Treatment of Cartilage Defects of the Knee: Expanding on the Existing Algorithm

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Objective: The purpose of this review is to survey the literature regarding factors used in determining a course of surgical treatment for symptomatic cartilage lesions of the knee to determine which factors affect treatment outcomes and should be incorporated in the treatment algorithm.

Methods: A systematic review was performed using PubMed, Cochrane Review, and SportDiscus databases for studies investigating factors affecting cartilage lesion treatment and outcomes. Inclusion criteria were clinical and basic science studies in English, on human or animal specimens that focus on factors affecting the initiation, progression, and treatment of focal knee chondral defects.

Results: Twenty-seven studies examining 1450 human (1416 in vivo; 34 cadaveric) and 90 animal subjects met inclusion criteria. Female sex and higher body mass index (BMI) significantly predicted cartilage loss rates and recovery after microfracture (MFx) and autologous matrix-induced chondrogenesis. Defect size and location significantly predicted treatment outcomes. Sizes >2 to 4 cm^2 demonstrated worse outcomes after MFx treatment. Defect size did not consistently affect autologous chondrocyte implantation or osteochondral autograft transplantation outcomes. Intra-articular lesion location was related to intralesional subchondral bone contact and MFx outcome. Corrected patellofemoral and tibiofemoral alignment improved clinical outcome when realignment procedures were done concurrently with cartilage repair.

Conclusions: Choice of the appropriate repair technique for focal knee cartilage defects is multifactorial. A treatment algorithm should consider frequently used factors such as defect size, location, knee alignment, and patient demand. However, patient sex and BMI could also be considered. Patient age was not significantly associated with clinical outcome.

Submitted for publication August 22, 2012; accepted July 29, 2013.

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The authors report no conflicts of interest.

Disclosure: David C. Flanigan is a consultant for Sanofi and Smith & Nephew.

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Key Words: cartilage lesions, treatment algorithm, defect size, defect location, knee alignment, BMI, age

(*Clin J Sport Med* 2013;0:1–10)

INTRODUCTION

Focal chondral defects or lesions are commonly seen in knee arthroscopy.[1,2] These defects vary in thickness,[3] ranging from partial to full.[4] Many chondral defects are asymptomatic and, thus, it is difficult to estimate true incidence or prevalence. In a recent systematic review, more than half of asymptomatic athletes were found to have full-thickness defects.[5] Although the natural history of lesion progression may be unclear, they may eventually cause symptoms and functional impairment.[6] If left untreated, biomechanical overload of the defect may cause further degenerative changes in adjacent tissue and intralesional subchondral bone, leading to progression to osteoarthritis.[7]

Current cartilage repair algorithms[6,8,9] aim for the optimal treatment to reduce symptoms and restore functionality. These algorithms stress the importance of lesion-specific factors such as size and intra-articular location (patellofemoral or tibiofemoral). Patient knee demand level, as well as other knee-specific co-morbidities (meniscal deficiency, mechanical malalignment, ligamentous laxity) also affect treatment choice. Patient-specific factors such as age and physical activity level are also common considerations.[9–13]

Several factors have been found to affect cartilage defect treatment outcomes, yet have not been included in most existing algorithms. For instance, the intra-articular location of the lesion, specifically the medial femoral condyle, has been shown to predict better outcomes of autologous chondrocyte implantation (ACI) and microfracture (MFx) than lateral defects.[14] Higher patient body mass index (BMI) has also been associated with worse outcomes of MFx.[15] Further, female sex has been linked to greater cartilage loss and defect progression.[16]

Despite supportive studies regarding the importance of commonly used factors in the algorithm, other evidence regarding the effects of patient, knee, and defect-specific factors on cartilage defect treatments exists. There is a need to further identify and characterize these factors and expand and refine the current treatment algorithm. We investigate the patient-related, knee-related, and defect-related factors that may influence cartilage lesion treatment and could be used as criteria in treatment selection. The study hypothesis is that patient age, BMI, and sex, defect size and location, and alignment all play a significant role in the outcome of knee

cartilage lesion treatment and could be considered in an expanded algorithm.

