and wear revision TKA patients was greater than the general population. As previously discussed, a similar effect has been observed in primary TKA populations and has been primarily attributed to selection

bias (i.e. a "healthy patient effect"). It is possible that a similar bias is present in selection of patients for aseptic loosening and wear-related revisions. While periprosthetic joint infection and fracture are emergent conditions, aseptic loosening and wear can be managed conservatively. Future investigation is necessary to determine whether selection bias or other factors such as functional status, mobility, or prosthesis related contribute to the shift to excess mortality at ten years seen in aseptic loosening and wear patients.

Our study findings need to be interpreted in light of a number of potential limitations. Firstly, the study cohort was assembled retrospectively at a single, tertiary care institution. Therefore, the findings may not be representative of all revision TKA patients due to differences in ethnicity, socioeconomic status, comorbidity frequencies and health care access. Although the case-mix of the revision TKA cohort may not be representative of other institutions, comparisons across groups are still valid. Secondly, as in many revision TKA outcome studies, classification of patients by surgical indications was challenging due to multiple revisions for multiple indications. Although we were able to account for multiple revision procedures at our institution, it was not possible to track all revision procedures at other institutions, either before or after the revision TKA at our institution. As our registry is a joint-specific implant based registry, the total lifetime number of revisions is not comprehensively documented. Therefore, the lack of a significant association with the number of revisions in this cohort should be interpreted with caution. Thirdly, the data presented in this study should not be necessarily viewed as predictive. While comorbidity and surgical indication data are presented, the primary goal of this epidemiologic study was to characterize mortality trends and identify potential etiological clues. Further study is needed to identify comorbidities and other risk factors as etiologically important predictors of long term mortality in revision TKA. Finally, this study extends over four decades and surgical practice evolved over time. Surgeons in the present era may be more aggressive than in the past in operating on patients with multiple comorbid conditions.

Furthermore, some patients who developed aseptic loosening and/or wear may have also developed periprosthetic joint infection, instability or fracture. Under our classification scheme this would lead to the patient being classified as a periprosthetic joint infection or fracture patient. Therefore, periprosthetic joint infection, fracture, and instability patients would be more likely to have multiple revisions with multiple indications. This selection might exaggerate any existing survival disadvantage. However, this is difficult to overcome in a

retrospective study. Patients can be analyzed in regards to number of revisions, however while our institutional total joint registry does record previous revisions, patient provided documentation can be unreliable unless all previous revisions were performed at our institution. Therefore for the purposes of this investigation, patients were stratified according to their most severe complication.

Conclusion

Revision TKA patients have a higher mortality risk than individuals in the general population, particularly patients who underwent revision TKA for periprosthetic joint infections and fractures. Revision TKA patients who underwent surgery for aseptic loosening and wear initially had a lower mortality risk, but experienced a shift to excess mortality risk after the first postoperative decade. Further studies are warranted to better understand and manage risk factors for long-term mortality after revision TKA.

Table 1: Baseline Characteristics of the Revision Total Knee Arthroplasty Patients

Surgical Indication	**N**	**Age at Surgery, Years Mean (±SD)**	**Male Gender N (%)**	**Charlson Comorbidity Index, Severity-weighted Mean (±SD)**
Infection	1370 (28%)	67.8 (11.2)	727 (53%)	1.4 (1.7)
Fracture	399 (8%)	71.7 (11.5)	167 (42%)	1.1 (1.6)
Loosening/Wear	1740 (35%)	69.5 (10.6)	854 (49%)	0.7 (1.2)
Instability	990 (20%)	65.9 (10.8)	390 (39%)	0.7 (1.1)
Other	408 (9%)	63.9 (12.6)	163 (40%)	0.8 (1.3)
Total	4907	68.0 (11.2)	2301 (47%)	0.9 (1.4)

Table 2: Mortality Rates Following Revision Total Knee Arthroplasty According to Surgical Indications

	1 Year		5 Year		10 Year		15 Year	
Surgical Indication	**Mortality rate**	**95% CI**	**Mortality rate**	**95% CI**	**Mortality rate**	**95% CI**	**Mortality rate**	**95% CI**
Fracture	0.04	(0.02, 0.06)	0.18	(0.14, 0.22)	0.46	(0.40, 0.52)	0.72	(0.64, 0.78)
Infection	0.04	(0.03, 0.05)	0.21	(0.19, 0.24)	0.47	(0.43, 0.51)	0.73	(0.69, 0.77)
Instability	0.01	(0.01, 0.02)	0.11	(0.09, 0.13)	0.31	(0.27, 0.35)	0.58	(0.52, 0.64)
Loosening/Wear	0.02	(0.01, 0.02)	0.12	(0.10, 0.13)	0.34	(0.32, 0.37)	0.60	(0.57, 0.63)
Other	0.02	(0.00, 0.03)	0.09	(0.06, 0.13)	0.26	(0.20, 0.32)	0.50	(0.41, 0.58)
Total	0.02	(0.02, 0.03)	0.15	(0.13, 0.16)	0.37	(0.36, 0.39)	0.63	(0.61, 0.65)

Table 3: Standardized Mortality Ratios (SMR; 95% Confidence Intervals) Following Revision Total Knee Arthroplasty According to Surgical Indications.

Surgical Indication	N	Expected no of Deaths	Observed no of Deaths	SMR	Lower CI	Upper CI	P-Value
Infection	1370	384.4	557	1.45	1.33	1.57	<0.001
Fracture	399	161.7	188	1.16	1.00	1.34	0.04
Loosening/Wear	1740	892.0	850	0.95	0.89	1.02	0.16
Instability	990	284.4	285	1.00	0.89	1.13	0.95
Other	408	122.2	114	0.93	0.77	1.12	0.50
Total	4907	1844.7	1994	1.08	1.03	1.13	<0.001

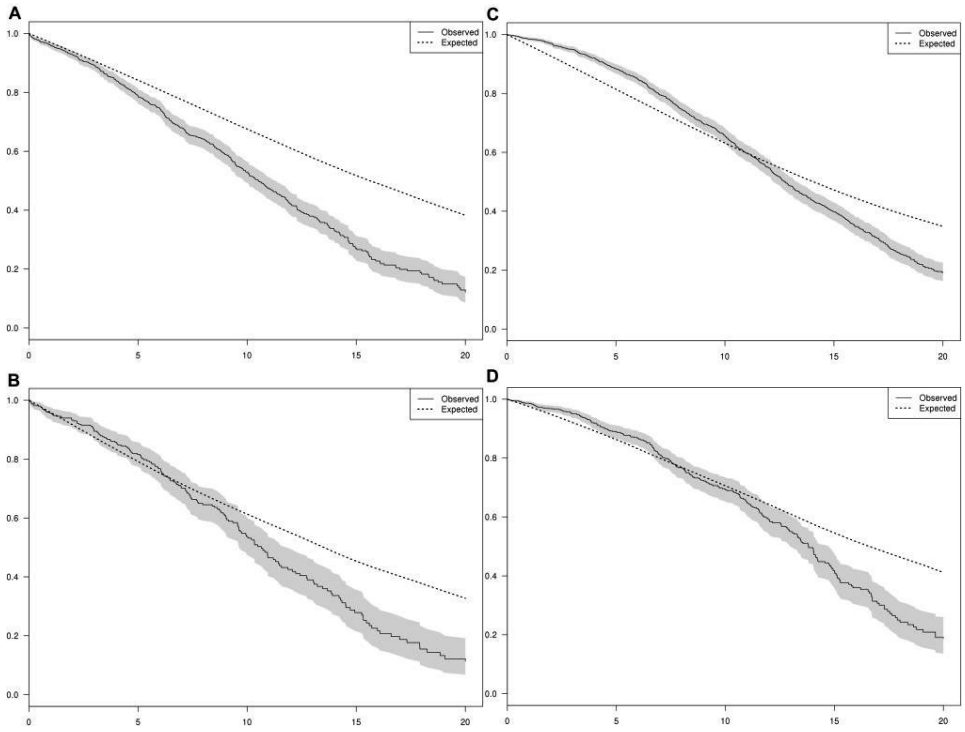

Figure 1: Kaplan-Meier patient survival curves following revision total knee arthroplasty for prosthetic joint infection (A), for fracture (B), for aseptic loosening and/or wear (C), and for instability (D). Observed patient survival is shown in black solid line along with shaded confidence intervals. Expected age-adjusted and sex-adjusted survival is shown in dotted line. Observed survival above the dotted line indicates a lower mortality risk relative to the general population. Observed survival below the dotted line indicates a higher mortality risk relative to the general population.

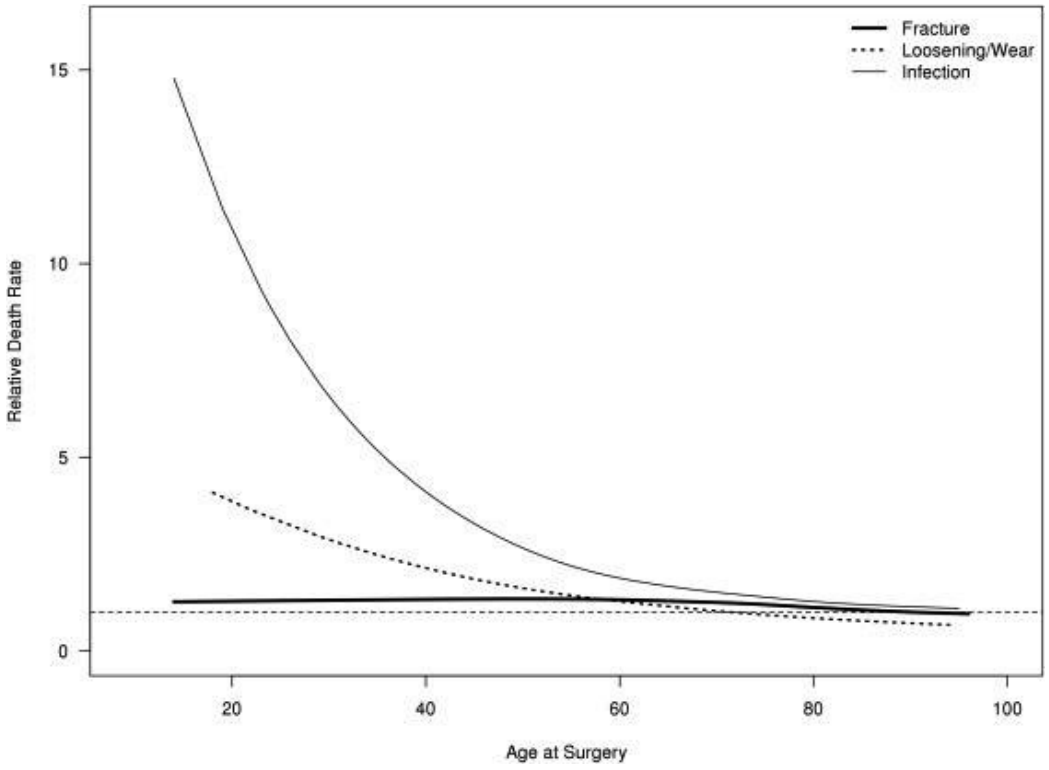

Figure 2: Relative death rate by age at surgery. Relative mortality rate (observed deaths/expected deaths) by age at surgery and surgical indications. Each surgical indication group is represented by a different line. The dotted horizontal line at a relative mortality rate of 1 represents a relative mortality rate that is the same as the general population. Relative mortality above the dotted line at 1 indicates that risk of mortality is higher than the general population. Relative mortality below the dotted line at 1 indicates that the risk of mortality is lower than the general population.

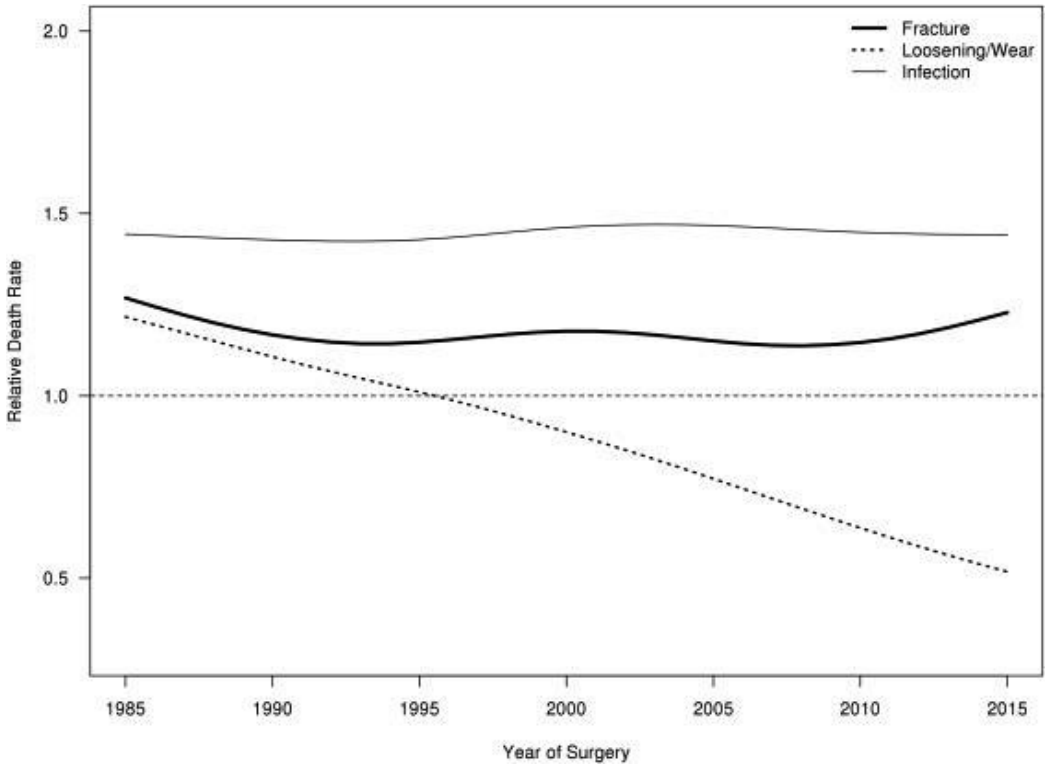

Figure 3: Relative death by year of surgery. Relative mortality (observed deaths/expected deaths) by year of surgery and surgical indications. Each surgical indication group is represented by a different line. The dotted horizontal line at a relative mortality rate of 1 represents a relative mortality rate that is the same as the general population. Relative mortality above the dotted line at 1 indicates that risk of mortality is higher than the general population. Relative mortality below the dotted line at 1 indicates that the risk of mortality is lower than the general population.

Revision THA for Fracture: More Expensive, More Complications, Same DRG. A Local and National Cohort Study.

Hevesi M, Wyles CC, Maradit-Kremers H, Habermann EB, Glasgow AE, Bews KA, Ransom JE, Visscher SL, Lewallen DG, Berry DJ.

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Introduction

The number of primary total hip arthroplasty (THA) procedures performed in the United States is growing, with numbers predicted to increase by 174% between 2005 and 2030 and an estimated 505,170 THAs performed nationwide in 2014[1, 225, 260, 417]. Concurrently, the age at which patients undergo THA has demonstrated a significant, sustained trend towards younger patients [11, 418]. As such, there has been an increase in the volume of revision hip arthroplasties (rTHA)[225]. While primary THA is predominantly performed for osteoarthritis, rTHA occurs for a variety of indications including fracture, loosening, and dislocation [398]. Considering that rTHA adverse outcome rates have been significantly higher than for primary procedures, rTHA patients pose a unique challenge in terms of preoperative optimization, in-hospital care, and post-discharge management [160, 256].

Little is known regarding the hospital cost and complication profile of rTHAs by indication, with most series limited to single institutions, often without access to line-item billing details [160, 256]. Cost is an increasingly important factor in patient care, reimbursement, and sustainable healthcare access. Currently, rTHA procedures are billed under the Diagnosis-Related Groups (DRGs) 466, 467, and 468, representing arthroplasty without complication or comorbidity, arthroplasty with complication or comorbidity (CC), and arthroplasty with major complication or comorbidity (MCC). As such, the Medicare Severity DRG system does not distinguish between rTHA performed for fracture and rTHA performed for wear/loosening or dislocation/instability, which together comprise the three most common aseptic rTHA indications [98, 228, 398]. This is important in that there are potential inherent differences between rTHA indications, whether manifested directly in the form of in-hospital costs, or indirectly in the form of early complications. Furthermore, studies have determined that within the rTHA

population, Medicare is the primary payer class, comprising 60 – 70% of patients undergoing revision procedures [49, 213].

Therefore, the purpose of this study was to answer (1) Do aseptic rTHAs performed for fracture cost more than revisions performed for aseptic wear/loosening or dislocation/instability; and (2) Do aseptic rTHAs performed for fracture experience increased 30-day complication rates as compared to revisions performed for aseptic wear/loosening or dislocation/instability? We hypothesized that rTHA performed for fracture would demonstrate higher in-hospital costs and 30-day complications rates than rTHA performed for wear/loosening or dislocation/instability.

Methods

The present study is a retrospective comparative cohort of patients undergoing aseptic rTHA between 2009-2014 from three data sources: local high-volume single-institution data, the National Inpatient Sample (NIS), and the American College of Surgeons National Surgical Quality Improvement Program (ACS-NSQIP). rTHA for fracture was defined as revision procedures in the setting of a previous THA occurring for periprosthetic fractures (femoral and acetabular) as well as fractures involving the prosthesis itself. Open reduction internal fixation (ORIF) around stable implants was not included in the analysis. Granular single-institution costs and complications data were analyzed and subsequently, locally observed patterns were compared with the NIS and ACS-NSQIP databases.

The local study population included 1,422 rTHAs performed at the Mayo Clinic, Rochester, MN in the period 2009-2014. All aseptic rTHAs were eligible for inclusion. We excluded patients who had undergone bilateral procedures during the same hospitalization, rTHA performed for infection upon chart review, and patients not consented for research. The study was Institutional Review Board (IRB) approved prior to commencement.

We obtained demographic and clinical data using the Mayo Clinic Total Joint Registry which has been in operation since 1969 and previously described in detail [38]. The registry records demographics, operative data, and standardized postoperative medical and surgical complications selected by a committee of orthopaedic surgeons. Patients are followed on a standardized basis, with two follow-up appointments in the first surgical year and regular

follow-up at years 2, 5, and beyond. Records are reviewed by trained Total Joint Registry coders with standardized documentation of complications for the life of the patient and prosthesis. Complications were grouped into five categories: wound complications and infections (superficial and/or deep), vascular complications (i.e. deep venous thrombosis, pulmonary embolism, myocardial infarction), neurologic complications (i.e. sciatic palsy), dislocation, and fracture of bone or prosthetic components.

Cost data was obtained from the Mayo Clinic Cost Data Warehouse using line-item details for every service or procedure billed to patients[404]. Recognizing discrepancies between billed charges and true resource use, bottom-up microcosting valuation techniques were employed to generate standardized inflation-adjusted cost estimates[189, 241, 262].

The national cost comparison cohort comprised all NIS patients with charge data from 2009-2014. The NIS dataset collects a stratified sample of 20% of all discharges from U.S. hospitals with corresponding documentation of total inpatient charges. Procedures were identified by ICD-9 procedure code for rTHA (82.53, 00.70, 00.71, 00.72, and 00.73) and associated ICD-9 diagnosis codes for fracture (996.44), wear/loosening (996.41 and 996.46), and dislocation/instability (996.42). Patients with a concurrent diagnosis of infection (ICD-9 996.6 or 996.66) were excluded from analysis.

National complication rates were obtained using the ACS-NSQIP database which employs trained local surgical clinical reviewers to collect 30-day complications using a HIPAA-compliant platform on randomly assigned patients at 602 participating U.S. study sites [12]. Of note, ACS-NSQIP complications encompassed those included in the local registry with the exception of neurologic and prosthetic (dislocation/fracture) complications and additionally provided a national perspective on a greatly expanded list of medical complications. Complications were analyzed for patients undergoing rTHA (Current Procedure Terminology codes 27134, 27137, 27138) between 2009-2014 and meeting the primary ICD-9 diagnosis code criteria defined above.

Primary outcomes were local in-hospital cost and 30-day complication rates. Secondary outcomes were national in-hospital costs and 30-day complication rates, which served as a comparison cohort for local outcomes. Costs were defined as total 2016 line-item

costs for Mayo Clinic patients and total NIS charges converted into 2016 dollars using Healthcare Cost and Utilization Project cost-to-charge ratios.

Statistical analysis:

Comparisons were performed using chi-squared tests for categorical outcomes, Fisher's exact tests for rare complications such as pulmonary embolism, and Kruskal-Wallis testing for ordinal values. Multivariable linear modelling was used to examine the relative effect of operative indication in determining in-hospital cost after accounting for American Society of Anesthesiologists (ASA) classification, age, and sex in light of the current comorbidity-based DRG reimbursement system. Statistical analyses were performed using SAS Version 9.4 (SAS Institute, Inc, Cary, NC, USA) and R Version 3.4.3 (R Core Team, Vienna, Austria).

Results

A total of 1,422 local rTHA patients were obtained (Table 1). Of these, 1,225 (86.1%) underwent rTHA for one of the three indications studied (150 fracture, 854 wear/loosening, 221 dislocation/instability). Other reasons for revision included painful arthroplasty, adverse metal reactions, and trunnionosis. These procedures were included in determining overall mean costs of aseptic rTHA at our institution since they would have been eligible for billing under DRGs 466-468. However, they were not included in national analyses considering the non-specific ICD-9 indication coding (i.e. ICD-9 996.77 – Other complications due to internal joint prosthesis). Nationally, 28,150 rTHA patients (3,494 fracture; 13,768 wear/loosening; 10,888 dislocation/instability) were obtained using the NIS (Table 2) and 3,224 rTHA patients (317 fracture; 1,789 wear/loosening; 1,118 dislocation/instability) were obtained using the ACS-NSQIP (Table 3).

The local fracture population demonstrated a trend towards older fracture patients (mean age: 69.3 ± 13.9 years) when compared to other aseptic rTHA indications (wear/loosening: 67.1 ± 13.1 years; dislocation/instability: 66.5 ± 12.0 years, $p = 0.059$, Table 1). This pattern of older fracture patients was present in the NIS and ACS-NSQIP databases as well, where larger patient volumes demonstrated statistical significance ($p<0.001$, Tables 2-3). While no significant difference existed amongst the distribution of ASA classification in the local population, estimates for Class 3: Severe Systemic Disease and Class 4: Life Threatening in the

fracture population (48.7% and 2.0%, respectively) were higher than those observed for both the wear/loosening (41.8% and 1.4%) and dislocation/instability (42.5% and 1.4%) groups (p=0.756, Table 1) [109]. The proportion of fracture patients in the ACS-NSQIP database with Class 3 (58.7%) and Class 4 (14.2%) comorbidities was significantly higher than in the wear/loosening (48.3% and 3.5%, respectively) and dislocation/instability groups (58.6% and 7.2%, respectively, p<0.001, Table 3).

Hospitalization Costs by Revision Indication:

Median local, line-itemized cost for rTHA performed for fracture was $25,672 (interquartile range [IQR]: $21,897 – 30,988), which was significantly higher than $20,228 (IQR: $17,397 – 24,066) for wear/loosening (p<0.001), $17,911 (IQR: $15,608 – 20,620) for dislocation/instability (p<0.001) and $19,768 (IQR: $16,845 – 24,104) for all-cause aseptic rTHA at our institution (p<0.001) (Table 1). Fracture patients represented 33% or $6,366 higher median costs compared to non-fracture local rTHA cohort. After adjusting for patient comorbidities using ASA Class, age, and sex, fracture indication remained a significant driver of cost, with $7,023 increased costs compared to wear/loosening (p<0.001) and $9,209 increased costs compared to dislocation/instability (p<0.001). In multivariable analysis, ASA score (p<0.001) but not age (p=0.550) or sex (p=0.117) was found to predict cost. The average operative time for fracture (201.8 minutes) was significantly higher than for dislocation/instability (108.9 minutes, p<0.001) or wear/loosening (151.6 minutes, p<0.001)

Local patterns were mirrored in the NIS database wherein rTHA for fracture had a median in-hospital cost of $27,605 (IQR: $20,068 – 38,051), which was significantly higher than $19,658 (IQR: $14,646 – 27,198) for wear/loosening (p<0.001) and $17,509 (IQR: $13,048 – 24,355) for dislocation/instability (p<0.001, Table 2).

30-day Complication Rates:

Locally, 30-day orthopaedic database complication rates for rTHA for fracture were 20.7%, significantly higher than 9.0% observed for dislocation/instability (p=0.007) and similar to the 17.6% observed for wear/loosening (p=0.434) (Table 1). There was no complication for wear/loosening or dislocation/instability that was significantly higher than rTHA for fracture (p≥0.450). In comparison, risk of postoperative dislocation within 30 days for fracture patients

(6.0%) was significantly higher than for wear/loosening (2.0%, p<0.012) and dislocation/instability (0.5%, p=0.002).

In the ACS-NSQIP database, which comprises an expanded panel of surgical and medical complications, 71.3% of rTHAs performed for fracture experienced at least one 30-day complication, significantly higher than 35.2% for wear/loosening (p<0.001) and 35.1% for dislocation/instability (p<0.001). In pairwise comparisons of the complications listed in Table 3, non-fracture indications demonstrated no complication which was significantly higher than for fracture (p≥0.053).

Discussion

THA is one of the most successful orthopaedic procedures, with demonstrated safety and efficacy[211, 240]. As the number of primary procedures continues to rise, the incidence of rTHA continues to increase [225, 260, 417]. The costs of rTHA are poorly understood and, while primary THA occurs principally for osteoarthritis, aseptic rTHA represents a broad variety of indications, the most common of which are wear/loosening, dislocation/instability, and fracture. In the modern, cost-conscious era of bundled payments, it is of great importance to create value-based reimbursement schedules accounting for indication-specific differences in cost and risk. In this study, rTHA for fracture was 33-48% more expensive and demonstrated increased complication rates locally and nationally, confirming our previous hypotheses.

While the costs of THA have been described in the literature, there is a paucity of information regarding the costs of rTHA [110, 238, 264, 309]. It has been previously determined that resource utilization in THA for fracture is higher than arthroplasty for osteoarthritis, however this was done indirectly through complications, length of stay, and discharge to an inpatient facility [356]. Our study improves on this type of analysis by providing line-item costs in our institutional setting. Furthermore, the increased operative times observed in the fracture population suggest that in addition to being more costly in terms of hospitalization fees (Medicare Part A), rTHA for fracture is also more demanding in terms of surgical time and effort. This suggests that rTHA for fracture may warrant consideration as a separate Current Procedural Terminology (CPT) code. By employing the NIS database, locally-observed 33% increased costs in the fracture population could be compared to national data for 28,150 rTHAs with the benefit of larger samples and greater statistical power. The analogous cost distribution

by rTHA indication between the local and NIS data supports that cost patterns observed locally are applicable nationally.

Revision THA for fracture has been previously documented to have high, unpredictable complication rates estimated to be 18-44% with long-term reoperation rates of up to 21-33% [247, 263, 378, 431]. While revisions for various etiologies have been examined on an individual basis, to our knowledge, this is the first study to compare complication rates between rTHA indications. Both the local and national data suggests that the rTHA for fracture demonstrates higher 30-day complication rates than other aseptic indications. These findings are likely related to the fact that rTHA for fracture is performed on an urgent or semi-urgent basis during the course of an otherwise unplanned admission for a patient not previously optimized for surgery. Furthermore, in terms of high-resource complications, the return to OR rate in the local and national fracture groups is approximately double that of wear/loosening, which represents the most common rTHA indication both locally and nationally. This further supports that rTHA for fracture represents a fundamentally unique group of patients in terms of preoperative, postoperative, and post-discharge management.

A striking finding is the higher age and comorbidity burden demonstrated by the fracture population in Tables 1-3. We believe this highlights the fact that patients undergoing rTHA for fracture comprise a distinct population and as such, billing for the three rTHA indications under the same DRG is inappropriate. This is further demonstrated by the proportion of the three indications between our local tertiary referral center and general NIS and ACS-NSQIP figures. Dislocation/instability, which was the least costly indication for rTHA, made up 44% of the NIS population, 35% of the ACS-NSQIP population, and only 16% of the tertiary center population, indicating that large referral centers perform a higher percentage of the more costly rTHA indications. It is well understood that small and private hospitals make up the majority of both the NIS and ACS-NSQIP databases, with approximately 26 – 37% contribution by academic centers[155, 365]. A DRG scheme which does not distinguish between indications for rTHA sets the stage for disincentivising the care of fracture patients and incentivising referrals. This is highlighted by the fact that by using the national 2016 Medicare reimbursement for DRGs 466 ($29,756; with MCC), 467 ($20,298; with CC) and 468 ($16,245; without CC), one could only cover the median standardized costs of Medicare Part A hospital services for fracture ($22,050) by coding all fracture patients as MCC. This is likely untenable considering that all patients, regardless of health status, would have to be coded as MCC, leaving

no mechanism to account for other comorbidities or complications aside from rTHA indication. Such a system places local quality fracture care and sustainable reimbursement at odds and could readily be addressed and corrected through indication-specific DRGs.

This study had a number of important limitations. First, while our local registry has the distinct advantage of allowing for manual review of patients with unclear indications for rTHA, national databases are contingent upon complete and accurate coding by providers and reviewers, which has not been validated specifically for orthopaedic-related complications. Second, while local complication rates were obtained from a well-established standardized total joint registry designed by orthopaedic surgeons, the complications captured were different than for the ACS-NSQIP database which is based on a greatly expanded list of both medical and surgical complications and thereby reflected in the high rates of observed complications. A unique strength of the local database is that orthopaedic-specific complications such as dislocation and periprosthetic fracture are recorded. However, inclusion of ACS-NSQIP data allows for comparison to national trends as well as capture of additional medical complications which may potentially contribute to resource utilization. It would be of future utility to determine the rate of rTHA for fracture within the first 90 days of other hip procedures in differentiating iatrogenic versus traumatic or pathologic fractures. Due to the significant number of outside referrals we receive as a tertiary institution, defining these rates is difficult to achieve and thus a limitation of this study. Finally, while the NIS provides inpatient charge data, professional services (surgeon fees) and post-discharge costs are not included. This highlights the value of local, high-resolution data with subsequent comparisons to broadly generalizable national datasets.

Conclusion

Due to the 33-48% increased in-hospital costs and high 30-day complication rates observed for patients undergoing rTHA for fracture as compared to other etiologies, we strongly recommend indication-based DRGs for rTHA in the growing and evolving era of bundled payments. This is particularly true for the Medicare population, which makes up 60-70% of rTHAs. Such indication-appropriate codes will allow for developing sustainable, data-driven solutions to promote and support access to rTHA for patients.

Table 1: Demographics, Complications, and Inpatient Costs of Locally Treated Aseptic Revision THA Patients*

Variable	All Revision THAs (N = 1,422)	Fracture (N = 150)	Wear/Loosening (N = 854)	Dislocation Instability (N= 221)	P Value
Age† *(yr)*	66.4 ± 13.0	69.3 ± 13.9	67.1 ± 13.1	66.5 ± 12.0	0.059
Sex‡					
Male	649 (45.6%)	55 (36.7%)	410 (48.0%)	78 (35.3%)	<0.001
Female	773 (54.4%)	95 (63.3%)	444 (52.0%)	143 (64.7%)	
BMI† *(kg/m²)*	29.8 ± 6.7	29.9 ± 7.9	29.7 ± 6.4	29.6 ± 6.7	0.658
Length of stay§ *(days)*	3 (3, 4)	4 (3, 6)	3 (3, 4)	3 (3, 4)	<0.001
ASA class‡					
I - no disease	26 (1.8%)	3 (2.0%)	15 (1.8%)	3 (1.4%)	0.756
II - mild disease	791 (55.6%)	71 (47.3%)	470 (55.0%)	121 (54.8%)	
III - severe disease	586 (41.2%)	73 (48.7%)	357 (41.8%)	94 (42.5%)	
IV - life threatening	19 (1.3%)	3 (2.0%)	12 (1.4%)	3 (1.4%)	
30-day orthopaedic registry-specific complications‡#					
Any complication	238 (16.7%)	31 (20.7%)	150 (17.6%)	20 (9.0%)	<0.001
Return to OR	32 (2.3%)	5 (3.3%)	12 (1.4%)	7 (3.2%)	0.082
In-hospital mortality	2 (0.1%)	1 (0.7%)	0 (0%)	0 (0%)	0.122
30-day mortality	7 (0.5%)	3 (2.0%)	0 (0%)	1 (0.5%)	0.003
Wound					
Any	83 (5.8%)	19 (12.7%)	35 (4.1%)	18 (8.1%)	<0.001
Superficial infection	4 (0.3%)	1 (0.7%)	3 (0.4%)	0 (0%)	0.520
Deep infection	18 (1.3%)	4 (2.7%)	7 (0.8%)	4 (1.8%)	0.077
Vascular					
Any	62 (4.4%)	9 (6.0%)	34 (4.0%)	3 (1.4%)	0.043
DVT	7 (0.5%)	2 (1.3%)	4 (0.5%)	0 (0%)	0.177
PE	3 (0.2%)	1 (0.7%)	2 (0.2%)	0 (0%)	0.398
Neurologic	8 (0.6%)	2 (1.3%)	5 (0.6%)	0 (0%)	0.244
Dislocation	35 (2.5%)	9 (6.0%)	17 (2.0%)	1 (0.5%)	0.002
Fracture	106 (7.5%)	11 (7.3%)	85 (10.0%)	4 (1.8%)	<0.001
2016 adjusted standardized costs§ *($)*					
Total in-hospital cost	19,768 (16,845-24,104)	25,672 (21,897-30,988)	20,228 (17,397-24,066)	17,911 (15,608-20,620)	<0.001
Part A hospital services	16,815 (13,951-20,815)	22,050 (18,552-27,127)	17,266 (14,531-20,715)	14,885 (12,725-17,329)	<0.001
Part B professional costs	3,079 (2,762-3,465)	3,594 (3,132-4,294)	3,043 (2,760-3,432)	3,050 (2,763-3,396)	<0.001
OR and anesthesia	7,114 (6,303-7,583)	7,529 (6,989-8,307)	6,876 (6,314-7,577)	6,677 (6,219-7,303)	<0.001
Prostheses	3,294 (2,157-5,435)	5,279 (3,835-6,773)	3,850 (2,371-5,850)	2,361 (1,757-3,080)	<0.001
Room and board	3,848 (3,480-4,947)	5,820 (4,132-8,157)	3,848 (3,480-4,835)	3,787 (2,910-4,947)	<0.001
Pharmacy	1,081 (903-1,324)	1,292 (1,030-1,622)	1,060 (905-1,295)	1,032 (841-1,285)	<0.001
Laboratories and pathology	654 (497-855)	810 (550-1,131)	665 (541-855)	565 (313-708)	<0.001

* BMI = body mass index, OR = operating room, DVT = deep venous thrombosis, and PE = pulmonary embolism. †Data are presented as the mean and the standard deviation. ‡Data are presented as the number of THAs with the percentage of the total THAs in that cohort in parentheses. §Data are presented as the median with the interquartile range in parentheses. #Any complication and return to the OR are calculated on a per-patient basis, and individual complications are listed as the number of events.

Table 2: Demographics and Inpatient Costs of National Aseptic Revision THA Patients in the NIS Database

Variable	All Revision THAs (N = 28,150)	Fracture (N = 3,494)	Wear/Loosening (N = 13,768)	Dislocation Instability (N = 10,888)	P Value
Age* ***(yr)***	68.7 ± 12.9	72.4 ± 12.5	67.3 ± 12.7	69.3 ± 13.0	<0.001
Sex†					<0.001
Male	11,183 (39.8%)	1,208 (34.6%)	6,182 (44.9%)	3,907 (34.9%)	
Female	16,950 (60.2%)	2,285 (65.4%)	7,574 (55.1%)	7,273 (65.1%)	
Length of stay‡ ***(days)***	3 (3, 5)	5 (4, 8)	3 (3, 4)	4 (3, 6)	<0.001
2016 total adjusted in-hospital costs‡ ***($)***	19,517 (14,339-27,569)	27,605 (20,068-38,051)	19,658 (14,646-27,198)	17,509 (13,048-24,355)	<0.001

*Data are presented as the mean and the standard deviation. †Data are presented as the number of THAs with the percentage of total THAs in that cohort in parentheses. Seventeen (0.06%) patients have missing sex data. Distribution of the missing data cannot be shown due to NIS data-use licensing agreement. Missing values were excluded from analysis. ‡Data are presented as the median with the interquartile range in parentheses

Table 3: Demographics and Complications of National Aseptic Revision THA Patients in the ACS-NSQIP Database*

Variable	All Revision THAs (N = 3,224)	Fracture (N = 317)	Wear/ Loosening (N = 1,789)	Dislocation/ Instability (N = 1,118)	P Value
Age† *(yr)*	68.3 ± 12.8	73.9 ± 12.0	67.2 ± 12.4	68.4 ± 13.1	<0.001
Sex‡§					<0.001
Male	1,318 (40.9%)	118 (37.2%)	829 (46.4%)	371 (33.2%)	
Female	1,903 (59.1%)	119 (62.8%)	957 (53.6%)	747 (66.8%)	
BMI† *(kg/m²)*	29.4 ± 6.7	29.2 ± 8.5	29.8 ± 6.2	28.8 ± 6.9	<0.001
ASA class‡#					<0.001
I - No disease	50 (1.6%)	3 (0.9%)	36 (2.0%)	11 (1.0%)	
II - Mild disease	1,280 (39.7%)	83 (26.2%)	826 (46.2%)	371 (33.2%)	
III - Severe disease	1,704 (52.9%)	186 (58.7%)	863 (48.3%)	655 (58.6%)	
IV - Life threatening	189 (5.9%)	45 (14.2%)	63 (3.5%)	81 (7.2%)	
30-day postoperative ACS-NSQIP complications (medical and surgical)‡					
Any complication**	1,248 (38.7%)	226 (71.3%)	630 (35.2%)	392 (35.1%)	<0.001
Return to OR††	195 (6.1%)	32 (10.1%)	70 (3.9%)	93 (8.3%)	<0.001
Any readmission (2012+)‡‡	208 (8.6%)	27 (11.1%)	82 (6.1%)	99 (11.9%)	<0.001
Wound					
Any	117 (3.6%)	9 (2.8%)	47 (2.6%)	61 (5.5%)	<0.001
Superficial infection	27 (0.8%)	0 (0%)	12 (0.7%)	15 (1.3%)	0.035
Deep infection	41 (1.3%)	2 (0.6%)	17 (1.0%)	22 (2.0%)	0.033
Vascular					
Any	49 (1.5%)	5 (1.6%)	34 (1.9%)	10 (0.9%)	0.097
DVT	14 (0.4%)	1 (0.3%)	8 (0.4%)	5 (0.4%)	1.000
PE	13 (0.4%)	2 (0.6%)	6 (0.3%)	5 (0.4%)	0.548
Myocardial infarction	19 (0.6%)	3 (0.9%)	15 (0.8%)	1 (0.1%)	0.025
Stroke/CVA	6 (0.2%)	0 (0%)	6 (0.3%)	0 (0%)	0.118
Other medical complications					
Pneumonia	17 (0.5%)	6 (1.9%)	5 (0.3%)	6 (0.5%)	0.001
Urinary tract infection	58 (1.8%)	17 (5.4%)	19 (1.1%)	22 (2.0%)	<0.001
Sepsis	33 (1.0%)	5 (1.6%)	14 (0.8%)	14 (1.3%)	0.278
Transfusions§§	1,010 (31.3%)	203 (64.0%)	534 (29.8%)	273 (24.4%)	<0.001

* Values not reported were excluded from analysis. BMI = body mass index, OR = operating room, CVA = cerebrovascular accident, SSI = surgical site infection, CPR = cardiopulmonary resuscitation, DVT = deep venous thrombosis, and PE = pulmonary embolism. †Data are presented as the mean and the standard deviation. ‡Data are presented as the number of THAs with the percentage of total THAs in that cohort in parentheses. §Three (0.17%) wear/loosening sex data points not reported in ACS-NSQIP database. #One (0.06%) wear/loosening ASA class data point not reported. **Includes superficial SSI, deep incisional SSI, organ space SSI, wound disruption, pneumonia, unplanned intubation, pulmonary embolism, ventilation >48 hr, progressive renal insufficiency, acute renal failure, urinary tract infection, stroke/CVA, cardiac arrest requiring CPR, myocardial infarction, transfusions, DVT/thrombophlebitis, sepsis, septic shock, any readmission, and return to OR. ††One (0.06%) wear/loosening return to OR data point not reported. ‡‡Seventy-three (23.0%) fracture, 436 (24.4%) wear/loosening, and 283 (25.3%) dislocation/instability readmission data points not reported given 2012+ timeline. §§For intraoperative bleeding or given postoperatively.

Chapter III:

Pre-Operative Assessment of Cartilage Damage: Large-Scale Clinical Predictive Modeling and the Importance of Addressing Underlying Pathology

The Recurrent Instability of the Patella (RIP) Score: A Statistically-Based Model for Prediction of Long-Term Recurrence Risk after First-Time Dislocation

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Introduction:

The functional anatomy of the patellofemoral joint allows for significant freedom of patellar motion, but also risk of instability and dislocation.[114, 115, 172, 194, 199] It has been estimated that 2-3% of orthopedic presentations involving the knee will involve patellar dislocation and that the annual incidence of lateral dislocation ranges from approximately 6 to 30 per 100,000 in the general population, with highest incidence during the teenage years.[16, 19, 90, 124, 138, 229, 351] Notably, active duty military members comprise a special high-demand and high-risk subpopulation, with greater than twice the risk of dislocation compared to the general teenage population.[188]

The vast majority of dislocations occur laterally during non-contact knee twisting and valgus loading.[124] Advanced imaging at the time of first dislocation using magnetic resonance imaging (MRI) is generally recommended due to the high rate of concurrent osteochondral lesions, with up to a 58% incidence of osteochondral loose bodies, only 29% of which are identified on plain radiographs.[229, 249, 379, 429] With repeated dislocation, the chance for significant articular injury increases.[348, 369, 393] Concurrently, greater than 85% of primary dislocations involve partial or complete rupture of the medial patellofemoral ligament (MPFL), the primary restraining force to lateral patellar translocation.[115, 205, 393] As such, with the first episode, patients lose previous protective factors, causing further risk for recurrent instability and associated osteochondral injury leading to arthritis.[352]

Non-operative management remains the mainstay of initial patellar dislocation treatment; however, approximately 30% of patients experience recurrent instability and 10% undergo surgical intervention.[90, 351] Risk factors for recurrent instability include trochlear dysplasia, young age, patella alta, and lateralization of the tibial tubercle.[19, 114, 172, 194, 229, 245]

While risk factors have been individually described, a clinically-robust stratification system for determination of risk for recurrent dislocation has remained elusive. Currently available stratification systems are few in number and have been significantly limited by multiple factors including 1) limited risk stratification, 2) exclusion of operatively managed cases decreasing generalizability, 3) short-term follow-up, and 4) reporting risk as odds ratios which are difficult to interpret clinically.[22, 90, 199]

Accordingly, a scoring system that is able to demonstrate long-term accuracy for predicting instability is highly desirable in deciding upon initial operative versus non-operative management in patients presenting with first-time episodes of instability. This is particularly true given the potential for further cartilage injury with repeated episodes of instability. Therefore, the purpose of this study was to describe the clinical history of a series of primary, lateral patellar dislocations and to determine long-term predictors of recurrent instability while accounting for patients undergoing early operative management. We hypothesized that using a statistically based scoring system, patients will be readily stratified into low-, intermediate-, and high-risk groups for recurrent instability on the basis of demographic and biomechanical factors such as age and the presence of trochlear dysplasia.

Methods:

Study Population and Design

Following approval of the institutional review boards of the Mayo Clinic and Olmsted Medical Center (#15-009310 and #077-OMC-15), subjects who experienced a first-time lateral patellar dislocation between January 1, 1990 and December 31, 2010 were identified using the Rochester Epidemiology Project (REP). The REP is an established database for medical research that consists of the complete medical records of all residents of Olmsted County, MN and neighboring counties for use in research activities. This database has previously been described in detail and allows for the capture of all medical records and procedures for patients within its catchment area, independent of treating institution.[342] Using the International Classification of Diseases 9 (ICD-9) diagnosis code for closed patella dislocation (836.3), patient charts were reviewed by hand to confirm the diagnosis of a first-time lateral patellar dislocation.

Inclusion criteria consisted of 1) first-time, closed lateral patellar dislocation requiring manual reduction or history of a frank dislocation with spontaneous reduction, and 2) patients consented for research. Exclusion consisted of 1) patients with a history of chronic patellar subluxation, 2) patients without knee MRI at the time of injury, 3) patients with previous surgery involving the affected knee, and 4) patients with less than 4 years of follow-up.

Patient demographics including age, sex, body mass index (BMI), and clinically documented ligamentous laxity were noted using standardized data collection forms by orthopedic residents (MH, MJH) based on the documentation provided by board certified Orthopedic Surgeons in the comprehensive epidemiological healthcare database analyzed (REP). Clinical and surgical notes were reviewed to determine episodes of recurrent instability and patients undergoing patellar stabilization surgery such as lateral retinacular release, medial retinacular imbrication, and MPFL repair or reconstruction.

Imaging

Anteroposterior and lateral knee radiographs acquired at the time of injury were obtained and analyzed in addition to patellar views (Merchant or Sunrise). Skeletal maturity was defined as closed distal femoral and proximal tibial physes on plain radiographs. Caton-Deschamps Index (CDI) was measured using lateral radiographs at 30 degrees of knee flexion.[72]

All MRI studies were obtained at a single institution using 1.5- or 3.0 Tesla General Electric scanners (GE Healthcare, Waukesha, Wisconsin) with imaging cuts ranging from 3 to 4 mm in thickness. The imaging protocol involved the patient positioned supine with the extremity of interest placed in full extension with surrounding pads to minimize motion artifact. The presence of trochlear dysplasia was evaluated using plain films and MRI employing the classification set forth by Dejour et al.[114] Tibial tubercle to trochlear groove (TT-TG) distance was measured using previously validated and described methods.[67, 172] In brief, the medial-lateral distance between the deepest cartilaginous portion of the trochlear groove and the midpoint of the patellar tendon at its most cephalad insertion on the tibial tubercle was measured in millimeters using axial MRI images. Patellar length (PL) was measured on sagittal images to obtain the longest proximal-to-distal length of the patellar cartilage.[172] Subsequently tibial tubercle to trochlear groove distance was divided by patellar length to obtain the TT-

TG/PL ratio as this radiographic measure has been previously demonstrated to best predict recurrent instability in the population investigated.[172] All measurements were obtained on T2-weighted images.

Statistical Analysis

Descriptive statistics were used to present demographic data with means, standard deviations, and percentages, as appropriate. Patients who experienced recurrent patellar instability during the course of follow-up were compared to those without recurrent instability using Fisher's exact test for proportions and Mann-Whitney U testing for nominal values.