METHODS

A systematic review of the literature on cartilage defects was conducted using the PubMed, Cochrane Reviews, and SportDiscus databases. The search was performed April 20, 2012, and repeated April 22, to ensure the inclusion of all relevant studies. The key words used for the search included knee cartilage repair, defects, chondral lesions, treatment, algorithm, size, location, shape, mechanics, alignment, gender, sex, BMI, and ethnicity. Included studies were graded as levels I, II, III, IV, or V evidence by the Oxford Centre for Evidence-Based Medicine.[17]

The inclusion criteria were the following:

- English language
- Clinical outcome and basic science studies
- In vivo or cadaveric human or animal subjects
- Publication between 1970 and 2012
- Studies reporting treatment outcomes of partial-thickness and full-thickness chondral defects in the knee
- Studies reporting treatment outcomes of focal defects, not osteoarthritis.

Exclusion criteria included the following:

- Non-English language
- Non-knee joint
- Studies reporting treatment outcomes of osteoarthritis

The initial keyword search in 3 databases yielded a total of 7826 potentially relevant citations. Further screening by the primary author eliminated studies in joints other than the knee, non-English language studies. Figure 1 illustrates how the list was filtered through inclusion/exclusion criteria and narrowed down to 27 studies.

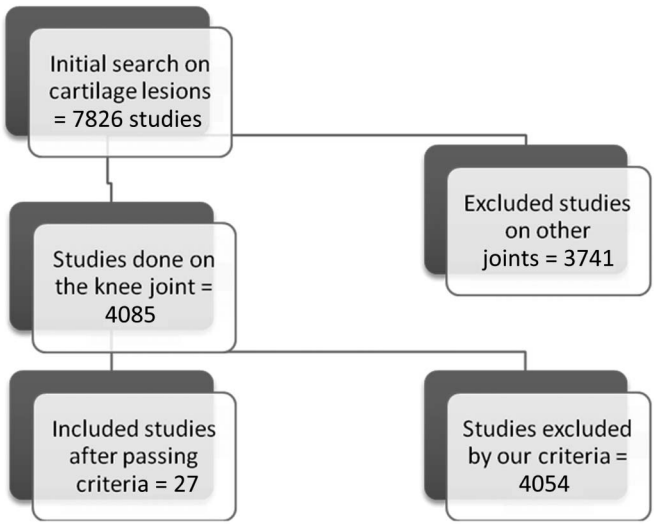

FIGURE 1. Flowchart demonstrating selection of studies for our review.

The scope of the search included studies investigating the influence of patient-related (age, sex, BMI), knee-related (tibiofemoral or patellofemoral alignment and menisco-ligamentous status), and lesion-related (surface area, depth, intra-articular location) factors on the choice of treatment of knee chondral defects. Further, studies that reported the association of such factors with tissue biomechanical properties were investigated.

Application of exclusion criteria led to final inclusion of 27 studies[14–16,18–41] for detailed analysis. The 27 studies (21 in vivo and 6 in vitro) examined a total of 1416 human subjects (in vivo), 90 animal subjects (both in vivo and in vitro), and 34 cadavers (in vitro). These included 2 randomized controlled trials (RCTs), 12 prospective cohort studies, 4 retrospective case series, 5 animal experiments, and 4 cadaveric laboratory studies.

RESULTS

Each of the 27 studies investigated the association between patient-specific, knee-specific, and defect-specific factors and various outcomes. The heterogeneity of the selected studies (in terms of study design, outcomes measured, factors studied, and patient populations) prevented performance of a meta-analysis.

Evidence Supporting Factors Currently Considered in Treatment Selection

Lesion Size

The evidence, with a variety of study designs, showed an effect of lesion size on cartilage biomechanics (Table 1). Several biomechanical and animal studies highlighted the importance of defect size and the threshold at which articular cartilage undergoes biomechanical changes.[20–24,28] An in vitro canine study showed that lesion size alters circumferential cartilage contact stress levels, which are lower in intact cartilage surface.[20] Other human cadaveric studies showed that peak stress concentration, which may be related to the stability of the cartilage adjacent to defects, was significantly greater ($P < 0.05$) around the rim of defects that were $\geq$10 mm in diameter. Defects $\leq$5 mm showed no deviation in contact pressure at the defect from the surrounding healthy tissue.[21,23,24] In a separate study, defects 6 mm in diameter did not result in degradation to cartilage that is adjacent to the defects in canine knees after 1 year of follow-up.[22] In a bovine study, lesions larger than 0.97 cm^2 showed significant subchondral bone contact[28] which may be related to defect progression.[42]

In clinical evidence consisting of prospective studies and RCTs, defect size has also been found to affect treatment choice and outcomes. A recent randomized comparative trial found that lesion size is related to the outcome of MFx but not osteochondral autograft transplantation (OAT).[26] Lesions >2 cm^2 in area demonstrated a worse International Cartilage Repair Society (ICRS) score after MFx surgery than those <2 cm^2 ($P = 0.04$). A separate randomized comparative trial[27] found that among patients who underwent MFx, significantly higher postoperative Short Form 36 (SF-36)[43] scores were observed for lesions <4 cm^2, suggesting that

TABLE 1. Outcomes and Conclusions of Studies Highlighting the Importance of Lesion Size

Study	Design	Evidence Level	Factor(s)	Treatment (s)	Outcome(s)	Results	Conclusions
Micheli et al[18]	50 human subjects in vivo prospective study	II	Lesion size	ACI	Modified Cincinnati Knee Rating System	Improvements at 36 mo after ACI ($P < 0.001$). Size of defect did not impact the results with ACI	Excellent graft survivorship using ACI irrespective of lesion size
Rose et al[19]	27 human subjects in vivo prospective study	II	Lesion size	OAT	Lysholm score	The wide range of outcome Lysholm scores did not show significant differences in: follow-up, concomitant injuries, or defect size	Defect size was not associated with differences in Lysholm score in these patients undergoing OAT
Brown et al[20]	13 dog knees in vitro experiment	V	Lesion size	—	Contact stress distribution assessed	Circumferential mean cartilage contact stress around defect rim was higher (10%-30%) than intact surface's peak local contact stress	Defect size is associated with varying levels of cartilage contact stress levels
Guettler et al [21]	8 cadaver knees in vitro experiment	V	Lesion size	—	Defect rim stress	Increasing radius of peak pressure as defect size increased from 10 to 20 mm ($P = 0.0011$)	Rim stress concentration was demonstrated for defects 10 mm and greater. This altered loading may cause degeneration of adjacent cartilage
Nelson et al[22]	16 defects in 5 dogs in vivo observational study	V	Lesion size	—	Contact pressures and histological evaluation	No degeneration of cartilage adjacent to defects. No high stress observed in this adjacent cartilage	Cartilage degeneration may not be related to elevated contact stress in defects (6-mm diameter)
Guettler et al[23]	10 cadaver knees in vitro experiment	V	Lesion size	—	Contact pressure measured	5-mm defects did not lead to significant alterations in local contact pressure	Morbidity may be minimized if defects are limited to 5 mm and smaller
Papaioannou et al[24]	8 cadaver knees in vitro experiment	V	Lesion size	—	Contact pressure assessed	Insignificant stress concentration around the rims of defects 8 mm and smaller. In defects 10 mm and greater, distribution of peak pressures followed the rim of the defect	A size threshold of 10 mm may be a useful guide to clinical decision-making
Qiu et al[25]	33 rabbit knees in vivo observational study	V	Lesion size	—	Contact pressure and histological repair scores	Repaired defects had lower contact pressure and greater indentation than the normal controls at all time ($P < 0.05$)	Presence of an advanced and irregular subchondral plate was associated with degradation of repaired articular surface
Gudas et al[26]	60 human subjects in vivo RCT	I	Lesion size	OAT, MFx	ICRS	ICRS clinical outcome in MFx was worse if the lesions were >2 cm^2 ($P = 0.04$). No association in the OAT group	Lesions size affects the outcome of MFx repair but not OAT
Knutsen et al[27]	80 human subjects in vivo RCT	I	Lesion size	MFx	SF-36	Higher SF-36 scores in MFx group associated with lesion <4 cm^2 ($P = 0.003$)	Lesion size associated with MFx outcome