A statistically-based scoring system for recurrent instability risk was created using the methods described by Sullivan et al. in their description of the mathematic origins of the Framingham Heart Study risk score which serves as one of the first and most published methods in generating risk models for medical applications.[384] We used competing risk analysis as the primary analysis method, where patellar stabilization surgery was considered as a competing rather than a censoring event of recurrent dislocation, to assess the factors associated with recurrent instability. Competing risks modelling was used as patient recurrence risk and the decision for early operative management are likely correlated and should therefore be directly addressed and accounted for in analytic approach rather than simply excluded or censored, as has been done in previous studies.[22, 199, 302]

In short, a Fine and Gray proportional hazards model with competing risks for recurrent instability and patellar stabilization surgery was generated and the estimated coefficients from the subdistribution hazards were used as the basis for point value standardization for the scoring system. Total point values were then assigned to each patient and the observed rates of recurrent instability over time for point-stratified groups were plotted and analyzed using cumulative incidence curves. *Post hoc* power analysis was subsequently performed to determine the power achieved for the RIP score in differentiating patellar recurrence risk at alpha = 0.05. Further information regarding the theoretical basis and methods used for implementation of our model is provided by Austin et al.[20] P-values < 0.05 were considered significant. Analyses were conducted in R 3.4.3 (R Core Team, Vienna, Austria) and JMP Pro 13.0.0 (SAS Institute, Cary, NC, USA).

Results:

This study population represented a subset of 87 patients previously reported in a radiographic analysis; six (6.9%) were excluded due to less than 4 years of follow-up (range: 0.2 – 2.7 years).[172] 81 patients (38 males, 43 females) met criteria for inclusion in this study. Mean age at the time of primary dislocation was 19.9 ± 9.4 years and patients were followed for a mean of 10.1 years (range 4.1 – 20.2) (Table 1). Over the course of follow-up, 38 (46.9%) patients experienced an episode of recurrent instability and 30 (37.0%) patients underwent surgical management for instability-related pathology (Figure 1). Mean time to recurrent instability was 3.0 years (range 0.2 – 11.8) and mean time to patellar stabilization surgery was 3.1 years (range: 1 week – 18.5 years).

Seven patients, comprising 8.6% of the entire study population and 23.3% of patients managed operatively, underwent stabilization surgery prior to recurrent instability at an average of 0.2 years (range: 1 week to 9 months) following primary dislocation. Early surgical management was driven primarily by intra-articular loose bodies, which were present in six patients. All seven early operative cases underwent primary MPFL repair, with concurrent medial retinacular imbrication in three patients and combined lateral release and medial imbrication in one patient. Two additional patients demonstrated medial patellar facet fractures and underwent patellar ORIF. Of the 23 patients that underwent stabilization surgery following recurrent instability, 11 (47.8%) underwent medial advancement, 7 (9.1%) lateral release, 10 (43.5%) MPFL reconstruction, and 9 (39.1%) underwent tibial tubercle osteotomy (TTO). Of these patients, 12 (52.2%) had combined procedures.

Univariate comparisons were made between those patients who experienced recurrent instability and those who did not. Factors associated with recurrent dislocation were young age (< 25 years, $p < 0.025$), low BMI ($p = 0.003$), skeletal immaturity ($p = 0.026$), trochlear dysplasia ($p < 0.001$), increased Caton-Deschamps index (CDI ≥ 1.3, $p = 0.040$), increased TT-TG distance ($p = 0.002$) and increased TT-TG/PL ratios ($p < 0.001$, Table 1).

Potential demographic and radiographic variables were entered into a multivariate competing risk model and a risk scoring system, the Recurrent Instability of the Patella Score (RIP Score), was generated using the point standardization methods described previously.[20, 384] The resulting set of variables encompassed age, skeletal maturity, trochlear dysplasia, and TT-

TG/PL ratio (Table 2). BMI and Caton-Deschamps index resulted in zero point values when accounting for the above predictive factors during multivariable analysis and are thus not included in the final RIP Score. No difference was found when assigning points values for low grade Dejour A-B dysplasia as compared to higher grade Dejour C-D dysplasia, with both categories demonstrating 1 point standardized risk; therefore the two subcategories of trochlear dysplasia were combined.

RIP Scores were calculated and applied to our dataset in order to determine its characteristics. Scores of 0-1 points were deemed low-risk, 2-3 points deemed intermediate-risk, and 4-5 points deemed high-risk. Significant differences existed in recurrence-free survival between the three risk stratification categories ($p < 0.001$, Figure 2) and *post hoc* power analysis demonstrated that the RIP score was able to differentiate between the low- and high-risk group's recurrence risk with a power of 1.00 at alpha = 0.05.

Patients demonstrated reasonable distribution between the three risk stratification groups, with 12 (14.8%) patients classified as low-risk, 37 (45.7%) intermediate risk, and 32 (39.5%) high risk. No patient in the low-risk category experienced a recurrent dislocation. At 10-years of follow-up, recurrent instability-free survival for the low-, intermediate-, and high risk groups was observed to be 100.0%, 69.4%, and 20.8%, respectively (Table 3). Receiver operating characteristics of the RIP score were also investigated. The area under the curve (AUC) for the score was determined to be 0.875 (Figure 3, $p < 0.001$). On the basis of the ROC curve, it was observed that a cut-off of RIP Scores of 0-1 being considered low risk carried was highly sensitive (100.0% sensitivity, 12.3% specificity) for predicting the absence of recurrent dislocation. In contrast, a RIP Score of 4-5 was highly specific (89.7%) with moderate sensitivity (68.4%) for predicting high recurrence risk.

Discussion:

This study demonstrated that recurrence of primary lateral patellar dislocations can be readily predicted using age, physeal status, the presence of dysplasia, and TT-TG / PL ratio. Furthermore, the data presented describes the recurrent instability and surgical history of patients followed for an average of over 10 years, demonstrating that second-time dislocation continues to occur throughout mid- and long-term follow-up, a factor previously not addressed by proposed stratification systems. Our hypothesis was confirmed in that we found that

patients could be readily stratified into low-, intermediate-, and high-risk groups with the RIP Score on the basis of patient age, skeletal immaturity, trochlear dysplasia, and TT-TG / PL ratio.

Patellar dislocation is a relatively common injury sustained by the young athletic patients and carries significant risk of functional limitations, recurrent instability, and progressive osteochondral damage with repeated episodes. Risk factors for recurrent dislocation are well-described, but existing scoring systems are derived from case series with short-term follow-up and have classically excluded surgical cases, limiting clinical utility by biasing scores to patients that had already been selected for non-treatment. Balcarek et al. proposed the Patellar Instability Severity Score which was the first multivariable scoring system and provided a 7 point scale for recurrent instability.[22] However, recurrence risk was quantified in relative terms using odds ratios and the actual percentage risk for redislocation with a given score was not reported. In addition, the median score for patients without recurrence was 3 points and the median for those patients who experienced a recurrent episode was 4 points. As such, the ability of this score to risk-stratify patients is limited.

Jaquith et al. also proposed a predictive score for use in pediatric patients.[199] However, in both the Jaquith and Balcarek scoring systems, patients who required initial operative management were excluded from analysis making scores best applicable to lower-risk, non-operative patients as opposed to the general population. A competing risk model which accounts for patients undergoing early surgical stabilization is necessary to create a broadly-applicable score for recurrence prognosis. In addition, large epidemiological studies have demonstrated that the natural history of recurrent instability is lengthy, but the above mentioned scoring systems are based on a median/mean follow up of only 1.3 to 3.1 years.[22, 90, 199] Given an average time to recurrence of 3.7 years in a long-term study of 584 patients, it is expected that greater than 50% of recurrence episodes occurred outside the study period of the previously proposed risk-assignment systems. Accordingly, we chose a minimum follow-up of 4 years for our study population.

Risk factors for recurrent patellar dislocation have been previously identified on an individual basis and are included in the multivariate point scoring system presented in the RIP Score model.[19, 114, 172, 194, 229] It is noteworthy that age-related factors are used twice in the RIP Score, with skeletally immature patients gaining points both due to their open physes as well as

age below 25 years. This is consistent with previous literature demonstrating higher rates of recurrent dislocation in patients less than 15 years of age (52-60%) than those 15 – 18 years of age (26-33%) as well as studies that have demonstrated that adolescents have a significantly higher risk of patellar instability than older adults.[19, 56, 71, 124] Our data mirror these findings, with an observed rate of recurrent instability of 64.1% in patients with open physes, 41.7% recurrence in skeletally mature patients under 25, and 21.4% recurrence in patients 25 years of age or older. This supports the inclusion of both physeal status and an additional age category for young adults. Currently available risk scoring systems have either focused exclusively on pediatric patients or have not made distinctions between those in early adolescence, teenage years, and later adulthood, limiting generalizability to broad patient populations.[22, 199] It is advantageous to include both factors (age and skeletal maturity) in the recurrence risk model since the age at which skeletal maturity is achieved varies between patients.

Trochlear dysplasia, as categorized by the Dejour classification, was found to be a significant predictor of recurrent instability. In a study that compared 103 patients who presented with primary lateral patellar dislocations to 69 controls without instability, trochlear depth < 3 mm, which was used as a surrogate to measure dysplasia, was the most divergent anatomic risk factor between the study and control groups, with 74% of patients in the instability group and only 4% of control patients observed to have a dysplastic trochlea.[18] Of note, the most common instability risk factor present in the control group (36%) was Caton-Deschamps index (CDI) ≥ 1.2, which was found to be a univariate predictor of patellar dislocation and deemed to be only marginally contributory in models assessing multiple factors.[18] These findings mirror ours which indicate that CDI provides some univariate predictive value but loses prognostic ability when other, more specific factors such as trochlear dysplasia are taken into account.

We previously investigated radiographic predictors of recurrent instability and found that of the multiple parameters and ratios described, patellar length-adjusted tibial tubercle to trochlear groove distance (TT-TG/PL) served as the best predictor, with an odds ratio of 6.1 for recurrent instability in those patients with TT-TG/PL ratio greater than or equal to 0.5.[172] Given that in our database, TT-TG/PL was the best performing radiographic predictor of recurrence, with demonstrated reliability and inter-rater agreement, we sought to add other potential clinical factors such as age into a comprehensive scoring system for recurrent instability risk.[67]

Comparisons of TT-TG/PL ratio to other radiographic measures such as TT-TG standardized to patellar width and trochlear length are not included in order to avoid duplication of data.

This study has a number of limitations. The scoring system provided is based on the 20-year retrospective review of first-time patellar dislocations; hence, conclusions drawn may be susceptible to the inherent bias of retrospective processes, such as reliance on accurate and complete recordkeeping, which may also be prone to subjectivity, such as in the case of documentation of ligamentous laxity. The use of a geographic database that captures all medical records for the patients involved partially mitigates this limitation. In addition, while a competing risk model better accounts for patients undergoing surgery following primary patellar instability, the true rate of recurrence if left untreated cannot be determined without randomization of patients between operative and non-operative management. Finally, validation-focused study of a larger sample size of patients with primary lateral patellar dislocations would further strengthen the scoring system presented and efforts for prospective application of the presented RIPS Score are currently underway.

Conclusion

Patients who sustain a first-time, lateral patellar dislocation can be readily classified into low-, intermediate-, and high-risk categories employing the RIP Score based on age, skeletal maturity, trochlear dysplasia, and TT-TG/PL ratio. This long-term risk stratification holds significant potential clinical utility for determination of patients who are at high risk for recurrent instability following primary patellar dislocation.

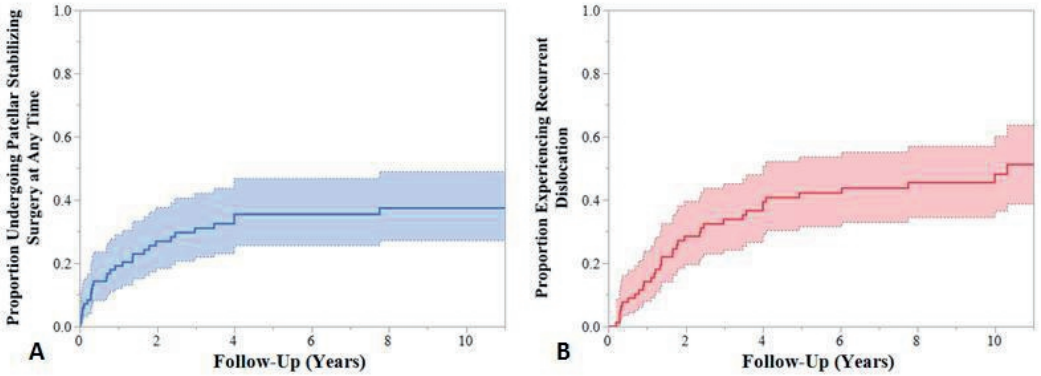

Figure 1: Rates of (A) Patellar stabilization surgery and (B) Recurrent patellar instability. 95% Confidence interval provided as shaded area.

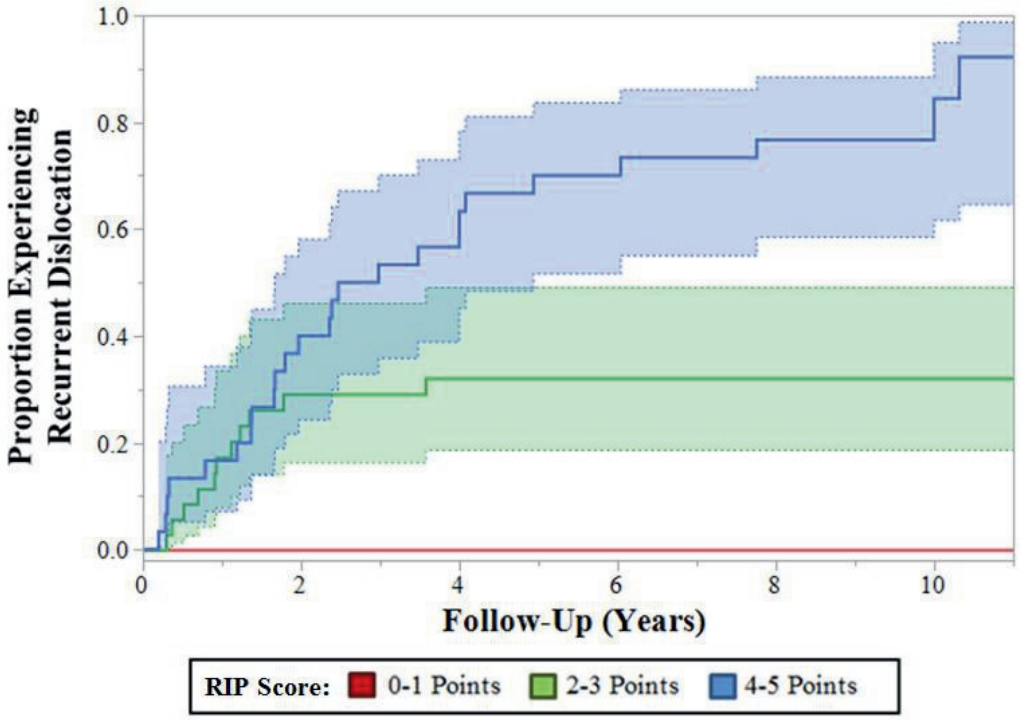

Figure 2: Observed cumulative patellar instability recurrence rate by RIP Score. 95% Confidence interval provided as shaded area.

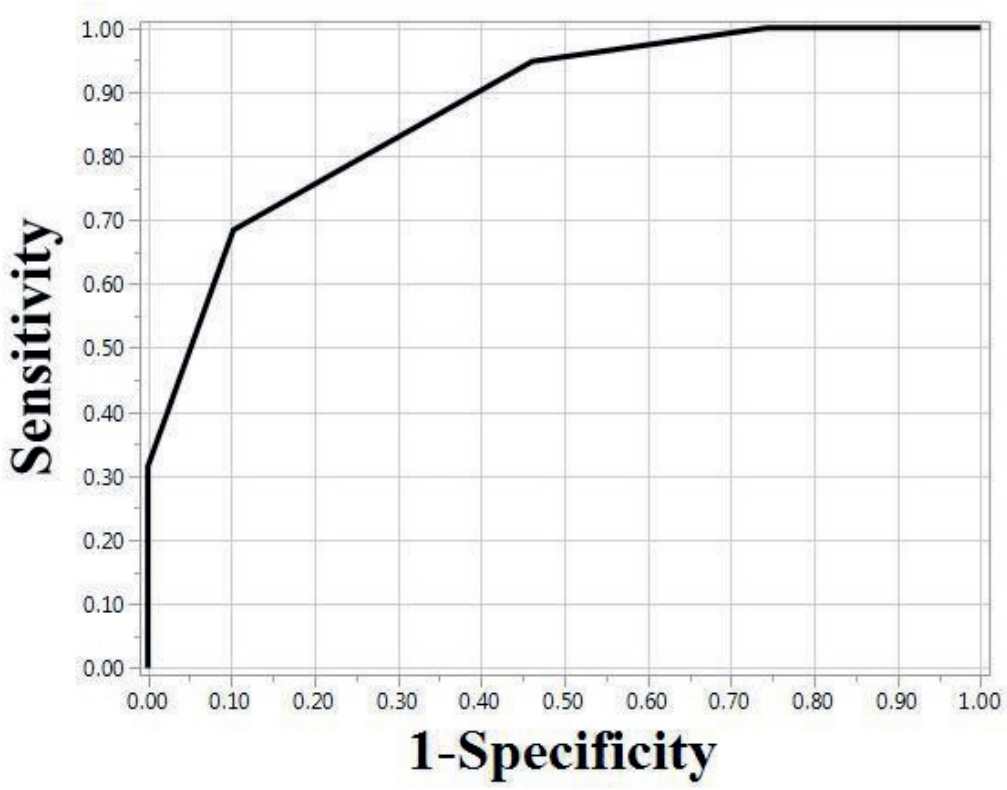

Figure 3: Receiver-operator curve for the RIP score in predicting recurrent dislocation. AUC = 0.875.

Table 1: Patient Demographics and Radiographic Parameters

Variable	All Patients (n = 81)	Recurrent Instability (n = 38)	No Recurrence (n = 43)	p-value
Age at Index	19.9 ± 9.4	16.5 ± 7.0	23.0 ± 10.3	**< 0.001**
Instability				
Sex				
Female	43 (53.2%)	22 (57.9%)	21 (48.8%)	0.505
Male	38 (46.9%)	16 (42.1%)	22 (51.2%)	
BMI, kg/m^2	25.0 ± 6.0	22.7 ± 5.5	26.7 ± 5.9	**0.003**
Ligamentous Laxity	1 (1.2%)	1 (2.6%)	0 (0.0%)	0.469
Skeletally Mature				
No	42 (51.8%)	25 (65.8%)	17 (39.5%)	
Yes	39 (48.2%)	13 (34.2%)	26 (60.5%)	**0.026**
Dejour Dysplasia				
None	48 (59.3%)	11 (28.9%)	37 (86.0%)	
Grade A-B	20 (24.7%)	16 42.1%)	4 (9.3%)	
Grade C-D	13 (16.0%)	11 (28.9%)	2 (4.7%)	**< 0.001**
Caton-Deschamps				
Index	71 (87.6%)	30 (78.9%)	41 95.3%)	
< 1.3	10 (12.4%)	8 (21.1%)	2 (4.7%)	**0.040**
≥ 1.3				
TT-TG, mm	15.5 ± 4.0	17.1 ± 4.2	14.1 ± 3.3	**0.002**
PL, mm	30.9 ± 2.8	30.6 ± 2.7	31.1 ± 2.9	0.408
TT-TG / PL				
< 0.5	43 (53.1%)	12 (31.6%)	31 (70.1%)	
≥ 0.5	38 (46.9%)	26 (68.4%)	12 (27.9%)	**< 0.001**

Table 2: RIP Score components and associated point values.

Risk Factor	Point Value
Age < 25 years	2 points
Skeletal immaturity	1 point
Dejour A-D dysplasia	1 point
TT-TG / PL ≥ 0.5	1 point
Total:	0 to 5 points

Table 3: Cumulative recurrent instability-free survival over time for the three RIP risk stratification groups. Values are patellar-stabilization surgery censored and presented as Mean ± Standard Deviation.

	Observed Recurrent Instability-Free Survival			
Risk Group	**1-Year**	**2-Year**	**5-Year**	**10-Year**
Low Risk (0-1)	100.0%	100.0%	100.0%	100.0%
Intermediate Risk (2-3)	83.3 ± 6.3%	72.2 ± 7.6%	69.4 ± 7.8%	69.4 ± 7.8%
High Risk (4-5)	84.4 ± 6.5%	62.5 ± 8.7%	34.4 ± 8.7%	20.8 ± 9.6%

The Rapidly Assessed Predictor of Intraoperative Damage (RAPID) Score: An In-Clinic Predictive Model for High-Grade Acetabular Chondrolabral Disruption.

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Introduction

Chondrolabral injury is manifested as progressive shear-induced separation of acetabular cartilage from the subchondral plate near the chondrolabral junction.[207, 333] Mild forms of disease can consist of isolated cartilage softening, whereas progressive disease leads to peelback, generation of large flaps, and subsequent full-thickness cartilage loss. Intraoperative visualization of damage occurs commonly in hip arthroscopy and open hip preservation surgery, with rates in femoroacetabular impingement (FAI) and dysplasia series ranging from 33% to 68%.[14, 33, 328, 383, 397] Given the significant influence of chondrolabral injury on perioperative planning and preparation for potential cartilage intervention such as microfracture or future cell-based treatment options, the ability to predict which patients have high grade cartilage injury would be of significant clinical utility, both for preoperative planning and possible prognostication.[220, 280, 377]

To date, both simple x-ray and advanced imaging modalities including magnetic resonance imaging (MRI), have yielded little in the way of diagnostic accuracy or precision.[257] In the 2018 study by Rajeev et al using gadolinium injected under fluoroscopic guidance, the sensitivity of magnetic resonance arthrography (MRA) for predicting damage was 7%, with 98% specificity.[333] Overall diagnostic accuracy was 73.5% and the area under the curve (AUC) for detecting damage was 0.52. These results, which demonstrate very low sensitivity but high specificity mirror others, which have noted sensitivity ranging from 22 – 30%.[14, 328] Without the creation of a full-thickness cartilage defect or subchondral cyst to allow for highly specific fluid accumulation under the delaminated area, it is difficult to visualize these pathologic changes without direct articular interrogation and dynamic probing.

Male gender, age, and the presence of a cam lesion have all been described as individual risk factors for high grade acetabular damage and the odds ratios for each of these risk factors has been published by high-volume hip arthroscopy groups.[14, 28, 201, 383] However, to date, no validated multivariable scoring system has outlined an approach for simultaneously assessing the damage risk factors that may be present in any given patient. This information is vital for preoperative discussion with the patient and planning. If a cartilage treatment such as microfracture is performed, the intraoperative surgical procedure and postoperative rehabilitation is significantly altered for the surgeon and patient.[330] Preoperative knowledge of these defects is essential, but currently lacking.

Therefore, the purpose of this study was to 1) describe easily assessed preoperative risk factors for intraoperatively visualized high grade chondrolabral damage, 2) to generate a readily employable in-clinic scoring system with which patients can be assessed for likelihood of chondrolabral damage, and 3) apply the scoring system to a prospectively collected validation cohort. Our hypotheses were 1) established risk factors such as sex, the presence of cam morphology, and Tönnis grade would predict high grade damage; 2) using multiple factors, a scoring system with significant preoperative predictive value will be generated; and 3) the resultant score will demonstrate satisfactory performance on the prospectively collected validation cohort.

Materials and Methods

Study Population and Design

This intraoperative and radiographic study included all patients undergoing hip arthroscopy following failure of comprehensive non-operative management at two high-volume hip arthroscopy centers (Mayo Clinic, Rochester, MN, USA; Mayo Clinic, Phoenix, AZ). Patients were consented for research participation following Institutional Review Board approval (IRB# 08-002259). Inclusion criteria consisted of (1) primary hip arthroscopy between December 2007 and April 2017, (2) preoperative hip radiographs, and (3) consent for research participation. Exclusion criteria consisted of (1) no digitally retrievable preoperative radiographs, and (2) previous ipsilateral hip surgery (Figure 1). A second, prospective cohort was collected between April 2017 and February 2018 with the above-described inclusion and exclusion criteria in order to serve as a validation cohort for the scoring system generated based

on the original study group. Values for this cohort served as a prospective application of the RAPID Score and were not available at the time of original score generation, to ensure true, prospective testing and validation.

Imaging

All patients had non-weight bearing anteroposterior, Dunn view, and cross-table lateral imaging of the symptomatic hip performed in addition to a centered anteroposterior view of the pelvis. Plain radiographs were used to assess Tönnis grade[395], lateral center edge angle (LCEA)[292], Tönnis angle[394], alpha angle[303], cam morphology[227], and the presence of an ischial spine sign[203], indicative of acetabular retroversion. Cam morphology was defined as alpha angles > 55° on Dunn view x-rays. Acetabular dysplasia was defined as patients with lateral center edge angles < 25°. Pincer lesions were defined as patients with LCEA > 40° or Tönnis angles < 0°.

Surgical Technique

Surgery was performed by experienced hip arthroscopists (AJK, BAL, DEH) in a dedicated operative setting for arthroscopy. Patients were positioned in the modified supine position and anterolateral and mid anterior portals were created. Additional use of the anterior, distal anterolateral, and posterolateral portals was employed as needed. Patient positioning and operative approach has been described in detail previously.[68, 86-88]

Diagnostic arthroscopy was performed to evaluate labral and acetabular chondral status and documented in operative notes as well as on standardized research forms. Damage observed at the time of direct arthroscopic visualization was graded according to the Acetabulum Labrum Articular Disruption (ALAD) classification system, with grade 1 changes defined as softening of the cartilage adjacent to the labrum, grade 2 changes defined as early peelback of cartilage, large chondral flaps classified as grade 3 disease, and complete loss of cartilage classified as grade 4.[207] Following diagnostic arthroscopy, subsequent intraoperative procedures included labral repair, cam and pincer resection, microfracture, and chondroplasty, as indicated.

Statistical Analysis

Descriptive statistics were used to present demographic data with means, standard deviations, and percentages, as appropriate. Patients with high grade (ALAD grade 3-4) lesions were compared to those without high grade lesions using Fisher's exact test for proportions and Mann-Whitney U testing for nominal values to determine univariate predictors of chondrolabral damage.

A predictive scoring system was generated by entering all variables with univariate predictive value into a multivariable binary regression model. Subsequently, the ideal set of predictive variables was determined using stepwise regression employing the Akaike Information Criterion (AIC).[5] Using the AIC, goodness of fit could be quantified and optimized for univariate predictive variables while penalizing over-fitted models that contain more parameters than justified by the data. The area under the curve (AUC) was used to evaluate the predictive ability of the RAPID score on the retrospectively and prospectively collected cohorts. Additionally, analysis of variance (ANOVA) testing was performed to determine whether cartilage damage stratification using the RAPID score was similar between the retrospective and prospective groups.

A priori analysis was used to determine the mean group sample size needed to demonstrate a 15% difference of the proportion of patients with high grade damage at alpha = 0.05 and power of 0.95. The resulting estimated mean sample size was 252 per damage group. Testing was two-sided and p-values < 0.05 were considered statistically significant. Analyses were conducted in G*Power 3.1.9.2 (G*Power Team, Dusseldorf, Germany)[131, 132] and R 3.4.3 (R Core Team, Vienna, Austria).

Results

Six hundred fifty-two primary hip arthroscopies performed between December 2007 and April 2017 in 614 patients (390 females, 224 males) were analyzed. Mean age was 33.2 ± 12.5 years and mean BMI was 26.9 ± 5.5 kg/m^2. Of the study patients, 97% of patients underwent surgery for labral tears (93% repair, 7% debridement), and 61% had concurrent indications for FAI (81% isolated cam, 9% isolated pincer, 10% combined), 2% underwent synovectomy, and 40% had intraoperatively addressed subspine impingement. Two hundred ninety-eight patients were noted to have ALAD grade 3-4 lesions (high grade) and 354 patients

were found to have ALAD grade ≤ 2 (low grade), meeting the n = 252 patients per group necessary on *a priori* power analysis.

Significant differences were observed in age at surgery, sex, BMI, Tönnis grade, and alpha angle between patients with intraoperatively documented high and low grade lesions (Table 1). 70.2% of patients in the high grade group and 44.2% of patients in the low grade group had cam morphology ($p < 0.01$), whereas a similar proportion of the high (15.1%) and low grade patients (12.8%) had pincer morphology ($p = 0.51$).

Univariate predictors of high grade chondrolabral damage were subsequently analyzed using binomial models. Age ≥ 35 years (OR: 1.96, $p < 0.01$), male sex (OR: 3.11, $p < 0.01$), the presence of cam morphology (OR: 3.0, $p < 0.01$), and Tönnis grade 1-2 changes (grade 1 OR 4.1, $p < 0.01$; grade 2 OR: 9.3, $p < 0.01$) were determined to be significant univariate risk factors for intraoperatively-documented ALAD grade 3 and 4 lesions (Table 2). While the observed difference of 1.2 kg/m^2 in BMI between the high and low grade groups was found to be significant in group-wise comparisons ($p < 0.01$), this small absolute difference was considered to have poor clinical discriminatory value.

Following univariate analysis, multivariable analysis for predictors of high grade chondrolabral damage was performed employing stepwise regression with the Akaike Information Criterion and assessment of the relative damage risk represented by each predictive factor. The optimal model generated a readily employable, multivariable in-clinic scoring system, the Rapidly Assessed Predictor of Intraoperative Damage score (RAPID Score), which was based on the sex, Tönnis grade, and cam morphology presence (Table 3). Age and BMI were found to be of poor predictive value and therefore not included in the final model.

RAPID scores were calculated and applied to our dataset in order to determine operating characteristics. Patients with increasing RAPID scores demonstrated increased rates of intraoperatively visualized ALAD grade 3 and 4 lesions, with 10.5% risk in the 0 point score group and 88.0% risk in the 5 point group ($p < 0.01$, Figure 2). Patients were also well stratified with 29.5% of patients falling into a low risk category with RAPID 0-1 scores, 44.8% with intermediate RAPID scores of 2-3, and 25.6% of patients with high risk RAPID 4-5 scores. The receiver-operator characteristics of the RAPID score demonstrated an AUC of 0.754.

Prospective Score Verification

Following score generation, the RAPID score was validated using a cohort of 167 primary hip arthroscopies performed immediately following the initial study period, which included the April 2017 to February 2018 time frame. Validation data served as a unique set of primary arthroscopies, previously blinded and not viewed nor analyzed during the creation of the RAPID score. The observed proportion of validation patients with high grade damage predicted by the RAPID score was similar to that observed in the original study group from which the RAPID score was generated ($p = 0.09$, Figure 3), supporting generalizability of the score.

For further analysis of the operating characteristics of the RAPID score, receiver-operator curves and their associated AUC were generated for both the study patients and the validation cohort (Figure 4). The two curves were observed to be similar, with AUCs that differed by 0.003 ($p = 0.943$), demonstrating that the RAPID score had similar predictive value for both the study group and the previously blinded validation data.

Discussion

Preoperative prediction of high grade chondrolabral damage is of significant clinical value due to consequences on perioperative planning and preparation. Treatment of cartilage defects can potentially require special equipment and preoperative planning for the surgeon, and alters the postoperative rehabilitation for the patient. To date, damage risk factors such as increasing age, Tönnis grade, and the presence of cam deformities have been described on an individual basis. However, there is no readily-available multivariable system on which to preoperatively stratify patients by damage risk. Our hypotheses were confirmed in that established risk factors such as sex, cam morphology, and Tönnis grade predicted damage, and that the combination of such factors could be used both retrospectively and prospectively to predict high grade damage.

Our finding that male gender is predictive of damage is consistent with previous literature including 64 arthroscopies described by Anderson et al.,1502 patients reported by Suarez-Ahedo et al. and 167 patients in the series by Beaulé et al., all of which provided odds ratios for males ranging between 2.24 and 4.00.[28, 383] While males with FAI have been observed

to more commonly demonstrate cam morphology as opposed to females, both male gender and the presence of a cam lesion were found to be independent predictors of damage in our final multivariable model.

The significance of cam morphology in predicting damage is likely biomechanical in nature.[28, 201] It is thought that outside-in shearing contact of the abnormal femoral head-neck junction with the anterosuperior acetabulum during hip flexion and internal rotation is the causative factor for damage.[28] The association between cam morphology and premature arthroplasty is well documented and a mechanical etiology is further supported by published increases in degenerative risk observed with increasing cam severity.[28, 144, 294, 426] A biomechanical basis is also supported when considering our female population in isolation. Although classically associated with male sex, when we performed a female-only subanalysis, the presence of cam morphology conferred a 99% increased risk of high grade damage ($p < 0.01$).

While Tönnis grade is a described damage risk factor, previous literature has assessed this variable on its own.[33] This limits clinical utility as damage is likely the product of the interaction of multiple variables. To our knowledge, Anderson et al. is the only previous group to investigate multivariable predictors of damage. However, their study was not well-powered, consisting of only 64 arthroscopies.[14] Only odds ratios were presented for the factors described and the operating performance of this model was not reported, significantly limiting clinical utility. The group also investigated risk scores for damage as they relate to measures of cam and pincer morphology (pistol grip deformity, femoral neck impingement cyst). Neither score attained statistical significance.

By using the Akaike Information Criterion, we believe we have been able to produce a system which maximizes the predictive ability of the data while providing a parsimonious solution with three simple variables (sex, Tönnis grade, presence of cam morphology) that can be readily and rapidly assessed in clinic using history and radiographs. In addition, the use of a validation cohort is a particular strength of our study. We find it self-evident that a predictive score, based on a study dataset, should perform well when applied to the dataset from which it was calculated. The observation that the RAPID score, when applied to the previously-blinded two-center validation cohort, performed with an AUC statistically equivalent to the original

study data greatly strengthens the notion that this score is generalizable. However, further study is warranted for patient populations found outside our health system.

The receiver operating characteristics of the proposed RAPID score are also worth discussion. The RAPID score was able to predict progressively increasing risks of intraoperatively observed damage, from 10.5% for RAPID score 0 patients to 88.0% for RAPID score 5 patients, providing clinically useful stratification. The observed AUCs of 0.75 and 0.76 for the study and validation groups, respectively, also demonstrate predictive capabilities which are approximately 50% greater than the AUC of 0.52 published for MRA by Rajeev et al.[333] RAPID scores of 5 were found to be highly indicative of damage, with a specificity of 99.1%. While there is certainly room for predictive improvement, the easily assessed nature of the RAPID score, requiring only history and hip radiographs, lends added clinical value to this assessed score.

An example of the clinical utility of the RAPID score are patients with indeterminate MRI findings or artifacts such as those left by motion or nearby implants. In this case, the RAPID score can serve to better inform non-specific data, especially given the previously demonstrated limitations of magnetic resonance imaging in the femoroacetabular joint. A patient with indeterminate imaging but a RAPID score of 4 to 5 (74 - 88% high grade cartilage damage risk) should be pre-operatively counselled for the high likelihood of the performing surgeon's preferred intervention for high grade pathology (i.e. microfracture which can require partial weight bearing status during the course of recovery or the potential for two-stage surgery in the setting of ACI or MACI). In the case of cell-based procedures such as ACI, high RAPID scores can also serve to prompt listing for case preparations in anticipation of cartilage biopsy for expansion.

The RAPID score is generalizable and able to stratify the cartilage damage risk for patients with varying pathology patterns. A female with a Tönnis grade of 1 and no cam lesion and also a male with a cam lesion and Tönnis grade 0 would both have a RAPID score of 2 yet appear as quite distinct entities clinically. In our series, of the 95 patients that meet the criteria of the female described above, 38% of them were intraoperatively documented to have high-grade cartilage damage, whereas of the 39 male patients meeting the scenario described above, 33% of them had high grade damage. This further highlights the value of the easily calculated RAPID score in clinic. While these patients represent two distinct clinical entities, the Akaike

Information Criterion optimized RAPID score accurately predicts intraoperatively documented high grade delamination for both patients, with an estimated risk of 37%, thus providing a simple scoring method to assist clinical decision making.

Our study has important limitations. While variables for the study cohort were prospectively collected, they were retrospectively analyzed and remain reliant on accurate and complete documentation by providers. This is greatly mitigated by the use of standardized forms filled out at the time of arthroscopic intervention. Additionally, while the RAPID score demonstrated satisfactory, comparable operating characteristics when applied to the validation cohort, the validation group is limited to 167 patients or 26% of the original study group, limiting statistical power in comparisons between the score's performance in the two cohorts. Finally, the study presented is the product of two high-volume institutions which, aside from performing primary hip arthroscopy, also perform a many revisions procedures annually. Further research is warranted to ensure the broad applicability of the RAPID score at other institutions and this is currently under way.

Conclusion:

While preoperative MRI imaging has diagnostic value for hip arthroscopy, the RAPID score provides added benefit as a readily employable, in-clinic system for predicting high grade damage. The discriminatory value of the RAPID score compares favorably with previous MRI and arthrography studies. We have found this to be of significant value when evaluating patients, counseling them on likely intraoperative findings and possible alteration in postoperative rehabilitation, and making preparations for hip arthroscopy.

Table 1: Study population demographics by intraoperatively visualized ALAD grade.

Demographic	**ALAD Grade 3-4 (n = 298)**	**ALAD Grade 0-2 (n = 354)**	**p-value**
ALAD Grade			
Grade 0	0 (0%)	89 (25.1%)	
Grade 1	0 (0%)	57 (16.1%)	
Grade 2	0 (0%)	208 (58.8%)	
Grade 3	181 (60.7%)	0 (0%)	
Grade 4	117 (39.3%)	0 (0%)	**< 0.01**
Age at Surgery, years	35.9 ± 11.8	31.0 ± 12.6	**< 0.01**
Sex			
Female (%)	147 (49.3%)	266 (75.1%)	
Males (%)	151 (50.7%)	88 (24.9%)	**< 0.01**
Laterality			
Left (%)	134 (45.0%)	150 (42.4%)	
Right (%)	164 (55.0%)	204 (57.6%)	0.53
BMI, kg/m^2	27.5 ± 4.9	26.3 ± 6.0	**< 0.01**
Tönnis Grade			
Grade 0	53 (17.8%)	179 (50.6%)	
Grade 1	190 (63.8%)	155 (43.8%)	
Grade 2	55 (18.4%)	20 (5.6%)	
Grade 3	0 (0.0%)	0 (0.0%)	**< 0.01**
LCEA	30.4 ± 6.5°	30.1 ± 5.6°	0.55
Tönnis Angle	6.3 ± 4.3°	5.5 ± 4.3°	0.12
Ischial Spine Sign	122 (40.9%)	162 (45.8%)	0.36
Alpha Angle	61.9 ± 11.2°	54.2 ± 12.8°	**< 0.01**

Table 2: Univariate predictors of high grade chondrolabral damage

Variable	Odds Ratio (95 % CI)	p-value
Age		
< 35 years	Reference	
≥ 35 years	1.96 (1.31, 2.97)	**< 0.01**
Sex		
Female	Reference	
Male	3.11 (2.24, 4.34)	**< 0.01**
BMI		
< 30 kg/m^2	Reference	
≥ 30 kg/m^2	1.27 (0.84, 1.92)	0.26
Tönnis Grade		
Grade 0	Reference	
Grade 1	4.14 (2.87, 6.05)	**< 0.01**
Grade 2	9.29 (5.19, 17.20)	**< 0.01**
Cam Morphology		
Not present	Reference	
Present	2.96 (2.08, 4.26)	**< 0.01**

Table 3: RAPID Score and associated point values

Risk Factor	**Point Value**
Sex	
Female	0
Male	1
Tönnis Grade	
Grade 0	0
Grade 1	2
Grade 2	3
Cam Morphology Present	
No	0
Yes	1
Total:	0 to 5 points

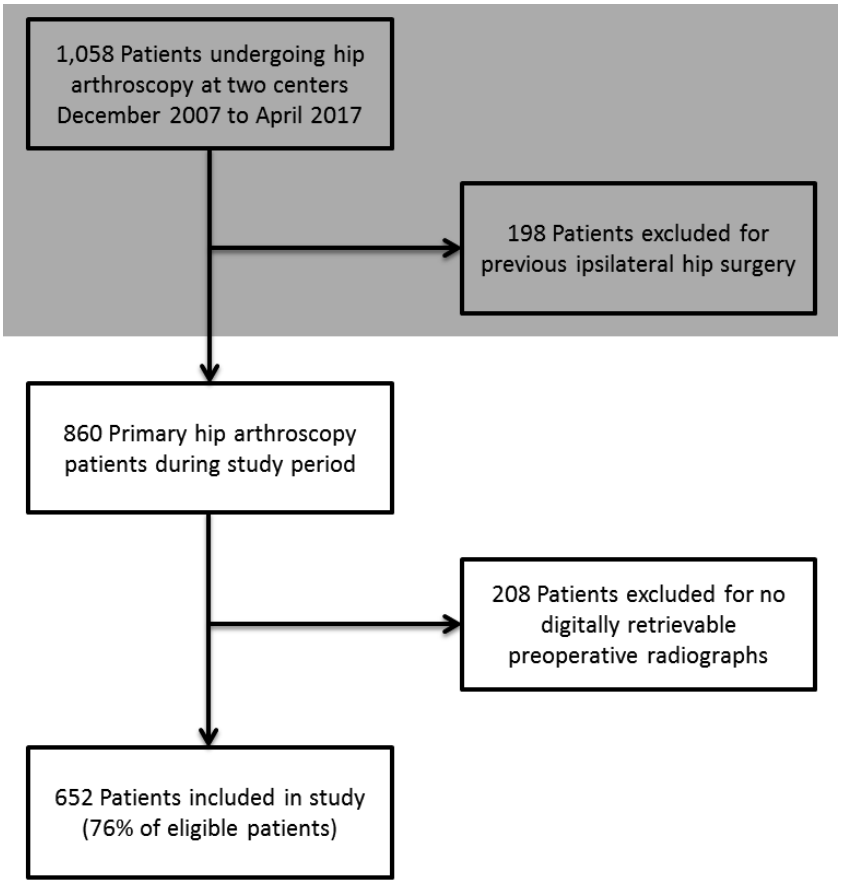

Figure 1: Inclusion and exclusion of patients based on study criteria.

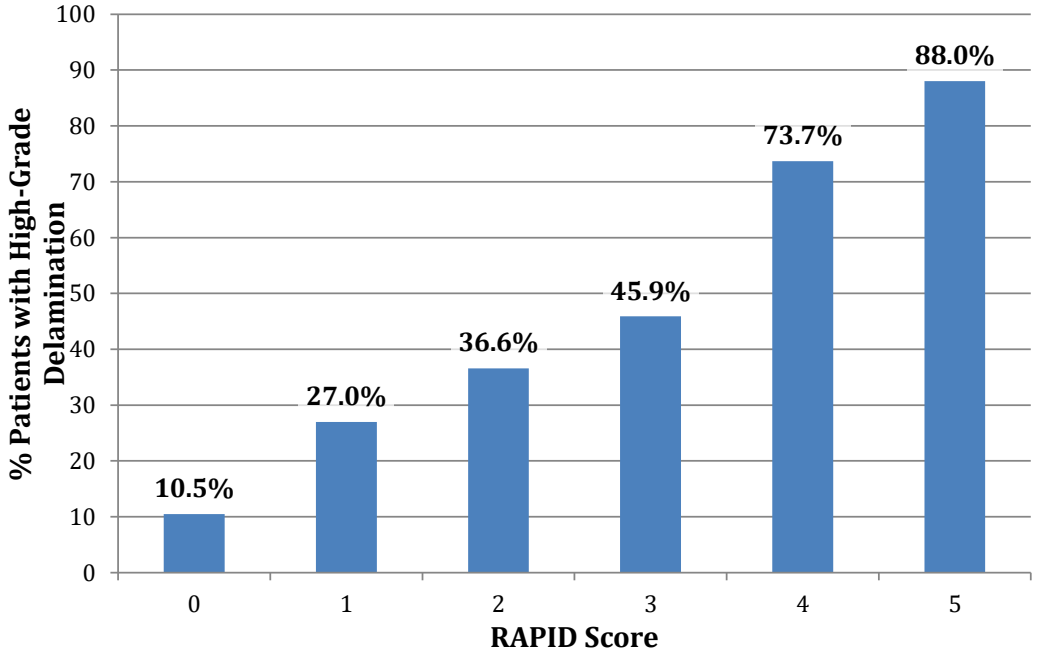

Figure 2: Intraoperatively documented ALAD grade 3 and 4 lesions by RAPID score.

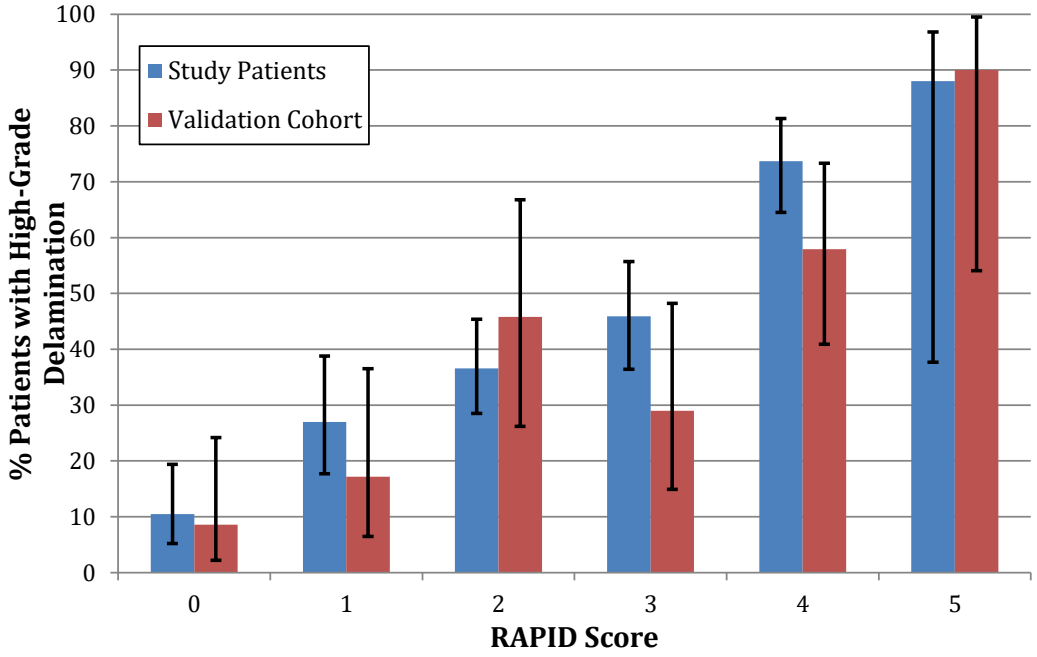

Figure 3: Comparison of validation cohort observed rates of high grade damage by RAPID score to study patients. 95% binary confidence interval for validation cohort provided with solid bars.