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TABLE 1. (*Continued*) Outcomes and Conclusions of Studies Highlighting the Importance of Lesion Size

Study	Design	Evidence Level	Factor(s)	Treatment (s)	Outcome(s)	Results	Conclusions
Flanigan et al[28]	9 bovine knees in vitro experiment	V	Lesion size and intra-articular location	—	Subchondral bone contact	No significant contact in any lesions <0.97 cm^2. Different area thresholds of significant ($P < 0.05$) subchondral bone contact between lateral (1.61 cm^2) and medial (1.99 cm^2) condyles	Subchondral bone contact depends on defect size and intra-articular location
Karataglis et al[29]	36 human subjects in vivo prospective study	II	Lesion size or location (patellofemoral vs femoral condyles)	OAT	Tegner Activity Scale, Activities of Daily Living Scale of the Knee Outcome Survey	No correlation between the size or site of the chondral lesion and the functional outcome	Size and location of lesion were found to be not associated with outcomes of OAT

Evidence level is determined based on the Oxford Centre for Evidence-Based Medicine grading system.

MFx may be better suited for smaller lesions. Despite the size-specific outcome association with MFx, lesion size was not found to be a predictor of Lysholm scores[19] or functional outcome[29] in OAT. Additionally, outcomes of ACI measured by the Cincinnati Knee Rating System were also not affected by defect size.[18] These findings suggest that larger lesions could be treated with OAT, although limited by donor tissue availability, or ACI, whereas smaller lesions (<4 cm^2) could be effectively treated by any technique.

Defect Location

Intra-articular defect location was found to affect cartilage biomechanics in animal studies and defect progression in clinical studies, mostly prospective in design (Table 2). Defects on the medial femoral condyle showed a tendency to progress to larger sizes and involve subchondral bone changes.[33] In a prospective study,[30] lesions located in the weight-bearing central region of the medial compartment had the highest progression in the rate of cartilage loss compared with other regions of the medial compartment and the lateral compartment. Differences in intralesional subchondral bone contact were also observed between the medial and lateral compartments.[28] In this study, the intralesional subchondral bone contact threshold differed significantly ($P < 0.05$) based on defect location (medial condyles = 1.99 cm^2 or lateral condyles = 1.61 cm^2), stressing the importance of defect location on cartilage biomechanics.

Clinical results of certain cartilage treatments are also influenced by location. In a cohort study with 55 subjects on MFx and ACI treatments, defects in the medial femoral condyle showed better improvements in Knee Injury and Osteoarthritis Outcome Score (KOOS) than lesions in the lateral femoral condyles ($P < 0.05$).[14] Outcome measures after MFx (Cincinnati score, ICRS, and MRI assessments) were statistically better for lesions that were on the femoral condyles versus those on tibial, trochlear, or patellar regions.[32] In contrast, ACI treatment showed successful outcomes in trochlear lesions.[31] However, OAT was shown to be unaffected by lesion location,[29] perhaps due to the viability of the intact transplanted cartilage.