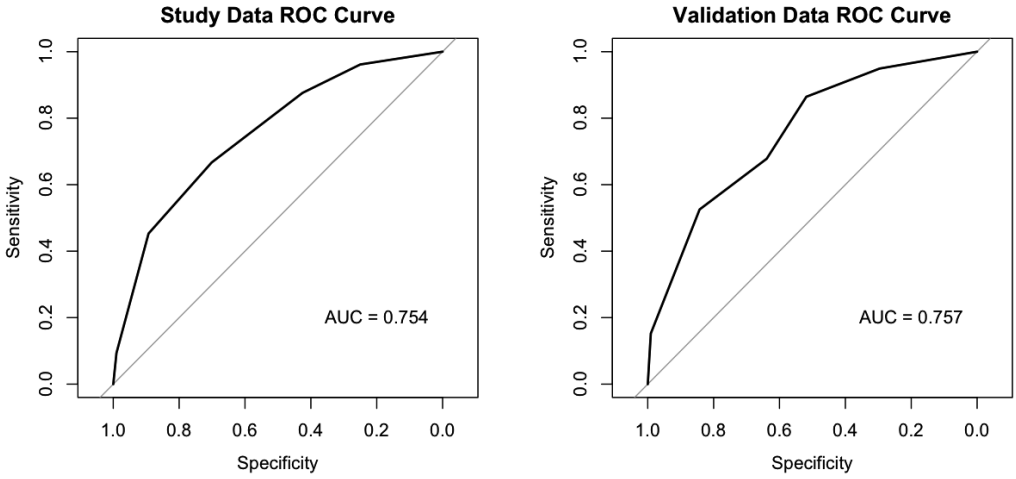

Figure 4: ROC Curves for Study Data and Validation Data.

Learning from Failure in Cartilage Repair Surgery: An Analysis of the Mode of Failure of Primary Procedures in Consecutive Cases at a Tertiary Referral Center.

Krych AJ, **Hevesi M**, Desai VS, Camp CL, Stuart MJ, Saris DBF.

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Introduction

It has been reported that focal cartilage defects impair quality of life in a similar fashion to severe osteoarthritis (OA), causing long-term deficits in knee function.[175] When non-operative management fails, surgery may be indicated with a variety of surgical options available to treat cartilage lesions. Overall, these interventions have been shown to improve quality of life and be cost-effective.[285] Palliative treatment options offer limited and short-term symptom relief for cartilage defects, but articular cartilage restoration has demonstrated cost-effectiveness in reducing pain and functional disability.[96, 285] A variety of surgical options are available to treat cartilage lesions and over 90,000 cartilage repair and restoration cases were performed in the United States in 2010.[271] Surgical options include microfracture, autologous chondrocyte implantation (ACI), osteochondral autograft transfer (OAT), osteochondral allograft transplantation (OCA) and particulated chondral tissue transplantation.[69] Microfracture remains the most commonly performed procedure for cartilage defects.[276]

While these procedures have demonstrated satisfactory results, not all patients do well. Many patients have relevant pathology in addition to the isolated cartilage defect such as: patellar maltracking/instability, malalignment, meniscus deficiency, and instability of the tibiofemoral articulation.[52] It is critical to understand how the cartilage defect occurred prior to considering any attempt at restoration surgery. Treatment with cartilage restoration may fail or outcome durability may be compromised if all possible influential factors are not corrected. In addition, the incidence of articular cartilage defects, the number of surgical procedures, and the variety of techniques have all risen over the past two decades. More surgeons are being trained in these complex procedures with narrow indications, including many who do not subspecialize in cartilage restoration. This is comparable to trends in ACL reconstructions, the majority of which are performed by surgeons that perform less than ten ACL procedures per year.[242, 409] The

most common reason for failure of an ACL reconstruction is technical error with misplacement of the femoral socket by the surgeon.[349, 425] On the contrary, the mode of failure in cartilage repair surgery has not been well elucidated.

Revision surgery will also be more common as a result of the frequent primary cartilage procedures. These revision procedures may have satisfactory outcomes, but they are typically inferior to the initial cartilage restoration.[186] Consequently, it would be instructive to evaluate the current methods of failure in order to optimize patient outcomes and limit the number of failures. The purpose of the present study is to determine the mode of failure of a consecutive series of failed primary cartilage repair procedures presenting to a specialized cartilage clinic at our tertiary referral center. We hypothesize that a large number of failures are due to unrecognized or untreated, concomitant influential factors, such as malalignment, meniscus deficiency, and instability.

Methods

Following institutional review board approval (IRB #15-000601), patients who underwent revision surgery following a failed cartilage repair between September 2011 and May 2017 were identified. Inclusion criteria consisted of all cases of all referred patients undergoing revision cartilage surgery by the first author (AJK) at a single institution in the above-defined time period. Exclusion criteria consisted of 1) patients presenting with failed cartilage surgery that were not candidates for revision cartilage surgery, 2) those that required arthroplasty, and 3) patients choosing not to participate in research. Patients who were not candidates for revision cartilage surgery were those with generalized degenerative changes and osteoarthritis of the knee, leading to conservative non-operative management or arthroplasty following their index cartilage procedure.

Cases were reviewed by two fellowship trained experts in cartilage surgery in a blinded fashion in order to arrive at a consensus for cause of failure. Failure was defined as lack of improvement of preoperative symptoms including pain, function, activity level, and overall quality of life leading to an indication for revision surgery. Index (failed) surgeries were performed at outside institutions and included microfracture technique, osteochondral autograft transfer (OAT), fresh osteochondral allograft transplantation (OCA), nonviable/decellularized osteochondral allograft (*Chondrofix*®, Zimmer Biomet, Warsaw, IN),

and particulated juvenile chondral allograft (*DeNovo® NT Natural Tissue Graft,* Zimmer Biomet, Warsaw, IN). All revision surgeries were performed by a single surgeon and included OAT, OCA, high tibial osteotomy (HTO), tibial tubercle osteotomy (TTO), autologous chondrocyte implantation (ACI), distal femoral osteotomy (DFO), medial meniscus allograft transplant (MMAT), and particulated juvenile chondral allograft. A total of 53 patients, comprising 59 failed cases, were identified for this review of prospectively collected data. Basic demographic information including age, gender, BMI, and level of education, was collected from the medical records for all cases. Surgical details including size and location of lesion, laterality, type of failed intervention, and revision strategy was gathered from pre-operative and intra-operative notes. Patients with failure of bilateral cartilage restoration procedures and those with repeat revision surgeries were eligible for inclusion. Lesion dimension data was available for 53 of the 59 failed cases and was combined from all anatomic locations of the knee joint. Surgical notes in all cases provided maximal width and height dimensions (in millimeters) that were used to calculate a total lesion area estimate.

Mechanism of failure was determined by physical examination, pre- and post-index procedure imaging and intraoperative findings during revision surgery. While imaging obtained prior to index surgery at outside institutions varied, standard anteroposterior, lateral, patellar views (sunrise or merchant), and full-length standing films were obtained in addition to magnetic resonance imaging (MRI) in preparation for revision surgery. Mechanisms of failure were categorized into four broad categories:

1. Malalignment: Defined as 5 degrees or more of mechanical axis deviation.[82, 177]
2. Meniscus deficiency: Defined as less than 50% functioning meniscus tissue.
3. Instability: Defined as unaddressed or persistent clinically symptomatic instability. In the patellofemoral joint, this was typically patellar subluxation/dislocation that required MPFL reconstruction and/or TTO during the revision surgery. In the femorotibial joint, this was typically persistent instability following an ACL reconstruction requiring revision ACL reconstruction.
4. Graft failure: Defined as biologic failure of the index cartilage repair or restoration procedure without other identified contributing factors.

Statistical Analysis

Patient characteristics, including demographics and risk factors for cartilage failure, were summarized using descriptive statistics including means, standard deviations, and percentages, as appropriate. Descriptive statistics predominated due to the nature of this case series of failed procedures and referrals to a tertiary surgical center. Where appropriate, proportions were compared using Chi-squared testing. Statistical analysis was performed in R 3.4.0 (R Core Team, Vienna, Austria). P-values < 0.05 were considered statistically significant.

Results

59 failed cartilage procedures on 53 patients were surgically revised between September 2011 and May 2017. Average patient age at time of revision surgery was 27.6 (Range, 14.0-49.0, Table 1). The study sample included 32 males (60%) and 21 females (40%). The average duration from the failed index surgery to revision was 41.5 months (SD: 38.4).

Failed index surgeries included 35 microfractures (59%), 12 OCA (20%), 10 OAT (17%), 2 non-viable osteochondral allograft (3%), and 2 particulated juvenile chondral allograft (3%; Table 2). Thirty-two patients had lesions involving the medial femoral condyle (MFC) (60%), 21 involving the lateral femoral condyle (LFC) (40%), 12 involving the patella (23%), and 9 involving the trochlea (17%; Table 3). 48 failures involved lesions affecting only one area of the knee joint (81.4%), 7 affected 2 regions (11.8%), and 4 affected three regions (6.8%).

Reason for index surgery failure was divided into four categories as follows: 33 due to malalignment (56%), 11 due to meniscus deficiency (19%), 16 due to graft failure (27%), and 3 due to instability (5%; Table 4). Four of the 59 failed cases involved more than one failure mechanism. Six patients had bilateral disease (11%). Of these, 1 had simultaneous revisions of both sides whereas the remaining were performed serially. Ten of the index cases involved an initial insult that was traumatic in nature (17%). In total, 74 distinct lesions were found, accounting for the 59 failed cases. Sixty-six of these lesions provided dimension data in either the surgical or radiology note, and mean lesion size was 4.4 cm^2.

Overall, the most common failed procedure was microfracture, and the majority failed due to malalignment. While most of the failures were attributable to one mechanism, 4 cases were found to have failed by two mechanisms. The most commonly affected region of the joint was the medial femoral condyle followed by the lateral femoral condyle. Although some patients

did have cartilage failure at multiple locations, the majority of patients only had one point of failure. The reasons for failure were statistically similar in distribution ($p = 1.00$) for outside institutions and tertiary referral center (Table 5). Detailed patient data is organized below (Table 6).

An illustrative example has been provided (Figures 1-3). This patient was a 32 year old active golfer who developed an osteochondritis dissecans lesion and underwent excision and microfracture. Because the microfracture failed, he underwent cell-based particulated juvenile chondral allograft which was later revised with decellularized osteochondral allograft, which also failed. His initial radiographs demonstrate significant varus malalignment through the osteochondral lesion. At presentation to our cartilage center, he was offered surgery with valgus osteotomy and revision fresh osteochondral allograft. This case represents the only patient in this series with more than one procedure at presentation.

Discussion:

Healthy articular cartilage is essential for normal, pain-free knee function and focal cartilage defects can impair quality of life similar to severe osteoarthritis.[175] With the evolution of cartilage restoration techniques, the number of cartilage procedures performed in the United States has substantially increased, with an associated increase in failed cartilage surgeries and subsequent revisions.[272] The purpose of this study was to determine the mode of failure for primary cartilage procedures referred to a tertiary referral center in order to perform a descriptive casual analysis and identify treatable risk factors for failure. Our hypothesis was confirmed in that the majority of failures were due to a lack of treating underlying factors such as malalignment, meniscus deficiency, and ligament instability.

The most common reason for failure of cartilage restoration procedures was residual malalignment (56%). In cases of malalignment, the affected cartilage compartment is overloaded, with potentially profound changes in force distribution at relatively low degrees of angulation. In previous native joint and total knee model analyses, it has been suggested that an increase of 4-6° varus angulation leads to a 20-50% increase in medial tibiofemoral stresses.[390, 420] There exists strong evidence that malalignment plays a role in both the development and subsequent progression of osteoarthritis.[54, 364, 387] In particular, Sharma et al, in their age, sex, and BMI adjusted model, demonstrated that varus malalignment was associated in a 4-fold

increase in progression in Kellgren-Lawrence arthritis of ≥ 1 grade at 18 months follow-up while valgus malalignment was associated with a near 5-fold increased incidence of arthritic progression.[364] Severity of both varus and valgus deformity correlated with risk of disease progression. As such, we believe long-leg standing hip to ankle films are of utmost importance in the cartilage patient. Without addressing the underlying increased contact stresses that may have caused the primary cartilage injury, any restorative procedures are at increased risk to fail under continued increased stresses. While osteotomy alone in patients with chondral pathology and underlying malalignment may provide short-term symptomatic improvements, we recommend concurrent operative treatment of cartilage defects as restoration of the articular surface is necessary for optimal load-sharing in order to prevent asymmetric kinematics and resultant cartilage defects. In light of optimizing even articular load distribution, we recommend restoration of the normal anatomic axis as opposed to overcorrection when performing osteotomies for focal defects. Accordingly, sports medicine surgeons who perform cartilage restoration in their practice need to be well equipped and comfortable doing periarticular osteotomies about the knee. We also recommend avoiding microfracture for lesions encountered at the time of arthroscopy without knowledge of preoperative alignment as it is possible that a significant number of microfracture failures are due to addressing such findings without sufficient evaluation of contributing background factors.

Another common reason for cartilage failure was meniscal deficiency, which was observed in 11 of the 59 cases of revision surgery (18.6 %). Meniscectomy and untreated meniscal tears have an extensive track record for leading to increased osteochondral degenerative changes over time when compared to uninvolved contralateral knees or population controls.[9, 62, 128, 320] In cadaveric studies, it has been demonstrated that after partial meniscectomy of the inner one third of meniscus, tibiofemoral contact areas decrease by 10% while peak local contact stresses increase by 65%.[23] Furthermore, in total meniscectomy, contact area decreases by 75% and peak local contact stresses increase 2.35-fold.[23] Of additional significance is definitive intraoperative examination of the meniscal roots, as tears in these difficult to image areas has demonstrated significant subsequent increases in articular contact stresses.[8, 231, 234, 265] Consideration should also be given for meniscal allograft transplantation for cases where meniscal repair or conservative, partial debridement is not possible. Although there is controversy regarding the long-term results of meniscal transplantation, biomechanical studies support a possible protective role in increasing contact area and stability as well as decreasing peak contact stresses within the knee joint.[7, 183, 317, 344, 361, 372]

The importance of concomitant instability in patellofemoral cartilage defects is considerable and provides a treatment challenge. In the landmark series by Brittberg and Peterson, overall results for ACI were quite promising with 16 of the 23 patients reporting good to excellent results.[52] However, positive outcomes were concentrated in the femoral condylar transplant group (14 of 16 good-to-excellent) while failures were concentrated in the patellar group (2 of 6 good-to-excellent). At the time of publication, patellar maltracking and instability were not well-recognized in the literature and thus not addressed intraoperatively. In their discussion, the authors suggest that malalignment and subluxation may play a role in their modest results and that these may be better addressed by correction of the underlying abnormalities. In more contemporary series reporting on patellar ACI with concomitant biomechanical normalization procedures such as tibial tubercle osteotomy (TTO) with anteromedialization, trochleoplasty, and medial patellofemoral ligament (MPFL) reconstruction, outcomes have been significantly improved. A recent multicenter experience demonstrated greater than 80 % good-to-excellent outcomes and more than 90 % of patients stated they would undergo the procedure again.[148] Special care should also be taken to evaluate for sagittal and coronal instability. There is an abundance literature suggesting that for patients with laxity, coronal instability precedes and predisposes to osteoarthritic changes, with the degree of laxity positively associated with a degree of cartilage loss.[362] In terms of sagittal instability, it has been demonstrated that meniscus tears with concomitant ACL tears fare worse following meniscectomy than patients with isolated meniscectomy without ACL pathology.[62] Similarly, MRI and biomechanical studies have suggested that PCL deficiency causes both acute chondral damage and increased cartilage deformation and altered tibiofemoral load, leading to chronic cartilage degeneration which is potentially preventable by addressing the underlying ligamentous source of instability.[79, 337, 402] As such, patients with ligamentous laxity should be counselled on their increased risk for failure following cartilage procedures while patients with surgically correctable factors such as ACL and/or PCL deficiency should undergo treatment of both cartilage and associated ligamentous procedures to minimize the risk of subsequent failure.

Despite the correction of background factors and improvements in techniques and outcomes, cartilage surgery will not have uniformly excellent results. Graft failure was the reason for approximately one quarter of revision cases. While storage and optimization efforts are underway to improve graft quality and surgical techniques continue to evolve, the cartilage

patient continues to pose a complex clinical entity which is often the result of multiple, overlapping biomechanical and patient-specific factors. While surgical factors can be optimized, other variables such as age, BMI, and patient activity level will continue to impact the rates of cartilage surgery success. Accordingly, cartilage surgery candidates must be preoperatively counselled in light of established risk factors for failure such as increased BMI and patient age where non-operative optimization or arthroplasty may provide more durable approaches. We recommend that every cartilage patient undergo an extensive clinical history, physical examination including analysis of gait and alignment, full length radiographs, and scrutinization of all imagining in order to recognize contributing background factors. Surgical management of the cartilage patient should only be considered in the practice of the physician facile in osteotomy, meniscus repair, meniscus transplantation techniques, and patellofemoral procedures such as TTO, MPFL reconstruction, lateral retinacular lengthening, and trochleoplasty.[305]

This review of failed cartilage procedures has some limitations. Defining failures as revision surgery at a tertiary referral center underestimates the number of procedures with poor results, as patients may elect for non-operative management or even total knee arthroplasty following suboptimal outcomes following primary cartilage surgery. However, including patients with poor initial indications for cartilage surgery, such as diffuse degenerative changes, was not felt to add instructive insight to the mode of failure of cartilage repair surgery. The results of this study were also subject to a degree of referral bias as the revising surgeon had no control over the nature of failed cartilage repair patients presenting for re-evaluation or the previous surgeries they had undergone. In light of this bias, the relative predominance or absence of primary procedures such as microfracture and ACI should be interpreted with caution as these values are influenced by not only failure rate but also prevalence and referral patterns. The original surgeons did not assess alignment and provided no long-leg radiographs to the revising surgeons. Therefore, it is unknown if alignment changed from normal to malalignment between the primary and revision surgeries. Similarly, an assumption was made that the status of the meniscus at the time of revision was similar to after the primary surgery was performed. And finally, when reporting surface area, the maximum length and width of lesions are presented. It is important to note that lesions were often irregular in shape and thus, these total surface area measurements likely tend to overestimate lesion size.

Conclusion:

Cartilage restoration procedures play an important and evolving role in managing knee pathology, which often exists with a spectrum of contributing background factors. In the current series, the most common failed cartilage procedure treated with revision surgery was microfracture, and the most commonly recognized reason for failure was untreated coronal malalignment. While biologic and graft failures do occur, the majority of failures were attributed to untreated background factors such as malalignment, meniscus deficiency and instability. Thorough preoperative recognition and consideration of treatment of these background factors is critically important in cartilage surgery. By following a step wise approach that first addresses alignment, meniscus volume, and joint stability prior to, or concurrently with, the cartilage defect, patient care and functional outcomes are more likely to be optimized.

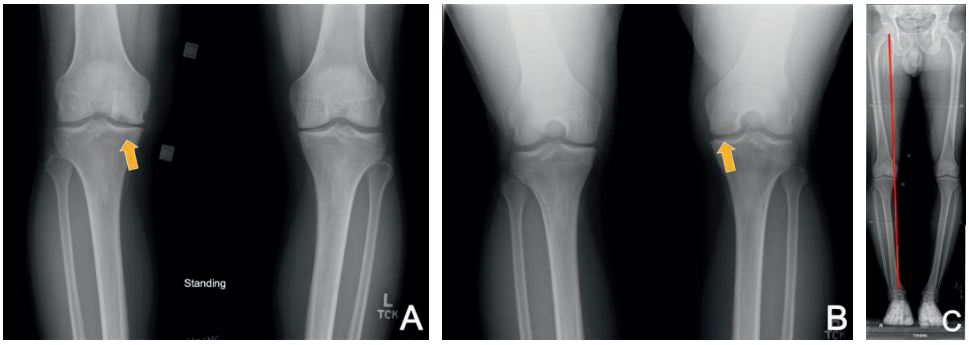

Figure 1A-C: A-B: Initial radiographs with AP demonstrating luceny in the medial femoral condyle consistent with an osteochondral defect and a preserved joint space on PA flexion film. C: Long-leg radiographs demonstrate significant 10 degree varus deformity with malalignment through the affected compartment.

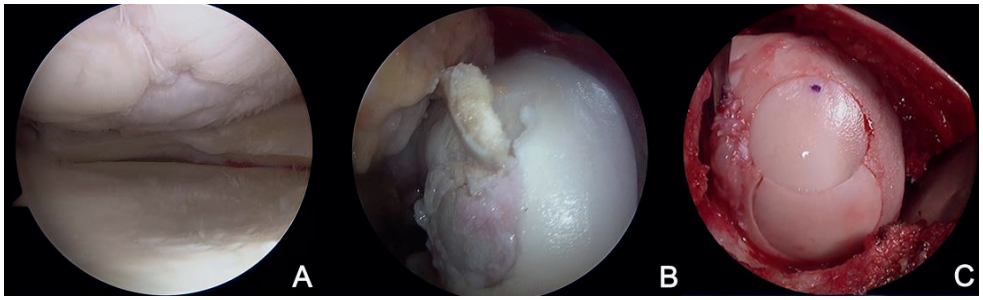

Figure 2A-C: (A-B) Intra-operative pictures demonstrating failed OCA transplant. (C) Final images after revision fresh osteochondral allograft with snowman technique.

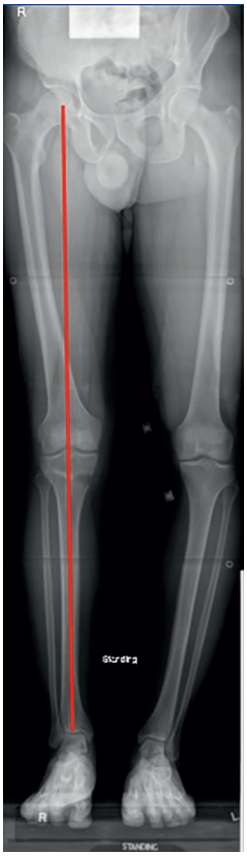

Figure 3: Long-leg radiographs demonstrate correction of varus deformity with valgus-producing proximal tibial osteotomy

Table 1: Patient Demographics at Time of Revision\

Variable	Value
Age (years)	27.6 ± 9.0
Gender	
Male	32 (60 %)
Female	21 (40 %)
BMI (kg/m^2)	28.4 ± 5.3
Laterality	
Right	32 (54 %)
Left	27 (46 %)
Time to Revision (months)	41.5 ± 38.4

Table 2: Summary of Reason Procedures were Performed

Primary Cartilage Procedures		
	N	**% of cases**
MFX	35	59.3
OCA	12	20.3
OAT	10	16.9
deNovo	2	3.4
chondrofix	2	3.4
TOTAL:	**61**	
Concurrent Procedures		
TTO	14	23.7
HTO	12	20.3
DFO	7	11.9
LMAT	7	11.9
MMAT	3	5.1
Meniscal Repair	2	3.4
Other	3	5.1
TOTAL:	**48**	

Table 3: Number of Cases involving Each Location

Medial Femoral Condyle	32	(54%)
Lateral Femoral Condyle	21	(36%)
Patella	12	(20%)
Trochlea	9	(15%)

4 failed cases involved lesions at 3 locations and 7 involved lesions at 2 locations. The remainder involved one lesion.
% represents percentage of cases involving that location

Table 4: Reason Cited for Index Procedure Failure

Malalignment	33	(56%)
Graft Failure	16	(27%)
Meniscal Deficiency	11	(19%)
Instability	3	(5%)
TOTAL	**63**	

Table 5: Reason for Index Procedure Failure for Procedures performed at OSH and Tertiary Center

Reason for Failure	Outside Hospital		Tertiary Center	
Malalignment	20	50%	12	52%
Meniscus Deficiency	8	20%	4	17%
Graft Failure	11	28%	6	26%
Instability	1	3%	1	4%

Table 6: Patient Data

#	Sex	Age at Revision (years)	Side	Failed Index Surgery	Lesion Location	Lesion Size (cm squared)	Reason for Failure	Time from Index to Revision (mos)	Revision Procedure
1	F	43	R	failed MFX	MFC	1.44	varus malalignment	-	OAT, HTO
2	F	17	L	failed OAT	LFC	1.2	meniscus deficiency	12.6	OC allograft, LMAT
3	M	31	L	failed MFX	MFC	1	varus malalignment	40.0	OAT, HTO
4	F	24	R	failed MFX	MFC	1.65	varus malalignment	31.7	OAT, HTO
5	F	34	R	failed MFX	MFC	1.12	varus malalignment	-	OAT, HTO
6	M	20	L	failed MFX	MFC	-	varus malalignment	-	OAT, HTO
7	F	20	R	failed MFX	Patella	1.44	patella maltracking, graft failure--fibrocartilage	67.2	MACI, TTO
8	F	16	L	failed OAT	LFC	3.96	meniscus deficiency	-	OCA, LMAT
9	M	39	L	failed MFX	MFC	6.25	varus malalignment	30.8	OCA, HTO
10	F	14	R	failed OAT	MFC	3.3	varus malalignment	-	OCA, HTO
11	F	32	R	failed OAT	MFC	4.5	meniscus deficiency	-	OCA, MMAT
12	F	24	R	failed OAT	MFC	-	graft failure	18.1	OCA--pre-op wt loss
13	M	20	L	failed MFX	LFC	4.84	valgus malalignment	-	OCA, DFO
14	M	17**	R	failed OCA	MFC	6	graft failure	-	revision OCA
		17**	L	failed OCA	MFC	6	graft failure	-	Revision OCA
		19	R	failed OCA	MFC	6.72	graft failure	15.6	revision OCA
		21	R	failed OCA	MFC	6	graft failure	24.8	revision OCA
15	M	14	L	failed OAT	LFC	2	meniscus deficiency	7.7	OCA, LMAT
16	M	31	L	failed OCA	LFC	-	valgus malalignment	4.2	revision OCA, DFO
17	M	32	R	failed MFX, deNovo, chondrofix	MFC	8.75	varus malalignment	36.0	OCA, HTO
18	F	29	R	failed OCA	MFC	2.34	graft failure	39.9	ACI sandwich technique
19	M	39	L	failed MFX	MFC, LFC, Trochlea	-	graft failure	120.9	Multifocal OCA
20	M	37	R	failed chondrofix	MFC	-	varus malalignment, graft failure	25.6	HTO, revision OCA
21	F	47	L	failed MFX	MFC	3.24	graft failure	96.6	OCA
22	M	28	R	failed OCA	LFC	7.29	meniscus deficiency	-	revision OCA, LMAT
23	F	20	R	failed MFX	Patella	4.4	patella maltracking	28.9	deNovo, TTO
		21	L	failed MFX	Patella	8.68	patella maltracking	44.8	deNovo, TTO
24	M	26	L	failed MFX	Patella	5	patella maltracking	83.3	deNovo, TTO
25	F	34	L	failed deNovo	Patella, Trochlea, MFC	Patella: 3.12; Trochlea: 1.3; MFC: 5.67	patella maltracking	40.5	ACI, TTO
		35	R	failed MFX	MFC, Trochlea, Patella	MFC: 4; Trochlea: 1.68; Patella: 4.2	patella maltracking	22.5	ACI, TTO
26	M	33	L	failed MFX	MFC, Patella	MFC: 3.6; Patella: 6.8	varus malalignment	3.1	ACI, HTO
		33	R	failed MFX	Patella, Trochlea	Patella: 6; Trochlea:	patella maltracking	5.8	ACI, TTO

						1.44			
27	M	22	R	failed MFX	MFC	1	patella instability	96.4	ACI patella, TTO, MPFL
28	M	20	L	failed MFX	LFC	5	valgus malalignment	42.1	DFO, ACI
29	F	20	R	failed MFX	Patella	3.96	patella instability	74.8	ACI MPFL
30	F	32	L	failed MFX	Patella	3.75	patella maltracking	24.7	ACI, TTO
31	M	24	R	failed OCA	LFC	7.56	valgus malalignment	4.5	revision OCA, DFO
32	M	33	R	failed OAT	LFC	3.24	valgus malalignment	-	OCA, DFO
33	M	49	L	failed MFX	MFC	4	varus malalignment	33.5	OCA, HTO
34	M	31	L	failed MFX	MFC	6	varus malalignment	8.9	OCA, HTO
35	M	39	L	failed MFX	Patella, MFC	Patella: 1.5; MFC: 5.29	MFX for an osteochondral lesion (bone and cartilage)	-	OCA
36	M	25	R	failed OAT	LFC	4.84	Meniscus deficiency	-	LM root repair, OCA
37	M	23	L	failed MFX	LFC	4	Meniscus deficiency	72.4	LMAT, LFC OCA
38	M	45	R	failed MFX	MFC	6	MFX for an osteochondral lesion (bone and cartilage)	7.3	OCA
39	M	25	L	failed OAT	LFC	1	meniscus deficiency	-	OAT LFC, root repair
40	M	23	L	failed MFX	MFC	6.25	graft failure	113.5	OCA
41	F	22	R	failed OCA	MFC	5.29	meniscus deficiency	35.9	revision OCA, MMAT
42	F	16	L	failed MFX	LFC	-	meniscus deficiency, valgus malalignment	23.9	DFO, LMAT
43	M	18	R	failed OCA	LFC	8	valgus malalignment	21.8	DFO, revision OCA
44	M	21	R	failed OCA	LFC	6.25	meniscus deficiency, ACL failure	-	DFO, revision ACLR, MMAT
45	F	36	R	failed MFX	Patella	4	patella maltracking	116.4	Cartiform, TTO
46	M	20	R	failed OCA	MFC	7.56	graft failure	-	revision OCA
47	F	33	R	failed MFX	Trochlea, MFC, LFC	Trochlea: 4; MFC:1.6; LFC: 2.8	patella maltracking	4.1	ACI, TTO
48	M	30	R	failed MFX	LFC, Trochlea	LFC: 2.99; Trochlea: 9	patella maltracking	8.0	ACI, TTO
49	F	22	L	failed OAT	LFC	4.84	meniscus deficiency	59.9	OCA, LMAT
50	M	42	R	failed MFX	Trochlea, MFC	Trochlea: 4; MFC: 8 LFC: 4.6;	graft failure	54.9	OCA
51	M	32	L	failed MFX	LFC, Trochlea	Trochlea: 6.6	patella maltracking	2.6	MACI, TTO
52	M	42	L	failed MFX	Trochlea, LFC	Trochlea: 5.06; LFC: 1.76	patella maltracking	12.5	MACI, TTO
53	F	36	R	failed MFX	MFC	5.94	graft failure	166.0	OCA

**Surgeries were performed simultaneously

Chapter IV:

Optimization of Osteochondral Tissues for Transplantation in Cartilage Repair

Fresh Osteochondral Allograft Transplantation in the Knee: A Viability and Histologic Analysis for Optimizing Graft Viability and Expanding Existing Standard Processed Graft Resources using a Living Donor Cartilage Program

Hevesi M*, Denbeigh JM*, Paggi CA, Galeano-Garces C, Bagheri L, Larson AN, Stuart MJ, Saris DBF, van Wijnen AJ, Krych AJ.

Cartilage.
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Introduction

Osteoarthritis remains a central challenge of orthopedics, affecting more than 1 in 4 American adults and more than 300 million patients worldwide.[73, 117] Focal articular cartilage defects are common in young patients and play a key role in disrupting joint homeostasis and driving the inflammation- and degradation-based pathogenesis to generalized osteoarthritis.[58] In addition to significant long-term sequelae, focal cartilage defects can cause acute pain and disability similar to that of severe arthritis.[174]

Articular cartilage defects have limited reparative potential due to the poor inherent regenerative capacity and the avascular nature of cartilage. Therefore, articular defects have been classically treated with surgical interventions including microfracture, cell-based therapies such as autologous chondrocyte implantation, and tissue-based therapies such as osteochondral allograft (OCA) transplantation.[215]

First described as early as 1908, OCA has become the gold standard for the treatment of cartilage defects greater than 2 cm^2, with well-established safety, efficacy, and durability.[210, 212, 244, 273, 282, 300, 334] The use of osteochondral tissue allows for the simultaneous transplantation of cartilage and underlying bone, enabling clinicians to address pathology extending beyond the subchondral plate if needed. Using classically obtained fresh allografts which were often implanted within the first 24 – 48 hours of donor expiration, long-term graft survival rates of 66 – 69% have been described at 20 years of follow-up.[129] Furthermore, in addition to durability, OCA has demonstrated a broad range of clinical applications, with a proven track-record spanning the knee, ankle, hip, shoulder, elbow, and other joints.[35, 210, 286, 297, 334, 336]

With the emergence of uniform cartilage banking and testing protocols embodied in part by the 2004 adoption of United States Pharmacopeia (USP) <71>, OCA tissues were stored at 4°C for a minimum of 14 days and up to 28 - 35 days following procurement and prior to implantation.[399] Subsequently, it has been well-demonstrated that cellular demise, driven by apoptosis and cell-stress at sub-physiologic temperature significantly deteriorates allograft viability and quality, even within the first 14 days of storage.[248, 284, 382] Alternative storage methods at room temperature (22 – 25°C) and physiologic 37°C temperatures have subsequently been proposed and demonstrated to be superior to refrigerated storage, as is current clinical practice.[146, 381] Despite this, no direct comparison of alternative cartilage storage and sourcing has been made to clinical-grade tissues, which are currently poorly characterized given their high cost and relative rarity. Accordingly, many previous studies employed caprine and canine cartilage, which may possess different storage and viability profiles as compared to human tissues.

Therefore, the central limitation of increasing clinical implementation of gold-standard OCA is that allografts are currently obtained from young deceased donors, leading to logistical scheduling challenges and lack of scalability of this efficacious resource. The purpose of this study was to 1) determine and validate living cartilage allograft transplantation as a novel source for viable OCA tissues and 2) to perform histologic and viability comparisons of living donor cartilage tissues to currently available clinical-grade standard processed grafts.

Methods

Tissue Collection and Processing

Joint resections were collected from young patients (< 60 years) undergoing total knee arthroplasty (TKA) for varus or valgus pathology with well-preserved contralateral compartments demonstrating Kellgren-Lawrence Grade 0 or 1 pathology. Patients with Grade 2+ pathology in the preserved compartment (lateral for varus, medial for valgus) were ineligible for tissue collection and subsequent analysis. Screening was performed on the basis of pre-operative TKA templating radiographs, without further advanced imaging or additional formal criteria for meniscus and ligamentous pathology. Importantly, the decision for TKA was made clinically and independently of subsequent osteochondral tissue donation, with radiographs of listed TKA patients screened to determine the presence of a minimally affected compartment appropriate for cartilage characterization. Twenty-seven young TKA donors (16 males, 11 females, age: 56.2 ± 3.3 years) were screened using standard American Association of Tissue Banks (AATB) tissue donation criteria and were eligible for inclusion in this study. In addition, 10 femoral OCA specimens, obtained immediately following operative implantation of the harvested osteochondral plug in clinical practice, were collected in order to characterize currently utilized OCA tissues and serve as a point of

comparison to TKA tissues (i.e. living donor cartilage). Therefore, a total of 37 osteochondral samples were analyzed. All aspects of this study were performed following Institutional Review Board approval (IRB 13-005619).

Upon collection of the living donor TKA joint resections and deceased donor OCA samples, photos were taken to enable gross observation and scoring of the tissues according to the International Cartilage Repair Society (ICRS) grading system.[53] Subsequently, osteochondral samples were harvested from each sample by the creation of 4 mm cartilage discs using biopsy punches for use in histologic and cellular-level characterization. Cartilage discs were stored in 2 mL of serum-free osteochondral media at 37°C with hypoxia (2.0 + 0.5% O_2) for experimental time points ranging from 1 – 4 weeks following harvest, with media changes every 7 days.

Histologic Tissue Characterization

Discs undergoing histologic analysis were transferred to 10% neutral buffered formalin for preservation. After 24 hours of fixation, samples were transferred to 70% ethanol for storage prior to embedding. Tissues were subsequently bisected and embedded in paraffin and sectioned (5 μm) along a vertical plane to get cross-sectional views simultaneously demonstrating both the superficial and deep aspects of the osteochondral samples. Slides were stained for hematoxylin-eosin (H&E) and Safranin-O using standard methods.

Additional sample sections underwent immunohistochemical staining for aggrecan (mouse anti-aggrecan antibody, Novusbio NB110-6524, Dilution 1:150 in PBS/BSA 5%), collagen I (rabbit monoclonal anti-Collagen 1, Abcam EPR7785, Dilution: 1:400 in PBS/BSA 5%) and collagen II (mouse monoclonal anti-Collagen II, DSHB, University of Iowa, Dilution 1:100 in PBS/BSA 5%) with normal mouse or rabbit IgG used as a negative controls.

Cell Viability Quantification

Osteochondral discs were assessed for cell viability using a two-color fluorescence assay based on the simultaneous determination of living (Calcein acetoxymethyl (AM): green) and dead cells (Ethidium homodimer-1: red) (Live-Dead Viability/cytotoxicity kit for mammalian cells; Molecular Probes). Fluorescent three dimensional confocal images (850 um x 850 um x ~ 100 um; 7.2 um slice thickness) were collected using an inverted LSM 780 multiphoton laser scanning confocal microscope (488 nm & 561 nm lasers) at 10x magnification. Maximum intensity projections were subsequently created in Zen (2.3 SP1, Zeiss 2015) using a threshold value of 25. The amount of red and green in each image was quantified objectively in an automated and

independent process using MatLab (R2015b, 8.6.0.267246) to provide red and green pixel counts. Viable Cell Density (VCD) was calculated by dividing the number of green (live) pixels by the sum number of green (live) and red (dead) pixels in order to provide a quantitative and non-subjective measure of percentage viable cells.

Microbiologic Testing

Culture-based microbiological testing was performed by a dedicated microbiologic laboratory (Mayo Clinic, Rochester, MN) by placing osteochondral samples into 35 ml of tryptic soy broth followed by vortexing and allowing the sample to mix for 10 minutes. Subsequently, 0.1 ml of culture was placed onto two sheep blood agar plates, one incubated in 37°C under aerobic conditions (21% O_2, 5% CO_2) and the other placed in 37°C anaerobic culture. In addition, for each sample, 8 ml of inoculated, mixed tryptic culture was placed into a sealed sterile container for anaerobic broth culture alongside the anaerobic plate specimen. Samples were monitored for 2 weeks for microbiological growth. Additionally, bacterial endotoxin (BET) quantification was performed using kinetic turbidimetric testing employing good laboratory practice (GLP) principles and test validation by an independent, third-party laboratory (Nelson Laboratories, Salt Lake City, UT) in accordance with Food and Drug Administration (FDA) standards.

Statistical Methods

Statistical analysis was performed by two formally trained statisticians. Histologic measurements and cell viability comparisons were made between groups using generalized linear models (GLM) and Kruskall-Wallis rank-sum testing. Multi-group p-values were adjusted for the number of comparisons performed during GLM modeling using the methods described by Benjamini and Hochberg (1995) [36]. P-values < 0.05 were considered significant. Statistics were performed using SAS 9.4 and JMP Pro 13.0 (SAS Institute, Cary, NC), and R Version 3.4.3 (R Core Team, Vienna, Austria).

Results

Physiologic Storage of Osteochondral Tissues

Baseline viable cell density (VCD) at the time of living donor TKA sample harvest was 91.8% ± 8.5%. Decreasing viability over time was observed, with average VCD of 86.1 ± 16.9% at Week 1, 86.4 ± 14.9% at Week 2, and 72.5 ± 15.6% at Week 3 (p = 0.01 for Day 0 versus Week 3, Figure 1). A significant progression of superficial GAG loss was also observed over time, with a mean depth of

GAG loss progression of 25.6 μm at Week 1, 70.0 μm at Week 2, and 71.7 μm at Week 3 ($p = 0.04$, Figure 2)

Living Donor Cartilage Compared to Clinical Grade Fresh-Stored OCA

The average age of clinical OCAs (Figure 3) at the time of implantation was 22.7 days (Range: 19 – 25) since donor death. Mean donor age was 23.1 years (Range 17 – 33), with 9 males and 1 female. The samples consisted of 4 whole distal femurs, 4 medial condyles, and 2 lateral condyles. The mean graft thickness was 7.2 mm (Range: 5 – 11) and mean plug diameter was 20.9 mm (Range: 18 – 25).

Macroscopic Comparisons

Living donor cartilage from unaffected TKA compartments exhibited healthy macroscopic architecture at the time of harvest, with median ICRS grade 0 pathology (range: 0 – 2). Patients without uniform grade 0 pathology demonstrated focal ICRS grade 1 – 2 defects, which were readily avoidable in both 4 mm disc and future allograft plug preparation. In contrast, the contralateral articular compartment demonstrated severe degenerative changes, with median ICRS grade 4 pathology (range: 3-4), as would be expected in the case of arthroplasty patients (Figure 4). Average living donor osteochondral allograft thickness was 12 mm (range: 8 – 15 mm), with full thickness cartilage and underlying subchondral bone present in the resected, healthy femoral condyle tissue (Figure 5). As expected, all clinical OCA samples demonstrated ICRS grade 0 pathology.

Living Donor Cartilage Histology

Living donor cartilage allograft samples exhibited substantial and uniform appearing collagen II staining throughout the superficial and deep cartilage layers, with no staining present on IgG controls (Figure 6). In contrast no significant collagen I staining was observed, supporting mature, hyaline cartilage predominance over fibrocartilage. Additionally, aggrecan staining was present throughout the healthy compartment samples, further supporting the use of living donor TKA tissues as a potential source of osteochondral allograft.

Cellular-Level Comparisons (Live / Dead Analysis)

The mean VCD for all living donor cartilage allograft samples undergoing viability testing at the time of harvest was 93.6% (Range 88.4 – 97.8 %). In comparison, the mean VCD for operatively implanted OCA samples was 45.6% (Range: 2.2% - 90.9%, $p < 0.01$, Figure 7). The lowest VCD

observed for living donor samples at the time of procurement was 88.4% which was superior to 9 out of 10 clinical OCA samples. Additionally, all living donor samples surpassed the 70% cell viability threshold previously proposed in the literature to predict operative graft success.[101] In contrast, only 20% (2 of 10) of stored deceased donor OCAs reached this threshold. Furthermore, following 21 days of storage at 37°C, the average VCD observed for living donor cartilage allograft samples kept at physiologic storage was 72.5 %, which remained superior to the 45.6% mean VCD for clinical OCAs at the time of implantation ($p = 0.01$).

Living Donor Cartilage Microbiological Proof-of-Concept

Samples for all nine LCAP patients were culture negative (0% contamination) on aerobic and anaerobic plates, as well as anaerobic tryptic broth culture at all time points, 0 – 4 weeks following harvest. In addition, in accordance with Food and Drug Administration (FDA) tissue standards, Bacterial Endotoxin Testing (BET) was performed following 2 and 3 weeks of storage for 4 samples as part of a validated, third-party analysis. All BET values in the tests that were performed were under the detection limit of 0.250 endotoxin units (EU) per mL, and this stringent threshold is well below the 0.5 EU/mL limit set by the FDA.

Discussion:

The main findings of this study are three-fold: 1) fresh osteochondral samples obtained at the time of TKA demonstrate a consistent decrease in viability and histologic quality during the first three weeks of storage, 2) decreased viability observed in laboratory-stored samples are also observed in clinical grade osteochondral allograft at the time of surgical implantation, and 3) living donor osteochondral allograft from relatively well-preserved compartments at the time of TKA demonstrates satisfactory graft viability and histology when compared to OCA samples from current clinical practice. These findings are substantial given the recent shift in delayed OCA implantation at 14-35 days following donor procurement to permit further sterility testing which has yet to be accompanied by assurance or disclosure of graft viability.[399] Furthermore, employing living donor transplantation from the time of TKA has the potential to simultaneously increase viability, ease logistic scheduling, and expand the availability of OCA, supporting the implementation of what is considered the gold standard treatment for large cartilage and osteochondral defects.

Articular cartilage defects and subsequent osteoarthritis remain central challenges of orthopedic surgery, causing significant disability and loss of productivity in a large portion of the global population.[117] Osteochondral allograft has become the gold-standard treatment for large focal cartilage and osteochondral defects, and has a long-standing track record in successful joint

preservation surgery. However, this resource remains rare due to the limited scalability of young deceased donor based solutions and the importance of viable tissues for clinical success.[101, 129, 381] The purposes of this study were to determine and validate living donor cartilage allograft transplantation as a novel source for viable OCA tissues, and to compare living donor cartilage transplantation to currently available clinical-grade tissues. These aims were achieved by showing that living donor cartilage TKA tissues have the appropriate clinical properties (i.e. macroscopic cartilage grade, cell viability, and microbiological sterility) for use as a novel and potentially improved OCA source as part of a Living Donor Cartilage Program (LDCP).

Previous studies have shown that storage of cartilage at room temperature and 37°C is superior over classical refrigerated methods, especially in animal tissues.[146, 248, 284, 381, 382] However, these storage temperatures have not been evaluated in human tissues, especially over multiple weeks of storage. Our work focused on determining tissue quality under ideal, physiologic temperatures for OCA storage during a clinically relevant time frame by monitoring the biological properties of cartilage. While studies employing intra-articular thermometers at the time of knee exercise have demonstrated that physiologic knee temperature varies on the range of approximately 33 – 39°C, other investigations into the efficacy of ice- and cryotherapy-based cooling systems have demonstrated that physiologic and even therapeutic temperatures rarely, if ever approach values near 25° C (i.e. room temperature).[31, 408] Therefore, it is intuitive that long-term maintenance of osteochondral tissues may be preferable within physiologic and biologic parameters near 37°C, as performed in this study.

Given that physiologic storage offers viability benefits for osteochondral tissues, it is also important to establish the ideal timeline for cartilage implantation following storage. While classic OCA surgeries were performed on the order of hours to days following procurement, sterility testing paradigms have shifted practice towards implantation at 14 – 35 days following graft harvest, without simultaneous testing or validation of tissue viability.[61, 300, 399] These changes raise the concern of decreasing clinical benefit given the established link between tissue viability and graft success.[101] Accordingly, we tested the viability and histology of osteochondral samples under optimal physiologic conditions during storage for up to 3 weeks, which is near the average time of 23 days to OCA implantation at our institution. The observed decreases in viability, as well as significant accompanying loss of glycosaminoglycan content in Safranin-O staining, certainly raises the concern of storing tissues on the order of weeks, even in the most optimal and physiologic of conditions.

Previous research by Schmidt et al has investigated whether storage time influences outcomes of osteochondral allograft transplantation performed after a mean of 6.3 days (early release) versus 20.0 days (late release) of storage at 4° C.[357] While the authors did not find a

significant effect of storage time on graft survival, grafts were considered early release for up to 14 days following procurement which is noteworthy considering that this methodology masks the effects of early graft degradation or loss of viability occurring within the first two weeks of storage. Furthermore, as noted by the authors, there is mounting evidence which includes animal data from their institution[318] as well as others[146] demonstrating that refrigerated storage at 4° C performs inferior to more physiologic temperatures such as 37° C in terms of viability. Finally, although their study was well-powered with 150 patients, no direct measurements of graft viability were performed. Therefore outcomes must be interpreted in light of the limitations and potentially dominant effects of non-physiologic refrigeration and indirect, correlation-based causality between viability and outcomes.[357].

In addition to the inherent limitations of scaling allografts obtained from deceased donors, the unexpected passing of donors adds an additional layer of logistical complexity for scheduling OCA transplantation. At the time of this study, our institution, which is a high-volume cartilage center, has three patients that have been on OCA waiting lists for greater than 6 months. Such limitations and volumes could be improved by the implementation of Living Donor Cartilage Programs (LDCPs), considering the high volume of varus and valgus total knee replacements performed in the United States and worldwide and the fact that TKAs are performed on an elective and pre-scheduled basis.[363, 364] We have demonstrated that candidate living donors can be successfully screened to provide optimal osteochondral grafts, and that safety testing can be performed immediately prior to tissue donation. Therefore, patients in need of living donor cartilage allograft could also be scheduled in advance to follow operative dates for living donors undergoing TKA. Given that distal femoral OCA costs are on the order of $8,500 – $15,000 per graft, significant cost savings may also result and fund the establishment of the necessary tissue banks, infectious disease screening for donors, and more advanced preoperative testing such as magnetic resonance imaging (MRI) for donors.

To further assess the sterility and safety of tissues harvested in the OR for use as allograft, the sterility record of our facility Bone Bank, which employs identical personnel and sterile containers as those used in this study to intraoperatively harvest femoral head cancellous allograft was queried. Over the course of the 2017 calendar year, of the 377 femoral head samples obtained, 1 sample (0.27%) was determined to be contaminated at the time of storage. These values, in addition to our LDCP culture and BET testing data, indicate that concerns about the potential for microbial contamination are minimal. These encouraging findings support the clinical implementation of physiologic storage of osteochondral allograft as well as the expansion of currently limited OCA supply with living donor cartilage allograft. Given the evolution of new, rapid microbiological testing machinery such as that embodied by 3-dimensional colorimetry or DNA based methods, expedited

sterility clearance and OCA implantation within hours to days of allograft procurement comprise goals that are well supported by the literature and may serve to optimize patient outcomes.

The current study is not without limitations. First, the presented living donor allografts comprise a highly selected subset of TKA patients with varus or valgus pathology with well-preserved contralateral compartments. While approximately 15 – 20 patients per month at our institution meet local and American Association of Tissue Banks (AATB) criteria for osteochondral donation, less than a third demonstrate single compartment predominant varus or valgus pathology amenable for osteochondral donation. It is important to note that all patients are independently evaluated and consented for TKA based on clinical exams and imaging, prior to being contacted by this study or future Living Donor Cartilage Allograft Project efforts. Second, further research on the biomechanical properties of living donor cartilage would better characterize this novel tissue source and assist with determining the utility and durability of such tissues obtained at the time of well-selected TKA. Third, while our outcomes are supported by previous studies demonstrating significantly decreased graft viability with storage over time and decreasing glycosaminoglycan content[10, 414], the absolute magnitude of the observed decrease in viability has varied from paper to paper. This is likely partially related to variations between species given that animal data may not be directly applicable to clinical human experience and also related to variations between research institutions and private entities and their individual and sometimes proprietary storage solutions. Finally, both obtaining and maintaining physiologic storage of osteochondral tissues requires high-volume arthroplasty institutions with dedicated staff for patient consenting, tissue transportation, and storage.

Conclusion

Osteochondral tissue viability and histologic quality progressively decreases with ex vivo storage, even when kept at physiologic temperatures. Currently available clinical OCAs are stored for 2 – 5 weeks prior to implantation and demonstrate inferior viability to that of fresh osteochondral tissues that can be made available through the use of a Living Donor Cartilage Program (LDCP).

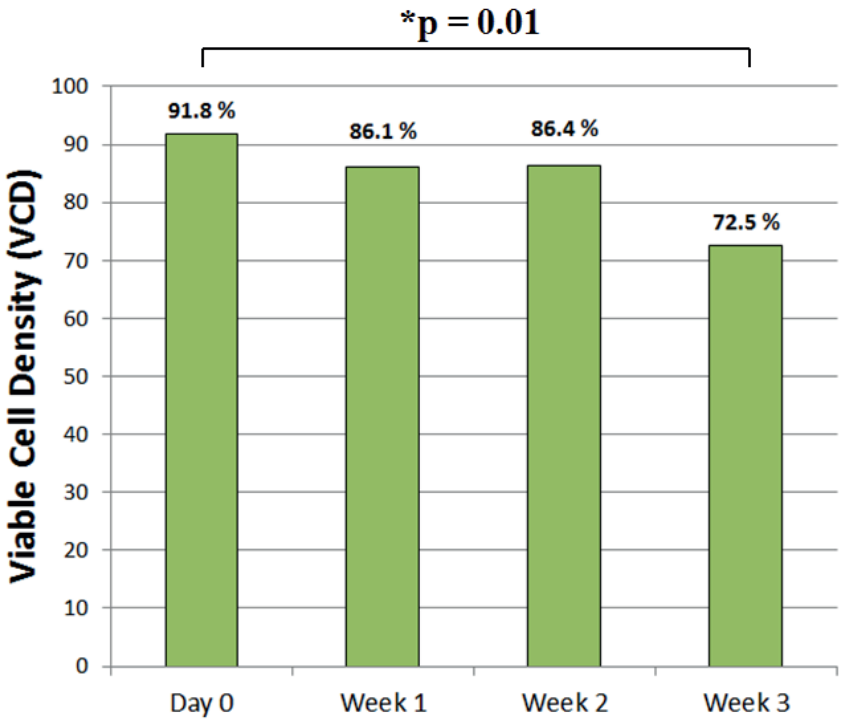

Figure 1: Viable Cell Density (VCD) of well-preserved TKA compartment tissues over three weeks of physiologic (37°C + hypoxia) storage.

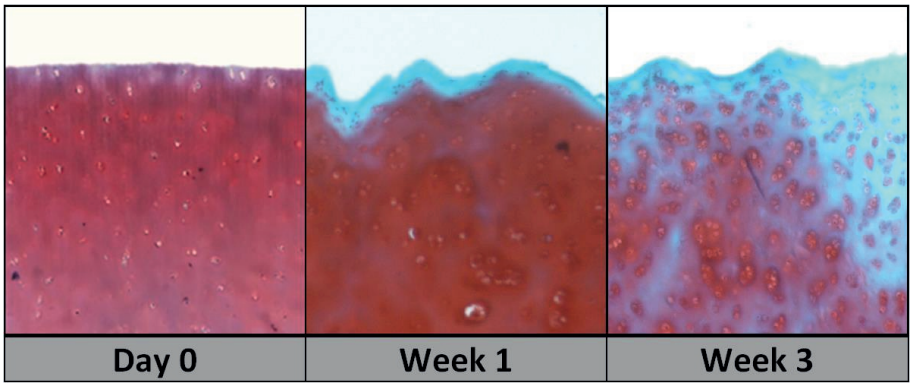

Figure 2: Representative images of decreasing Safranin-O staining (red), indicative of decreasing glycosaminoglycan content at articular surface of stored cartilage samples over 3 weeks with substituting fibrosis (light blue) and associated atypical chondrocyte hypertrophy.

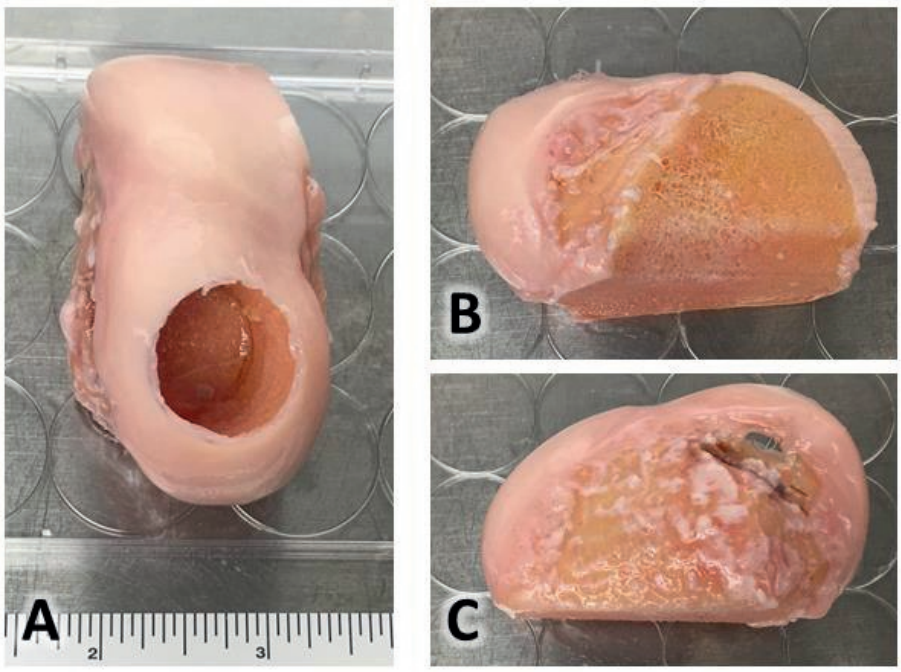

Figure 3: Medial femoral condyle OCA obtained immediately after clinical use with A) articular surface, B) lateral cut, and C) medial views.

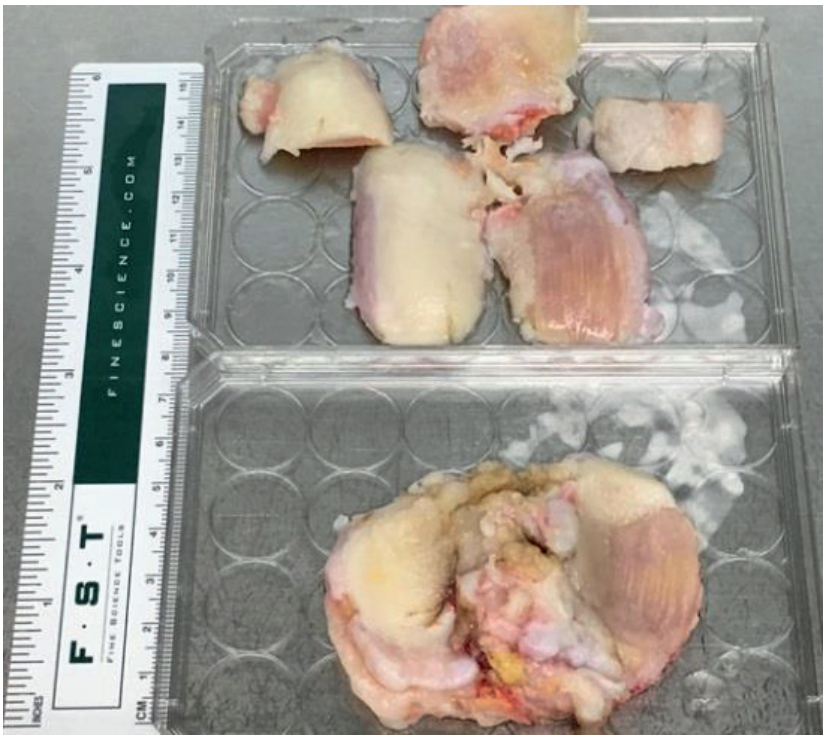

Figure 4: Representative Living Donor Cartilage osteochondral sample demonstrating full thickness medial compartment cartilage loss with a well-preserved lateral compartment.

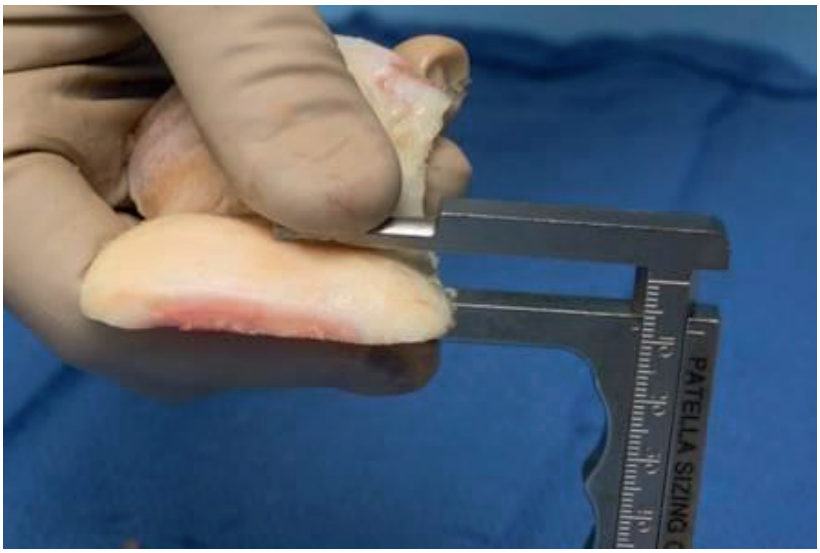

Figure 5: Intraoperative measurement of TKA graft thickness for living donor cartilage allograft osteochondral sections.

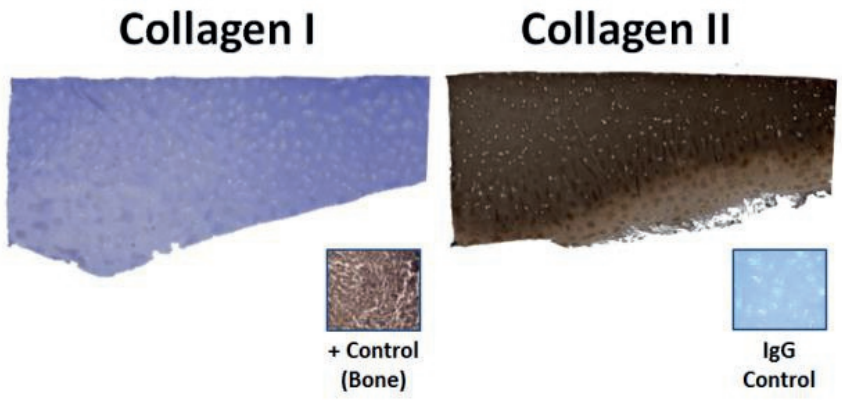

Figure 6: Collagen I and II staining for Living Donor Cartilage osteochondral samples with bone and IgG controls. Articular surface oriented upwards.

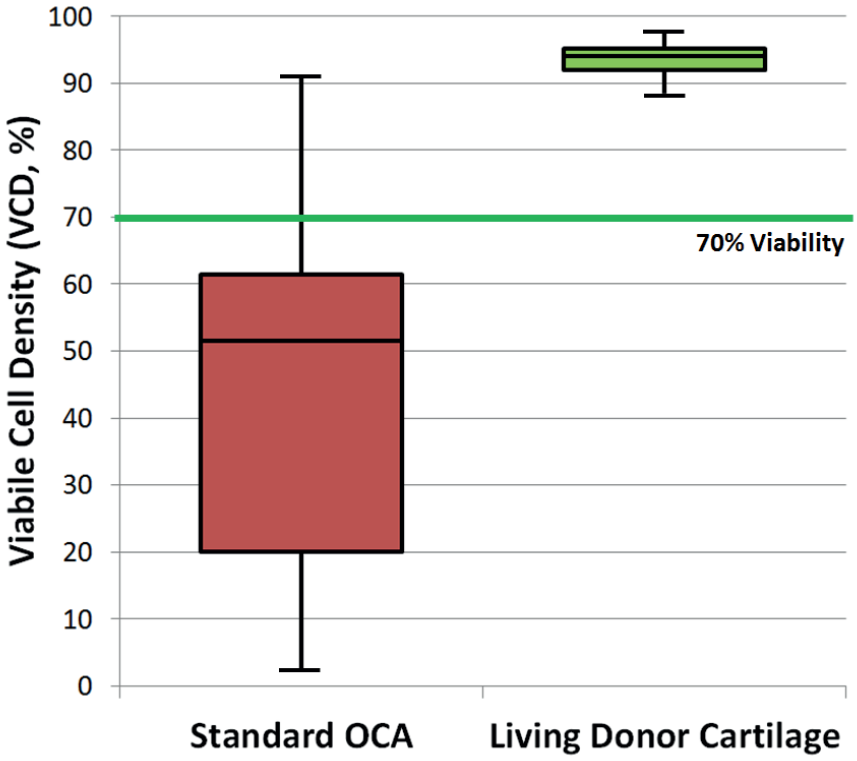

Figure 7: Box and whisker plot of OCA and living donor cartilage allograft VCD. Whiskers represent the minimum and maximum values while boxes show the first quartile, median, and third quartile.

Modernizing Storage Conditions for Osteochondral Allograft: Time to Store at Physiologic Temperatures

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Introduction

Osteoarthritis (OA) is a painful and debilitating joint disease, affecting more than 46 million Americans over the age of 25 [176, 307] and resulting in annual costs of more than $60 billion dollars [59, 343]. Loss of articular cartilage is considered a hallmark of OA. The inflammation, degradation, and dysfunction caused by a focal articular cartilage injury affects all tissues that comprise the joint organ, leading to loss of homeostasis and generalized degenerative changes throughout the joint [298].

Articular cartilage defects, resulting from acute joint trauma, are common in younger patients with active lifestyles[57], and, left untreated, can cause generalized post-traumatic OA, thereby severely impairing quality of life[174]. Such lesions have limited spontaneous reparative potential due to the poor regenerative capacity and avascular nature of cartilage [298]. Relief of symptoms therefore often requires operative intervention including micro-fracture, cell-based therapies such as autologous chondrocyte implantation (ACI), or osteochondral allograft transplantation (OCA) [125, 165, 373, 382].

Osteochondral allograft (OCA) transplantation has been associated with consistently positive functional outcomes, with 69% graft survival at 20 years [146] and established long-term clinical safety [111, 368, 382]. Furthermore, this technique enables transplantation of both cartilage and underlying bone, enabling surgeons to address pathology extending beyond the subchondral plate. Although OCA has a proven record of clinical efficacy, the limited availability and logistical difficulties of procuring suitable grafts from deceased donors restricts widespread implementation of this technique [304, 318]. This is due in part to concerns related to contamination and disease transmission [232, 424]. Current cartilage banking and testing protocols, recommended and mandated by the American Association of Tissue Banks (AATB) according to the United States Pharmacopeia (USP) <71>, requires implementation of a 14-day culturing and disease-screening period before release of grafts for clinical use [105, 111, 146, 237, 318].

To confound matters, cartilage allograft viability has been shown to decrease in storage over time [232]. Using the standard tissue bank practice of 4°C storage, chondrocyte viability deteriorates significantly within the initial 14-day tissue clearance period [60, 101, 105, 122, 146, 318, 323, 326, 381, 389, 414, 416] with cellular demise driven by both apoptosis [270, 340] and stress response [246]. Because chondrocyte viability influences the long-term clinical success of OCA [21, 29, 101, 154, 307, 319, 381, 415], optimization of storage conditions during the early period after harvesting is crucial. Proposed preservation goals suggest maintaining a minimum viable chondrocyte density (VCD) consisting of 70% living chondrocytes[101, 382]. Key variables of interest have included type of preservation solution[270, 311, 414, 416, 424], choice of supplementation (see Bian et al., 2008[41] and other factors [146, 326, 389]), temperature[27, 252, 270, 318, 381, 424], and level of oxygenation[318]. Conditions have been assessed across several animal species [424](including rabbit[391], pig[27], goat[270, 318], canine[42, 101, 381]), but there is only a very limited number of human studies[252, 382]). While both room temperature storage and physiologic storage at 37°C have demonstrated promise in animal models, no comparisons between non-refrigerated conditions have been made. Furthermore, validation of animal models, in which variables such as species-specific core temperature and cartilage morphology may differ from humans, is necessary using clinical human tissues.

Even with improvements to preservation techniques, healthy cadaveric cartilage candidates remain scarce, and there is significant interspecimen and intrastudy variability in chondrocyte viability of OCAs at the time of implantation [10, 381]. Differences in harvest timing, technique, location, and the initial condition of the cartilage are all expected to have significant influence on the quality and performance of the graft[410]. To alleviate this shortage, we propose the implementation of a Living Donor Cartilage Program (LDCP). This approach would improve availability of grafts, provide grafts with high cell viability, allow for pre-screening of donors for safety, facilitate more convenient scheduling of surgery, and offer a potentially less expensive alternative. In fact, the successful transplantation of OCAs from living donors has been previously reported [163]. Given that much of the long-term data regarding OCAs is based on patients that had grafts implanted within 7 days of harvest[381], the clinical goal for this pilot program is to preserve osteochondral allografts for only a short time (approximately a week) at temperatures greater than 4°C, in an effort to avoid deterioration in chondrocyte viability and to preserve extracellular matrix (ECM) integrity.

Therefore, the purpose of this study was to evaluate the quality of macroscopically healthy cartilage from relatively young middle-aged patients upon storage by testing chondrocyte histology, viability, and gene expression after one week of incubation in a number of modern storage conditions (i.e. in chondroprotective media incubated at normoxia (21% O_2) at 22°C and 37° C or hypoxia (2% O_2) at 37° C). In addition, we aimed to perform a limited validation experiment to compare physiologic storage (37°C with hypoxia) to the current industrial standard of 4°C to further evaluate

and compare modern storage conditions in light of currently used clinical protocols. We hypothesized that storage at physiologic conditions (37°C, hypoxia) would lead to improved tissue viability and gene expression as compared to storage at room temperature or refrigerated storage at 4°C. The short term storage of healthy OCAs from donors has the potential to provide efficacious treatment through the novel utilization of this post-operative product, with high chondrocyte viability, to overcome the persistent global shortage of cartilage allografts.

Methods

Tissue Collection and Processing

Joint resections were collected from young patients (< 60 years) undergoing total knee replacement surgery for varus or valgus pathology with well-preserved contralateral compartments demonstrating Kellgren-Lawrence Grade 0 or 1 pathology. Eleven young TKA donors (6M, 5F, age: 56.4 ± 2.2 years) were screened using standardized inclusion/exclusion criteria (Figure 1) and eligible for inclusion in this study.

Upon collection of joint resections, photos were taken to enable gross observation and scoring of the tissues according to the ICRS grading system (Figure 2a). Subsequently, osteochondral samples were harvested from each resection by the creation of 4 and 8 mm discs using biopsy punches (Figure 2b-d), with a scalpel introduced below the calcified layer and within the superficial bone to include subchondral bone along with the cartilage and create true osteochondral discs. Discs of 4 mm from each tissue section were transferred immediately to 10% formalin for preservation. These served as baseline samples for histology at the time of tissue harvest. All other cartilage discs were transferred into serum-free media and maintained for seven days at room temperature (22 ± 0.5°C, normoxia (21%O_2)), incubated at 37°C with normoxia, or incubated at 37°C under hypoxic conditions (2.0 $\pm$ 0.5% O_2) (Figure 3. for timeline). Excess cartilage was frozen in liquid nitrogen for RNA preservation for real-time quantitative PCR (RT qPCR) analysis.

Histologic Tissue characterization

Four millimeter discs from the time of tissue harvest and following 7 days of incubation for each treatment group were transferred to 10% neutral buffered formalin for preservation. After 24 hours of fixation, samples were transferred to 70% ethanol. Tissues were bisected and embedded in paraffin and sectioned (5 µm) along a vertical plane to get a cross-sectional view of the different cartilage zones. Slides were stained for hematoxylin-eosin (H&E) and safranin-O/fast green using standard methods (Figure 4a,b). Additional sections of each sample underwent

immunohistochemical staining for aggrecan (mouse anti-aggrecan antibody, Novusbio NB110-6524, Dilution 1:150 in PBS/BSA 5%), Collagen type I (rabbit monoclonal anti-Collagen 1/COL1A1, Abcam EPR7785, Dilution: 1:400 in PBS/BSA 5%) and Collagen type II (mouse monoclonal anti-Collagen II/COL2A1, DSHB, University of Iowa, Dilution 1:100 in PBS/BSA 5%) with normal mouse or rabbit IgG used as a negative controls (Figure 4c-e). For the 11 patients studied, 3 blinded and independent reviewers scored histologic sections from each of the samples at each of the four conditional time points: Day 0 and Day 7 at 22°C, 37°C + O2, and 37°C with hypoxia, for a total of n=246 . Samples were scored using the modified HHGS by Mankin method for histological quality and histomorphometry [106, 259].

Cell Viability Quantification with Live-Dead Staining

At Days 1 and 7, 4 mm pellets were collected from each culture condition (22°C + O_2; 37°C + O_2; 37°C + hypoxia) and assessed for cell viability using a two-color fluorescence assay based on the simultaneous determination of live (Calcein acetoxymethyl (AM): green) and dead (Ethidium homodimer-1: red) cells (Live-Dead Viability/cytotoxicity kit for mammalian cells; Molecular ProbesFluorescent z-stack images (850 um x 850 um x ~ 100 um; 7.2 um slice thickness) were collected for each tissue section and culture condition using an inverted LSM 780 multiphoton laser scanning confocal microscope (488 nm & 561 nm lasers) at 10x magnification. Maximum intensity projections were created in Zen (2.3 SP1, Zeiss 2015) (Figure 5). The amount of red and green staining in each image was quantified in MatLab (R2015b, 8.6.0.267246) by setting an intensity threshold to 25 and calculating the percentage of red and green pixels relative to the total number of pixels in the image. Viable Cell Density (VCD) was calculated by dividing the number of green (live) pixels by the combined number of green (live) and red (dead) pixels in order to provide a measure of percentage viable cells.

Molecular characterization of cartilage by gene expression analysis

To ascertain whether the different storage conditions produced distinct molecular responses in the cartilage discs, gene expression was analyzed using reverse transcriptase-based real-time quantitative PCR (RT-qPCR). RNA was isolated from the frozen cartilage samples using a modified Biochain Protocol (Cartilage RNA Isolation Kit, K2031010, Biochain Institute, Newark CA). Detailed methods are provided in Supplementary Methods and Table 1. Gene expression for selected gene markers (ACTB, HPRT1, AKT1, COL1A1, COL2A1, COL10A1, ACAN, HAPLN1, MFAP5, MMP13, CD14, CD117, CD163, CD4) was quantified using RT-qPCR whereby each reaction was performed with 10 ng/µL of cDNA, QuantiTect SYBR Green PCR kit (Qiagen, Hilden, Germany), and a CFX384 real time quantitative PCR system (Bio-Rad, Hercules, California, USA). Transcript levels were quantified using

the $2^{\Delta\Delta Ct}$ method and normalized to the housekeeping gene AKT1 (set at 100). Technical qPCR triplicates were run for each sample at each condition. \

Statistics

Statistical analysis was performed by a formally trained institutional statistician. The total sample size for the study was 11 samples (patients) employed for the core viability, histology, and qPCR analysis performed at baseline (Day 0) and at the Day 7 22°C, 37°C + O2, and 37°C with hypoxia conditions. Each patient was analyzed at the above timepoints for all three outcome measures (viability, histology, and qPCR). An additional n = 3 samples were employed in our validation experiment comparing physiologic storage (37° C with hypoxia) to the current industrial standard of 4°C on the basis of viability.

Comparisons for live-dead quantification and RT-qPCR results were made between groups using generalized linear models utilizing generalized estimating equations (GEE). P-values were adjusted for multiple comparisons using the false discovery rate method described by Benjamini and Hochberg (1995) [36]. For histology, the weighted Kappa statistic with Cicchetti-Allison weights was used to assess the agreement in measures between the observers. Areas and conditions were compared using GEE, taking into account multiple measurements taken from the same person. Power and sample size calculations for the study were chosen based on a primary viability endpoint at alpha = 0.05, power = 0.80 and the viability values provided by Pallante et al in their caprine model for temperature-based osteochondral allograft preservation, resulting in a goal sample size of n = 11 per group[318]. P-values < 0.05 were considered significant. Statistics were performed using SAS Version 9.4 and JMP Pro 13.0 (SAS Institute, Cary, NC).

Results

Macroscopic and Histologic Tissue Characterization

Eleven osteochondral specimens from relatively young middle-aged TKA patients (6M, 5F, age: 56.4 ± 2.2 years) were stored in chondroprotective media and incubated at normoxia (21% O_2) at 22° and 37° C and hypoxia (5% O2) at 37° C for seven days. Cartilage from the unaffected compartments demonstrated healthy macroscopic architecture, with median ICRS grade 0 pathology (range: 0 – 2) and focal ICRS grade 1 – 2 changes. In contrast, the median contralateral compartment demonstrated mean grade 4 pathology (range: 3-4).

Upon histologic embedding and staining, the obtained Day 0 samples exhibited excellent Collagen II staining and no significant Collagen I staining, supporting mature, hyaline cartilage predominance over fibrocartilage, and supporting the use of these TKA resection samples in determining osteochondral tissue viability over time during storage (see Figure 4 for representative images). Aggrecan staining was present throughout the healthy compartment samples. In addition, all samples were stained for H&E and Safranin-O for cartilage morphology grading.

Cartilage morphology was scored according to the modified Histological Histochemical Grading System (mHHGS, Figure 6) by three independent and blinded reviewers. This system evaluates differences in structure, cell composition, and safranin-O staining, with a minimal score of 0 (normal cartilage) and a maximum score of 11 (complete structure disorganization with hypocellularity and no safranin-O dye staining noted). The mean mHHGS score of all histological samples at the time of harvest was 3.9 ± 1.8, indicating mild degenerative changes (see Figure 6). Following 7 days of storage, mean mHHGS scores were 4.5 ± 2.0 for 22° C + O_2, 3.8 ± 1.6 for 37° C + O_2, and 4.3 ± 1.3 for 37° C + hypoxia with no significant difference noted between groups or as compared to baseline ($p \geq 0.54$).

Cellular level characterization with Live-Dead staining

At the time of baseline measurements within the first 24 hours of storage (Day 1), all three conditions demonstrated similar, high VCDs (94.0 ± 2.7 %, range: 87.5 – 99.2 %, $p = 0.13$). Following 7 days of storage, incubation at room temperature caused a significant decrease in the presence of viable cells, with a final mean VCD of 65.6 % (Range: 22.8 – 98.9 %, $p < 0.01$). In comparison, at Day 7 the mean VCD for 37°C normoxic storage was 95.1 % (Range: 87.2 – 97.1 %) and mean VCD for 37°C hypoxic storage was 92.2 % (Range: 79.7 – 97.4 %), with no significant difference between the two 37°C storage conditions ($p = 0.39$). No significant difference in VCD was observed when comparing baseline (Day 1) VCD to viability at Day 7 for the 37°C incubation groups, suggesting that VCD was maintained throughout storage for these groups ($p \geq 0.27$). For comparison, the Day 7 VCDs for samples incubated at 37°C under either oxygen condition were significantly higher when compared to the Day 7 VCD for samples incubated at room temperature ($p = 0.0001$, Figure 7).

Molecular Level Characterization with RT-qPCR

COL1A1, COL1A2, and ACAN qPCR expression following 7 days of storage was unchanged from baseline ($p > 0.05$) for all three storage conditions tested (see Figure 8). CD163 expression, indicative of inflammatory activity including macrophages and monocytes, was significantly lower in the 37° C groups (normoxia and hypoxia) compared to 22° C ($p < 0.01$). Of the genes tested, MFAP5,

COL10A1, CD4 (associated with helper T-cells) and CD117 (KIT; mast cell) demonstrated trace to no detectable expression (data not shown).

Validation Experiment: Viability Comparisons with Current 4°C Industrial Standard

When comparing physiologic storage at 37°C with hypoxia to the current industrial standard of refrigeration at 4°C, a validation group of n = 3 additional patient samples (3F, mean age: 52.3 ± 1.2 days) demonstrated that the 4°C group had a substantially lower mean VCD of 56.1 ± 6.0 % after 7 days as compared to 88.9 ± 4.8 % for the 37°C + hypoxia condition (p = 0.004). These results are included in Figure 7a.

Discussion:

Articular cartilage defects can cause chronic pain and progression to osteoarthritis and there is a critical need for safe and cost effective interventions. Osteochondral allograft transplantation is a safe and effective treatment option for large cartilage defects, with demonstrated positive long-term clinical outcomes[154, 273, 334]. However, OCA suffers from a limited supply of viable tissues. This is compounded by AATB mandates for OCA storage for culture-based infectious disease testing, with this storage classically performed at 4°C with documented deleterious on tissue viability [304]. The purpose of this study was to test macroscopically healthy cartilage from discarded varus and valgus total knee arthroplasty (TKA) tissue in patients with localized cartilage degeneration and to evaluate and compare chondrocyte viability after one week of storage in a number of modern storage conditions. Our hypothesis was confirmed in that storage at physiologic conditions (37°C ± hypoxia) demonstrated improved viability when compared to room temperature storage.

Previous studies have suggested that the success of an OCA is a function of the viability of the graft's chondrocytes, which diminishes over storage time[304] and that storage at physiological temperatures results in favorable chondrocyte viability[111, 146, 270, 318, 381] compared to 4°C. The storage conditions examined in this study were selected based on previously published findings, which have compared storage at 4°C to storage at room temperature or 37°C on an individual basis [111, 146, 270, 318, 381]. Both Pallante et al. [318] and McCarty et al. [270], for example, have demonstrated that caprine chondrocyte viability is maintained for up to 28 days at 37°C, while 4°C incubation showed a 30% decrease in viability. In canine cadaver studies, Garrity et al. have reported a mean 28 day tissue viability of 40% in samples maintained at 4°C compared to ~76% viability for OCAs stored at 37°C and Day 0 control of 77% viability[146]. Other work has focused on prolonging viability when OCAs are stored at room temperature[100, 382]. Given that there is considerable evidence pointing to reduced chondrocyte viability following storage at 4°C, we focused on comparing storage of OCAs for two of

the most commonly proposed storage temperatures, ~ 22-25°C and 37°C, as they have not been compared side by side for human tissues, and this comparison is important for development and future standardization of osteochondral allograft storage conditions. Furthermore, we have included a validation experiment of an additional 3 patient samples comparing physiologic storage at 37°C to the current industrial practice of storage at 4°C. While limited in sample size, the results, which demonstrate increased viability in the physiologic storage group, provide further human-tissue specific support which favors non-refrigerated storage at conditions which approximate those temperatures seen in vivo.

The effects of different storage times and different media recipes on cellular viability have been widely studied in the past, and have been summarized nicely by De Caro et al.[111] and Wright et al. [424]. In an effort to limit variables in this study, we tested only a single type of preservation media to enable the comparison of multiple storage conditions while controlling media environment. We focused on the use of a formulation similar to that developed in the MOPS protocol [382], which avoids the use of FBS supplements, as studies have presented conflicting reports as to their benefits[41, 381] This proprietary media is able to maintain sufficient (70%) chondrocyte viability for greater than 56 days at room temperature, and is well documented in the literature[100-102, 146, 304, 381, 382]. We elected to use a a serum free, growth-factor free solution to limit concerns related to disease-transmission, batch variability, or contamination [146, 381]. We also opted to avoid multiple media changes, because media replacement does not result in appreciable improvements in chondrocyte viability [382]. Furthermore, our clinical goal is to preserve cartilage for only a short time (1 week) and regular media changes have not been associated with significant improvements in chondrocyte viability, according to Stoker et al. [382]. Our studies replicate a best surgical practice solution for OCA, which has classically been performed within 7 days of donor expiry.

To date, storage at 37°C has not become standard practice, due to pre-existing tissue banking regulations and concerns related to cost or microbial contamination at temperatures above 4°C. A recent study by Stoker and colleagues [382] indicates that storage at room temperature is safe, because all tissue and media samples passed sterility testing, with no presence of microbial growth. Garrity and colleagues [146] have also shown that microbial cultures of the media collected at the end of storage at 37°C caused no increased incidence in bacterial contamination. Of note, storage at 4 °C was originally desired and recommended due to theoretic decreased microbiological viability and growth, analogous to the common practice of food refrigeration. However, as demonstrated in previous canine and caprine models, sub-physiologic storage has parallel negative consequences on desirable cartilage viability. Considering that it is increasingly well-established that aseptic storage is possible at 37°C, it appears that a microbiological rationale for cold storage is less tenable at present.

Histologically, healthy articular cartilage is comprised of smooth collagenous tissue with chondrocytes comprising less than 10% of the total volume[187, 307]. Collagen type II is abundant, while limited if any collagen type I is present[339]. In the histological staining of our Day 0 samples, we observed mild degeneration, suggestive of early osteoarthritic changes, as anticipated in the relatively preserved compartment of varus and valgus total knee arthroplasty specimens. However, tissues were generally healthy, with absence of collagen I staining, strong collagen II staining, and only mild to moderate disease present on mHHGS scoring. Most importantly, we did not observe significant histologic deterioration of samples during storage at any of the three conditions tested. This finding indicates that tissue architecture and composition are well maintained during osteochondral storage,in agreement with similar studies. Stoker et al.[382] have presented data showing no significant changes in OCA material properties after OCA storage in MOPS media at room temperature at 28, 56 or 70 days after procurement. Histological assessments indicated the maintenance of cell morphology, ECM staining for collagen, and articular surface integrity. Others have also suggested that ECM is maintained during graft storage even when chondrocyte viability falls[10, 318]. This highlights the need for nuanced measures of graft health such as viability (live-dead) and gene expression assays[382].

Most existing OCA studies have focused on quantifying chondrocyte viability at 14 days post harvest or later, presumably to fall in line with AATB testing recommendations; the rate of cell death generally appears to increase after this time point[381]. Numerous factors, including OCA source (human vs animal), disease state, media composition, level of oxygenation, and time point measured, as well as quantification technique are likely to influence viability measurements. Our analysis of live-dead viability in different storage conditions shows that human OCA tissues stored at 37°C achieved superior VCD results as compared to osteochondral specimens, stored in serum free media at 22°C, with > 90% viability following 7 days of incubation at 37°C as compared to a mean VCD of 66% for storage at 22°C. These results suggest the utility of physiologic storage and highlight that, after only 7 days of incubation, the mean VCD of storage for our human OCAs at room temperature (22°C) falls below the proposed 70% cutoff for OCA viability. Considering that graft viability is considered the leading predictor of clinical success in OCA transplantation, we believe these results strongly support human OCA storage at physiologic 37°C conditions, at least for programs aimed at minimizing storage time and maximizing chondrocyte viability. Of note, a change in oxygen content did not appear to significantly affect the viability of the chondrocytes in our samples. Because physiologic hypoxia is present in the articular environment and may suppress the growth of aerobic bacteria, hypoxic storage may represent a preferred storage environment that could reduce the possibility of infectious disease. Future studies should investigate the potential benefits of reduced oxygen tension by testing a broader range of oxygen conditions for chondrocyte storage.

order to perform comprehensive characterization of cartilage under the three experimental storage conditions, we performed RT-qPCR on baseline and stored osteochondral discs to ascertain the presence of key matrix deposition and maintenance markers, and investigate the presence of inflammatory infiltrates. Following 7 days of storage, there was no change in collagen or aggrecan expression for all three non-refrigerated storage conditions, while high expression of collagen II and aggrecan and low expression of collagen I were maintained. Remarkably, we did observe increased expression of the macrophage/monocyte biomarker CD163 with storage at 22°C. The latter indicates the presence of inflammatory activity which may reflect the immunological effects of storage below physiologic conditions, consistent with previous literature suggesting that stress-response gene expression can be driven by both supra- and infra-physiologic environments [246]. Increased CD163 expression observed at 22°C samples in our study provides molecular-level support for the potential utility of physiological storage at 37°C. Other groups looking at gene response have observed a significant increase in apoptotic gene expression in human (femur) OCA tissues stored at 4° C, indicating that loss of chondrocyte viability observed during storage is at least partially due to apoptosis [340]. We did not observe matrix degeneration at 7 days, which supports the findings of Robertson et al.[340] who concluded that there was little to no upregulation of genes involved in ECM degradation even at their latest time point of 35 days. Since both histologic and gene expression markers appear to be limited to long-term storage effects, we reiterate the importance of having reliable and robust measurements of chondrocyte viability for short term storage when assessing OCA quality, when decreases in metabolic activity and increased chondrocyte death may become apparent[414].

Our study is not without limitations. Paired analyses, performed by having all three storage conditions tested for each osteochondral donor, enabled better accounting for inter-sample tissue variance. However, the absolute amount of tissue per donor remains limited and thus, additional temperature conditions such as 4°C could not be tested in parallel to the three methods of storage compared. These limitations were mitigated by the addition of a validation cohort to provide comparisons and a context including standard 4°C storage, next to which our main results can be interpreted. For the same reasons, we did not use clinically relevant sized discs although we note that the size of clinical OCA lesions can vary considerably, with one estimate describing ranges of 2.3 -11.5 cm2[392]. We also did not measure the bone-to-cartilage ratio in our discs. It is possible that a larger bone presence in the discs could have adversely affected cartilage during storage, although Pennock et al.[325] suggest that the bone-to-cartilage ratio plays little to no role in the degradation of allografts during prolonged storage. We did not attempt to quantify this factor, or OCA size in these experiments. Additionally, we did not include microbiological testing in this cohort in an effort to ensure tissue availability for histologic, live-dead, and qPCR analysis. Finally, further expansion of

sample sizes and metabolic comparisons in follow-up studies may provide a more stringent physiologic proof-of-concept.

Conclusion:

Storage of human osteochondral tissues in serum free media at 37°C, with or without hypoxia, demonstrates maintained macroscopic tissue quality and chondrogenic gene expression, improved chondrocyte viability, and decreased inflammatory CD163 activity when compared to storage at 22°C. These data provide guidance for a novel yet simple method that optimizes tissue viability during short-term storage of fresh OCA and has the potential to improve long-term clinical results of surgical cartilage repair.

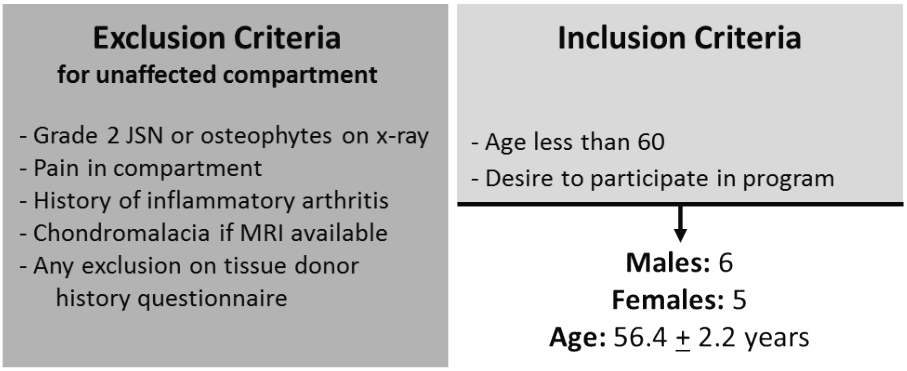

Figure 1: Screening for inclusion/exclusion criteria. Volunteer total knee arthroplasty donors were screened for the following criteria. 11 donors were included in the pilot study.

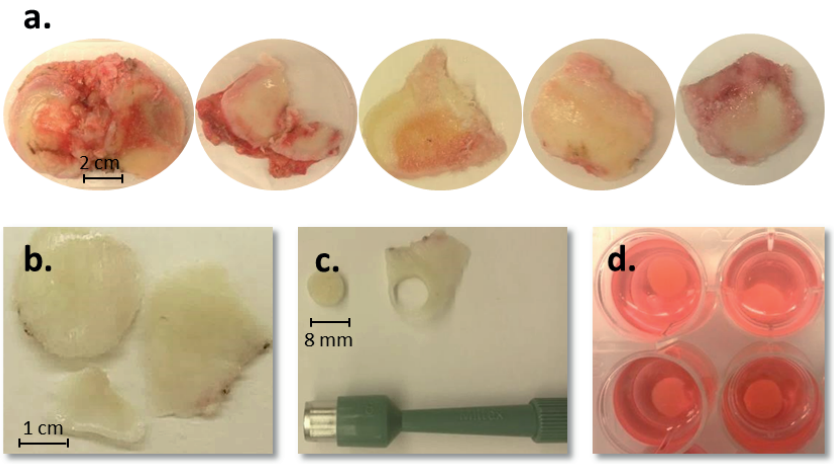

Figure 2: Collection of tissue resections and creation of cartilage discs. (**a**) Representative images of the joint resections. Bone and cartilage joint resections are collected from patients undergoing total knee replacement surgery and scored for disease severity. (**b**) Healthy cartilage pieces are harvested and cartilage discs are created using a biopsy punch (shown here: 8 mm disc) (**c**) before transfer to storage cocktail (**d**).

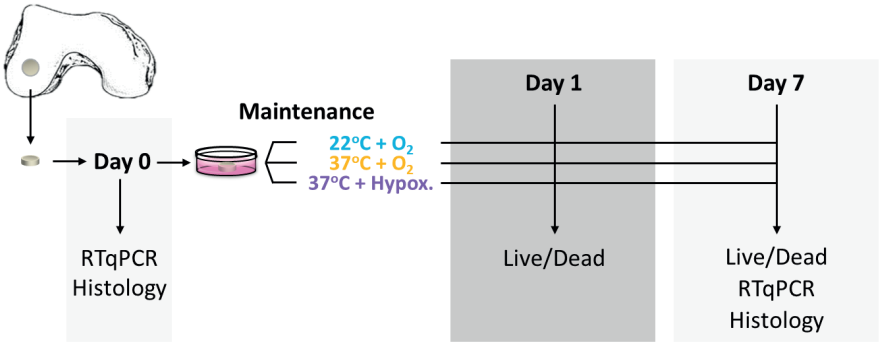

Figure 3: Timeline for storage and tissue characterization. Schematic representation of punched cartilage discs, the 3 storage conditions, and the timeline for the different levels of tissue characterization.

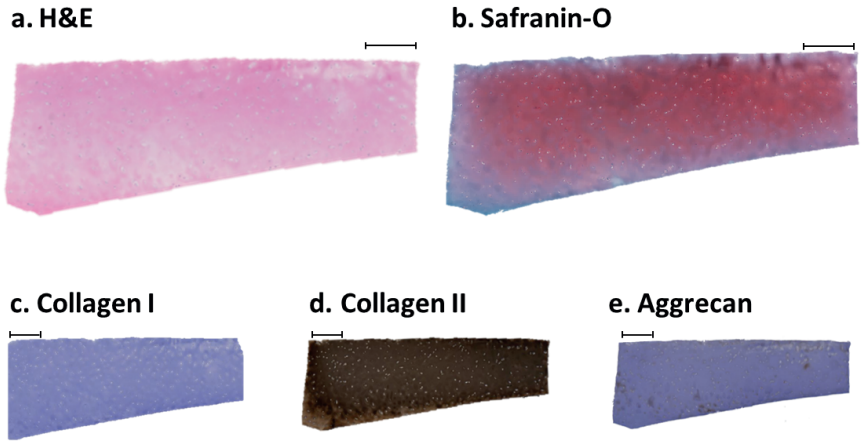

Figure 4: Histology staining. Representative joint resection sample demonstrating good cartilage architecture by H&E (**a**) and Safranin-O (**b**) staining. Immunohistochemisty demonstrates an absence of Collagen I staining (**c**), strongly positive Collagen II staining throughout (**d**), and scattered areas of positive aggrecan staining (**e**) within the cartilage disc. Scale bar = 500 μm

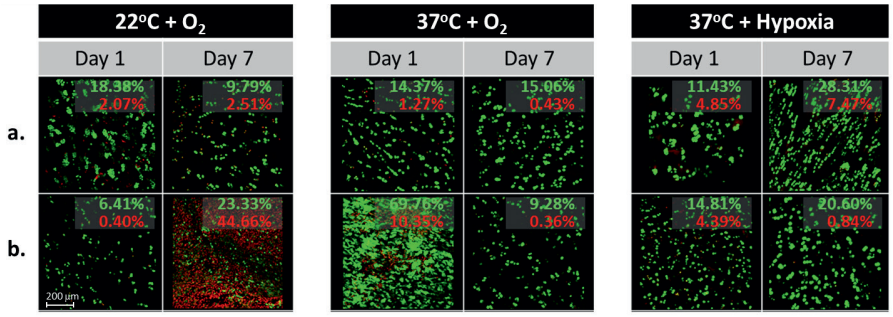

Figure 5: Representative Live/Dead staining of cartilage discs. Representative images from five different cartilage discs (**a**-**e**, collected from a single donor) obtained during live/dead microscopy at days 1 and 7 following storage at various temperature and oxygen conditions. Samples stored at 22° C demonstrated significantly decreased proportions of live (green) cells at day 7 compared to baseline (day 1) and matching samples stored at 37° C. Green (red) values represent the percentage of all pixels that are green (red).