Knee Alignment

Knee alignment can influence defect loading and clinical outcomes of cartilage restoration. However, the evidence summarizing these findings is not of the highest quality (Table 3). Two of the studies were case series,[34,35] one was a clinical prospective study[36] but with a small sample of 14 subjects and another was a cadaveric experiment.[37] In the cadaveric biomechanical study on unloading isolated cartilage defects through high tibial osteotomy, medial contact pressure and area both decreased as tibiofemoral alignment moved from varus to valgus alignment ($P < 0.001$).[37] Furthermore, between 6 and 10 degrees of anatomical-axis valgus alignment, there was complete unloading of the medial compartment. This study, along with another clinical study,[35] supports the use of corrective tibial osteotomy for medial lesions in the situation of varus malalignment. Patellofemoral alignment can also play a significant role in patellofemoral compartment loading and clinical outcomes. Pascual-Garrido et al[34] found that outcomes were improved by combining anteromedialization with ACI compared with ACI alone. Similarly, improved outcomes were found in patients who had corrective distal realignment with ACI for combined patellar cartilage lesions and patellar malalignment.[36] Therefore, improving alignment and unloading the articular cartilage in the patellofemoral joint can affect the results of restorative procedures.

Evidence for the Consideration of New Factors in Treatment Selection

Current literature suggests that patient sex and BMI may play a role in cartilage injury and repair outcomes. The role of patient age in treatment outcomes is inconclusive.

Patient Sex

There are sex differences in cartilage loss in the knee that may influence outcomes according to 2 clinical prospective

TABLE 2. Outcomes and Conclusions of Studies Highlighting the Importance of Lesion Location

Study	Design	Evidence Level	Factor(s)	Treatment (s)	Outcome(s)	Results	Conclusions
de Windt et al[14]	55 human subjects in vivo prospective study	II	Lesion location (medial vs lateral)	ACI, MFx	KOOS	Clinical outcome was better for medial than lateral lesions ($P < 0.05$)	Defect location is related to clinical outcome of ACI, MFx
Biswal et al[30]	43 human subjects in vivo prospective study	II	Lesion location	—	Cartilage loss	Progression rate of lesions in the medial compartment: Central (28%), anterior (19%), posterior (17%). Lesions in the lateral compartment (average progression rate 15%)	Lesion location affects cartilage loss rates
Mandelbaum et al[31]	40 human subjects in vivo case series	IV	Lesion location (trochlear)	ACI	Cincinnati Knee Rating System	Significant improvement in mean overall condition, pain, and swelling scores	ACI improves function and reduces symptoms in full-thickness trochlear lesions
Kreuz et al[32]	85 human subjects in vivo prospective study	II	Lesion location	MFx	ICRS, Cincinnati scores, MRI parameters	Lesions in the femoral condyles had the highest improvements in Cincinnati score ($P < 0.0001$) and ICRS ($P < 0.0001$). MRI showed best defect filling in femoral condyle lesions ($P < 0.02$)	MFx is best in femoral condyle lesions vs tibia, trochlea, and retropatellar regions
Jackson et al[33]	30 goat knees in vivo experiment	V	Lesion location	—	Histological assessment, MRI	Weight-bearing areas of cartilage show progression of defects and subchondral bone involvment	Lesion location with respect to weight bearing is related to lesion progression
Flanigan et al[28]	9 bovine knees in vitro experiment	V	Lesion size and intra-articular location	—	Subchondral bone contact	No significant contact in any lesions <0.97 cm^2. Different area thresholds of significant ($P < 0.05$) subchondral bone contact between lateral (1.61 cm^2) and medial (1.99 cm^2) condyles	Subchondral bone contact depends on defect size and intra-articular location
Karataglis et al[29]	36 human subjects in vivo prospective study	II	Lesion size or location (patellofemoral vs femoral condyles)	OAT	Tegner Activity Scale, Activities of Daily Living Scale of the Knee Outcome Survey	No correlation between the size or site of the chondral lesion and the functional outcome	Size and location of lesion were found to be not associated with outcomes of OAT

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studies (Table 4).[16,41] Women had higher MRI-assessed annual tibial cartilage loss (1.6% vs 0.4%, $P = 0.05$) and higher patellar cartilage loss (2.3% vs 0.8%, $P = 0.02$) than men.[16] Moreover, women's risk of progression of tibiofemoral cartilage defects was higher than men ($P = 0.03$). This study provides compelling evidence, assessed prospectively, in a large sample of 271 patients. In the latter study, which had much fewer subjects (27), autologous matrix-induced chondrogenesis yielded higher ICRS scores in males than in females.[41] These findings show a difference in the pattern of cartilage loss between men and women and that a difference in treatment outcome may exist between both sexes in certain treatments.