I Structure	
A. Normal	0
B. Surface irregularities	1
C. Clefts to transitional zone	2
D. Clefts to radial zone	3
E. Complete disorganization	4
II Cells	
A. Normal	0
B. Diffuse hypercellularity	1
C. Cloning	2
D. Hypocellularity	3
III Safranin-O staining	
A. Normal	0
B. Slight reduction	1
C. Moderate reduction	2
D. Severe reduction	3
E. No dye noted	4

Minimal	**0**
Maximal	**11**

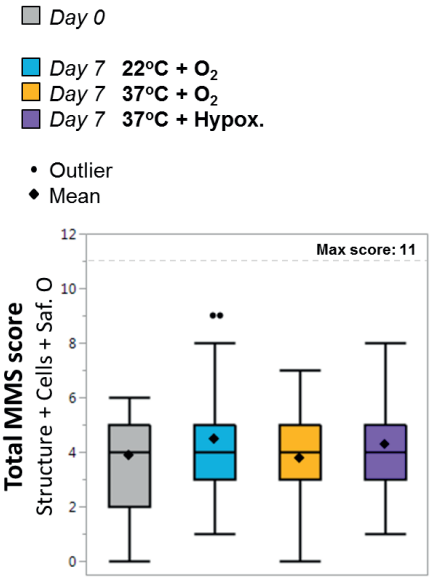

Figure 6: Histology scoring. (**a**) Breakdown of MMS scoring table. (**b**) Box (IQR) and whisker (max, min) plots of the total MMS histological scores (Structure [0-4] + Cells [0-3] + Safranin-O staining [0-4]; three independent observers) for Day 0 samples harvested immediately at tissue collection, and for samples cultured for 7 days in storage at 22° C + O_2, 37° C + O_2 or 37° C + Hypoxia. Mean $\pm$ standard deviation are included (diamonds) for each treatment group. No significant difference was found across treatment.

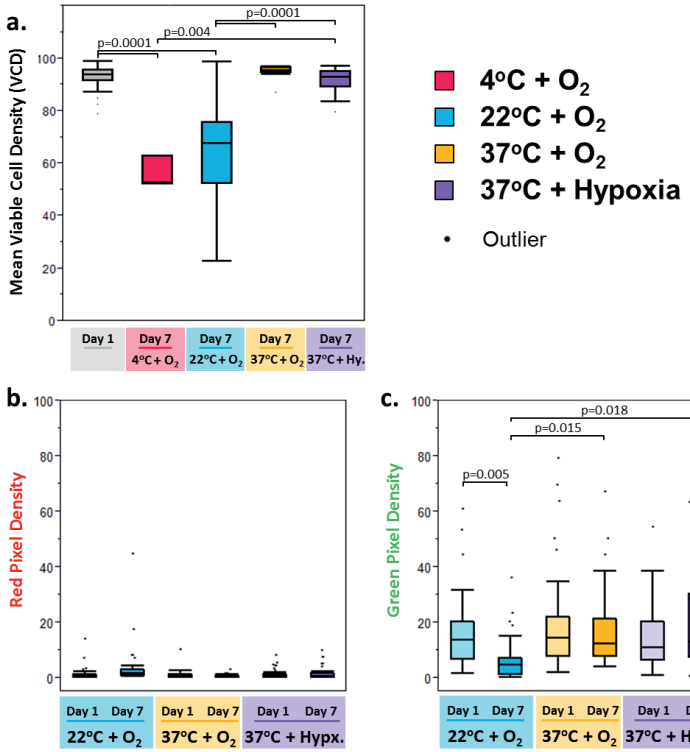

Figure 7: Live/Dead staining results. Box and whisker plots of live/dead staining demonstrate significantly better maintenance of cell viability, as measured by percentage of green pixels at 7 days of storage for cells cultured at 37° C as compared to cells cultured at 22° C. (**a**) Change in cell viability over one week is illustrated by plotting the ratios of green pixels: all stained pixels to determine viable cell density [VCD]). All Day 1 samples are pooled, while average Day 7 results are grouped by condition. There was no significant change in VCD from Day 1 to Day 7 for cartilage preserved at 37°C, while samples stored at 4°C (validation cohort) and at 22°C had a significant drop. Percentage of (**b**) red pixels (dead cells) and (**c**) green pixels (live cells) are shown as a function of the total number of pixels in each image to represents the change in cell density for each condition and time point.

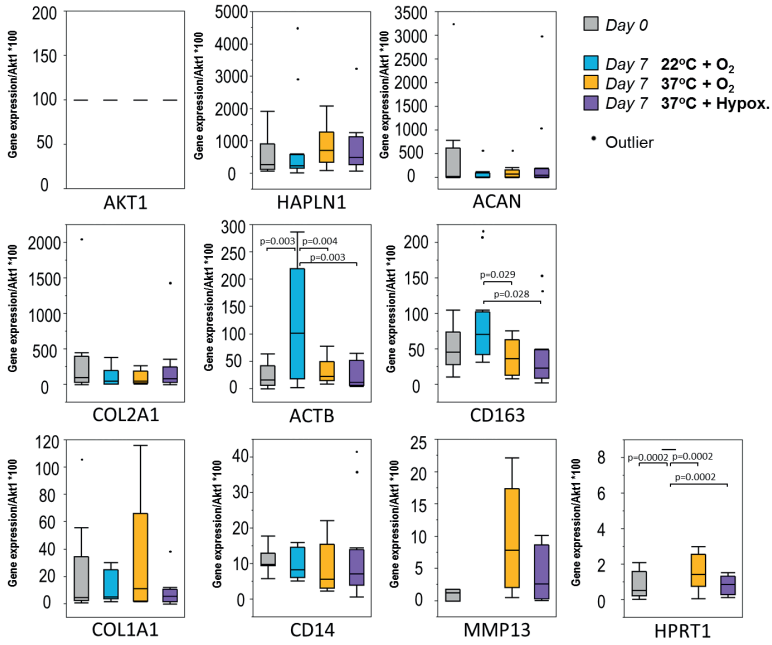

Figure 8: RTqPCR data from three different week-long maintenance conditions. Box and whisker plots of gene expression levels (obtained by RT-qPCR; normalized to Akt1) that allow comparison of samples collected from different treatment conditions at 2 distinct time points: Day 0 samples (gray) and Day 7 samples stored at 22°C + O_2 (blue), 37°C + O_2 (yellow), or 37°C + Hypoxia (purple). Samples were assessed for changes in housekeeping genes (AKT1, ACTB), matrix deposition associated markers (COL1A1, COL2A1, COL10A1, ACAN), matrix maintenance-associated markers (HAPLN1, MFAP5, MMP13) and inflammatory infiltrate markers (CD4, CD14, CD163, KIT). Genes with no detectable expression are not plotted. Anova with FDR adjustments made for multiple comparisons were performed to compare treatments. p-values less than 0.05 are significant.

Chapter V:

Modernizing Surgical Interventions and Clinical Outcomes of Hip and Knee Preservation

Chapter V, Section I: Hip Preservation

Multicenter Analysis of Midterm Clinical Outcomes of Arthroscopic Labral Repair in the Hip: Minimum 5-Year Follow-up.

Hevesi M, Krych AJ, Johnson NR, Redmond JM, Hartigan DE, Levy BA, Domb BG.

American Journal of Sports Medicine.
February 2018; 46(2):280-287.
PMID: 29065275

Introduction

Hip pain and development of osteoarthritis has been strongly associated with structural abnormalities of the hip joint including chondral pathology, labral tears, and femoroacetabular impingement (FAI) [32, 145, 209, 295]. Traditionally, treatment of hip pathology required open approaches; however, there has been a contemporary shift to less invasive management of these lesions [47]. Hip arthroscopy was popularized in the late 2000s and there has been a dramatic increase in recent use, as it has been shown to be safe and efficacious in short-term studies [48, 159].

Initial arthroscopic management of acetabular labral pathology was in the form of debridement and this has been shown to have modest outcomes at mid-term follow-up, with 20% of hips requiring surgery and an additional 25% of hips rating function as abnormal or severely abnormal at 5 years' follow-up [219]. Subsequent efforts to preserve the labrum through repair have demonstrated promising short-term outcomes, with significantly greater improvements in Hip Outcome Score activities of daily living (HOS-ADL) and sports specific subscale (HOS-SSS) when compared to isolated debridement[222]. However, longer follow-up is currently underreported. As such, it is largely unknown whether early improvements following labral repair will be durable over time.

Short-term studies have additionally established that BMI and increased patient age are risk factors for decreased patient reported outcomes postoperatively[152, 185, 243, 411]. However, preoperative Tonnis grade, which had previously been postulated to be a negative predictor of outcome, has not been shown have significant postoperative effects in large, matched cohorts[76, 78]

Therefore, the purpose of this study was to (1) outline the clinical mid-term patient reported outcomes of arthroscopic hip labral repair at a minimum five years of follow-up, (2) to determine the applicability of short-term risk factors on mid- to long-term outcomes, and (3) to establish novel risk factors as patient groups differentiate over time. Our hypotheses were that patients would (1) demonstrate durable improvements in patient reported outcome scores at mid-term follow-up, (2)

previously established short-term risk factors such as increased BMI and patient age would predict worse midterm outcomes, and (3) increased preoperative Tonnis grade will negatively affect mid- to long-term outcomes as patients with varying degrees of pre-existing osteoarthritis differentiate over time.

Materials and Methods:

Study Population and Design

This retrospective clinical and radiographic study included all eligible patients undergoing hip arthroscopy following failure of non-operative management at four high-volume hip arthroscopy centers (Mayo Clinic, Rochester, MN; Mayo Clinic, Phoenix, AZ; Mayo Clinic, Jacksonville, FL; American Hip Institute, Westmont, IL). Patients were consented to participate in research following Institutional Review Board approval of the study design (IRB# 08-002259). Inclusion criteria consisted of all patients undergoing primary hip arthroscopy between February 2008 and December 2011 consented for research participation with labral repair performed at the time of surgery. Exclusion criteria consisted of less than five years of clinical follow-up, patients choosing not to participate in outcome score surveys, labral debridement, labral reconstruction, and previous hip surgery. Cases with bilateral hip arthroscopy, both simultaneous and staged, were included and noted in our database. Indications for arthroscopy included labral tears, chondral injury, and femoral acetabular impingement (FAI) which had failed conservative, non-operative management. The prospectively collected institutional databases contained the records of 449 primary hip arthroscopies with labral repair performed during the study period for potential inclusion. Of these, 146 cases were excluded due to less than 5 years of clinical follow-up resulting in 303 cases for inclusion in this study.

Surgical Technique

Arthroscopic hip surgery was performed by experienced arthroscopists (AJK, JMR, DEH, BAL, BJD) in an operative setting designed for hip arthroscopy. Patients were positioned in a modified supine position and two or more portals were employed, including the anterolateral and mid anterior portals. Positioning and approach has been described in detail [63, 288, 413]. Diagnostic arthroscopy was performed to directly evaluate articular and labral status. Correction of cam and pincer lesions was performed when present [86, 87]. All patients underwent labral repair with concurrent debridement as indicated employing standard techniques [88, 142, 208]. Psoas release was performed in the setting of clinically painful iliopsas snapping reproduced on physical examination. Capsular repair was performed at the discretion of the operating surgeon with use favored in the

setting of young patients participating high-demand activities, patients demonstrating hip or generalized laxity such as those that easily translated under femoral head traction, and those with dysplastic radiographic features[68, 85].

Rehabilitation Protocol

Patients underwent standard postoperative rehabilitation and pain relief protocols which were consistent between physicians at the same institution and similar between institutions. Patients were placed on crutches for 2 – 4 weeks with foot-flat partial weight bearing. Passive motion was started at 0 weeks. As crutches were weaned, patients progressed through institutional rehabilitation protocols which have been previously outlined in detail for the centers involved (Mayo clinic, Rochester, M; Southeast Orthopedic Specialists, Jacksonville, FL; and Mayo Clinic, Phoenix, AZ[376] American Hip Institute, Westmont, IL[120]). Jogging exercises began at 3 months, as tolerated, and return to sport was allowed at 5-6 months.

Outcomes Collected

Demographic data such as age at the time of surgery, BMI, and gender were collected. In addition, preoperative radiographic measures such as Tonnis grade [395], alpha angle [25], and lateral central edge angle (LCEA) [292] were noted. Hips with LCEA < 25° were classified as dysplastic. Surgical diagnoses such as presence of cam and/or pincer lesions, femoral and acetabular chondromalacia as defined by the Outerbridge [313] and acetabular labrum articular disruption (ALAD) [66] classification systems, and surgical techniques such as ligamentum teres debridement and psoas release were documented using a standardized data form. Subjective pre- and postoperative outcomes were documented using visual analog pain score (VAS) [230], modified Harris Hip Score (mHHS) [166], and Hip disability and osteoarthritis Outcome Score – Sports Specific Subscale (HOS-SSS) [301]. Outcome score completion for each individual score was ≥ 89.3 %. Failure rate was defined as subsequent ipsilateral hip surgery, including revision arthroscopy, open hip surgery, and conversion to hip replacement.

Statistical Analysis

Descriptive statistics were used to present demographic data employing means and standard deviations, percentages, and medians with interquartile ranges (IQR), as appropriate. Factors such as BMI, gender, laterality, and intra-operative cartilage grade were examined for their association with outcome measures such as VAS, mHSS, and HOS-SSS scores using Spearman's rank correlation coefficient for continuous variables, independent sample t-testing for differences

between nominal values, and analysis of variance (ANOVA) for categorical variables such as Tonnis, femoral, and acetabular cartilage grade. Following analysis of single factor predictors, stepwise linear regression was performed employing the Akaike Information Criterion (AIC) in order to identify the optimal set of explanatory variables for postoperative outcome scores[5]. Wilcoxon rank sum testing (Mann-Whitney U) was used to compare ordinal variables such as pre- and postoperative VAS, mHHS, and HOS-SSS scores. Cox proportional hazards regression was performed to determine predictors of postoperative failure.

A priori analysis was used to determine the mean group sample size needed to demonstrate minimal clinical important differences (MCID) for patient reported outcome scores at alpha = 0.05 and power of 0.80. Using the study by Chahal et al wherein MCID cutoffs were determined for mHHS and HOS-SSS at 3, 6, and 12 months following hip arthroscopic labral repair for FAI, the most conservative MCID value presented for each outcome measure was selected, resulting in a cutoff of 9.0 points improvement for mHSS and 25.0 points for HOS-SSS[74]. Additionally, based on a study of arthritic hip pain in 211 patients, an MCID of 2.0 points improvement was established for VAS[396]. Employing these values and outcome score distributions derived from previous studies on hip arthroscopic labral repair, the mean group sample size needed to demonstrate MCID was determined to be 48 for mHHS, 12 for HOS-SSS, and 21 for VAS[197]. P-values < 0.05 were considered significant. Analyses were conducted in R 3.4.0 (R Core Team, Vienna, Austria).

Results

Using institutional databases comprising of hip arthroscopy cases performed from 02/2008 to 12/2011 at four institutions, we identified 303 cases with five years or more of clinical follow-up. Mean age at the time of surgery was 32.0 years, mean BMI was 24.4, and mean duration of follow-up was 5.7 years (Range: 5.0 – 7.9) (Table 1). In terms of preoperative radiographic measures, Tonnis grade 0 predominated (72.1 %) followed by grade 1 (24.2 %) and grade 2 changes (3.7%). Median alpha angle was 56.9 degrees (IQR: 49.0 – 67.0) and median lateral central edge angle was 30.0 degrees (IQR: 26.5 – 34.0). Of note, right-sided surgery (58.1 %) was significantly more common than left (41.9 %) ($p < 0.01$) and females were represented to a greater proportion (66.7 %) than males (33.3 %) ($p < 0.001$).

Four patients had bilateral hip surgeries with both hips included in the dataset with minimum five years of follow-up. Of these, one pair of hips was performed simultaneously and another three pairs were performed in a staged manner, with the two procedures separated by 4.5 to 24.6 months. An additional five patients had hip arthroscopy performed in a staged manner with the

second hip performed after December 2011 and thus having less than 5 years of follow-up. In these cases, the first hip was included in the dataset.

Patients underwent hip arthroscopy for a combination of hip dysplasia (n = 50), cam (n = 200), pincer (n = 66), and labral lesions (n = 303) in the setting of varied acetabular and femoral chondromalacia (Table 2). For patients with dysplasia, mean LCEA was 21.5° (Range: 13.0° – 24.9°). Ligamentum teres debridement was performed in 37.6% of the study population, psoas release in 38.3 %, and capsular repair in 48.5%. Total failure rate was observed to be 16.2%, with 49 of 303 patients undergoing revision hip surgery during the course of follow-up. Of these, seven went on to total hip arthroplasty, two underwent hip resurfacing, two underwent periacetabular osteotomy alone, 37 underwent revision arthroscopic management, and one patient underwent revision arthroscopic management followed by periacetabular osteotomy at a later time. All patients going on to periacetabular osteotomy did so in the setting of hip dysplasia.

A multivariable Cox proportional hazards model was constructed to evaluate pre- and intraoperative findings predictive of subsequent failure and progression to ipsilateral hip surgery. No significant predictors of failure were noted (Table 3). Dysplasia did not predict subsequent ipsilateral hip surgery, whether defined as LCEA < 25° ($p = 0.56$) or LCEA < 20° ($p = 0.60$).

Visual analog pain score, modified Harris Hip Score, and HOS-SSS were all observed to significantly improve ($p < 0.001$) between their preoperative values and final follow-up at 5.0 to 7.9 years postoperatively (Figure 1). Visual analog pain score decreased a mean of 3.5 points following surgery whereas mHHS and HOS-SSS increased by 20.1 and 29.3 points, respectively. Analysis was conducted to explore whether institution or performing surgeon had an effect on outcome scores. Location and provider were found to be non-significant in predicting VAS, mHHS, and HOS-SSS at final follow-up ($p \geq 0.11$) when accounting for patient age, BMI, and Tonnis grade.

BMI was found to be significantly and negatively correlated to final modified Harris Hip Score ($p < 0.001$) and HOS sports specific subscale ($p < 0.001$). It was non-significant for predicting VAS ($p = 0.33$). This pattern was also present for age at the time of surgery, with a significant, negative correlation with final modified Harris Hip Score ($p = 0.02$) and HOS-SSS ($p < 0.01$) and non-significance in terms of VAS ($p = 0.66$).

On average, patients with BMI > 30 had final mHHS 9.5 points lower (mean mHHS = 74.0) than those with BMI ≤ 30 (mean mHHS = 83.5) ($p < 0.01$) and demonstrated a HOS-SSS 15.9 points lower (mean HOS-SSS = 57.0) than those with BMI ≤ 30 (mean HOS-SSS = 72.9) ($p < 0.001$) (Figure

2). Patients aged > 35 years at the time of surgery had a final mHHS 4.5 points lower (mean mHHS = 79.8) than those aged ≤ 35 years (mean mHHS = 84.3) (p = 0.03) and similarly demonstrated HOS-SSS 6.7 points lower (mean HOS-SS = 67.1) than those aged ≤ 35 (mean HOS-SSS = 73.8) (p = 0.03) (Figure 3). Patients with BMI >30 achieved mean improvements in VAS of 4.0, mHHS of 19.1, and HOS-SSS of 29.2 postoperatively whereas patients with age >35 years had mean improvements of 3.2 in VAS, 17.5 in HOS-SSS, and 27.3 in HOS-SSS. As such both groups, while statistically inferior in outcome as compared to patients with BMI ≤ 30 and age ≤ 35, surpassed the MCIDs for each patient reported score (2.0, 9.0, and 25.0, respectively).

Additionally, patients with Tonnis grade 2 changes preoperatively were found to have 12.5 point worse mHHS (p = 0.02) and 23.0 point worse HOS-SSS outcomes (p < 0.01) at the time of follow up as compared to patients with grade 0 pre-operative radiographs (Figure 4). VAS demonstrated no significant association with Tonnis grade. No significant differences in mHHS or HOS-SSS were found when comparing patients with grade 0 and grade 1 changes preoperatively. Patients presenting with Tonnis grade 2 radiographs achieved final mean improvements in VAS of 3.7 points (p = 0.0.01), surpassing the MCID. However, mean mHHS decreased non-significantly from 72.1 preoperatively to 71.0 postoperatively (p = 0.84) while mHHS scores decreased from 68.8 preoperatively to 49.5 postoperatively (p = 0.66) in the Tonnis grade 2 group.

Preoperative alpha angle, lateral central edge angle (LCEA), gender, operation laterality, intra-operative femoral and acetabular cartilage grade, ligamentum teres debridement, psoas release, and capsular repair were found to be non-significant at predicting VAS, mHHS, and HOS-SSS.

Following univariate analysis, multifactorial analysis for predictors of each of the three patient reported outcomes was performed using stepwise regression employing AIC. As previously observed in the univariate analysis, no significant predictors of final VAS were found. It was determined that the optimum model for both mHHS and HOS-SSS at final follow-up was through the combination of BMI and Tonnis Grade. As such, patients with BMI > 30 and Tonnis grade 2 changes preoperatively were modeled to have the worst outcomes whereas patients with BMI ≤ 30 and Tonnis grade 0-1 changes were predicted to experience the most favorable results following arthroscopic labral repair (Table 4).

Discussion:

The purpose of this study was to determine the clinical outcomes of arthroscopic hip labral repair at a minimum five years of follow-up, as well as to determine risk factors for worse patient outcomes. Our hypothesis was supported in that patients demonstrated durable improvements in

VAS, mHHS, and HOS-SSS at mid-term follow-up. In addition, we found that increasing Tonnis grade, patient BMI, and age at the time of surgery significantly predicted worse outcomes.

Our finding that patient outcomes demonstrate significant and sustained improvement at five years status post hip arthroscopy is an extension of previous literature that has demonstrated well-established short-term efficacy and favorable outcome in terms of VAS [76], modified Harris Hip Score [70, 108, 204] and HOS-SSS scores [108]. As longer-term outcomes become available for analysis, recent studies have demonstrated mid-term benefit of hip arthroscopy in the setting of FAI and labral tears [306]. However, sample size for most studies has been relatively small and we believe this study is amongst the largest cohorts with the longest mean follow-up when reviewing the current literature [147, 190, 306, 331, 371]. As such, we believe this paper supports the durable outcomes previously described at mid-term follow-up whilst adding statistical power and decreasing the propensity for type II error present in smaller sample sizes.

In terms of VAS, our findings demonstrate a mean postoperative VAS within a standard deviation of the overall VAS score observed for 935 hips previously described at 2+ years of follow-up [76]. It is noteworthy that our mean VAS falls below the point estimates for the Tonnis grade 0, 1, and 2 subgroups reported in the prior study, however, our population was 12.8 years younger at the time of surgery making direct comparisons between study populations difficult. In terms of our findings associating increasing Tonnis grade with decreasing outcome scores, it has been previously reported in large matched-cohort studies that VAS, mHHS, and HOS-SSS are not significantly affected by preoperative Tonnis grade at two years of follow-up [76, 78]. Our findings are significant in that they suggest preoperative osteoarthritis evolves over time, causing significant effects in mHHS and HOS-SSS at mid-term follow-up which are not apparent earlier in patients' clinical course. This was especially noticeable in mHHS and HOS-SSS scores for Tonnis grade 2 patients, which non-significantly decreased postoperatively, failing to meet MCID. In comparison, patients with Tonnis grade 0-1 changes demonstrated significant postoperative improvements in mHHS and HOSS-SSS as well as VAS which surpassed MCID. This highlights the importance large cohorts with extended follow-up as outcomes can differentiate over the course of many years. Future studies should aim to investigate outcome score trends over time as well as correlate these outcomes to postoperative radiographic signs of arthritis.

In terms of mHHS, we observed postoperative outcome scores which approximated the findings of Kamath et al who demonstrated a mean mHHS of 80.4 at 4.8 years in their sample of labral tears managed arthroscopically [204]. When comparing our subgroup of patients aged over 35 years to their sample which had an average age of 42 years, the difference in observed post-operative mHHS is 0.6, suggesting relative homogeneity between our outcomes and those found at the University and private hospital included in their study. Similarly, our HOS-SSS scores are similar to

values previously presented for both adolescents and for recreational athletes at short-term follow-up [108, 411].

A meta-analysis comprising of 81 studies and 9,317 hips at 1+ year by Levy et al demonstrated that increasing patient age negatively predicts mHHS and HOS-SSS [243]. Similarly, the study suggested that increasing BMI predicts worse HOS-SSS. In terms of age, there has been a significant amount of data associating age-related chondropathy with worse outcomes as well as identifying increasing age as an independent negative predictor of postoperative outcome and as a risk factor for subsequent conversion to total hip arthroplasty, especially in those patients over 40 years of age [152, 185]. However, meta-analyses have focused on stratifying risk of revision and have been limited by differences in outcome scores collected by various studies as well as by their combination of relatively dissimilar, individually small sample sizes. We believe this cohort serves as the first single-study sample to describe the association between increased age and worsened mid-term outcomes following hip arthroscopy.

Our finding of BMI being associated with worse patient outcome scores has also been described previously in the short-term literature. A recent outcomes paper correlated increasing BMI and decreased mHHS and HOS-SSS values at two years follow-up in a population of relatively young recreational and amateur athletes [411]. These findings have also been described in larger cross-sectional samples, such as the previously mentioned meta-analysis by Levy et al which demonstrated a significant correlation between increasing BMI in 3,149 hips and decreasing HOS-SSS and HOS-ADL scores [243]. Finally, a two-study meta-analysis associated BMI ≥ 30 with both decreased mHHS and NAHS as compared to non-obese controls as well as an increased risk of revision arthroscopy and THA at 2.5 years of follow-up [30]. The current study, however, remains the only study to extend these findings to mid-term follow-up, suggesting that increased BMI and patient age have lasting effects on patient outcomes. It is noteworthy that there is likely a considerable degree of interplay between age, BMI, and osteoarthritis for most patients; however, each has been established as an independent risk factor for failure following hip arthroscopy [185, 243, 329]. With the exception of the VAS but not mHHS or HOS-SSS improvements observed in patients presenting with preoperative Tonnis grade 2 radiographs, patients at risk for poorer outcomes due to increased BMI and age achieved significant improvements in VAS, mHHS, and HOS-SSS, reaching MCID in all three scales, albeit to a lower magnitude than their younger, lower BMI counterparts. As such, our findings suggest that while outcomes are compromised in these patients, hip arthroscopic labral repair may still provide significant relief and improvement in function.

While the four institution nature and use of three outcome scales (VAS, mHHS, and HOS-SSS) are relative strengths of our study, future investigations should aim to include additional arthroscopy centers and outcomes measures as prior literature contains a variety of measurement tools, such as

the Non-Arthritic Hip Score [70, 89], iHOT-12 [137, 151], and Functional Activity Assessment [37, 338] for which further outcomes research is merited. An associated limitation of our study is the inherent difficulty of mid- to long-term clinical follow-up in a young and healthy patient population and ensuring patients fill out multiple time-consuming scales at each clinical visit. Although we believe our data performs well at ≥ 89% completion for each scale, future studies should aim to achieve near 100% response rates, as relationships may exist between patient outcome and patient propensity to complete surveys. Additionally, while Tonnis grade is a reasonable surrogate degree of joint involvement for chondral damage, further studies may also consider noting intraoperative surface area of chondral damage in addition to Outerbridge grade of chondral damage. Our study also contains biases inherent to a retrospective review, namely selection bias and reliance of accurate and complete recordkeeping.

Conclusion

Our data suggests that improvements in VAS, mHHS, and HOS-SSS outlined in previous studies are durable through mid-term follow-up. Additionally, this study reinforces the association between increased BMI and patient age and worse patient outcomes following hip arthroscopy. Our finding that patients with higher preoperative Tonnis grade have worse outcomes at mid-term follow-up is novel in that this differentiation was not apparent in previous short-term studies, suggesting that patients grouped by preoperative radiographic arthritis clinically differentiate over the course of extended follow-up. As such, we believe this study's significance lies in its ability to support hip arthroscopy in providing sustained relief for labral pathology and FAI as well as in providing both univariate and multivariate preoperative measures that can serve as enduring predictors of clinical outcomes for the surgeon selecting and counseling patients for hip arthroscopy.

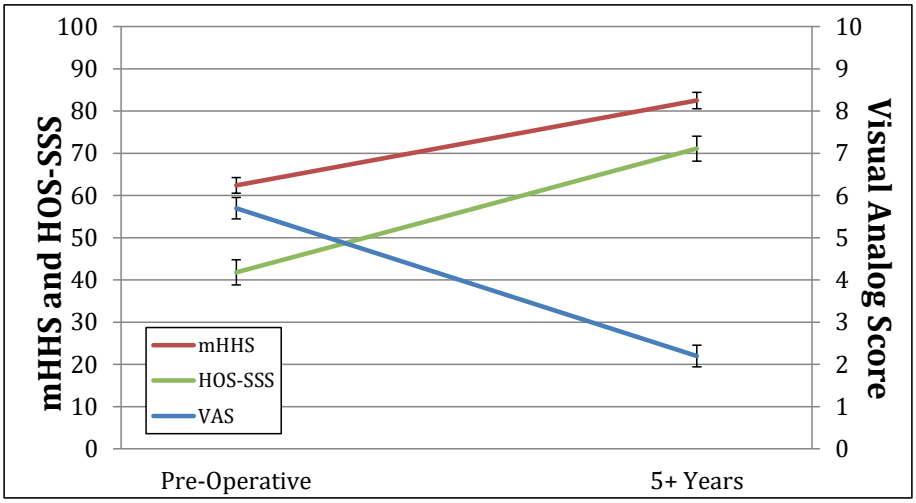

Figure 1: Pre- and postoperative outcome scores by predictors of outcome. Postoperative values are provided at the time of final follow-up, 5.0 – 7.9 years. 95% Confidence interval provided as error bars.

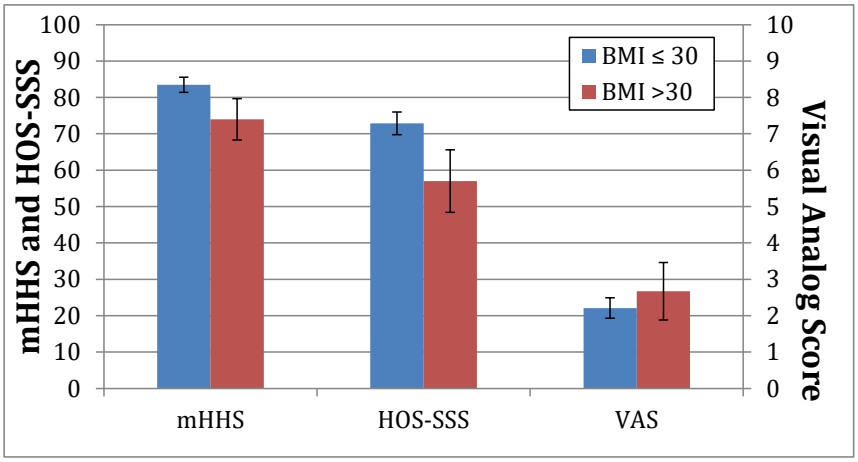

Figure 2: Postoperative outcome scores for VAS, mHHS, and HOSS-SSS by BMI. Error bars provided as the 95% confidence interval.

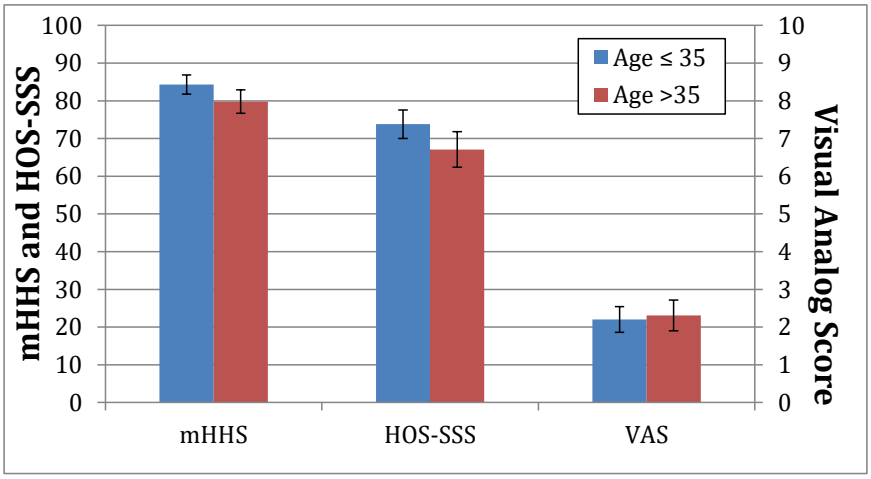

Figure 3: Postoperative outcome scores for VAS, mHHS, and HOSS-SSS by age. Error bars provided as the 95% confidence interval.

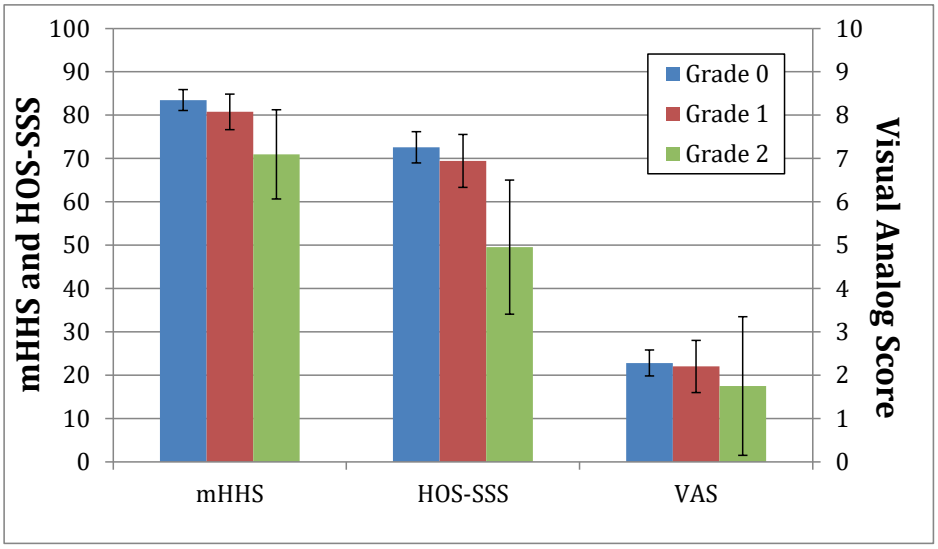

Figure 4: Postoperative outcome scores for VAS, mHHS, and HOSS-SSS by Tonnis grade. Error bars provided as the 95% confidence interval.

Table 1: Preoperative Demographic and Radiographic Measures. Values provided as Mean ± SD.

Pre-Operative Variable	Value
Age at Surgery	31.97 ± 12.02
BMI	24.35 ± 5.01
Gender	
Females (%)	202 (66.7 %)
Males (%)	101 (33.3 %)
Laterality	
Right (%)	176 (58.1 %)
Left (%)	127 (41.9 %)
Bilateral Procedures[a]	
Total	13
Simultaneous	2
Staged	11
Alpha Angle	58.15 ± 12.14
LCEA	30.16 ± 6.09

[a]Number of hips

Table 2: Diagnoses and Surgical Techniques Performed

Diagnosis / Procedure	**Number of Hips**
Isolated Cam Lesion	151 (49.8 %)
Isolated Pincer Lesion	17 (5.6 %)
Combined Cam and Pincer Lesions	49 (16.2 %)
Hip Dysplasia	50 (16.5 %)
Labral Tear	303 (100 %)
Femoral Chondromalacia	
Grade 1	7 (2.3 %)
Grade 2	26 (8.6 %)
Grade 3/4	29 (9.6 %)
Acetabular Chondromalacia	
Grade 1	90 (29.7 %)
Grade 2	83 (27.4 %)
Grade 3/4	64 (21.1 %)
Tonnis Grade	
Grade 0	214 (72.1 %)
Grade 1	72 (24.2 %)
Grade 2	11 (3.7 %)
Ligamentum Teres Debridement	114 (37.6 %)
Psoas Release	116 (38.3 %)
Capsular Repair	147 (48.5 %)

Table 3: Cox proportional hazards model for pre- and intraoperative predictors of failure

Variable	Hazards Ratio (95% CI)	p-value
Age		
≤ 35 years	Reference	
> 35 years	0.71 (0.19 – 2.63)	0.61
BMI		
≤ 30	Reference	
> 30	1.44 (0.48 – 4.33)	0.51
Gender		
Female	Reference	
Male	1.31 (0.29 – 5.88)	0.72
Laterality		
Left	Reference	
Right	1.04 (0.50 – 2.14)	0.92
LCEA		
≥ 25° (Normal)	Reference	
< 25° (Dysplasia)	0.80 (0.39 – 1.68)	0.56
Femoral Chondromalacia		
Grade 1-2	Reference	
Grade 3-4	0.57 (0.14 – 2.21)	0.41
Acetabular Chondromalacia		
Grade 1-2	Reference	
Grade 3-4	0.95 (0.42 – 2.16)	0.90
Alpha Angle		
< 55° (Normal)	Reference	
≥ 55° (suggestive of FAI)	0.80 (0.40 – 1.57)	0.51

Table 4: Estimates of mHHS and HOS-SSS at final follow-up based on predictive measures determined by multivariate stepwise regression using AIC.

Risk Factor Combination	**mHHS Estimate (95% CI)**	**HOS-SSS Estimate (95% CI)**
BMI ≤ 30, Tonnis Grade 0-1	83.5 (49.0 – 118.0)	73.0 (21.9 – 124.2)
BMI > 30, Tonnis Grade 0-1	74.9 (40.0 – 109.9)	58.0 (6.2 – 109.8)
BMI ≤ 30, Tonnis Grade 2	70.4 (34.2 – 106.5)	48.6 (-5.0 – 102.1)
BMI > 30, Tonnis Grade 2	61.8 (25.3 – 98.3)	33.6 (-20.5 – 87.6)

Are Results of Arthroscopic Labral Repair Durable in Dysplasia at Midterm Follow-up? A 2-Center Matched Cohort Analysis.

Hevesi M, Hartigan DE, Wu IT, Levy BA, Domb BG, Krych AJ.

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Introduction

Hip pain and the development of osteoarthritis have been associated with structural abnormalities including dysplasia, femoroacetabular impingement (FAI), and labral tears [32, 145, 209, 295, 412]. The advent of hip arthroscopy and subsequent rapid adoption and evolution of techniques has led to safe and effective management of chondrolabral lesions and FAI without traditional open approaches[47, 48, 159]. However, arthroscopic management in the setting of the dysplastic hip remains a controversial topic[236, 322, 345]. In particular, questions have been raised regarding the durability of the procedure and the potential for destabilization of the already shallow acetabulum with labral excision[322].

Initially, arthroscopic management of acetabular labral pathology consisted of labral debridement and this has been shown to demonstrate modest outcomes at mid-term follow-up with nearly half of patients requiring revision surgery or reporting their hip function as abnormal to severely abnormal at mid-term follow-up[219]. Subsequent efforts to repair and preserve the labrum have demonstrated promising outcomes and improved subjective outcome scores when compared to isolated debridement [222, 288]. In addition, arthroscopic closure employing capsular repair is a relatively modern technique with ongoing discussion regarding its efficacy, especially in the setting of hip dysplasia[118, 121, 267, 268]. Short-term studies on arthroscopic capsular repair have demonstrated promising results with significant postoperative improvements in patient-reported outcome scores[77, 140, 236]. Due to the presence of multifactorial decision-making including degree of dysplasia, tissue laxity, and patient activity demand involved in electing for or against capsular repair, studies on modern arthroscopic techniques such as labral repair in the setting of dysplasia would ideally control for the presence of capsular repair as a potential confounding variable.

The management of the dysplastic hip is of importance since patients with dysplasia comprise 0.49% to up to 51.8% of the population in contemporary studies [251, 421]. Dysplasia has been demonstrated to be one of the most common causes of hip pain, dysfunction, and arthritis, as well as a leading cause of total hip arthroplasty[167, 347, 412]. In addition to its relation to osteoarthritis,

dysplasia has been demonstrated to be a strong independent predictor for cartilage degeneration and labral tears[134, 168]. Accordingly, dysplasia and associated pathologies have special significance for the orthopedic arthroscopist attempting to preclude or delay open hip surgery. Previous studies have postulated that dysplastic hips pose an increased risk of failure following hip arthroscopy, yet a significant limitation is that cross-sectional studies are unable to account for potential differences in age, BMI, gender, and other factors that may exist between dysplastic and non-dysplastic hips[46, 345]. A **cohort** study of mid-term outcomes would provide the significant benefit of decreasing the amount of confounders at play while extending the follow-up currently available in the literature so that the predictors of interest can be better analyzed.

The purpose of this study was to (1) determine the clinical mid-term failure rate and patient-reported outcomes of arthroscopic labral repair in the setting of hip dysplasia, (2) to compare dysplasia failure rates and patient-reported outcomes to a rigorously matched control group without dysplasia, and (3) to assess factors which lead to higher failure rates or worse outcomes. Our hypotheses were (1) that patients undergoing primary hip arthroscopy in the setting of dysplasia would demonstrate satisfactory failure rates and outcomes at mid-term follow-up, (2) that failure rate and patient-reported outcomes would be similar to a control group without dysplasia, and (3) factors such as age, body mass index (BMI), gender, and Tonnis grade may play a role in predicting outcome.

Materials and Methods:

Study Population and Design

This clinical and radiographic study included all eligible patients undergoing hip arthroscopy following failure of comprehensive non-operative management at two high-volume hip arthroscopy centers (Mayo Clinic, Rochester, MN; American Hip Institute, Westmont, IL). Patients were consented for research participation following Institutional Review Board approval (IRB# 08-002259) using an established multi-center research initiative and standardized rehabilitation protocol. Inclusion criteria consisted of: (1) primary hip arthroscopy between February 2008 and December 2011, (2) consent for research participation, and (3) arthroscopic labral repair performed at the time of surgery (Figure 1). Exclusion criteria consisted of (1) less than five years of clinical follow-up, (2) isolated labral debridement or reconstruction, and (**3**) previous ipsilateral hip surgery.

Surgical Technique

Surgery was performed by experienced hip arthroscopists (AJK, BAL, BJD) in a dedicated operative setting designed for arthroscopy. Patients were positioned in the modified supine position and anterolateral and mid anterior portals were created. Additional use of the anterior, distal anterolateral, and posterolateral portals was employed, as needed. Patient positioning and operative approach has been described in detail previously[63, 288, 413]. Diagnostic arthroscopy was performed to evaluate labral and chondral status and correction of cam and pincer lesions was performed when present[86, 87]. All patients included in this study underwent labral repair[88, 142, 208]. Psoas release was performed in patients with painful iliopsoas snapping reproducible on physical examination and capsular repair was performed using standard techniques on the basis of the operating surgeon's assessment of ease of femoral head translocation, intraoperative laxity, and patient factors including hip dysplasia and participation in high demand activities[68, 85]. Not all dysplastic hips during the time period underwent capsular repair due to the combination of the evolving approach and techniques of capsular repair as well as above-described intraoperative assessment of hip stability by the performing surgeon.

Rehabilitation Protocol

Patients underwent a standard postoperative rehabilitation and analgesic protocol which was consistent between physicians within the same institution, similar between institutions, and outlined in detail in previous publications (Mayo Clinic, Rochester, MN[376] American Hip Institute, Westmont, IL[120]). Namely, patients were placed on crutches with foot-flat partial weight bearing for 2-4 weeks, with passive motion started at 0 weeks. As crutches were weaned, patients progressed through the institutional rehabilitation protocols, with jogging exercises beginning at 3 months, as tolerated, and return to sport allowed at 5-6 months.

Outcomes Collected

Demographic data such as age, BMI, and gender were collected in addition to preoperative radiographic measures including Tonnis grade[395], alpha angle[25], and lateral central edge angle (LCEA)[292]. Dysplasia was defined as hips with LCEA < 25°. The presence of cam and pincer lesions, femoral and acetabular chondromalacia as defined by the Outerbridge[313] and acetabular labrum articular disruption (ALAD)[66] classification systems, and procedures such as ligamentum teres debridement and psoas release were documented pre- and intraoperatively using a standardized data collection form. Pre-and postoperative patient-reported outcome measures (PROMs) were prospectively collected and documented employing visual analog pain score (VAS)[230], modified Harris Hip Score (mHHS)[166], and Hip disability and osteoarthritis Outcome Score – Sports Specific Subscale (HOS-SSS)[301]. Outcome score completion was 94.4%. Failure was defined as subsequent

ipsilateral hip surgery, including revision arthroscopy, open hip surgery, and conversion to total hip replacement.

Statistical Analysis

Following identification of 48 patients with hip dysplasia, 96 patients were matched on a 1:2 case-control basis from a pool of 223 possible patients meeting inclusion and exclusion criteria (Figure 1). Patients were matched on the basis of age at surgery, gender, operation laterality, BMI, Tonnis grade, and capsular repair using a validated nearest-neighbor matching algorithm[182]. Case and control group validation was performed using Fisher's exact test for proportions and Mann-Whitney U testing for nominal values to ensure the dysplasia and control groups were statistically similar in terms of the demographic variables upon which they were matched (Table 1). Within the unmatched dysplasia population, patients undergoing capsular repair had an average BMI 3.8 kg/m^2 lower (23.1 versus 26.9, $p < 0.01$) and were more likely to be female (76% versus 35%, $p < 0.01$) when compared to dysplastic patients not undergoing repair ($p < 0.01$), supporting the need for matching the controls on the basis of capsular repair in addition to baseline demographics. Following matching, it was determined that population differences underlying capsular repair ($p = 1.00$) and its interaction with gender ($p = 0.78$) and BMI biases ($p = 0.72$) were balanced between the dysplasia and control groups.

Mid-term failure rate was examined for the dysplasia cohort using Kaplan-Meier curves. Wilcoxon rank sum testing (Mann-Whitney U) was used to compare pre- and postoperative VAS, mHHS, and HOS-SSS scores. Subsequently, dysplasia failure rates and PROMs were compared to the rigorously matched control group. Additionally, potential risk factors such as patient demographics and the presence of capsular repair were evaluated using Cox proportional hazards analysis to determine their relationship to failure rate and clinical outcomes below the minimal clinically important difference (MCID).

A priori analysis was used to determine the sample sizes needed to demonstrate PROM improvements equivalent to MCID. Using the study on arthroscopic labral repair in the setting of FAI by Chahal et al, MCID cutoffs were determined for mHHS and HOS-SSS using the most conservative MCID value presented by the authors. The resultant MCIDs were 9.0 points for mHHS and 25.0 points for HOS-SSS[74]. Additionally, an MCID of 2.0 points was established for VAS employing a previous study on osteoarthritic hip pain[396]. Employing these values, the mean group sample size needed at alpha = 0.05 and a power of 0.80 to demonstrate MCID was determined to be 48 for mHHS, 12 for HOS-SSS, and 21 for VAS[197]. P-values < 0.05 were considered significant. Analyses were conducted in R 3.4.1 (R Core Team, Vienna, Austria).

Results

Forty-eight patients with dysplasia (LCEA < 25°) were matched with 96 controls (LCEA ≥ 25°) on the basis of age, gender, operation laterality, BMI, Tonnis grade, and capsular repair (Table 1, Figure 1). Both the dysplastic and the control groups met the minimum sample sizes needed in the *a priori* power analysis. Furthermore, no significant difference existed in preoperative VAS (p = 0.11), mHHS (p = 0.08), or HOS-SSS (p = 0.48) between the dysplastic and control groups, supporting subsequent postoperative comparisons between the two populations. In addition, institution and performing surgeon were found to be non-significant in predicting VAS, mHHS, and HOS-SSS when accounting for patient age, BMI, and Tonnis grade.

The mean age of the dysplasia group was 31.8 ± 12.7 years and the mean preoperative LCEA was 21.6° (range: 13.0° – 24.9°) (Table 1). Patients underwent arthroscopic labral repair with intraoperative assessment of femoral and acetabular cartilage lesions and were followed for a mean of 5.7 years (range: 5.0 – 7.7) (Table 2). The 5-year failure-free survival rate for the dysplasia population was 83.3%, with an overall failure rate at final follow-up of 18.8 %. Of the nine failures observed, six (66.7%) resulted in revision hip arthroscopy, two (22.2%) were periacetabular osteotomies (PAO), and one (11.1%) was total hip arthroplasty (THA). One revision arthroscopy was followed two years later by PAO. The mean time to revision surgery was 3.0 years. The dysplastic group demonstrated significant improvements in patient-reported outcome scales, with mean improvement of 3.0 points for VAS, 15.3 points for mHHS, and 27.3 points for HOS-SSS at final-follow up (p < 0.01).

The mean LCEA for the control population was 32.1° (range: 25° – 52°). 52.1% of both the control and dysplasia population underwent capsular repair. When compared to the dysplasia population, no significant difference was found between the dysplasia and matched control populations in terms of failure on Kaplan Meier analysis (p = 0.53, Figure 2), with the matched controls demonstrating a 5-year failure-free survival rate of 78.1%. For the 22 failures observed in the control population, 18 (81.8%) were revision arthroscopy, one was resurfacing (4.5%), and three were THA (13.6%). The mean time to revision surgery was 2.0 years. The failure rate for the dysplasia and control groups at the time of final follow-up (mean = 5.7 years) was 18.8% and 22.9%, respectively (p = 0.67), with not statistically different rates of revision arthroscopy (p = 0.62) and conversion to THA (p = 0.66). Additionally the failure rate for both populations was found to be not statistically different (p = 0.39 and 0.06, respectively) to the failure rate of the general population of 271 hip arthroscopies (16.6%) from which the dysplasia and matched controls were obtained. The dysplasia group and matched controls were found to be not statistically different in terms of final VAS (p = 0.52), mHHS (p = 0.87), and HOS-SSS (p = 0.98).

We performed a Cox proportional hazards analysis of potential univariate pre- and intraoperative predictors of failure for the dysplastic and control populations in our study and found that BMI ≤ 30 was a risk factor for failure in the dysplasia group ($p < 0.01$, Table 3). All nine failures occurred in patients with a BMI less than 30 (mean BMI = 22.8, range: 19.4 – 28.5). Age > 35 years, gender, operation laterality, Tonnis grade, femoral and acetabular chondromalacia, alpha angle ≥ 55°, capsular repair, ligamentum teres debridement, and psoas release were found not to be significant risk factors for failure.

Failure to achieve MCID in any of the three patient-reported outcome scales was also analyzed as an alternate, competing risk to ipsilateral hip surgery. Namely, these patients had failed to achieve MCID at the time of final follow-up but had not elected for repeat operative intervention. It was determined using competing risk regression that for the dysplastic group, age > 35 years at the time of surgery carried a 3.17-fold increased relative hazard of failure to achieve MCID when compared to patients aged ≤ 35 years (Table 4). This trend was observed for mHHS however it did not reach significance (HR 2.96, $p = 0.06$). Tonnis grade 0 was a risk factor for failure to achieve MCID in VAS and mHHS ($p < 0.01$) but not HOS-SSS. Of the 12 dysplastic patients that failed to achieve MCID in VAS and 11 patients that failed to achieve MCID in mHHS, all had preoperative Tonnis grades of 0. BMI, gender, operation laterality, femoral and acetabular chondromalacia, alpha angle, capsular repair, ligamentum teres debridement, and psoas release were not found to significantly predict failure to achieve MCID.

Additionally, due to previous literature which has sub-categorized dysplasia into borderline (LCEA 20° - 25°) and more severe (LCEA < 20°) categories[46, 127], we described and analyzed the failure rates of these two subpopulations (Table 5). The two dysplasia subcategories demonstrated no significant demographic differences aside from mean LCEA ($p < 0.01$), with similar preoperative patient reported outcome scores between the two groups ($p \geq 0.33$). While we had previously demonstrated significant ($p < 0.01$) improvements in all three patient reported outcome scores in the overall dysplastic group, no significant difference was noted between the borderline and more severe dysplasia sub-groups' VAS, mHHS, and HOS-SSS scores at final follow-up ($p \geq 0.65$). Two of the nine severely dysplastic (28.6 %) and seven of the 41 borderline dysplastic patients (17.1 %) went on to revision surgery ($p = 0.60$). Survival trends over time for the two populations were not observed to be significantly different at this sample size (Figure 3, $p = 0.60$).

Discussion:

The purpose of this study was to determine the clinical mid-term failure rate and patient-reported outcomes of arthroscopic labral repair in the setting of hip dysplasia, to compare dysplasia failure rates and patient-reported outcomes to a rigorously matched control group without dysplasia, and to assess factors which lead to higher failure rates or worse outcomes. Our hypothesis was supported in that patients undergoing primary hip arthroscopy in the setting of hip dysplasia demonstrated failure rates and outcomes comparable to a rigorously matched control population at mid-term follow-up. In addition, we found that dysplastic patients with BMI ≤ 30 were more likely to go on to subsequent ipsilateral hip surgery and that patients older than 35 years of age or with Tonnis grade 0 radiographs at the time of surgery were more likely not to achieve postoperative improvements of at least MCID following arthroscopic management.

At mid-term follow-up, arthroscopic labral repair in the setting of dysplasia demonstrated significant postoperative improvements in VAS, mHHS, and HOS-SSS and a failure rate of 18.8% at a mean of 5.7 years of follow-up. There is little mid-term literature available for arthroscopic labral repair failure rates, especially in the setting of dysplasia, with most reports limited to case series of dysplastic hips or retrospective causal analyses for revision surgery[46, 345]. A cautionary series by Parvizi et al found that 16 (44%) of 36 patients with LCEA < 20° or global acetabular retroversion went on to revision surgery at a mean follow-up of 3.5 years following arthroscopic surgery for labral tears[322]. Of note, all patients had undergone labral debridement, which has previously been shown to have inferior outcomes as compared to labral repair[164, 219, 222].

In this study, three of the nine patients in the dysplastic population that went on to revision surgery underwent PAO, with two progressing directly to PAO while a third underwent revision hip arthroscopy with PAO two years later. This suggests that variants of labral tears in the setting of dysplastic hip pathology cannot be successfully managed arthroscopically alone. Of note, the median LCEA of those patients who underwent later PAO was 21.0° (range: 19.3° – 21.2°) while the median LCEA of the overall nine patients that underwent repeat surgery in the dysplasia group was 21.0° (range: 13.0° – 24.0°) suggesting that progression to PAO was not exclusive to patients with more severe dysplasia. This observation is supported by the findings of Ross et al who demonstrated that in 30 PAOs performed following failure of arthroscopic surgery, 27% had an LCEA between 20° and 25° [345].

Patients with dysplasia demonstrated failure rates statistically similar to the rigorously-matched control group. The fact that the rate of subsequent ipsilateral surgery for both the dysplasia and the control populations was similar to that of our general population of 271 primary arthroscopic labral repairs is important in that it supports the notion that our matched cohort is not a high risk group of non-dysplastic patients but rather a generalizable control for arthroscopic labral

repair. Of note, repeat hip arthroscopy dominated revision surgery for both the dysplasia (66.7%) and control (81.8%) populations, however; only members of the dysplasia cohort went on to PAO, as would be biomechanically expected. Our findings of similar revision rates in the dysplasia and non-dysplasia populations are also supported by those of Ricciardi et al who found that acetabular undercoverage was not overrepresented in their study of 152 revision hip preservation surgeries[335].

Other studies have suggested that mild to moderate acetabular dysplasia demonstrates inferior subjective outcomes and higher failure rates when compared to an FAI cohort, however, in these papers, labral repair, which was performed in all cases analyzed in this study, was linked to better patient-reported outcome scores as compared to debridement, the presence of which likely led to some degree of confounding[236]. Additionally, we believe that the effect of dysplasia on PROMs is better addressed in the setting of advanced matching algorithms, as age, BMI, and Tonnis grade in particular have been linked to statistically significant differences in subjective outcomes scores following hip arthroscopy[172].

The relative preponderance of FAI (71%) in the dysplasia group is noteworthy, especially in light of 56.3% females in the dysplasia cohort which is more consistent with FAI than the population classically described for dysplasia which has a proportion of females near 80%[97, 153, 251, 353]. In the clinical decision-making between hip arthroscopy and PAO, we believe that selection of dysplastic labral repair patients with concurrent FAI can be conducive to initial arthroscopic management as both the labral tear and FAI, which is likely contributory to tear etiology, can be simultaneously addressed arthroscopically. This is the likely contributor to the relative prevalence in males and FAI patients in our dysplastic hip arthroscopy practice. However, 29% of dysplastic patients did not have FAI. In these cases, we find it important to note that the patient's pain generator was clinically felt to be most consistent with labral etiology (i.e. mechanical locking on physical exam) as opposed to dysplasia and associated chondral loading and injury. In the case of the latter, we would favor the use of PAO as acetabular version cannot be adequately arthroscopically addressed at this time.

The finding that BMI ≤ 30 was linked to increased failure with subsequent surgical reoperation is a relatively novel finding of this study, although low BMI has been documented by the Academic Network of Conservational Hip Outcomes Research (ANCHOR) group and contributing authors in patients electing for revision hip arthroscopy or PAO[46, 353]. All nine of the failures present in the mild dysplasia group of this study had a BMI below 30. Traditionally, patients with increased BMIs have been associated with worse patient-reported outcome scores and failure rates following arthroscopic hip surgery[30, 243, 411]. However, multiple previous short-term studies have described young females with ligamentous laxity as being at risk for failure following arthroscopic hip surgery, especially in dysplastic cohorts [335, 345, 353].

Our finding that patient age above 35 years is associated with a near 3-fold increased risk of failure to achieve MCID between preoperative VAS and final-follow has been previously been described in short-term studies, with increased age predicting decreased patient-reported outcome scores [152, 185, 243]. Although the hazard ratios for mHHS and HOS-SSS did not reach significance, they were both estimated to be above 2.0, which suggests that with increased sample size, these outcome scores may demonstrate a significant negative association with patient age.

The association of low preoperative Tonnis grade and failure to achieve MCID in VAS and mHHS is a unique finding of this investigation. Previous short-term outcome hip arthroscopy studies have failed to demonstrate a difference in patient-reported outcome scores between populations with Tonnis grade 0, 1, and 2 radiographs, highlighting the importance of dysplasia-specific analysis[76, 78]. We believe our observed outcomes may be attributable to patients with relatively small labral tears and early, mild cartilage changes whose symptoms and underlying dysplasia may be best addressed through joint unloading procedures involving a PAO, which was performed in 33% of patients revised over the course of follow-up. Additionally, low Tonnis grade may play a part in the constellation of the young, thin, dysplastic female which represents a population documented to be at high risk for failure following arthroscopic hip surgery[335, 345, 353]. Of note, dysplastic patients failing to achieve MCID in VAS and mHHS demonstrated mean LCEAs (21.8° and 21.5°, respectively) no different than that of the general dysplasia population (21.6°). Additionally, the preoperative VAS and mHHS of the patients with Tonnis grade 0 failing to achieve MCID were not significantly different compared to those patients achieving MCID ($p = 0.75$ and 0.95, respectively), suggesting this effect is not due to patients with Tonnis grade 0 radiographs having milder symptoms and thus making more modest gains in subjective outcome scores.

The current study is not without limitations. While the inclusion of two institutions and use of three outcome scales are relative strengths of this study, we believe future investigations should aim to include additional centers and outcomes measures, as it is difficult to obtain statistically powerful sample sizes for arthroscopic intervention in the setting of hip dysplasia. Additionally, while there is reasonable consistency in the literature regarding a cutoff of LCEA < 25° for the definition of dysplasia, there remains significant controversy regarding whether borderline dysplasia represents a clinically separate entity and where such LCEAs cutoffs should be made[46, 107, 127, 236]. While sub-analyses for LCEA < 20° and LCEA 20° - 25° are presented in this study for the sake of completeness and demonstrate no difference in failure rates between the two groups, this study was neither designed nor powered to detect differences in subpopulations of the dysplastic cohort undergoing arthroscopic labral repair.

We elected to proceed with univariate proportional hazards regression for failure and MCID analysis in order to be well-powered on the basis of approximately ten events per variable modeled, as has been previously suggested[324]. While more recent literature suggests that five to nine events per variable may be appropriate, given our sample size of nine failures in the dysplasia group, we believe it would be statistically warranted and conservative to proceed with univariate analysis given our sample size[406]. Future studies should aim to collect populations sufficient for additional multivariate analysis. Additionally, while we believe our patient-reported outcome score completion of 94.4% was quite robust, a limitation of missing follow-up is the possible bias in failure rate and outcomes that may be present in those patients electing not to follow-up or complete surveys.

Conclusion:

Our findings support that with careful selection and modern arthroscopic techniques, patients with dysplasia can benefit significantly and durably from arthroscopic labral repair. Dysplastic patients had similar outcomes and failure rates to rigorously matched non-dysplastic controls at mid-term follow-up. BMI ≤ 30 was associated with increased risk of revision while age > 35 years and Tonnis grade 0 preoperative radiographs were associated with failure to achieve MCID.

Table 1: Study demographics for the dysplasia and control cohorts by matching criteria.

Demographics	**LCEA < 25 (n = 48)**	**LCEA ≥ 25 (n = 96)**	**p-value**
Age at Surgery	31.8 ± 12.7	31.4 ± 12.1	0.87
Gender			
Males (%)	21 (43.8 %)	47 (49.0 %)	
Females (%)	27 (56.3 %)	49 (51.0 %)	0.60
Laterality			
Right (%)	25 (52.1 %)	58 (60.4 %)	
Left (%)	23 (47.9 %)	38 (39.6 %)	0.37
BMI	24.9 ± 4.9	24.6 ± 5.5	0.55
Tonnis Grade			
Grade 0	37 (77.1 %)	70 (72.9 %)	
Grade 1	10 (20.8 %)	26 (27.1 %)	
Grade 2	1 (2.1 %)	0 (0.0 %)	0.28
Capsular Repair	25 (52.1 %)	50 (52.1 %)	1.00
LCEA	21.6 ± 2.7	32.1 ± 5.2	< 0.01
Alpha Angle	63.7 ± 11.4	59.4 ± 12.9	0.07
Preoperative ROM			
Flexion	120.7 ± 16.5	120.9 ± 21.0	0.47
Internal Rotation	26.8 ± 16.2	24.3 ± 14.8	0.13
External Rotation	48.6 ± 15.1	52.7 ± 15.8	0.42
Abduction	44.8 ± 14.0	46.2 ± 13.7	0.77
Preoperative PROMs			
VAS	5.0 ± 2.5	5.7 ± 2.0	0.11
mHHS	67.2 ± 14.2	61.2 ± 15.9	0.08
HOS-SSS	45.2 ± 20.3	41.1 ± 25.0	0.48
Postoperative PROMs			
VAS	2.0 ± 2.1	2.0 ± 2.2	0.52
mHHS	82.5 ± 18.4	83.2 ± 17.6	0.87
HOS-SSS	72.5 ± 23.3	71.0 ± 26.6	0.98

Table 2: Diagnoses and surgical techniques performed by dysplasia and control cohort.

Diagnosis / Procedure	**LCEA < 25**	**LCEA ≥ 25**	**p-value**
Isolated Cam Lesion	34 (70.8 %)	64 (66.7 %)	0.71
Isolated Pincer Lesion	0 (0.0 %)	5 (5.2 %)	0.17
Combined Cam and Pincer Lesions	0 (0.0 %)	2 (2.1 %)	0.55
Hip Dysplasia (LCEA < 25°)	48 (100 %)	0 (0 %)	< 0.001
Labral Tear	48 (100 %)	96 (100 %)	1.00
Femoral Chondromalacia			
Grade 1	0 (0 %)	3 (3.7 %)	
Grade 2	3 (6.5 %)	7 (8.6 %)	
Grade 3/4	10 (21.7 %)	7 (8.6 %)	0.13
Acetabular Chondromalacia			
Grade 1	14 (29.8 %)	26 (27.7 %)	
Grade 2	7 (14.9 %)	29 (30.9 %)	
Grade 3/4	14 (29.8 %)	28 (29.8 %)	0.08
Ligamentum Teres Debridement	25 (52.1 %)	39 (40.6 %)	0.22
Psoas Release	21 (43.8 %)	33 (34.4 %)	0.28

Table 3: Univariate Cox proportional hazards model for pre- and intraoperative predictors of failure in the dysplastic (n = 48) and matched (n = 96) cohorts.

	Dysplasia (n = 48) 9 failures (18.8 %)		**Controls (n = 96) 22 failures (22.9%)**	
Variable	**HR (95% CI)**	***P-value***	**HR (95% CI)**	***P-value***
Age				
≤ 35 years	Reference		Reference	
> 35 years	0.86 (0.21 – 3.56)	0.84	0.64 (0.27 – 1.53)	0.32
BMI				
≤ 30	Reference		Reference	
> 30	0 (0.00 – 0.00)*	**< 0.01**	0.60 (0.14 – 2.58)	0.49
Gender				
Female	Reference		Reference	
Male	0.35 (0.08 – 1.56)	0.17	0.46 (0.19 – 1.11)	0.08
Laterality				
Left	Reference		Reference	
Right	1.26 (0.36 – 4.46)	0.72	0.74 (0.32 – 1.70)	0.48
Tonnis Grade				
Grade 0	Reference		Reference	
Grade 1–2	0.70 (0.17 – 2.91)	0.62	1.20 (0.51 – 2.82)	0.70
Femoral Chondromalacia				
Grade 1–2	Reference		Reference	
Grade 3–4	0.28 (0.06 – 1.24)	0.09	1.32 (0.33 – 5.35)	0.70
Acetabular Chondromalacia				
Grade 1–2	Reference		Reference	
Grade 3–4	0.62 (0.15 – 2.48)	0.50	1.18 (0.48 – 2.87)	0.72
Alpha Angle				
< 55° (Normal)	Reference		Reference	
≥ 55° (FAI)	0.70 (0.14 – 3.57)	0.66	0.88 (0.38 – 2.04)	0.76
Capsular Repair				
No	Reference		Reference	
Yes	0.83 (0.23 – 2.99)	0.78	0.98 (0.43 – 2.24)	0.96
LT Debridement				
No	Reference		Reference	
Yes	0.43 (0.11 – 1.74)	0.24	0.54 (0.21 – 1.38)	0.20
Psoas Release				
No	Reference		Reference	
Yes	0.57 (0.14 – 2.32)	0.43	1.18 (0.50 – 2.81)	0.71

LT: Ligamentum teres

Table 4: Univariate Cox proportional hazards model for pre- and intraoperative predictors of failure to achieve MCID separate from revision surgery in the dysplastic cohort.

Variable	VAS		mHHS		HOS-SSS	
	HR (95% CI)	*P*	HR (95% CI)	*P*	HR (95% CI)	*P*
Age						
≤ 35 years	Reference		Reference		Reference	
> 35 years	3.17 (1.00 – 10.02)	**0.049**	2.96 (0.95 – 9.26)	0.06	2.11 (0.73 – 6.08)	0.17
BMI						
≤ 30	Reference		Reference		Reference	
> 30	2.07 (0.37 – 11.56)	0.41	2.23 (0.39 – 12.74)	0.37	2.90 (0.76 – 11.07)	0.12
Gender						
Female	Reference		Reference		Reference	
Male	2.72 (0.86 – 8.58)	0.09	2.38 (0.74 – 7.69)	0.15	2.11 (0.72 – 6.19)	0.18
Laterality						
Left	Reference	0.34	Reference	0.53	Reference	0.19
Right	0.58 (0.19 – 1.77)		0.69 (0.22 – 2.16)		0.49 (0.17 – 1.43)	
Tonnis Grade						
Grade 0	Reference		Reference		Reference	
Grade 1–2	0.00 (0.00 – 0.00)*	**< 0.01**	0.00 (0.00 – 0.00)*	**< 0.01**	0.25 (0.03 – 2.31)	0.22
Femoral Chondromalacia						
Grade 1–2	Reference		Reference		Reference	
Grade 3–4	1.04 (0.30 – 3.65)	0.95	0.65 (0.16 – 2.68)	0.55	0.28 (0.04 – 1.82)	0.18
Acetabular Chondromalacia						
Grade 1–2	Reference		Reference		Reference	
Grade 3–4	1.23 (0.36 – 4.20)	0.74	1.36 (0.40 – 4.65)	0.62	2.66 (0.92 – 7.66)	0.07
Alpha Angle						
< 55° (Normal)	Reference		Reference		Reference	
≥ 55° (FAI)	0.87 (0.22 – 3.44)	0.84	0.49 (0.14 – 1.75)	0.28	0.61 (0.18 – 2.05)	0.43
Capsular Repair						
No	Reference		Reference		Reference	
Yes	0.91 (0.30 – 2.72)	0.86	1.16 (0.36 – 3.67)	0.81	1.52 (0.51 – 4.56)	0.45
LT Debridement						
No	Reference		Reference		Reference	
Yes	1.44 (0.45 – 4.55)	0.54	1.38 (0.41 – 4.66)	0.61	1.90 (0.60 – 6.03)	0.27
Psoas Release						
No	Reference		Reference		Reference	
Yes	1.58 (0.53 – 4.73)	0.41	1.77 (0.55 – 5.70)	0.34	1.43 (0.49 – 4.15)	0.52

*All failures to achieve MCID in the VAS and mHHS groups had Tonnis grade 0 arthritis at the time of presentation.

Table 5: Demographics, clinical outcomes, and revision rates of the LCEA 20 – 25° and LCEA < 20° dysplasia subgroups**.**

Demographic	**LCEA < 20 (n = 7)**	**20° ≤ LCEA < 25° (n = 41)**	**p-value**
Age at Surgery	32.0 ± 14.2	31.8 ± 12.6	0.83
Gender			
Males (%)	3 (42.9 %)	18 (43.9 %)	
Females (%)	4 (57.1 %)	23 (56.1 %)	1.00
Laterality			
Right (%)	5 (71.4 %)	20 (48.8 %)	
Left (%)	2 (28.6 %)	21 (51.2 %)	0.42
BMI	24.5 ± 2.9	25.0 ± 5.2	0.94
Tonnis Grade			
Grade 0	6 (85.7 %)	31 (75.6 %)	
Grade 1	1 (14.3 %)	9 (22.0 %)	
Grade 2	0 (0 %)	1 (2.4 %)	1.00
LCEA	16.5 ± 2.7	22.5 ± 1.4	< 0.01
Alpha Angle	62.5 ± 11.8	64.0 ± 11.5	0.89
Preoperative ROM			
Flexion	122.1 ± 9.1	120.5 ± 17.6	0.91
Internal Rotation	20.0 ± 10.4	27.9 ± 16.8	0.24
External Rotation	50.0 ± 15.0	48.4 ± 15.3	0.87
Abduction	45.8 ± 15.9	44.6 ± 13.9	0.97
Preoperative PROMs			
VAS	5.3 ± 2.9	4.9 ± 2.4	0.71
mHHS	64.7 ± 12.2	67.6 ± 14.6	0.51
HOS-SSS	36.1 ± 24.4	46.7 ± 19.6	0.33
Postoperative PROMs			
VAS	2.0 ± 2.2	2.0 ± 2.1	0.88
mHHS	80.0 ± 20.5	83.0 ± 18.3	0.65
HOS-SSS	71.0 ± 23.9	72.8 ± 23.5	0.75
Revision Surgery	2 (28.6 %)	7 (17.1 %)	0.60

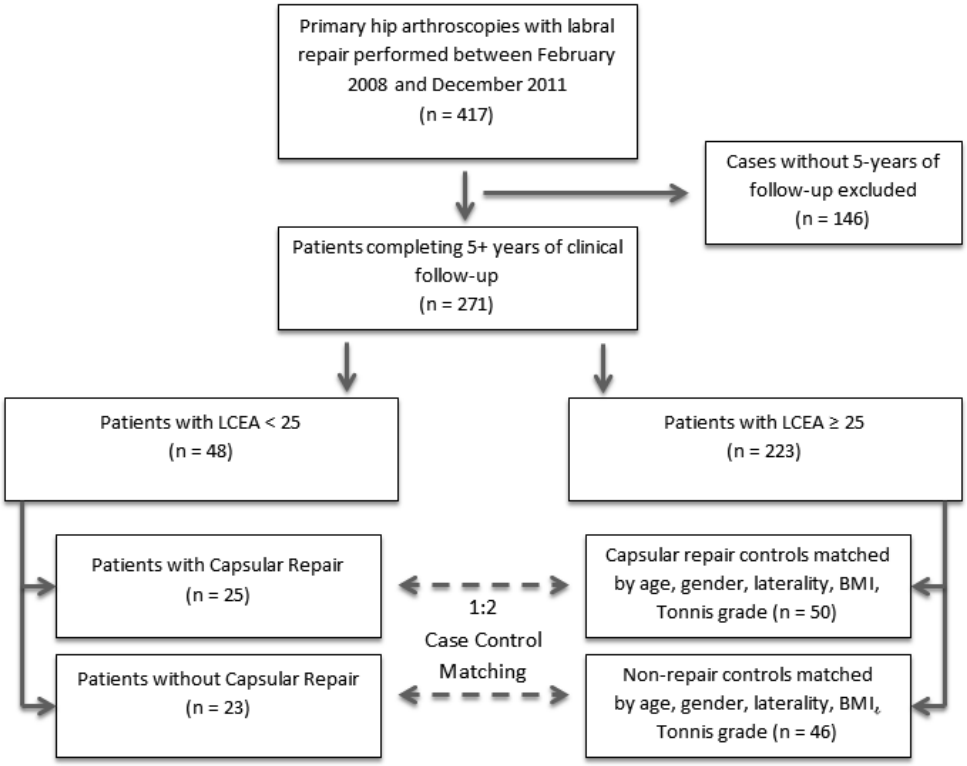

Figure 1: Flowchart of patient eligibility and case-control matching for study patients

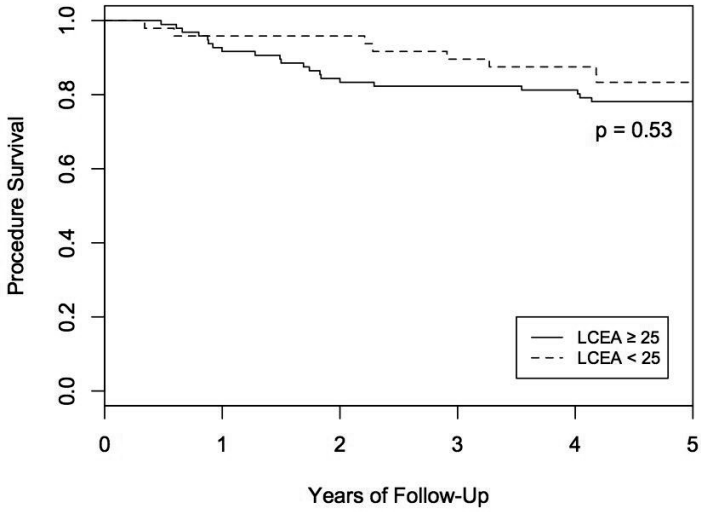

Figure 2: Procedure survival for the dysplasia (LCEA < 25°) and non-dysplastic control (LCEA ≥ 25°) groups.

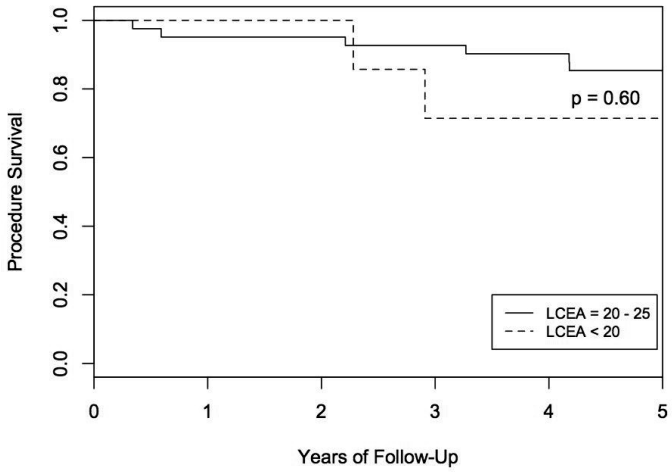

Figure 3: Subanalysis of the LCEA 20 – 25° and LCEA < 20° dysplasia subgroups.

Is Microfracture Necessary? Acetabular Chondrolabral Debridement/Abrasion Demonstrates Similar Outcomes and Survival to Microfracture in Hip Arthroscopy: A Multi-Center Analysis

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Introduction:

Hip pain and the development of osteoarthritis have been associated with structural abnormalities including femoroacetabular impingement (FAI) and labral tears [32, 145, 209, 295, 412]. The advent of hip arthroscopy and subsequent rapid evolution of arthroscopic techniques has led to safe and effective management of chondrolabral lesions without necessitating traditional open approaches[47, 48, 159, 180]. However, arthroscopic management of high-grade acetabular cartilage pathology spanning from large chondral flaps to complete loss of cartilage remains a controversial topic. In particular, questions have been raised regarding the utility of microfracture versus debridement/abrasion in patients with high-grade pathology.

Microfracture, which employs specialized awls to create subchondral plate perforations and release marrow elements to promote new tissue formation, was introduced and popularized by Steadman in the 1990s.[380] Subsequently, large increases in knee microfracture volume were observed, with this technique becoming one of the most common reparative orthopedic procedures performed in the United States.[99, 277, 380] The use of microfracture has been recently described in the setting of hip arthroscopy and is increasingly performed for full-thickness articular defects in weight bearing regions of the acetabulum.[330] Preliminary outcomes have demonstrated positive structural and patient reported outcomes, with 95 – 100% defect coverage in up to 89% of patients and clinically significant improvements in Visual Analog Scale (VAS), Harris Hip Score, and Non-Arthritic Hip Score.[65, 119, 330] However, these microfracture outcome studies all lack a control group, and it is not currently known whether the actual microfracture, or the associated surgical procedures, such as labral repair and cam/pincer resection, are responsible for the positive post-operative outcomes reported in the literature.

To date, no direct comparison of microfracture and chondral defect debridement/abrasion has been presented in the hip arthroscopy literature. This is of clinical importance given the

specialized resources including hip-specific microfracture awls, potentially greater operative time involved in undertaking microfracture following formal lesion debridement, which is performed with both techniques, and significant impact on patient rehabilitation that microfracture necessitates, with up to 2 months of limited weight bearing in order to promote tissue healing and minimize complications such as subchondral plate fracture and associated intralesional osteophytes.[65] Furthermore, recent knee literature has failed to demonstrate benefit of microfracture over chondroplasty/debridement, with studies demonstrating no difference in outcome scores between the two techniques[156] and a 4.4 lower return to play rate in National Football League (NFL) athletes undergoing microfracture as compared to chondroplasty.[360]

Debridement/abrasion of acetabular defects has the potential to remove pathologic tissues and provide immediate stable defect edges, limiting further chondral damage without prolonged post-operative weight restrictions.[65, 198] In addition, the ball-and-socket configuration of the acetabulum is such that focal acetabular deficiencies have the potential to be biomechanically better-tolerated , as is the case for the native acetabular cotyloid fossa, given the high degree of spherical articular congruency.[171] Therefore, the purpose of this study was to (1) describe patient reported outcomes of patients undergoing debridement/abrasion and microfracture of high-grade unipolar acetabular defects at the time of labral repair and 2) determine whether lesion treatment modality was predictive of outcomes and revision rates. Our hypotheses were (1) patients would demonstrate clinically significant improvements in patient reported outcomes for both debridement/abrasion and microfracture and (2) treatment modality would not predict outcome or revision rates.

Methods:

Study Population and Design

This clinical and radiographic study included all eligible patients undergoing hip arthroscopy following failure of comprehensive non-operative management at two high-volume hip arthroscopy centers (Mayo Clinic, Rochester, MN; American Hip Institute, Westmont, IL). Patients were consented for research participation following Institutional Review Board approval (IRB# 08-002259) using an established multi-center research initiative and standardized rehabilitation protocol. Inclusion criteria consisted of: (1) primary hip arthroscopy between November 2008 and April 2016, (2) age < 55 years, (3) isolated acetabular chondral damage present as Grade 3 or 4 acetabulum articular disruption (ALAD) changes upon diagnostic arthroscopy (4) arthroscopic labral repair performed at the time of surgery, (5) availability of preoperative radiographs, and (6) consent for research participation. Exclusion criteria consisted of (1) less than two years of clinical follow-up, (2) bipolar

cartilage lesions with femoral head Outerbridge Grade 3 or 4 changes, (3) lateral center edge angle (LCEA) < 20°, and (4) previous ipsilateral hip surgery (Figure 1).

Surgical Technique

Surgery was performed by experienced hip arthroscopists (AJK, BAL, BJD) in an operative setting designed for arthroscopy. Patients were positioned in the modified supine position and anterolateral and mid anterior portals were created. Additional use of the anterior, distal anterolateral, and posterolateral portals were employed as needed. Patient positioning and operative approach has been described in detail previously[63, 180, 288, 413]. Diagnostic arthroscopy was performed to evaluate labral and chondral status and correction of cam and pincer lesions was performed when present[86, 87]. All patients included in this study underwent labral repair[88, 142, 208]. Psoas release was performed in patients with painful iliopsoas snapping reproducible on physical examination and capsular repair was performed using standard techniques on the basis of the operating surgeon's assessment of ease of femoral head translocation, intraoperative laxity, and patient factors including participation in high demand activities[68, 85, 178].

Treatment of the acetabular chondrolabral delamination was determined by surgeon preference and preoperative discussion with the patient (Figure 2). Factors included in surgical decision making included the preferential use of abrasion/debridement for grade 3-4 defects with substantial surrounding cartilage damage as well as the use of abrasion/debridement for lesions whose orientation and location were technically suboptimal for arthroscopic microfracture. In both cases, lesions had stable vertical walls created with a curette and the calcified cartilage layer was removed. It is interesting to note that with scraping of the calcified layer, punctate bleeding from the subchondral bone was often visualized, especially with drilling for suture anchors. This may be likely equivalent to an abrasionplasty of the acetabular cartilage defect. For microfracture, this was typically performed using an arthroscopic hip awl with previously described techniques.[119]

Rehabilitation Protocol

Patients underwent a standard postoperative rehabilitation and analgesic protocol which was consistent between physicians within the same institution, similar between institutions, and outlined in detail in previous publications (Mayo Clinic, Rochester, MN[376], American Hip Institute, Westmont, IL[120]). Debridement/abrasion patients were placed on crutches with foot-flat partial weight bearing for 2-4 weeks, with passive motion started at 0 weeks. As crutches were weaned, patients progressed through the institutional rehabilitation protocols, with jogging exercises beginning at 3 months, as tolerated, and return to sport allowed at 5-6 months. Patients undergoing

microfracture were kept partial weight bearing for the first 6-8 weeks, with motion started at 0 weeks employing a continuous passive motion (CPM) machine for four hours per day for the first 6-8 weeks. Crutches were weaned during weeks 6-10 and patients progressed through physical therapies with jogging exercises beginning at 3-4 months and return to sport allowed at 5-6 months.

Outcomes Collected

Demographic data such as age, BMI, and gender were collected in addition to preoperative radiographic measures including Tonnis grade[395], alpha angle[25], lateral central edge angle (LCEA)[292], and RAPID score[179]. The presence of cam and pincer lesions, acetabular chondromalacia as defined by the Outerbridge[313] and acetabular labrum articular disruption (ALAD)[66] classification systems, and procedures such as ligamentum teres debridement and psoas release were documented pre- and intraoperatively using a standardized data collection form. ALAD grade 1 changes were defined as softening of the cartilage adjacent to the labrum, grade 2 changes were defined as early peelback of cartilage, grade 3 lesions consisted of large chondral flaps, and grade 4 changes represented complete full-thickness cartilage loss. Cam morphology was defined as hips with alpha angles >55°; pincer morphology was defined as LCEA >40°. Pre-and postoperative patient-reported outcome measures (PROMs) were prospectively collected and documented employing visual analog pain score (VAS)[230], modified Harris Hip Score (mHHS)[166], and Hip disability and osteoarthritis Outcome Score – Sports Specific Subscale (HOS-SSS)[301]. Outcome score completion rate was 87.4%. Failure was defined as subsequent ipsilateral hip surgery, including revision arthroscopy, open hip surgery, and conversion to total hip replacement.

Statistical Analysis

Demographics and outcomes scores for the debridement/abrasion and microfracture groups were compared using Wilcoxon rank sum testing (Mann-Whitney U) for nominal data and Fisher's exact testing for proportions. Subsequently, failure rates for the two groups were compared using Kaplan-Meier analysis with potential risk factors such as patient demographics or defect treatment modality evaluated using uni- and multivariate Cox proportional hazards analysis.

A priori analysis was used to determine the sample sizes needed to demonstrate PROM improvements equivalent to MCID. Using the study on arthroscopic labral repair in the setting of FAI by Chahal et al, MCID cutoffs were determined for mHHS and HOS-SSS using the median MCID values presented by the authors. The resultant MCIDs were 13.0 points for mHHS and 28.0 points for HOS-SSS[74]. Additionally, an MCID of 2.0 points was established for VAS employing a previous study on osteoarthritic hip pain[396]. Employing these values and previously presented PROMs for arthroscopic labral repair[180], the mean group sample size needed at alpha = 0.05 and a power of 0.90 to

demonstrate MCID was determined to be 29 for mHHS, 17 for HOS-SSS, and 27 for VAS[197]. P-values < 0.05 were considered significant. Analyses were conducted in R 3.4.3 (R Core Team, Vienna, Austria).

Results

A total of 113 hips in 110 patients (66 males, 44 females) undergoing treatment of unipolar ALAD grade 3 and 4 lesions at the time of labral repair met inclusion criteria and were followed for a mean of 4.9 years (range: 2.0 – 8.5). Of these, 82 hips (72.6%) underwent debridement/abrasion and 31 hips (27.4%) underwent microfracture. Both the debridement/abrasion and microfracture cohorts met the minimum sample sizes needed in the *a priori* power analysis. Furthermore, no significant difference existed in preoperative VAS ($p = 0.29$), mHHS ($p = 0.97$), HOS-SSS ($p = 0.84$), or lesion size (1.3 versus 1.4 cm^2, $p = 0.47$) between the debridement/abrasion and microfracture groups, supporting subsequent postoperative comparisons between the two populations. Patients undergoing microfracture were on average 6.3 years older ($p < 0.01$) and had LCEA angles which were 4.0° smaller ($p < 0.01$) compared to the debridement/abrasion cohort (Table 1).

While grade 3 ALAD lesions predominated both the debridement/abrasion (91.5%) and microfracture groups (64.5%), grade 4 lesions were less common in the debridement/abrasion cohort than the microfracture group (8.5% versus 35.5%, respectively, $p < 0.01$). The two cohorts were otherwise similar in terms of gender, laterality, BMI, Tonnis grade, presence of capsular repair, RAPID score, and preoperative diagnoses (Table 2).

Both groups achieved significant postoperative improvements in outcome scores, with the debridement/abrasion group achieving a mean decrease of 3.6 points in VAS ($p < 0.01$), 21.2 point increase in mHHS ($p < 0.01$), and 25.4 point increase in HOS-SSS ($p < 0.01$). Similarly, the microfracture group achieved a 2.5 decrease in VAS ($p < 0.01$), 15.8 point increase in mHHS ($p < 0.01$), and 20.7 point increase in HOS-SSS ($p < 0.01$). PROMs at the time of final follow-up were comparable between the two groups ($p \geq 0.20$, Table 1).

Revision rates were similar between the cohorts, with 15.9% of the debridement/abrasion group and 16.1% of the microfracture cohort going on to revision at the time of final follow-up ($p = 1.00$). Kaplan-Meier analysis demonstrated that the two groups had similar trends in revision procedures over time, with survival free of revision surgery of 89.0% and 93.6% at two years, and 84.0% and 85.6% at 5 years, respectively (Figure 3).

Nine debridement/abrasion patients (11.0%) underwent revision hip arthroscopy, three (3.7%) underwent THA, and one (1.2%) underwent hip resurfacing. In comparison, two microfracture patients (6.4%) underwent repeat arthroscopy and three (9.7%) underwent THA.

We performed Cox proportional hazards analysis of potential pre- and intraoperative predictors of failure for the debridement/abrasion and microfracture populations and determined that lesion treatment technique was not a significant univariate predictor of failure (Hazards Ratio: 1.01, p = 0.98, Table 3).

In order to account for the baseline population differences between the two populations, we subsequently performed a multivariate Cox proportional hazards regression while accounting for the factors determined to be different between the two groups, namely patient age, ALAD grade, and LCEA. There remained no significant difference in revision rate between the debridement/abrasion and microfracture cohorts (HR: 0.93, p = 0.90) when accounting for these factors (Table 4).

Discussion:

The purpose of this study was to describe patient reported outcomes of patients undergoing debridement/abrasion and microfracture of high-grade unipolar acetabular defects at the time of labral repair and to determine whether lesion treatment modality was predictive of outcomes and revision rates. Our hypothesis was confirmed in that patients undergoing both debridement/abrasion and microfracture demonstrated significant improvements in patient reported outcome scores. In addition, treatment modality was found not to predict subjective patient reported outcomes or revision rates at a mean of 4.9 years follow-up.

The findings of this study are significant in that they support the use of either debridement/abrasion or microfracture in the treatment of grade 3 and 4 acetabular defects. While various authors have advocated for the preferential use of one technique or the other, both microfracture and debridement/abrasion are well-established and described in the literature for treating both grade 3 and 4 lesions.[64, 65, 170, 184, 202] In the present study, the debridement/abrasion and microfracture populations demonstrated similar postoperative subjective outcomes and revision rates, both when compared on a populational and on an adjusted multivariate basis. Given clinically similar outcomes, these findings call to question whether clinical improvement is attributed to the fibrocartilage fill of microfracture in arthroscopic hip surgery, or whether improvement is secondary to the labral repair, cam resection and pincer treatment in these hip populations. Alternatively, it is possible that debridement/abrasion to stable vertical surrounding cartilage borders and scraping of

the calcified cartilage layer in a debridement/abrasion can produce equivalent fibrocartilage without penetration of the subchondral plate.

Benefits supporting the use of preferential debridement/abrasion include the avoidance of prolonged weight bearing restrictions, need for costly CPM machines, and extended recovery course associated with microfracture.[65] Furthermore, violation of the subchondral plate carries significant risk of subchondral fracture and intralesional osteophyte formation, both of which may contribute to joint degradation and necessitate revision surgery.[150] Previous research demonstrating evidence of subchondral cyst formation and advanced degenerative changes following microfracture in multiple small and large animal studies further support these conclusions.[39, 81, 141, 312] In addition, an analysis examining the return to play rates of 39 elite athletes undergoing hip arthroscopy with microfracture and 94 controls without microfracture demonstrated no significant difference in return to play rates (76% versus 84%, respectively), supporting that the debridement/abrasion may provide similar benefit as compared to microfracture, even in high demand patients.[275]

Perhaps the strongest data regarding the relative utility of microfracture stems from studies in the knee, for which well-designed, large studies of mid-term outcomes are available. In a prospective, randomized study in which articular cartilage lesions at the time of anterior cruciate ligament (ACL) reconstruction were randomized to microfracture, debridement/abrasion, or osteochondral allograft transplantation (OATs), no significant difference in International Knee Documentation Committee (IKDC) scores were observed between the microfracture and debridement/abrasion groups at a mean of 3 years of follow-up.[156] In contrast, microfracture and debridement/abrasion patients demonstrated worse scores than a control group of patients without articular cartilage injury at the time of ACL reconstruction or those undergoing OATs. Multiple, prospective randomized trials in the knee have also demonstrated the inferiority of microfracture outcomes as compared to more advanced techniques such as matrix-induced autologous chondrocyte implantation (MACI)[26, 355] and OATs.[157, 158] Furthermore, in a review of failed cartilage procedures presenting to a tertiary referral center, 58% of patients presenting with failed cartilage surgery had undergone microfracture prior to presenting for evaluation.[216] While this is certainly related to relative volume of cartilage procedures, it is striking that microfracture accounted for more failures than osteochondral allograft, osteochondral autograft, particulated juvenile chondral allograft, and all other reparative procedures combined. These findings further support that given similar outcomes, debridement/abrasion of chondral defects may be preferable to microfracture due to the significant differences in recovery between the two techniques. In addition, the ball-and-socket configuration of the acetabulum is such that focal acetabular deficiencies such as those created by debridement/abrasion may be biomechanically better-tolerated, as is the case for the native acetabular cotyloid fossa.[171] In contrast, the knee is subject to flexion-angle based contact loading of articular cartilage given the

variable radius of curvature of the femoral condyles and non-congruent, medially concave and laterally convex nature of the tibial plateau.[143, 169, 386]

The current study is not without limitations. While the inclusion of two institutions and use of three outcome scales are relative strengths of this study, we believe future investigations should aim to include additional centers and outcomes measures in order to provide further multi-center evidence regarding the indications and preferential use of debridement/abrasion and microfracture. Additionally, there is a degree of surgeon based technique selection bias due to intraoperative defect assessment given the retrospective allocation of patients to the microfracture and debridement/abrasion cohorts in this study. As such, we find it important to note that this study does not advocate for the abandonment of microfracture nor does it justify or support decreasing coverage for microfracture by health systems considering that similar and positive outcomes were achieved with both techniques when employed at the discretion of the treating physician. While the use of debridement/abrasion or microfracture was based on intraoperative assessment, factors which influenced the decision to perform debridement/abrasion instead of microfracture included grade 3 lesions with morphology and orientation not technically optimal for surgical takedown and microfracture as well as grade 3-4 defects with diffuse surrounding cartilage damage more amenable to debridement/abrasion to stable edges. To this end, multivariate analysis was performed to adjust for baseline differences between the debridement/abrasion and microfracture populations. An associated limitation is the relative predominance of grade 4 lesions in the microfracture group as compared to the debridement/abrasion cohort. Multivariate analysis accounting for this difference as well as the observed difference in age between the cohorts is included in the study, however, future studies should aim for prospective randomization between techniques to further eliminate associated biases. While we believe our patient-reported outcome score completion of 87.4% was relatively robust, a limitation of missing follow-up is the potential bias in failure rate and outcomes that may be present in those patients electing not to follow-up or complete surveys. Finally, this study is subject to the inherent limitations of retrospective analyses, including dependence on complete record keeping.