Patient Body Mass Index

Body mass index appeared to affect the outcome of defect repair as well as the incidence of defects in 2 clinical prospective studies (Table 5). Elevated baseline BMI, weight, waist circumference, and fat mass were found to increase the risk of the presence of patellar cartilage defects ($P < 0.03$) in a study of 297 patients.[40] These findings, in a sample with this magnitude, are particularly important in highlighting an association between BMI and the pathology of cartilage defects. In the only clinical study that examined BMI in relation to cartilage treatment outcomes in 48 subjects,[15] individuals with BMI >30 kg/m^2 showed lower outcome scores than those whose

TABLE 3. Outcomes and Conclusions of Studies Highlighting the Importance of Mechanical Alignment Factors

Study	Design	Evidence Level	Factor(s)	Treatment(s)	Outcome(s)	Results	Conclusions
Pascual-Garrido et al[34]	62 human subjects in vivo case series	IV	Mechanical alignment	ACI, anteromedialization	Lysholm, IKDC, KOOS, Tegner, Cincinnati	Higher outcome scores for patients with ACI and AMZ vs ACI only	Anteromedialization (realignment) with ACIs improves outcomes vs ACI alone
Parker et al[35]	10 human subjects in vivo case series	IV	Mechanical alignment, intra-articular location	HTO	MRI assessment of cartilage content	HTO was associated with lower cartilage degeneration in the medial compartment compared with the lateral	Improved mechanical environment through HTO indicates the potential to articular cartilage recovery in the medial compartment
Gigante et al[36]	14 human subjects in vivo prospective study	II	Mechanical alignment	ACI, distal realignment	Kujala, Lysholm, Tegner, and Modified Cincinnati scores	Improvement in Kujala, Lysholm, Tegner, and Modified Cincinnati scores. All $P < 0.05$	Improvement with distal realignment and ACI concomitantly in patients with patellar cartilage lesions and patellar malalignment
Mina et al[37]	8 cadaver knees in vitro experiment	V	Mechanical alignment	—	Medial contact pressure and area	A shift in tibiofemoral alignment from varus to valgus caused a decrease in both medial contact pressure ($P < 0.001$) and area ($P < 0.001$)	Alignment between 6 and 10 degrees of valgus favors cartilage repair

Evidence level is determined based on the Oxford Centre for Evidence-Based Medicine grading system.
AMZ, anteromedialization; HTO, high tibial osteotomy; IKDC, International Knee Documentation Committee score.

BMI was <30 kg/m^2. These findings highlight the importance of BMI consideration in the treatment of cartilage lesions.

Patient Age

There was conflicting evidence on the association between patient age and outcomes of different treatments for focal cartilage defects. The evidence was mostly in prospective cohort studies with adequate samples in addition to a RCT and a case series study (Table 6). In some studies, younger patients, especially <30 years of age, showed higher postoperative improvements in KOOS,[14] SF-36,[27] Lysholm,[38] Hospital for Special Surgery, and ICRS scores[26] than older patients regardless of treatment (ACI, MFx, or OAT). However, conflicting findings showed that age does not significantly predict outcomes with ACI[39] or OAT.[29]

DISCUSSION

We hypothesized that patient age, BMI, and sex, defect size and location, and knee mechanical alignment are