Conclusion:

Our findings support that patients undergoing debridement/abrasion of high-grade unipolar acetabular cartilage lesions demonstrate similar patient reported outcome scores and revision rates compared to patients undergoing microfracture. These outcomes support the consideration of preferential debridement/abrasion at the discretion of the treating surgeon in order to optimize recovery while maintaining established positive outcomes following hip arthroscopy.

Table 1: Demographics for the debridement/abrasion and microfracture cohorts.

Variable	Debridement/Abrasion (n = 82)	Microfracture (n = 31)	p-value
Age at Surgery	32.8 ± 11.4	39.1 ± 9.1	< 0.01
Gender			
Females (%)	34 (41.5%)	11 (35.5%)	
Males (%)	48 (58.5%)	20 (64.5%)	0.67
Laterality			
Right (%)	42 (51.2%)	16 (51.6%)	
Left (%)	40 (48.8%)	15 (48.4%)	1.00
BMI	26.2 ± 5.0	27.9 ± 4.5	0.05
Tonnis Grade			
Grade 0	65 (79.3%)	22 (71.0%)	
Grade 1	15 (18.3%)	8 (25.8%)	
Grade 2	2 (2.4%)	1 (3.2%)	0.54
ALAD Grade			
Grade 0-2	0 (0%)	0 (0%)	
Grade 3	75 (91.5%)	20 (64.5%)	
Grade 4	7 (8.5%)	11 (35.5%)	< 0.01
Lesion Size (cm^2)	1.3 ± 1.0	1.4 ± 1.0	0.47
Capsular Repair			
No	53 (64.6%)	23 (74.2%)	
Yes	29 (35.4%)	8 (25.8%)	0.38
LCEA	30.8 ± 5.1	26.8 ± 4.3	< 0.01
Alpha Angle	63.0 ± 17.9	68.6 ± 17.0	0.07
RAPID Score	1.7 ± 1.2	2.1 ± 1.0	0.11
Preoperative PROMs			
VAS	5.6 ± 2.3	5.1 ± 2.6	0.29
mHHS	64.9 ± 14.9	65.5 ± 16.8	0.97
HOS-SSS	47.1 ± 26.1	45.6 ± 27.5	0.84
Postoperative PROMs			
VAS	2.0 ± 2.0	2.6 ± 2.6	0.39
mHHS	86.1 ± 15.5	81.3 ± 18.4	0.22
HOS-SSS	72.5 ± 26.4	66.3 ± 26.5	0.20
Revision	13 (15.9%)	5 (16.1%)	1.00

Table 2: Diagnoses and surgical techniques performed by the debridement/abrasion and microfracture cohorts.

Diagnosis / Procedure	**Debridement/Abrasion**	**Microfracture**	**p-value**
Isolated Cam Lesion	56 (68.3%)	26 (83.9%)	0.23
Isolated Pincer Lesion	1 (1.2%)	0 (0.0%)	1.00
Combined Cam and Pincer	2 (2.4%)	0 (0.0%)	1.00
Labral Tear	82 (100.0%)	31 (100.0%)	1.00
Acetabular Chondromalacia			
Grade 0-2	0 (0%)	0 (0%)	
Grade 3	67 (81.7%)	20 (64.5%)	
Grade 4	15 (18.3%)	11 (35.5%)	0.08
Ligamentum Teres Debridement	26 (31.7%)	11 (35.5%)	0.82
Psoas Release	24 (29.3%)	7 (22.6%)	0.64

Table 3: Univariate analysis of risk factors for revision surgery.

Variable	**HR (95% CI)**	***P-value***
Treatment		
Debridement/Abrasion	Reference	
Microfracture	1.01 (0.37 – 2.77)	0.98
Age		
≤ 35 years	Reference	
> 35 years	1.36 (0.54 – 3.40)	0.51
BMI		
≤ 30	Reference	
> 30	1.60 (0.58 – 4.41)	0.36
Gender		
Female	Reference	
Male	0.85 (0.33 – 2.15)	0.73
ALAD Grade		
Grade 3	Reference	
Grade 4	0.97 (0.29 – 3.27)	0.96
LCEA		
≥ 25°	Reference	
< 25°	1.06 (0.32 – 3.55)	0.92
Capsular Repair		
No Repair	Reference	
Repair	0.88 (0.31 – 2.49)	0.81

Table 4: Multivariate Cox proportional hazards analysis of risk factors for revision surgery**.**

Variable	**HR (95% CI)**	***P-value***
Treatment		
Debridement/Abrasion	Reference	
Microfracture	0.93 (0.30 – 2.90)	0.90
Age		
≤ 35 years	Reference	
> 35 years	1.38 (0.53 – 3.64)	0.51
ALAD Grade		
Grade 3	Reference	
Grade 4	0.96 (0.28 – 3.35)	0.95
LCEA		
≥ 25°	Reference	
< 25°	1.10 (0.32 – 3.72)	0.88

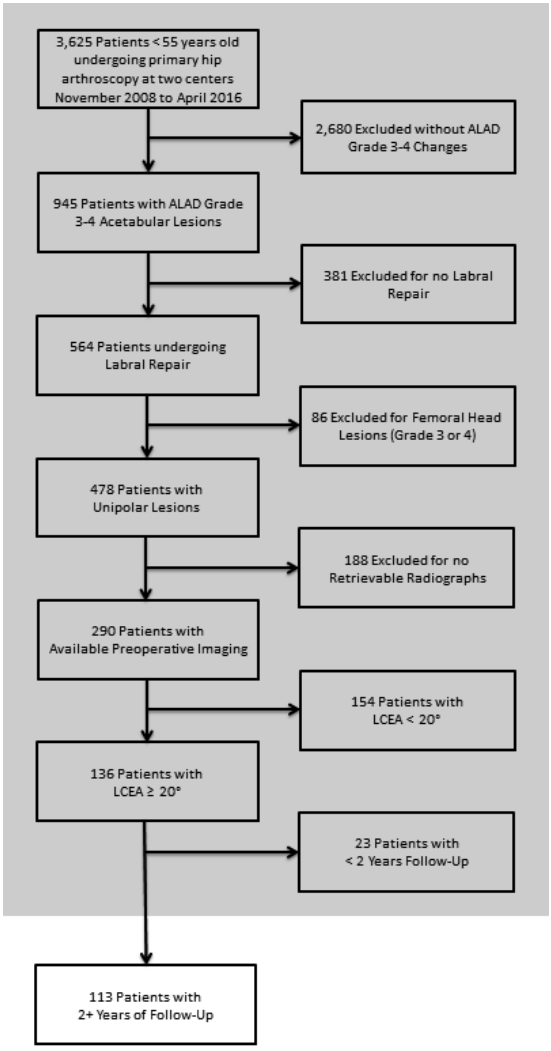

Figure 1: Inclusion and Exclusion of patients based on study criteria.

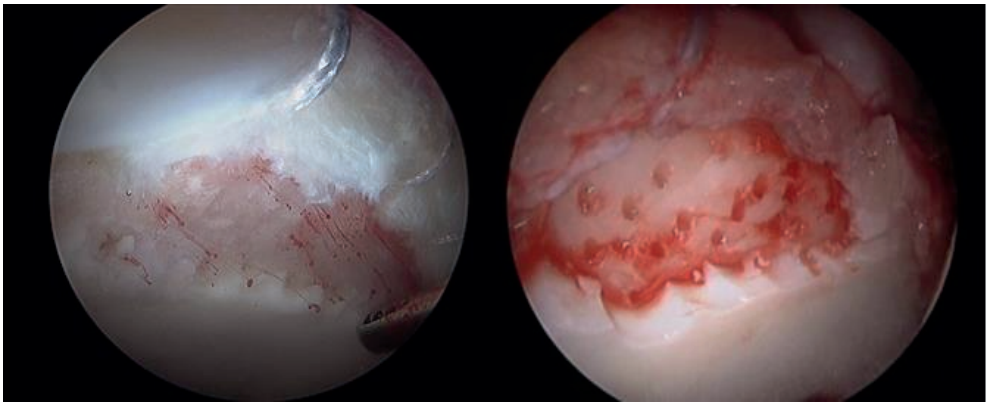

Figure 2: Intraoperative photos of right hip through anterolateral viewing portal following labral repair and preparation of two similar grade 4 cartilage lesions demonstrating (A) Debridement (abrasionplasty) and (B) Microfracture.

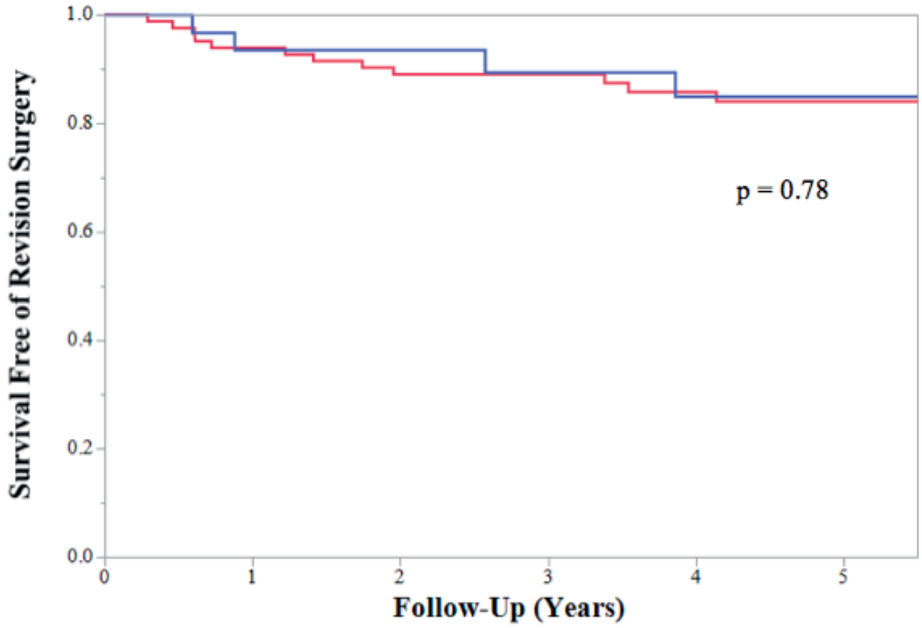

Figure 3: Survival free of revision surgery for the debridement/abrasion (red) and microfracture (blue) cohorts.

Chapter V, Section II: Knee Preservation

Medial Meniscus Root Repair: A Transtibial Pull-Out Surgical Technique

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Introduction

Meniscus root tears with associated extrusion have generated considerable interest since their initial description by Pagnani et al.[316] In 2008, Allaire and colleagues demonstrated that a medial meniscus posterior horn root avulsion is biomechanically equivalent to a complete meniscectomy due to the resulting abnormally high peak tibiofemoral contact pressures.[8] Several other studies have since associated meniscal extrusion with progressive, degenerative osteochondral damage in the setting of increased tibiofemoral joint forces.[3, 91, 130, 218, 221, 385]

Of significant concern, root tears represent a "silent epidemic" with many injuries often missed during the course of workup. [93, 214, 223] This highlights the importance of intraoperative meniscus root testing, especially given the potential for root-tear associated rapid articular cartilage damage, subchondral bone edema, and sometimes collapse, previously referred to as spontaneous osteonecrosis of the knee (SPONK). The authors are strong proponents of repair of meniscus root repairs, when technically feasible. In a comparison of medial meniscus posterior root tears treated with partial meniscectomy or non-operative management, no symptomatic benefit in IKDC or Tegner score was found for meniscectomy.[217] Furthermore, given the increased risk of conversion to arthroplasty with both meniscectomy and non-operative management, repair is a desirable alternative to non-preservation approaches.

Indications

Meniscus root tears can predominantly be classified into two categories: 1) traumatic tears which typically occur in younger patients in association with a knee ligament injury and 2) degenerative tears which result from low energy mechanisms in older patients, such as getting up from a deep seated position. Traumatic tears likely represent true avulsions of the posterior horn root attachment of the meniscus [Figure 1]. These tears should be repaired in all cases at the time of knee ligament reconstruction. In contrast, degenerative tears are usually full-thickness, radial tears near the root junction, but not a true avulsion of the meniscus attachment to bone [Figure 2]. These

tears are often associated with knee arthritis. Indications for repair in this setting are evolving and the optimal candidate has not yet been defined. Contraindications to meniscus root repair include subchondral bone collapse, radiographic joint space narrowing of the affected compartment, uncorrected varus or valgus malalignment, and obesity. Root repair in this setting is unlikely to heal or restore meniscus function. Two main meniscus root tear repair techniques have been described: 1) direct fixation employing suture anchors and 2) sutures pulled through a tibial tunnel. Given that meniscal root repair using a suture anchor technique is technically challenging, requiring a posterior portal, curved suture passing device, and constrained suture passing within the knee, the authors are proponents of the transtibial fixation, which has demonstrated positive mid- and long-term results.[91, 92, 422]

Author's Preferred Operative Technique

Standard knee arthroscopy portals are created, including an ipsilateral portal made under direct visualization to ensure access to the posterior meniscal root. The posterior horn attachment is inspected and palpated with a probe. In order to obtain adequate visualization of a medial meniscal tear and adequate space to introduce instrumentation, it may be necessary to lengthen the medial collateral ligament (MCL). This is accomplished by percutaneous fenestration of the proximal MCL using a spinal needle while applying a valgus force to the knee. In addition, a "reverse" notchplasty may be performed by removing a small amount of bone from the wall of the notch and by shaving down the medial tibial spine. Finally, removal of synovium from the posterior cruciate ligament can be beneficial.

Once the working space is optimized, a tibial socket is created at the meniscal root attachment. This is accomplished using a root specific tibial guide placed through the ipsilateral portal (Arthrex, Naples, FL). Alternatively, an anterior cruciate ligament guide can be used, but these tend to miss or skive from the root footprint due to the torque placed on the guide in a constrained space. Once the guide is positioned intra-articularly at the center of the meniscal root footprint, a 6-mm FlipCutter (Arthrex, Naples, FL) is introduced into the joint through a small incision on the proximal, medial tibia. The FlipCutter is deployed, and a 6 mm diameter socket is created to a depth of a few millimeters to access healing bone [Figure 3]. The device is then removed from the joint and replaced by a FiberStick (Arthrex), which is used for later passage of the meniscus sutures through the tibia [Figure 4]. The FiberStick passing suture is retrieved through the contralateral viewing portal to avoid tangling during suture passage into the meniscus.

A cannula is placed through the ipsilateral working portal to prevent a soft-tissue bridge and to aid in suture management. A free No. 0 nonabsorbable suture is then passed through the torn

meniscus in a simple cinch locking loop configuration using a self-retrieving suture passing device (Knee Scorpion, Arthrex or NovoStitch; Ceterix Orthopaedics, Menlo Park, CA) [Figure 5]. Two to three locking loop sutures are typically placed, depending on tissue quality [Figure 6]. The sutures should then be individually tightened to remove slack. All of the sutures are then shuttled through the tibial socket using the previously placed passing suture. The knee is cycled to remove the creep from the system. The stitches are tensioned to reduce the meniscus back to the root attachment [Figure 7]. If the meniscal root is not adequately reduced, the bone and cartilage in contact with the meniscus can be decorticated to allow for biologic healing with the suture fixation remaining in the anatomic socket using an arthroscopic curette. Tibial fixation is obtained with a 5.5-mm SwiveLock anchor (Arthrex) placed into the proximal-medial tibia through the previous incision, with the knee in 90 degrees of knee flexion.

A previous biomechanics studied has assessed suture configurations. When comparing a simple cinch versus locking loop configuration, there was significantly less displacement of the cinch sutures.[288] When comparing ultimate load to failure, both suture configurations were similar. Therefore, currently we utilize the simple cinch suture as it was significantly better at resisting displacement compared to the locking loop stitch configuration, and had similar ultimate load to failure. Practically, this is also easier to place the sutures with one pass in the posterior aspect of the compartment, and also creates fewer perforations in the meniscus tissue.

Postoperative Course

Postoperative protection of the repair is critical to healing. Therefore, during the first 6 weeks after surgery, weight bearing is limited to full extension toe-touch in a brace and knee flexion limited to 90 degrees. After 6 weeks, the brace is discontinued and the patient may begin full progressive weight bearing and full knee range of motion. Knee loading at flexion angles greater than 90 degrees is not allowed until 4 months postoperatively. Typically, a gradual increase in activities can occur beyond three months. Sporting activities are allowed at four to six months, once strength and movement symmetry has been achieved.

Outcomes

In two comparison studies, the results of root repair were superior to non-operative treatment for selected patients. Ahn et al compared 25 medial meniscus root repairs to 13 patients without surgery and found that the repair group had better subjective, activity, and knee function scores.[3] However, the repair group knees with greater than 5 degrees varus malalignment or greater than grade 3 cartilage changes at the time of arthroscopy did not have better results. Chung et al

compared 20 partial meniscectomies to 37 root repairs with a minimum 5 year follow-up.[91] They observed that the repair group had superior subjective knee rating and knee function scores as well as less radiographic progression of arthritis. In addition, none of the repair patients underwent subsequent knee arthroplasty compared to 35% of the debridement group. Recently, long-term results have also been reported by Chung et al utilizing the transtibial pullout repair technique.[92] In 91 patients with an average age of 59, only 4 failures were reported at an average 7-year follow-up (1 knee replacement, 3 failures defined as low clinical scores). In addition, Lysholm scores improved from 52.8 to 83.0 postoperatively. The overall survival of the repair was 92% at 8 years in these well-selected patients.

In an economic effectiveness study, meniscus repair, meniscectomy, and non-operative treatment were compared using a systematic literature meta-analysis and Markov cost model.[130] At beyond 10 years, osteoarthritis rates of 53.0%, 99.3%, and 95.1% and total knee replacement rates of 33.5%, 51.5%, and 45.5% were observed for repair, meniscectomy, and non-operative treatment, respectively. Repair was found to be both cost-effective and superior in terms of quality-adjusted life years. As such, we strongly believe that repair should be the preferred intervention for meniscus root tears, both in terms of patient outcomes and productivity, as well as societal costs.

Conclusion:

The results of medial meniscus root repair are good in selected patients, with demonstrated decreased rates of osteoarthritis and total knee arthroplasty compared to partial meniscectomy and non-operative management. Repair is advised when possible since patients treated with partial meniscectomy or non-operative management fare poorly in measures of subjective outcomes and quality-adjusted life years. Furthermore, repair has recently been demonstrated to be beneficial in terms of societal costs. Advantages of the presented medial meniscus root repair technique include a biomechanically strong suture construct, no need for a posterior portal, and instrumentation designed specifically for the knee. The methods described represent a readily-employable approach to meniscus repair and preservation, an undertaking which is critically important to normal knee function.

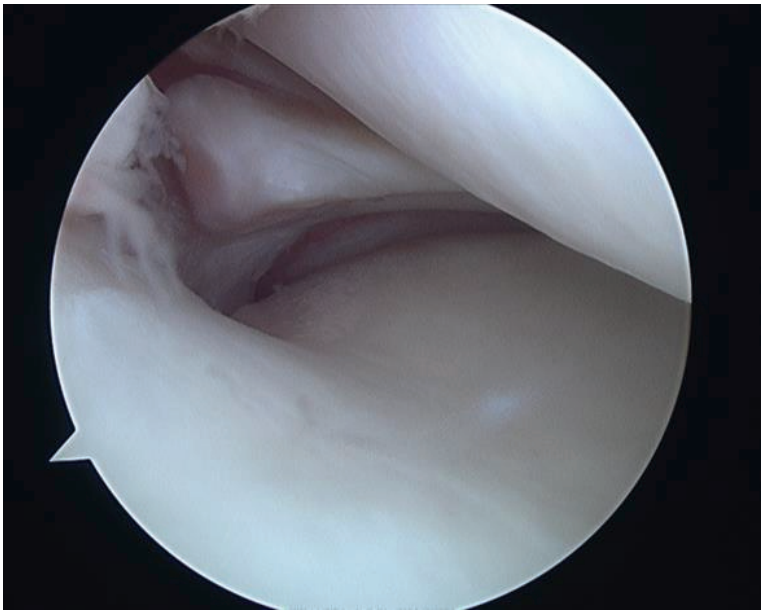

Figure 1: Arthroscopic view of a traumatic posterior horn medial meniscus root tear avulsion.

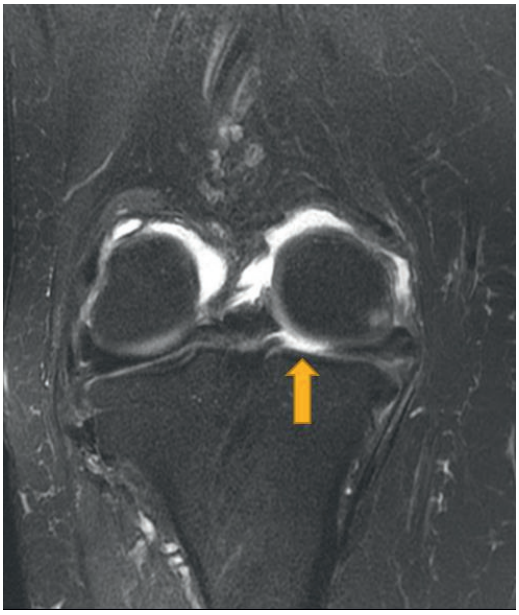

Figure 2: Coronal MRI appearance of a radial tear near the root junction of the posterior horn medial meniscus with extrusion.

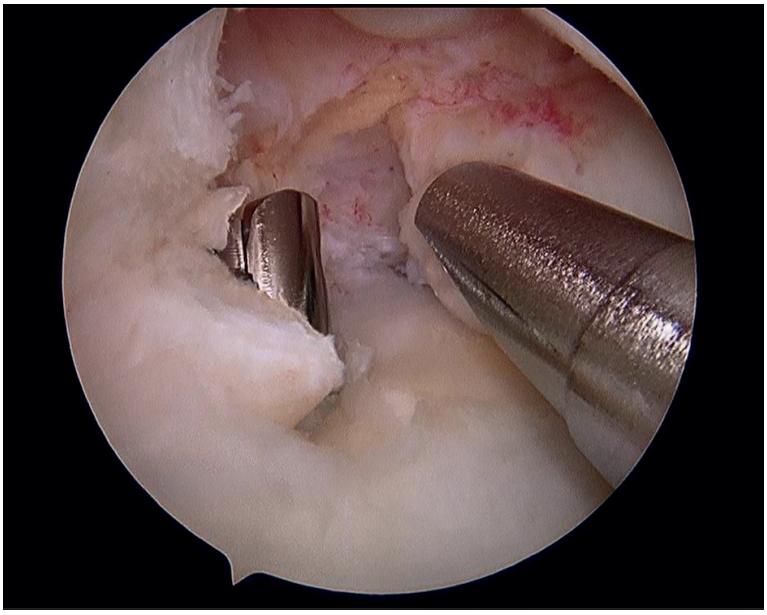

Figure 3: Arthroscopic view of flip cutter in root footprint remnant.

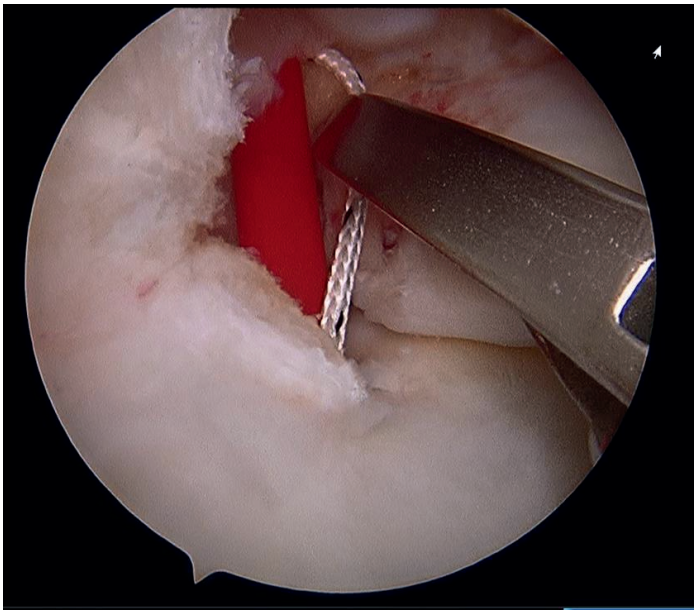

Figure 4: Arthroscopic view of shuttling suture through tibial socket.

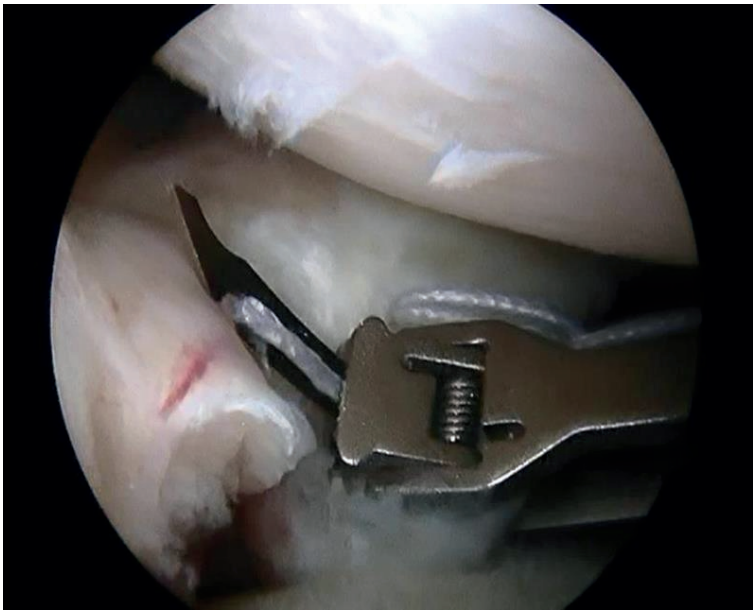

Figure 5: Arthroscopic view of self-retrieving suture passing device.

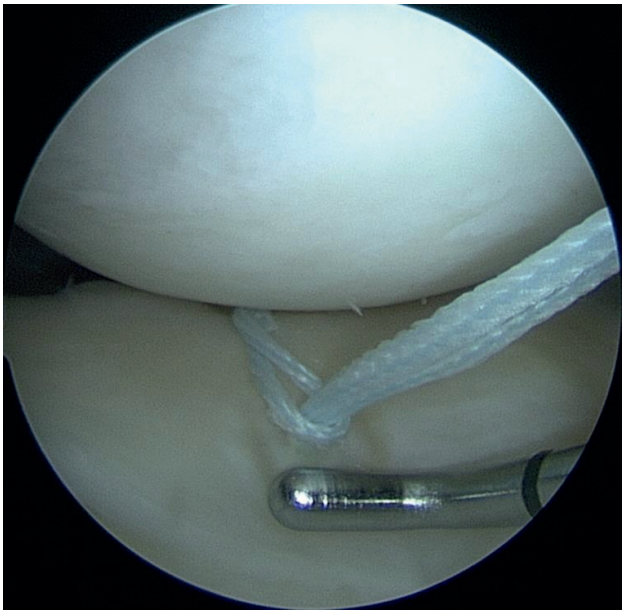

Figure 6: Arthroscopic view of a locking loop suture.

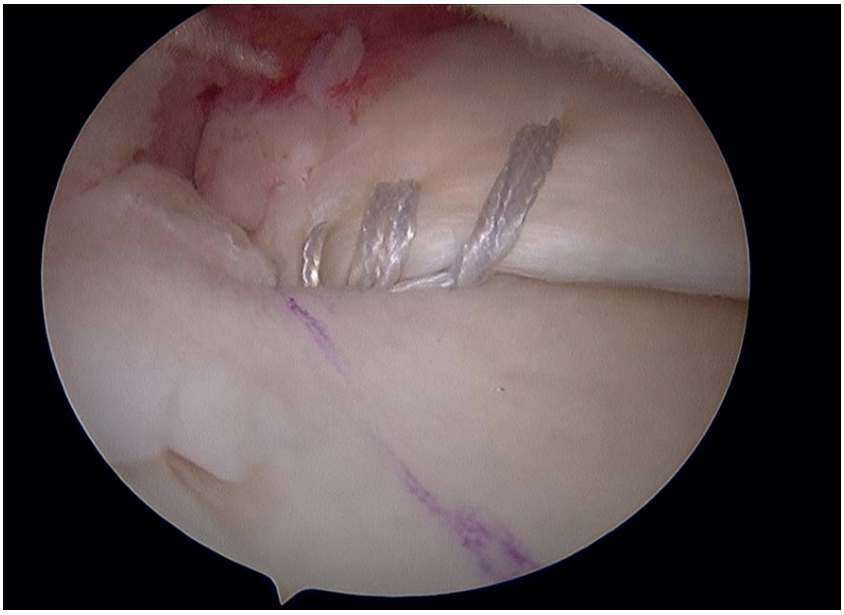

Figure 7: Arthroscopic view of a locking loop suture configuration and final root repair.

Comparative Outcomes of Radial and Bucket-Handle Meniscal Tear Repair: A Propensity-Matched Analysis.

Wu IT, **Hevesi M**, Desai VS, Camp CL, Dahm DL, Levy BA, Stuart MJ, Krych AJ.

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PMID: 30070592

Introduction

Menisci serve to disperse the axial load of body weight, provide shock absorption, improve joint congruity, and reduce friction during movement.[2, 15, 55, 139, 149, 274, 278] Both the lateral and medial meniscus are subject to a variety of traumatic tear patterns which often have poor healing potential and surgically prove difficult to repair.[289, 403] Radial tears have a very poor prognosis because the perpendicular orientation of the tear in relation to the meniscal fibers can compromise the circumferential distribution of vertical compressive loads on the tibia, described as "hoop" stresses.[34, 139, 296] Historically, partial meniscectomy has served as the cornerstone for operative management of radial meniscal tears,[44, 281, 358] despite the risk of post-meniscectomy arthrosis.[24, 320] A number of techniques have been developed for repairing radial meniscus tears since attention has increasingly turned towards meniscal preservation.[40, 321, 374, 375]

Radial tear repair has shown promise as an effective alternative to partial meniscectomy, with all-inside, inside-out, and transtibial techniques presented in the literature[13, 84, 94, 162, 332, 346, 375] Anderson et al. demonstrated successful repair in 92% of their patient cohort of 24 posterior radial tears.[13] However, studies often possess heterogeneous data of small sample sizes, limiting the strength of the conclusions that can be drawn. For example, a systematic review and meta-analysis of biomechanical studies conducted by Alentorn-Geli et al[6] was unable to establish any degree of superiority of either the inside-out or outside-in repairs, owing in part to a lack of available comparable studies. Similarly, a systematic review by Moulton et al[290] that examined clinical outcomes of meniscal radial tear repair generated a limited number of studies with none citing more than 15 patients.

In light of the current gap in the literature, a matched cohort study of radial repair techniques versus a comparison group of established repair techniques is indicated. Bucket-handle meniscus tears involve a large portion of the meniscus and are preferentially treated with repair due to favorable healing and the avoidance of downstream degenerative changes from meniscus deficiency.

The purpose of this study was to assess clinical postoperative outcomes and reoperation rates of radial meniscus repairs and then compare them to a group of robustly-matched bucket-handle meniscus repairs. We hypothesize that outcomes of radial tear repair will be satisfactory and comparable to a propensity-matched group of patients who underwent a bucket-handle meniscus repair.

Methods

This retrospective cohort study was approved by the institutional review board (IRB # 15-000601) prior to study commencement. The institutional medical record database was searched to identify all radial meniscal tears that underwent surgical repair by the senior authors (AJK, BAL, DLD, MJS) in the period from 2011 to 2015. All efforts were made to repair the meniscus, with partial meniscectomy performed only in the case of irreparable tears, such as those with extensive meniscus tissue loss or inability to coapt the tear. Patients undergoing repair of full-thickness radial tears were eligible for inclusion. Exclusion criteria consisted of 1) patients not consented for research, 2) less than 2 years of clinical follow-up, 3) grade 3-4 chondromalacia, 4) knee dislocation or combined ACL and PCL injury, 5) repair of a posterior meniscal root tear, and 6) repair of a partial radial tear. Twenty-four patients met criteria for inclusion in this study.

Surgical Technique

Radial meniscus repair was performed using either an inside-out[321] or all-inside[346, 375] technique, both of which have been previously described in detail. A brief overview of key steps is provided below.

First, the patient prepped and draped in a sterile fashion. Standard arthroscopic portals were created and the tear was directly identified. If the tear was deemed amenable to surgical repair, a shaver and double-sided rasp were used to debride the edges to promote healing.

For the inside-out technique, a posterolateral or posteromedial incision was made to expose the capsule in order to retrieve and tie the sutures. Preloaded No. 2-0 non-absorbable sutures, (Ethicon, Summerville, NJ) were then placed from inside-out using zone-specific cannulas in a horizontal mattress pattern to reduce the tear. A spoon retractor was used to deflect the needles and protect the neurovascular structures. The sutures were retrieved, tensioned under arthroscopic vision and, tied over the capsule to complete the repair (Figure 1).

In the all-inside technique, the repair was performed through the ipsilateral portal while viewing from the contralateral portal. An all-inside meniscal repair device (FastFix, Smith & Nephew, Andover, Massachusetts) was used to pierce the meniscus and deploy the first suture anchor. The same device was then used to penetrate the meniscus again on the other side of the tear, placing a second anchor. The suture was then pulled to reduce and compress the tear, and the knot advanced and cut to complete the stitch. Additional horizontal sutures were placed as needed to complete the repair.

For bucket-handle tears, standard arthroscopic portals were utilized and all tears underwent preparation in the form of rasping the tear site and adjacent synovium followed by anatomic reduction. The inside-out repair technique utilized standard medial or lateral incision in addition to zone specific cannulas and 2-0 non-absorbable sutures (Ethicon, Summerville, NJ) in a vertical mattress fashion. All-inside repairs were performed in accordance with the guidelines for the specific device utilized. Of the 8 all-inside and 6 hybrid repairs used in the bucket-handle group, 13 utilized Fast-Fix anchors (Fast-Fix 360, Smith & Nephew), and 1 utilized the MaxFire Marxman meniscal repair device (Biomet).

Post-Operative Rehabilitation

During the first 0 to 4 weeks after radial repair surgery, patients were kept non-weight-bearing. Range of motion was restricted to 90 degrees of flexion until week 4. In weeks 4 – 8, the patients were allowed to bear weight as tolerated. Range of motion was advanced but loading at flexion angles greater than 90 degrees was not permitted until 4 months postoperatively. At 4 months, patients were allowed to return to activity as tolerated. Bucket-handle repair patients followed a similar post-operative protocol, with the distinctions that patients were kept partial weight bearing for the first 0 to 4 weeks.

Outcome Data Collection

Patient demographics, surgery details, and clinical findings were extracted from the institutional electronic medical record. Pre- and postoperative range of motion (ROM) was recorded from the time of presentation and the most recent clinic visit with the operating surgeon. Tegner Activity Scale[51] and Visual Analog Scale (VAS) ratings[230] were documented before and after surgery. International Knee Documentation Committee (IKDC) Subjective Knee Evaluation scores[196] were calculated preoperatively and at the latest follow-up to assess functional and subjective outcomes after surgery. Use of the IKDC score has been shown in the literature to be reliable and valid in assessing outcomes of meniscus surgery.[104, 195, 401] All subsequent ipsilateral knee procedures were

reviewed and noted on a standardized documentation form. Failure was defined as any re-tear or insufficiency of the original meniscal radial tear repair, noting any revision repair or subsequent meniscectomy.

Statistical Analysis

A priori analysis was used to determine the radial repair group size needed to demonstrate postoperative efficacy of repair of radial meniscus tears, the primary endpoint of this study. Based on the IKDC validation and responsiveness data published by Irrgang et al., alpha = 0.05, and a power of 0.80, it was determined that 14 patients would be needed to demonstrate significant postoperative improvements following radial repair.[196] Propensity matching of the radial repair patients was performed on the basis of age at surgery, gender, meniscus laterality, BMI, and concomitant anterior cruciate ligament reconstruction (ACLR) using a comparison pool of 70 bucket-handle repairs performed by the same senior authors between 2007 and 2014. Kaplan-Meier curves were used to compare the survival rates between the radial repair and the bucket-handle repair groups. Continuous values (age, BMI) were compared using Student's t-test. Ordinal patient-reported outcome scores (VAS, Tegner and IKDC) were compared between groups, or between different time points, using Mann-Whitney U (Wilcoxon rank-sum) tests. P-values < 0.05 were considered significant. Analyses were conducted in R 3.4.1 (R Core Team, Vienna, Austria) and JMP Pro 13 (SAS Institute, Cary, NC).

Results

Radial Repair Group Characteristics

44 patients who underwent radial repair were initially retrieved. Of these, 6 were excluded for having grade 3 or 4 chondromalacia, 4 for knee dislocation or combined ACL and PCL injury, and 3 for having root repairs. Of the 31 eligible patients, 7 were not reached for two year follow-up and were thus excluded. The study included 24 patients (18 M, 6 F, mean age at surgery: 22.8 ± 11.9 years) undergoing surgical repair of full-thickness radial meniscus tears (Table 1). This sample size met *a priori* power analysis to demonstrate postoperative improvements in IKDC score. The majority (62.5%) of tears involved the posterior horn of the meniscus. Six radial tears involved the mid-third body of the meniscus or its junction with the anterior horn, and two patients had radial tears in both the posterior horn and body. Radial tears occurred acutely during sports or athletic activities and all were repaired within 1 year of injury. Mean time from injury to surgery was 48 ± 62 days. The mean preoperative range of motion was 4 degrees of extension (range: -3 – 10) to 106 degrees of flexion

(range: 60 – 145), with a mean preoperative arc of 103º (range: 50 – 142). No patient had a previous history of ipsilateral knee surgery.

An all-inside technique was utilized in 16 cases, 7 patients underwent inside-out repair, and one patient had a hybrid procedure involving both techniques. Repairs required a mean of 4.5 ± 3.8 (Range: 2-17) sutures. Six patients underwent partial resection or debridement of a secondary meniscal lesion: 5 on the same (lateral) meniscus and 1 on the opposite (medial) meniscus. Five patients with lateral meniscus radial repairs also underwent meniscal repair of the medial side. Other concomitant procedures included ACL reconstruction in 16 patients. Three patients received platelet rich fibrin matrix for meniscus repair augmentation. All concomitant ACLR were performed simultaneously.

Postoperatively, all patients achieved full extension with mean 136 degrees of flexion (range: 100° – 145°). Radial repair patients demonstrated improvements in patient reported outcome scales, with preoperative VAS improving from 3.0 ± 2.5 at rest and 5.8 ± 2.9 with activity to 0.3 ± 0.8 at rest ($p < 0.001$) and 0.8 ± 1.5 with activity ($p < 0.001$). IKDC improved from 39.8 ± 12.3 preoperatively to 89.0 ± 13.1 postoperatively ($p < 0.001$) and Tegner scores improved from 2.6 ± 1.4 immediately preoperatively to 6.5 ± 1.5 postoperatively ($p < 0.001$). Patients achieved statistically similar postoperative Tegner scores when compared to the patients' self-reported pre-injury scores (7.0 ± 0.7, $p = 0.10$).

Five cases (20.8%) progressed to meniscal re-tears or failed repairs at a mean time of 1.9 years (range: 0.18 – 5.14) after the initial repair. Two of the five failed repairs were directly visualized at the time of second surgery for a staged ACL reconstruction. Another two were noted when the patients re-tore their ACL grafts (one at 6 months after surgery and one at 5 years). The last failure was reported in a patient who underwent reoperation primarily for a tear of the medial meniscus, but had meniscal extrusion in the lateral radial repair location. One patient developed arthrofibrosis requiring lysis of adhesions two months following initial meniscal repair. No additional surgery-related complications were recorded. The patient who underwent PCL repair required a subsequent all-inside PCL reconstruction during which the medial meniscus radial repair was noted to be completely healed and stable upon probing.

Propensity-Matched Comparison of Outcomes

Following analysis of the entire radial repair group, 18 radial repairs were successfully matched to 18 bucket-handle repairs on the basis of age at surgery, gender, BMI, tear laterality (medial versus lateral) and the presence of concomitant ACLR (Table 1). Matching was successful in

that all match criteria were statistically similar between the two groups ($p \geq 0.49$). Thirteen (72%) radial tears were all-inside and 8 (44%) bucket-handle tears were all-inside. Mean preoperative outcome scores (VAS, IKDC, and Tegner) were statistically similar between the matched groups (Table 1) with only exception being post-injury, preoperative Tegner score (lower in the bucket-handle group [p=0.03]) and VAS with use (higher in the radial group [p = 0.03]). This suggests increased preoperative pain with use in radial tear group but greater limitations to activity in the bucket-handle group.

Bucket Handle Repair Group Surgical Characteristics

An all-inside technique was utilized in 8 patients, 4 patients underwent inside-out repair, and 6 patients had a hybrid procedure involving both techniques. Repairs required a mean of 7.7 ± 4.1 (Range: 3-15) sutures. Eleven patients underwent concomitant ACLR, with all concomitant ACLR were performed simultaneously. One patient received platelet rich fibrin matrix for meniscus repair augmentation.

Each group experienced statistically significant postoperative improvements in Visual Analog Scale, at rest and with use ($p < 0.001$) (Table 1, Figure 2). The mean IKDC scores in both matched groups also significantly increased between preoperative baseline and final follow-up ($p < 0.001$). Mean Tegner scores at final follow-up were significantly improved for both groups compared to their preoperative, post-injury value ($p < 0.001$). Both the radial repair and bucket-handle repair groups reported final Tegner scores that not significantly different from their baseline score prior to injury ($p = 0.32$ for radial, $p = 0.46$ for bucket-handle). No significant difference was observed when comparing final VAS, Tegner, and IKDC scores between matched radial and bucket-handle repair groups ($p \geq 0.17$, Table 1).

Additionally, matched radial and bucket-handle tear groups demonstrated similar survival, with 88.9% and 94.4% 2-year and 77.8% and 87.7% 5-year reoperation-free survival, respectively ($p = 0.17$, Figure 3).

Discussion:

The purpose of the present study was to assess clinical outcomes and reoperation rates of radial meniscus repairs and to compare them to a group of robustly-matched bucket-handle meniscus tear repairs. The hypothesis was supported in that arthroscopic repair of full-thickness radial tears demonstrated satisfactory outcomes, comparable to those observed in matched group of 18 bucket-handle meniscus tears. Furthermore, patients in both the radial and bucket-handle tear

groups were able to recover to a Tegner activity level statistically comparable to their pre-injury baseline.

Prior studies on the outcomes of radial repairs have been scarce until quite recently. A 2016 systematic review by Moulton et al[290] found that only 6 clinical series with minimum 2-year follow-up were published on outcomes of radial tear repairs between 1980 and 2014, with a combined number of 55 patients. The review demonstrated encouraging improvements in healing rates and patient-reported outcomes based on heterogeneous studies. The current investigation contributes to the literature by including a larger single-study volume of patients and employing a study design allowing for comparison of radial repairs to more extensively reported and understood bucket-handle repairs.

The overall radial repair survival rate at final follow-up (mean 3.5 years, range: 2.0 – 6.3) was 79% in this study. Notably, none of the failures involved a symptomatic re-tear. Four of the failed repairs were discovered during a primary or revision ACL reconstruction. The last failure was visualized during a repair procedure for the opposite meniscus. However, the observed failure rate in this series was still higher than those reported in previous studies. In a study by Ra et al,[332] follow-up MRI showed complete healing in 11/12 patients and partial healing in 1/12, which was similar to their findings on second-look arthroscopy (6 completely healed, 1 partially healed). Song et al[375] reported complete healing in 9/15, partial in 4/15, and no healing in 2/15 on second-look arthroscopy, but all patients were free of clinical symptoms. In another study, Choi et al[84] obtained MRIs at 6 months postoperatively on 14 repaired radial tears and found that 5/14 were completely healed, 8/14 were partially healed, and 1/14 was not healed. The results of this study are not directly comparable, as follow-up MRIs were not obtained and assessed for healing; however, our mean follow-up of 3.5 years compares favorably with the follow-up in the above three studies which ranged from 2.0 – 3.0 years. While repeat arthroscopies were all performed for indications other than symptomatic re-tear, we considered any meniscus repair failure reported in the second operative note to be a complete failure, without defining "partial" healing or failure. It is possible that one or more of the failed cases in this study would be considered partially healed depending on the imaging or arthroscopic criteria used. Due to the conservative nature of our reporting, the rate of clinically significant failures is likely overestimated.

Patients reported good clinical outcomes after radial repair, with mean Visual Analog Scale pain rating decreased significantly after surgery, both at rest and with use ($p < 0.001$). Patients on average reported little to no pain at rest and minimal pain with use after meniscus repair. Furthermore, the radial repair patients achieved a mean Tegner score of 6.5 at their latest clinical follow-up, which correlates with a recreational sports level, and was statistically comparable to the

included patients' preoperative baseline.[388] This represents significant improvements compared to the post-injury scores (mean 2.6 ± 1.4, $p < 0.001$). Our findings of excellent postoperative activity are supported in other studies which have reported mean postoperative Tegner scores ranging from approximately 5.7 to 6.7.[13, 84, 375] Subjective functional outcomes after surgery were also measured by IKDC score, which increased by a mean of 49.2 points postoperatively. The final mean IKDC score was 89.0 ± 13.1, which falls within the range of 81.6 to 92 reported in other radial repair case series.[13, 332, 346]

After propensity matching from a pool of 70 bucket-handle patients on the basis of age, sex, BMI, meniscus laterality, and concurrent ACLR, the radial repair group demonstrated patient-reported outcomes and failure rates comparable to the bucket-handle repair group. The preponderance of lateral tears amongst all radial tears (88%) and the matched groups (83%) were consistent with the high proportion of patients with concomitant ACLR (63% and 61%, respectively), a known risk factor for lateral-predominant tears.[135] Prior to surgery, most of the outcome scores were statistically equivalent. One difference in the bucket-handle tear group was greater preoperative reductions in activity level as a result of the meniscus tear and/or accompanying injuries (Tegner score, radial: 2.7 ± 1.5; bucket-handle: 1.9 ± 0.6; $p = 0.03$). However, radial tear patients perceived a greater level of pain with continued exertion (VAS with use, radial: 6.4 ± 2.6; bucket-handle: 4.1 ± 2.4; $p = 0.03$). After surgery, both groups showed significant improvements in all four outcome measurements: VAS at rest, VAS with use, Tegner, and IKDC ($p \leq 0.001$). Additionally there were no observed differences between the matched radial and bucket-handle repair groups in any of the mean postoperative outcome scores ($p \geq 0.17$), however these results must be taken in the light of a primary, powered outcome of postoperative improvements following radial repair and not pairwise comparisons between the two techniques. These results support that repair is a viable option for radial meniscus tears, producing outcomes that are statistically similar to those seen in bucket-handle repairs which were selected as a control group due to readily available reports of positive clinical outcomes in this tear pattern[4, 133, 161, 235, 308, 354, 366, 367]. Alternatively, recent literature has compared transtibial radial repairs with vertical longitudinal tears, with results supporting similar outcome scores and reoperation rates between the two groups.[94]

This study has several important limitations. While radial meniscal tears are not rare, small tears are frequently debrided to stable edges rather than repaired due to limited tissue for use in repair, limiting the number of patients available for study inclusion. Given the relatively low volume of eligible radial repairs, adequately powered studies randomized between repair and partial meniscectomy would be difficult to achieve. However, we hope the satisfactory outcomes observed in this study will contribute to increased consideration of this tear pattern for repair rather than meniscectomy—improving the size and power of future investigations both in our practice and

elsewhere. Another limitation is that the results of retrospective cohort studies are prone to selection bias, since the tears most amenable to repair are carefully evaluated and chosen. Given the nature of surgical practice, this is a necessary constraint and radial tears should continue to be prudently selected for repair. There also exist many potential confounding factors which can affect the clinical outcome. Propensity matching was performed to mitigate the effects of certain confounding variables, such as concomitant ACL reconstruction, but could not address all possible factors. Other characteristics of the radial and bucket-handle groups such as tear size and complexity, and repair technique (inside-out or all-inside) could not be included in the matching design given the current sample size. In future studies, it would be useful to analyze these additional variables for potential influence, or lack thereof, on patient outcomes and repair durability. Finally, post-operative magnetic resonance imaging (MRI) data was not consistently available for our patients and thus, we were unable to utilize "healing" on imaging as an outcome measure.

Conclusion:

Satisfactory clinical outcomes are achievable for radial meniscal tear repairs at short-term follow-up. In a robustly-matched comparison, radial and bucket-handle meniscus tears demonstrate similar improvements in VAS and IKDC scores, restoration of preoperative Tegner scores, and acceptable reoperation rates. Full-thickness radial meniscus tears should be considered for repair.

Table 1: Radial repair study population demographics and propensity-matched radial and bucket-handle repair groups with patient-reported outcome scores and survival. Values reported as Mean ± Standard deviation.

	All Radial Repairs (n = 24)	**Matched Radial Repair** (n = 18)	**Matched Bucket-Handle Repair** (n = 18)	**p-value***
Demographics and Matching Criteria				
Age, mean ± SD	22.8 ± 11.9	19.1 ± 9.1	20.8 ± 5.1	0.49
Males : Females	18 : 6	12 : 6	13 : 5	1.00
BMI	26.5 ± 5.8	27.0 ± 6.2	25.0 ± 3.5	0.68
Lateral meniscus	21	15	15	1.00
Concomitant Procedures				
Concomitant ACLR	16	11	11	1.00
Medial Meniscus Repair/Meniscectomy	5	4	1	0.34
LFC Chondroplasty	3	3	2	1.00
Other	4*	3**	3***	1.00
Baseline (Pre-injury) Scores				
Tegner	7.0 ± 0.7	6.9 ± 0.7	6.7 ± 1.0	0.51
Pre-op (Injured) Scores				
VAS, rest	3.0 ± 2.5	3.4 ± 2.7	2.1 ± 2.1	0.20
VAS, use	5.8 ± 2.9	6.4 ± 2.6	4.1 ± 2.4	**0.03**
Tegner	2.6 ± 1.4	2.7 ± 1.5	1.9 ± 0.6	**0.03**
IKDC	39.8 ± 12.3	39.2 ± 13.6	36.3 ± 16.3	0.36
Post-op (Final) Scores				
VAS, rest	0.3 ± 0.8	0.4 ± 0.9	0.0 ± 0.0	0.17
VAS, use	0.8 ± 1.5	0.9 ± 1.7	0.4 ± 0.8	0.64
Tegner	6.5 ± 1.5	6.6 ± 1.6	6.6 ± 1.2	0.80
IKDC	89.0 ± 13.1	89.9 ± 14.4	93.1 ± 3.3	0.43
Survival				
2 years	87.5%	88.9%	94.4%	--
5 years	83.3%	77.8%	87.7%	--
Overall	79.2%	77.8%	87.7%	0.17

BMI, body mass index; ACLR, anterior cruciate ligament reconstruction; VAS, Visual Analog Scale; IKDC, International Knee Documentation Committee Subjective Knee Evaluation Form.
*Other Concomitant Procedures: 1 PCL repair, 1 lateral tibial plateau debridement, 1 distal MCL repair, and 1 MCL internal brace.
**1 PCL repair, 1 lateral tibial plateau chondroplasty, 1 distal MCL repair
***1 MFC chondroplasty, 1 trochlear chondroplasty, 1 MCL reconstruction
†p-values calculated between matched groups

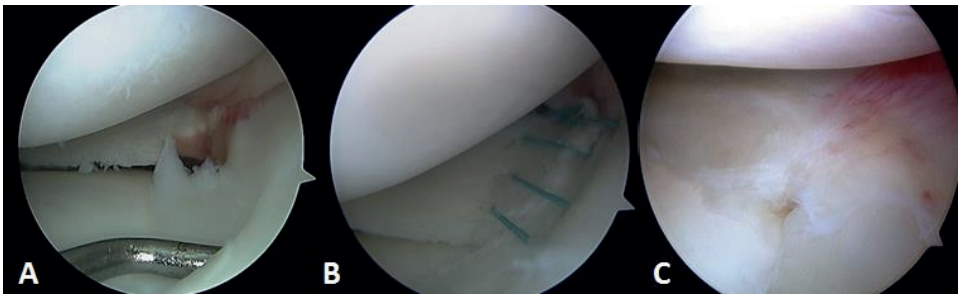

Figure 1A-C: A) Intraoperative visualization of a full-thickness radial meniscus tear. B) Tear visualization following completion of inside-out horizontal mattress suturing. C) Healed tear visualized at the time of repeat arthroscopy for revision ACL reconstruction.

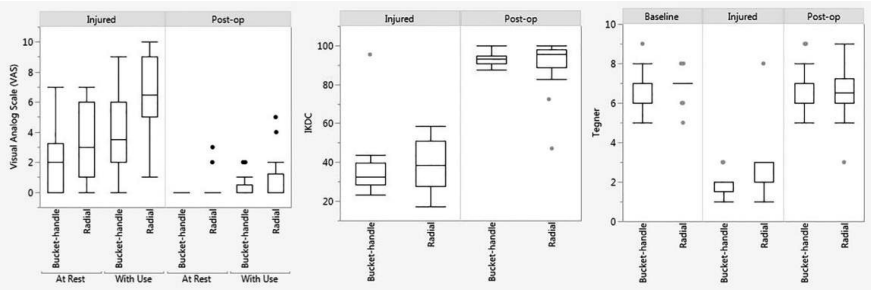

Figure 2: Patient-reported outcome scores in the matched radial repair and bucket-handle repair groups. IKDC, International Knee Documentation Committee Subjective Knee Evaluation Form.

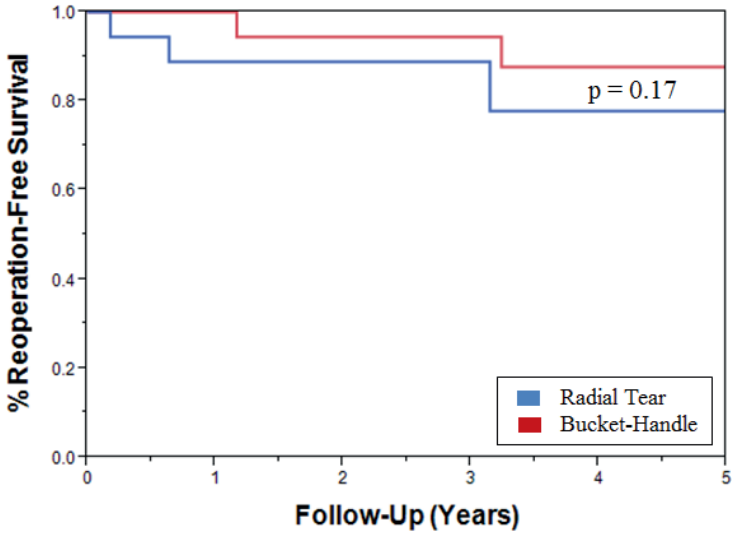

Figure 3 – Reoperation-free survival curves for propensity-matched radial and bucket-handle tears. No significant difference is seen in survivorship over 5 years of follow-up.

Chapter V, Section III:
Newly-Established Clinical Trials

IND16766: ASCLEPIOS

Autologous **S**tem **C**el**L** **E**xpansion and **P**rospective **I**njection for **O**steoarthritic hip **S**ymptoms: A Phase I Safety and Feasibility Trial of Autologous Culture Expanded Adipose Derived Mesenchymal Stromal Cells in the Treatment of Painful Hip Osteoarthritis

ClinicalTrials.gov Listing

Title	A Phase I Safety and Feasibility Trial of Autologous Culture Expanded Adipose Derived Mesenchymal Stromal Cells in the Treatment of Painful Hip Osteoarthritis
Running Title	Autologous AMSCs for osteoarthritis of the hip
Protocol Number	TBD
Phase	Phase I Safety and Feasibility
Methodology	Open label prospective clinical trial
Overall Study Duration	24 months for single injection cohort 25 months for two injection cohort
Subject Participation Duration	24 months for single injection cohort 25 months for double injection cohort
Single or Multi-Site	Single Site
Objectives	Determine the safety and feasibility of autologous, culture expanded, adipose derived mesenchymal stromal cell injections in the treatment of hip osteoarthritis
Number of Subjects	24
Diagnosis and Main Inclusion Criteria	Osteoarthritis of the hip, mild to moderate (Tönnis Grade 1-2)

Study Product, Dose, Route, Regimen	• Human, autologous, culture expanded, adipose derived mesenchymal stromal cells
	• Dosing protocol
	  ○ Single injection of 30 million AMSCs (S30)
	  ○ Two injections of 30 million AMSCs (M30)
	• Ultrasound guided intra-articular hip injection

Duration of Administration	Single administration by single ultrasound guided injection Two-dose administration (2 x ultrasound guided injections) with one month interval between doses
Reference therapy	None
Statistical Methodology	Descriptive

Current Status: FDA Approval to Proceed, Enrollment Active / Open

IND1898: RECLAIM

A Phase I Safety and Feasibility Trial of **RE**cycled **C**arti**L**age **A**uto/Allo **IM**plantation for the Treatment and Repair of Focal Knee Cartilage Defects

ClinicalTrials.gov Listing

Title	A Phase I Safety and Feasibility Trial of Recycled CartiLage Auto/Allo Implantation for Treatment and Repair of Focal Knee Cartilage Defects
Running Title	RECLAIM Cartilage Repair for Knee OA
Protocol Number	TBD
Phase	Phase I Safety and Feasibility
Methodology	Open label prospective clinical trial
Overall Study Duration	24 months
Subject Participation Duration	12 months
Single or Multi-Site	Single Site
Objectives	Determine the safety and feasibility of Recycled CartiLage Auto/Allo Implantation for the treatment and repair of Focal Knee Cartilage Defects
Number of Subjects	25
Diagnosis and Main Inclusion Criteria	Patients aged 18-50 with a symptomatic Modified Outerbridge Grade III or IV cartilage lesions of the knee ranging in size from 2 to 8 cm^2.

Study Product, Dose, Route, Regimen	• Human, autologous, chondrocytes in their pericellular matrix (chondrons)
	• Human, allogeneic adipose-derived mesenchymal stem cells (AMSCs)
	• Dosing protocol
	  ○ Single intra-articular surgical dosing
	  ○ 400,000 – 4,000,000 chondrons combined in 1:4 ratio with 1,600,000 – 16,000,000 AMSCs in 4 mL of fibrin glue
	  ○ Applied directly to cartilage defect
	  ○ Up to 4 mL additional fibrin glue solution with no cellular content to be used as sealant

Duration of Administration	Single administration by surgical arthrotomy
Reference therapy	None
Statistical Methodology	Descriptive

Current Status: FDA Approval to Proceed, Enrollment Active / Open

Chapter VI:

Summary, Discussion, and Implications

Key Findings

- There is exists a critical and global need for hip and knee preservation and restoration
- High volume tertiary care center experience combined with the RIP and RAPID scores provide valuable guidance tools for clinical decision making in cartilage surgery
- Living donor transplantation together with physiologic storage provide optimization and expansion of the existing resources available for the treatment of osteochondral defects
- Currently available and evolving biologic and restorative interventions demonstrate early clinical safety and efficacy in hip and knee preservation

Summary

The work presented in this thesis has directly influenced patient care. Hip and knee osteoarthritis remain central themes and challenges in orthopedics, given their profound impacts on patient quality of life, health, and wellbeing. While the rise and evolution of arthroplasty has substantially contributed to patient care, especially in elderly populations, arthroplasty remains limited by activity restrictions, wear, the potential for catastrophic periprosthetic joint infection, and an inability to restore native biomechanics and function.

In this thesis, we presented a four-tiered approach in improving biologic hip and knee preservation. In *Part I*, we demonstrated the value of hip and knee preservation on a societal level, showing that restoration of function benefits both the individual patient and the broader group within which they live and interact. We then followed the natural progression of patient presentation in *Part II* wherein we developed preoperative prognostic tools for identifying and risk stratifying patients with hip and knee chondropathology. A central theme in joint preservation is that form begets function and therefore restoration of function often necessitates recreation of native joint anatomy and mechanophysiology. This principle is embodied in the clinical success of treating osteochondral lesions with osteochondral allograft by replacing like with like. In *Part III*, we explored *in vitro* methods with which osteochondral allografts can be optimized and be made more viable. Additionally, we have explored novel living donor methods with which this precious and otherwise non-scalable graft source can be expanded. Finally, in *Part IV*, we have presented technical advances, outcomes, and two prospective clinical trials which have resulted from direct efforts from the work embodied in this thesis.

In summary, the thesis presented demonstrates the process, outcomes, and successes of modern hip and knee preservation. When evaluating the patient with hip and knee cartilage defects, our goal is to restore rather than replace.

Samenvatting *(Dutch Summary)*

Het werk dat in dit proefschrift wordt gepresenteerd, heeft de patiëntenzorg rechtstreeks beïnvloed. Heup- en knieartrose blijven centrale thema's en uitdagingen in de orthopedie, gezien hun grote invloed op de kwaliteit van leven, gezondheid en welzijn van de patiënt. Hoewel de opkomst en evolutie van artroplastiek substantieel heeft bijgedragen aan de patiëntenzorg, vooral in oudere populaties, blijft artroplastiek beperkt door activiteitsbeperkingen, slijtage, het risico op catastrofale periprosthetische infectie en een onvermogen om de eigen biomechanica en functie te herstellen.

In dit proefschrift hebben we een vierlagige aanpak gepresenteerd voor het bij het verbeteren van de behandelingen voor het behouden van heup- en kniegewricht. In deel I hebben we de waarde van het behouden van heup en knie gewricht op maatschappelijk niveau aangetoond, waaruit blijkt dat het herstel van de functie zowel de individuele patiënt als de bredere groep ten goede komt. Vervolgens volgden we de natuurlijke progressie van de patiëntpresentatie in deel II, waarin we pre-operatieve prognostische hulpmiddelen ontwikkelden voor het identificeren en risicostratificeren van patiënten met chondropathie van heup- en kniegewricht. Een centraal thema voor het behouden van een gewricht is het gegeven dat vorm functie verwekt en daarom vereist herstel van functie vaak recreatie van de oorspronkelijke gewrichtsanatomie en mechanofysiologie. Dit principe wordt aangetoond met het klinische succes van het behandelen van osteochondrale laesies met osteochondrale allografts door het vervangen articulair kraakbeen met articulair kraakbeen. In deel III hebben we in vitro methoden onderzocht waarmee osteochondrale allografts kunnen worden geoptimaliseerd en levensvatbaarder kunnen worden gemaakt Daarnaast hebben we nieuwe methoden ontwikkeld en onderzocht om kraakbeentransplantatie mogelijk te maken van levende donoren die gewrichtsvervanging ondergaan om dit beperkte en kostbare donor materiaal optimaal te kunnen gebruiken. Ten slotte hebben we in deel IV technische vooruitgang, resultaten en twee prospectieve klinische proeven gepresenteerd die zijn voortgekomen uit directe inspanningen van het werk dat in dit proefschrift is gedaan.

Samenvattend demonstreert het gepresenteerde proefschrift het proces, de resultaten en successen van moderne heup- en kniebehoud. Bij het evalueren van de patiënt met heup- en kniekraakbeendefecten is ons doel om te herstellen in plaats van te vervangen.

Összefoglalás *(Hungarian Summary)*

Az itt bemutatott tanulmány közvetlenül befolyásolja a betegellátást. A csípő és térd ízületi károsodása továbbra is központi téma és kihívás az ortopédia területén, mivel jelentős hatással van a betegek életminőségére, egészségére és közérzetére. Bár az artroplasztika elterjedése és evolúciója jelentősen hozzájárul a javuló betegellátáshoz, különösen idősebb korban, az artroplasztikát továbbra is limitálja az implantátum kopása , aktivitási korlátozások, a protézis körüli fertőzés lehetősége, és az eredeti ízület biomechanikai funkciójának hiányossága.

Ebben a tézisben egy négy-lépcsős formát használtunk a biológiai csípő és térd megőrzésének javítására. Az első részben az ízület megőrzésének fontosságát mutattuk meg, hangsúlyozva hogy a funkció javitása az egyén és a szélesebb társadalom számára is előnyös. A második részben preoperatív prognosztikai eszközöket fejlesztettünk ki. A harmadik részben in vitro módszert használva vizsgáltuk hogyan optimalizálható osteochondralis allograft átültetés sikeresen. Ezen felül, újfajta, élő donor módszert fejlesztettünk ki, amelyekkel kibővíthető ez az értékes, de egyébként nem kiterjeszthető porcforrás. Végül, a negyedik részben bemutattunk újabb fejlesztéseket és eredményeket a csípő és térd prezerválásban / megőrzése érdekében, miközben két első fázisisú klinikai vizsgálatot is inditotunk.

Összefoglalva, ez a tézis bemutatja a modern csípő- és térdkonzerválás új előrehaladásait/ lehetőségeit, eredményeit, és sikereit. A csípő és térd károsodása esetén a cél a javítás , nem a pótlás.

Discussion

Part I: Cost Modelling of Hip and Knee Preservation Durability and Efficacy

Modelling the costs and associated utility of hip and knee preservation can be intuitively done through a combined approach. First, the costs of the alternatives (TKA / THA) must be determined along with the expected failure modes, rates, and costs of revision. Next, indirect aspects such as morbidity of revision surgery should also be measured in order to further quantify the utility of preventing or delaying primary and therefore secondary arthroplasty.

We began our investigation into preservation costs by determining the reoperation, revision, and repeat revision rates of knee preservation in young total knee arthroplasty patients. In doing so, we were able to determine that even when analyzing only direct in-hospital costs, patients under 39 years of age undergoing primary TKA generated substantial costs within the first 20-years of post-operative management, not including the initial cost of arthroplasty, which is contemporarily estimated to be $17,662 USD.[262] Furthermore, the societal costs of [young] early TKA are likely even greater when accounting for indirect costs such as time lost from work and subsequent revisions occurring outside the analyzed timeframe of the first 20 postoperative years. Our investigation provides one of the first analyses of the natural history of patients undergoing TKA below the age of 50, a growing population that is likely to play an increasing role the societal cost of knee arthritis in the foreseeable future.[359, 370]

In parallel with our work on TKA and revision TKA costs, we also investigated the financial burden of revision hip arthroplasty for various surgical indications. While THA continues to be one of the most successful orthopedic procedures date, with demonstrated safety and efficacy, THA remains prone to the inherent mechanical limitations of artificial, non-biologic joint surfaces[211, 240]. To date, the costs of revision THA (rTHA) are poorly understood and, while primary THA occurs principally for osteoarthritis and therefore can be readily targeted for focused preservation efforts, aseptic rTHA represents a broad variety of indications and failure mechanisms. In the modern, cost-conscious era of bundled payments and scrutiny for cell-based and preservation-centered procedures, it is of great importance to understand the rates and reasons for failure of primary arthroplasty, a common salvage for joint preservation, and thus evaluate the utility and efficacy of early biologic repair interventions. In our presented investigation, the costs of rTHA were substantial, ranging from $17,911 to $25, 672 in our Mayo Clinic cohort and $17,509 – $27,605 in the national cohort. Furthermore, in our subanalyses which demonstrate the relative rates of revision

by indication, rTHA for fracture was 33-48% more expensive and demonstrated increased local and national complication rates. Therefore, given the many failure methods of primary THA and substantial associated costs for each of them, efforts to delay and preclude arthroplasty are intuitively worthwhile for both individual patients and society as a whole.

Having established the costs and cost utility of various aspects of hip and knee joint preservation, we sought to further characterize the effects of revision knee arthroplasty on patient mortality and thus investigate non-cost measures involved in revision. In doing so, we investigated long-term mortality trends in a large cohort of 4,907 revision TKA patients over a mean follow-up of 9.5 years and noted that the only group of patients who experienced a survival advantage following revision TKA were patients who underwent revision TKA for aseptic loosening/wear. This is particularly striking given that it is well established that the vast majority of primary TKA and THA patients experience a durable survival advantage following arthroplasty, supporting that primary arthroplasty improves not only patient quality of life but also patient longevity [261]. However, the substantial negative effects of revision TKA on patient mortality highlight the need for delayed TKA and more durable preservation and primary arthroplasty options given more guarded outcomes in those who go on to subsequent revision.

While non-arthroplasty interventions inherently carry surgical and peri-operative risks, those complications which are unique (wear and polyethylene induced osteolysis) and particularly devastating (i.e. PJI) in the setting of arthroplasty can potentially be better mitigated and avoided with early biologic intervention.

Part II: Pre-Operative Assessment of Cartilage Damage

Patient assessment and planning are critical for surgical and clinical success. In *Part II*, we employed validated statistical methods and our large scale hip and knee cartilage experience to examine predictors of recurrent patellar dislocation as well as preoperative acetabular cartilage damage in addition to evaluating common reasons for cartilage surgery failure. In doing so, we aimed to provide prognostic tools to help inform real-world medical decision making and patient care.

Our recurrent patellar dislocation investigation demonstrated that recurrence of primary lateral patellar dislocations can be readily predicted using age, physeal status, the presence of dysplasia, and TT-TG / PL ratio in the form of the novel RIP score. Furthermore, our data describes the recurrent instability and surgical history of patients followed for an average of 10+ years,

demonstrating that second-time dislocation continues to occur throughout mid- and long-term follow-up, a factor previously not addressed by existing stratification systems.

Risk factors for recurrent dislocation are well-described, but existing scoring systems are derived from case series with short-term follow-up and have classically excluded surgical cases, limiting clinical utility by biasing scores to patients that had already been selected for non-treatment. Balcarek et al. proposed the Patellar Instability Severity Score which was the first multivariable scoring system and provided a 7 point scale for recurrent instability.[22] However, recurrence risk was quantified in relative terms using odds ratios and the actual percentage risk for redislocation with a given score was not reported. In addition, the median score for patients without recurrence was 3 points and the median for those patients who experienced a recurrent episode was 4 points. As such, the ability of this score to risk-stratify patients is limited.

Jaquith et al. also proposed a predictive score for use in pediatric patients.[199] However, in both the Jaquith and Balcarek scoring systems, patients who required initial operative management were excluded from analysis making scores best applicable to lower-risk, non-operative patients as opposed to the general population. A competing risk model which accounts for patients undergoing early surgical stabilization is necessary to create a broadly-applicable score for recurrence prognosis. We believe that our RIP score has contributed substantially to the literature by providing a statistically founded system which is applicable to both adult and pediatric populations and has been developed in light of competing surgical management.

Having created a model for predicting recurrent patellar instability, we also sought to inform the practice of hip preservation, with a special focus on hip arthroscopy. Preoperative prediction of high grade chondrolabral damage is of significant clinical value due to consequences on perioperative planning and preparation. Treatment of cartilage defects can potentially require special equipment and preoperative planning for the surgeon and alters the postoperative rehabilitation for the patient. To date, there is no readily-available multivariable system on which to preoperatively stratify patients by damage risk. As such, similar to the opportunity and area afforded in the generation of the RIP score, we believed that true academic and clinical utility could be gained through multivariate, in-clinic prediction of acetabular chondrolabral delamination, presented in the form of the RAPID score.

In creating the RAPID score by using the Akaike Information Criterion, we believe we have been able to produce a system which maximizes the predictive ability of the data while providing a parsimonious solution with three simple variables (sex, Tönnis grade, presence of cam morphology) that can be readily and rapidly assessed in clinic using history and radiographs. In addition, the use

of a validation cohort is a particular strength of our study and scoring system. We find it self-evident that a predictive score, based on a study dataset, should perform well when applied to the dataset from which it was calculated. The observation that the RAPID score, when applied to the previously-blinded two-center validation cohort, performed with an AUC statistically equivalent to the original study data greatly strengthens the notion that this score is generalizable.

Perhaps an ultimate test of basic and translational medical science is its ultimate utility in affecting and informing clinical practice. We have been particularly pleased with the RIP in RAPID scores in terms of clinical value given their regular use in our practice and contribution to informing discussions with patients and other surgeons. A particularly striking example is their acceptance in MDCalc through peer review, where they are now available for free-of-charge graphical use by clinicians and patients globally (Please see RIP and RAPID).

Another key aspect of cartilage surgery is evaluating ongoing efforts at joint surgery and subsequently determining which factors influence outcomes and can be modified both pre- and perioperatively in order to optimize outcomes. With the evolution of cartilage restoration techniques, the number of cartilage procedures performed in the United States has substantially increased, with an associated increase in failed cartilage surgeries and subsequent revisions.[272] In this thesis, we sought to determine the mode of failure for primary cartilage procedures referred to our tertiary referral center in order to perform a descriptive casual analysis and identify treatable risk factors for failure. In doing so, our hope was to inform practice and decrease failure rates by addressing common targets for improvement.

In our investigation, the most common reason for failure of cartilage restoration procedures was residual malalignment (56%). This is intuitively and biomechanically logical, given that in cases of malalignment, the affected cartilage compartment is overloaded, with potentially profound changes in force distribution at relatively low degrees of angulation. In previous native joint and total knee model analyses, it has been suggested that an increase of 4-6° varus angulation leads to a 20-50% increase in medial tibiofemoral stresses.[390, 420] There exists strong evidence that malalignment plays a role in both the development and subsequent progression of osteoarthritis.[54, 364, 387] In particular, Sharma et al, in their age, sex, and BMI adjusted model, demonstrated that varus malalignment was associated in a 4-fold increase in progression in Kellgren-Lawrence arthritis of ≥ 1 grade at 18 months follow-up while valgus malalignment was associated with a near 5-fold increased incidence of arthritic progression.[364] Severity of both varus and valgus deformity correlated with risk of disease progression. As such, we believe long-leg standing hip to ankle films are of utmost importance in the cartilage patient and highlight the need and role of these even further in our clinical practice, demonstrating another area where this thesis has informed patient care. Without

addressing the underlying increased contact stresses that may have caused the primary cartilage injury, any restorative procedures are at increased risk to fail under continued increased stresses.

Another common reason for cartilage failure was meniscal deficiency, which was observed in 11 of the 59 cases of revision surgery. Meniscectomy and untreated meniscal tears have an extensive track record for leading to increased osteochondral degenerative changes over time when compared to uninvolved contralateral knees or population controls.[9, 62, 128, 320] Given this, we believe that consideration should be given for meniscal allograft transplantation for cases where meniscal repair or conservative, partial debridement is not possible. Although there is controversy regarding the long-term results of meniscal transplantation, biomechanical studies support a possible protective role in increasing contact area and stability as well as decreasing peak contact stresses within the knee joint.[7, 183, 317, 344, 361, 372]

Finally, we found that the importance of concomitant instability in patellofemoral cartilage defects is considerable and provides a treatment challenge. In the landmark series by Brittberg and Peterson, overall results for ACI were quite promising with 16 of the 23 patients reporting good to excellent results.[52] However, positive outcomes were concentrated in the femoral condylar transplant group (14 of 16 good-to-excellent) while failures were concentrated in the patellar group (2 of 6 good-to-excellent). At the time of publication, patellar maltracking and instability were not well-recognized in the literature and thus not addressed intraoperatively. In their discussion, the authors suggested that malalignment and subluxation may play a role in their modest results and that these may be better addressed by correction of the underlying abnormalities. In more contemporary series reporting on patellar ACI with concomitant biomechanical normalization procedures such as tibial tubercle osteotomy (TTO) with anteromedialization, trochleoplasty, and medial patellofemoral ligament (MPFL) reconstruction, outcomes have been significantly improved. A recent multicenter experience demonstrated greater than 80 % good-to-excellent outcomes and more than 90 % of patients stated they would undergo the procedure again.[148]

In light of our findings, we recommend that every cartilage patient undergo an extensive clinical history, physical examination including analysis of gait and alignment, full length radiographs, and scrutinization of all imagining in order to recognize contributing background factors. However, despite the correction of many of these factors, cartilage surgery does not uniformly excellent results and graft failure was the reason for approximately one quarter of the revision cases in our series. This leads naturally to the next area of focus of this thesis, namely graft tissue selection and subsequent storing and optimization.

Part III: Optimization of Osteochondral Tissues for Transplantation

When optimizing osteochondral tissues for transplantation, we pursued a two-pronged approach, namely, we explored novel sources of osteochondral tissues in the form of living donor allograft and furthermore, we sought to determine the ideal storage conditions for allograft tissues, both for living donor and existing sources of osteochondral allograft. The main findings of the living donor allograft study are three-fold: 1) fresh osteochondral samples obtained at the time of TKA demonstrate a consistent decrease in viability and histologic quality during the first three weeks of storage, 2) decreased viability observed in laboratory-stored samples are also observed in clinical grade osteochondral allograft at the time of surgical implantation, and 3) living donor osteochondral allograft from relatively well-preserved compartments at the time of TKA demonstrates satisfactory viability and histology when compared to OCA samples from current clinical practice. These findings are substantial given the recent private industrial shift in delayed OCA implantation to permit further sterility testing which has yet to be accompanied by assurance or disclosure of viability.[399] Furthermore, employing living donor transplantation from the time of TKA has the potential to simultaneously increase viability, ease logistic scheduling, and expand the availability of OCA, supporting the implementation of what is considered the gold standard treatment for large cartilage and osteochondral defects.

It is also important to establish the ideal timeline for cartilage implantation. While classic OCA surgeries were performed on the order of hours to days following procurement, sterility testing paradigms have shifted practice towards implantation at 14 – 35 days following graft harvest, without simultaneous testing or validation of tissue viability.[61, 300, 399] These changes raise the concern of decreasing clinical benefit given the established link between tissue viability and graft success.[101] Accordingly, we tested the viability and histology of osteochondral samples under optimal physiologic conditions during storage for up to 3 weeks, which is near the average time of 23 days to OCA implantation at our institution. The observed decreases in viability, as well as significant accompanying loss of glycosaminoglycan content in Safranin-O staining, certainly raises the concern of storing tissues on the order of weeks, even in the most optimal [physiologic] conditions.

In addition to the inherent and existing limitations of scaling allografts obtained from deceased donors, the unexpected passing of donors adds an additional layer of logistical complexity for scheduling OCA transplantation. At the time of this laboratory-based thesis investigation, our institution, which is designated a high-volume cartilage center, has three patients that have been on OCA waiting lists for greater than 6 months. Such limitations and volumes could be improved and overcome by the implementation of Living Donor Cartilage Programs, considering the high volume of varus and valgus total knee replacements performed in the United States and worldwide and the fact

that TKAs are performed on an elective and pre-scheduled basis.[363, 364] We have demonstrated that candidate living donors can be successfully screened to provide optimal osteochondral grafts, and that safety testing can be performed immediately prior to tissue donation. Therefore, patients in need of living donor cartilage allograft could also be scheduled in advance to follow operative dates for living donors undergoing TKA. Given that distal femoral OCA costs are on the order of $8,500 – $15,000 per graft, significant cost savings may also result and fund the establishment of the necessary tissue banks, infectious disease screening for donors, and more advanced preoperative testing such as magnetic resonance imaging (MRI) for donors.

The purpose of the second arm of our osteochondral allograft investigations was to evaluate and compare chondrocyte viability after one week of storage in a number of modern storage conditions, namely room temperature protocols (22°C) and physiologic conditions. In doing so, we demonstrated improved viability with physiologic storage when compared to room temperature storage, which has previously been suggested as an evolving standard from current 4°C practice.

Studies employing intra-articular thermometers at the time of knee exercise have demonstrated that physiologic knee temperature varies on the range of approximately 33 – 39°C, and other investigations into the efficacy of ice- and cryotherapy-based cooling systems have demonstrated that physiologic and even therapeutic temperatures rarely, if ever approach values near 25° C (i.e. room temperature).[31, 408] Therefore, it is intuitive that long-term maintenance of osteochondral tissues may be preferable within physiologic and biologic parameters nearer 37°C.

Our analysis of live-dead viability in different storage conditions demonstrated that human OCA tissues stored at 37°C achieved superior viable cell density (VCD) results as compared to osteochondral specimens stored in serum free media at 22°C, with > 90% viability following 7 days of incubation at 37°C as compared to a mean VCD of 66% for storage at 22°C. These results suggest the utility of physiologic storage and highlight that, after only 7 days of incubation, the mean VCD of storage for our human OCAs at room temperature (22°C) falls below the proposed 70% cutoff for OCA viability. Considering that graft viability is considered the leading predictor of clinical success in OCA transplantation, we believe these results strongly support human OCA storage at physiologic 37°C conditions.

Overall, our temperature-based data provide strong support that physiologic storage is a novel and facile method to optimize tissue viability during short-term storage of fresh OCA and has the potential to improve long-term clinical results of surgical cartilage repair. To this end, current efforts are currently underway for clinical grade, Good Manufacturing Practice (GMP) media manufacture and subsequent first-in-human trials of physiologically stored living donor allograft.

Part IV: Modernizing Interventions & Outcomes of Hip and Knee Preservation

Hip Preservation

Traditionally, treatment of hip pathology required open approaches; however, there has been a modern shift to less invasive arthroscopic management of femoroacetabular pathology[47, 48, 159]. In investigating the safety, outcomes, and efficacy of hip preservation, we aimed to evaluate hip arthroscopy for labral repair, one of the most common indications for arthroscopic management in our practice, and subsequently determine the utility of labral repair in well-selected dysplastic patients as well as evaluate the relative value of microfracture as compared to [conservative] acetabular debridement and abrasionplasty.

At mid-term follow-up, arthroscopic labral repair demonstrated durable improvements in VAS, mHHS, and HOS-SSS. In addition, we found that increasing Tonnis grade, patient BMI, and age at the time of surgery significantly predicted worse outcomes. Our finding that patient outcomes demonstrate significant and sustained improvement at five years status post hip arthroscopy is an extension of previous literature that has demonstrated well-established short-term efficacy and favorable outcome in terms of VAS [76], modified Harris Hip Score [70, 108, 204] and HOS-SSS scores [108]. However, sample size for most studies has been relatively small and we believe this investigation is amongst the largest cohorts with the longest mean follow-up when reviewing the current literature [147, 190, 306, 331, 371]. As such, we believe our research supports the durable outcomes previously described at mid-term follow-up whilst adding statistical power and decreasing the propensity for type II error present in smaller sample sizes.

Our findings are also substantial in that they suggest preoperative osteoarthritis evolves over time, causing significant effects in mHHS and HOS-SSS at mid-term follow-up which are not apparent earlier in patients' clinical course. This was especially noticeable in mHHS and HOS-SSS scores for Tonnis grade 2 patients, which non-significantly decreased postoperatively, failing to meet MCID. In comparison, patients with Tonnis grade 0-1 changes demonstrated significant postoperative improvements in mHHS and HOSS-SSS as well as VAS which surpassed MCID. This highlights the importance large cohorts with extended follow-up as outcomes can differentiate over the course of many years.

Having demonstrated the efficacy of arthroscopic labral repair at mid-term follow-up, we next sought to investigate various indications and underlying factors at the time of arthroscopy and their relationship to patient reported outcomes and revision rates. In particular, we aimed to determine the clinical mid-term failure rate and patient-reported outcomes of arthroscopic labral

repair in the setting of hip dysplasia and to assess factors which lead to higher failure rates or worse outcomes.

In our described series, arthroscopic labral repair in the setting of dysplasia demonstrated significant postoperative improvements in VAS, mHHS, and HOS-SSS and a failure rate of 19% at 5+ years of follow-up. This is substantial given that there is little mid-term literature available for arthroscopic labral repair failure rates, especially in the setting of dysplasia, with most reports limited to case series of dysplastic hips or retrospective causal analyses for revision surgery[46, 345]. A cautionary series by Parvizi et al found that 16 (44%) of 36 patients with LCEA < 20° or global acetabular retroversion went on to revision surgery at a mean follow-up of 3.5 years following arthroscopic surgery for labral tears[322]. Of note, all patients had undergone labral debridement, which has previously been shown to have inferior outcomes as compared to labral repair, again highlighting the importance of restoration-based intervention in joint preservation surgery[164, 219, 222].

In the clinical decision-making between hip arthroscopy and PAO, we believe that selection of dysplastic labral repair patients with concurrent FAI can be conducive to initial arthroscopic management as both the labral tear and FAI, which is likely contributory to tear etiology, can be simultaneously addressed arthroscopically. This is the likely contributor to the relative prevalence in males and FAI patients in our dysplastic hip arthroscopy practice. In contrast, in cases without FAI, we find it important to note that the patient's pain generator was clinically felt to be most consistent with labral etiology (i.e. mechanical locking on physical exam) as opposed to dysplasia and associated chondral loading and injury. In the case of the latter, we would favor the use of PAO as acetabular version cannot be adequately arthroscopically addressed at this time.

Overall, the findings of our dysplasia investigation support that with careful selection and modern arthroscopic techniques, patients with dysplasia can benefit significantly and durably from arthroscopic labral repair, with similar outcomes and failure rates to rigorously matched non-dysplastic controls at mid-term follow-up.

Given the growth of hip arthroscopy, we have observed a parallel growing potential role and availability of microfracture while there is a simultaneous movement away from microfracture-related methods in knee arthroscopy and preservation. Given this, we aimed to investigate patient reported outcomes of patients undergoing debridement/abrasion and microfracture of high-grade unipolar acetabular defects at the time of labral repair and to determine whether lesion treatment modality was predictive of outcomes and revision rates. We observed that patients undergoing both debridement/abrasion and microfracture demonstrated significant improvements in patient

reported outcome scores. In addition, treatment modality was found not to predict subjective patient reported outcomes or revision rates at a mean of 4.9 years follow-up.

Our findings are significant in that they support the use of either debridement/abrasion or microfracture in the treatment of grade 3 and 4 acetabular defects. Given clinically similar outcomes, these findings call to question whether clinical improvement is attributed to the fibrocartilage fill of microfracture in arthroscopic hip surgery, or whether improvement is secondary to the labral repair, cam resection and pincer treatment in these hip populations. Alternatively, it is possible that debridement/abrasion to stable vertical surrounding cartilage borders and scraping of the calcified cartilage layer in a debridement/abrasion can produce equivalent fibrocartilage without penetration of the subchondral plate.

Benefits supporting the use of preferential debridement/abrasion include the avoidance of prolonged weight bearing restrictions, need for costly CPM machines, and extended recovery course associated with microfracture.[65] Furthermore, violation of the subchondral plate carries significant risk of subchondral fracture and intralesional osteophyte formation, both of which may contribute to joint degradation and necessitate revision surgery.

Perhaps the strongest data regarding the relative utility of microfracture stems from studies in the knee, for which well-designed, large studies of mid-term outcomes are available. In a prospective, randomized study in which articular cartilage lesions at the time of anterior cruciate ligament (ACL) reconstruction were randomized to microfracture, debridement/abrasion, or osteochondral allograft transplantation (OATs), no significant difference in International Knee Documentation Committee (IKDC) scores were observed between the microfracture and debridement/abrasion groups at a mean of 3 years of follow-up.[156] In contrast, microfracture and debridement/abrasion patients demonstrated worse scores than a control group of patients without articular cartilage injury at the time of ACL reconstruction or those undergoing OATs. Multiple, prospective randomized trials in the knee have also demonstrated the inferiority of microfracture outcomes as compared to more advanced techniques such as matrix-induced autologous chondrocyte implantation (MACI)[26, 355] and OATs.[157, 158]

Overall, our findings contribute to a previous gap in the available literature and support that patients undergoing debridement/abrasion of high-grade unipolar acetabular cartilage lesions demonstrate similar patient reported outcome scores and revision rates compared to patients undergoing microfracture. These outcomes support the consideration of preferential debridement/abrasion at the discretion of the treating surgeon in order to optimize recovery while maintaining established positive outcomes following hip arthroscopy.

Knee Preservation

In evaluating modern techniques of knee preservation, we have found that meniscus repair is an area in which large advances have been made and can be newly justified and performed with modern techniques. Particular areas in which repair methods are evolving include the recent recognition and interest in meniscus root tears as well as the repair of radial tears which were often previously treated with benign neglect or resection.

Meniscus root tears were first described in 1991 by Pagnani et al.[316], and are defined as either radial tears located within 1 cm of the meniscal attachment or a bony/soft tissue root avulsion.[314] The prevalence of posterior root tears identified during knee arthroscopy has been reported to be 7-9% overall, with roughly 2/3^{rds} located medially and 1/3rd located laterally.[233, 266] Interest in these tears has continued to grow, with root injuries being increasingly recognized as a cause of early and rapid knee osteoarthritis.[288, 314, 315] In 2008, Allaire et al. demonstrated that avulsion of the medial meniscus posterior horn is biomechanically equivalent to a complete meniscectomy, with resultant abnormally high peak tibiofemoral contact pressures and decreased contact areas.[8] Subsequently, other studies have associated root tear associated meniscus extrusion with degenerative cartilage damage, particularly in the setting of increased tibiofemoral stresses during axial loading.[3, 91, 130, 173, 218, 288, 385]

The role of root repair over meniscectomy, when technically possible, is increasingly supported by available literature. Chung et al. compared 37 root repairs to 20 partial meniscectomies at a minimum of 5 years of follow-up and observed superior objective knee function scores in the repair group.[91] Furthermore, 35% of the partial meniscectomy group underwent conversion to total knee arthroplasty as compared to 0% of the repair group. These findings were mirrored by Krych et al., who demonstrated that patients undergoing partial meniscectomy for symptomatic medial meniscus posterior root tears demonstrated no substantial benefit in patient reported outcome scores and furthermore, 52% of meniscectomy patients progressed to arthroplasty at a mean of 4.5 years.[214]

In addition to providing a potential opportunity for operative intervention and joint preservation, recent studies have established the economic effectiveness of meniscus root repair. In a recent meta-analysis, meniscus repair, meniscectomy, and non-operative management were compared using a Markov cost model based meta-analysis.[130] Knee osteoarthritis rates of 53.0%, 99.3%, and 95.1% were observed at 10 years for the repair, meniscectomy, and conservative management groups, with associated 33.5%, 51.5%, and 45.5% rates of total knee arthroplasty,

respectively, highlighting the protective effect of root repair. In further cost-based analyses, meniscus repair was found to be both cost-effective as well as superior in terms of patient-experienced quality-adjusted life years (QALYs). As such, we believe that meniscus repair is not only surgically feasible, but also clinically and economically justified, therefore leading to the publication of our preferred transtibial pull-out technique, presented in *Part IV* above.

In addition to meniscus root repair, our outcomes-based research also aimed to investigate the potential utility and success of repairing radial meniscus tears, previously often treated with non-operative management or meniscectomy. In doing so, we demonstrated that arthroscopic repair of full-thickness radial tears demonstrated satisfactory outcomes, comparable to those observed in matched group of 18 bucket-handle meniscus tears. Furthermore, patients in both the radial and bucket-handle tear groups were able to recover to a Tegner activity level statistically comparable to their pre-injury baseline.

Prior studies on the outcomes of radial repairs have been scarce until quite recently. A 2016 systematic review by Moulton et al[290] found that only 6 clinical series with minimum 2-year follow-up were published on outcomes of radial tear repairs between 1980 and 2014, with a combined number of 55 patients. The review demonstrated encouraging improvements in healing rates and patient-reported outcomes based on heterogeneous studies.

The radial meniscus tear investigation presented in this thesis contributes to the literature by including a larger single-study volume of patients and employing a study design allowing for comparison of radial repairs to more extensively reported and understood bucket-handle repairs. The results presented support that repair is a viable option for radial meniscus tears, producing outcomes that are statistically similar to those seen in bucket-handle repairs which were selected as a control group due to readily available reports of positive clinical outcomes in this tear pattern[4, 133, 161, 235, 308, 354, 366, 367].

Newly Established Clinical Trials

In the process of performing bench side as well as pro and retrospective outcomes research, we believe a key and desirable intermediary is the transition of laboratory findings into clinical practice, which subsequently can be followed for short-, mid-, and long-term outcomes and efficacy. In the course of this hip and knee preservation thesis, two separate Phase I Clinical trials were co-written and co-generated, encompassing the administration of autologous, culture expanded, adipose derived mesenchymal stromal cell injections in the treatment of hip osteoarthritis (ASCLEPIOS) as well as recycled cartilage auto/alloimplantation with human autologous chondrocytes in their

pericellular matrix combined with allogeneic adipose-derived mesenchymal stem cells for the treatment and repair of knee focal cartilage defects (RECLAIM).

To date, these two trials have been written, submitted, gained FDA approval to proceed, and have enrolled greater than 25% of their respective 24 and 25 patient participants. Enrollment, outcomes collection, and evaluation remain ongoing. We believe that to see the future of hip and knee preservation, one need actively participate in the development of novel solutions to address the clinical challenges currently faced by the field. We look forward to analyzing and publishing publically the outcomes of these Phase I efforts in furthering cell-based hip and knee preservation.

Conclusions and Implications

The aims of this thesis were to 1) illustrate the critical need for hip and knee preservation, 2) provide prognostic tools for cartilage assessment to help clinical decision making, 3) optimize and expand available allografts for articular osteochondral defects, and 4) to assess the clinical efficacy of current modern interventions in hip and knee preservation and establish novel therapeutics with Phase I clinical trials in articular preservation of the hip and knee. In concluding the academic undertaking embodied in this thesis, we feel confident that we have demonstrated great patient and societal-level need for hip and knee preservation as well as expanded the clinician and surgeons' toolbox in preoperatively prognosticating the presence of hip and knee chondropathology as well as avoiding common failure mechanisms in cartilage surgery. Furthermore, we believe we have provided substantial proof-in-concept of a living donor system of expanding and improving upon osteochondral allograft tissue sourcing as well as storage. Finally, over the course of this investigation, multiple new treatment techniques and associated outcomes for hip and knee preservation have been undertaken, including the creation and successful initial enrollment of two Phase I Clinical Trials.

The implications of this body of work are substantial. Globally, hip and knee osteoarthritis affects more than 300 million patients. To date, there remains a large gap in cartilage care, where patients with early degeneration are predominantly offered symptomatic treatment together with limitations of activities and subsequently converted to arthroplasty when symptomatic management is no longer effective or sustainable. We believe the goal of cartilage care should be to restore native function and return patients to activities spanning from day to day occupations to high demand sport. By further expanding the predictive, material, and technical toolbox of orthopedic surgeons, we have enhanced the spectrum of care we offer and provide our patients and continue embody our mantra: **Restore, not Replace.**

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