TABLE 4. Outcomes and Conclusions of Studies Examining Patient Sex

Study	Design	Evidence Level	Factor (s)	Treatment (s)	Outcome(s)	Results	Conclusions
Hanna et al[16]	271 human subjects in vivo prospective study	II	Sex	—	MRI-assessed cartilage loss, risk for progression of defects	Women have higher tibial cartilage loss than men ($P = 0.05$). Risk of progression of tibiofemoral defects for women vs men (OR 3.0; $P = 0.03$). Higher patellar cartilage loss for women vs men (2.3% vs 0.8%) ($P = 0.02$)	Women have higher cartilage loss rates and risk for progression of cartilage defects
Gille et al[41]	27 human subjects in vivo prospective study	II	Sex	AMIC	Meyer, Tegner, Lysholm, ICRS, Cincinnati scores	Males showed significantly higher values in the ICRS score compared with their female counterparts	AMIC recovery was better for males

Evidence level is determined based on the Oxford Centre for Evidence-Based Medicine grading system.
AMIC, autologous matrix-induced chondrogenesis.

TABLE 5. Outcomes and Conclusions of Studies Examining Patient BMI

Study	Design	Evidence Level	Factor(s)	Treatment (s)	Outcome(s)	Results	Conclusions
Mithoefer et al[15]	48 human subjects in vivo prospective study	II	BMI (<30 or >30 kg/m^2)	MFx	IKDC, SF-36 activities of daily living score	Lower BMI correlated with higher scores for the activities of daily living and SF-36. Worst results for patients with a BMI of >30 kg/m^2	Best short-term results of MFx are observed in patients with low BMI
Teichtahl et al[40]	297 human subjects in vivo prospective study	II	BMI	—	MRI-assessed cartilage volume and defects	Higher BMI was associated with risk of the presence of patellar cartilage defects ($P < 0.03$)	Elevated BMI affects cartilage degeneration and defect incidence

Evidence level is determined based on the Oxford Centre for Evidence-Based Medicine grading system.
IKDC, International Knee Documentation Committee score.

associated with cartilage lesion treatment and should be considered in an expanded algorithm for the treatment of cartilage defects. Through this systematic review, there was evidence that each of these factors may be associated with treatment choice and outcomes of cartilage defects; however, not all of the evidence was consistent. Current treatment algorithms discussed in the literature[6,8,9] do not address patient age, sex, BMI, or intra-articular defect location (medial vs lateral femoral condyle) as parameters affecting treatment choice. Our results suggest that some of these parameters warrant consideration in the treatment algorithm.

Defect size affected the outcome for certain cartilage techniques, but not others. It can be inferred from evidence based on RCTs[26,27] that MFx treatment is not well suited for lesions larger than 2–4 cm^2. Autologous chondrocyte implantation, however, seems to give satisfactory outcomes even in larger lesions.[44–46] This provides good support for the current algorithm and its use of a 2 to 3 cm^2 guideline for treatment selection. The range in size may relate to differences in size and shape of the condyles.[28] A smaller threshold may be appropriate for a more petite person or potentially the lateral femoral condyle. The inherent differences in the shape, size

TABLE 6. Outcomes and Conclusions of Studies Highlighting the Importance of Patient Age

Study	Design	Evidence Level	Factor(s)	Treatment (s)	Outcome(s)	Results	Conclusions
de Windt et al[14]	55 human subjects in vivo prospective study	II	Age	ACI, MFx	KOOS	KOOS improvement was better for patients <30 years compared with older patients ($P < 0.05$)	Age influences clinical outcome of ACI, MFx treatment of lesions
Knutsen et al[27]	80 human subjects in vivo RCT	I	Age	ACI, MFx	SF-36	Subjects <30 years old show better SF-36 scores	Patient age is associated with better outcomes for MFx and ACI
Karataglis et al[29]	36 human subjects in vivo prospective study	II	Age	OAT	Tegner activity scale, Activities of Daily Living Scale of the Knee Outcome Survey	No correlation between patient age at operation and the functional outcome	Age is not a significant predictor of OAT outcomes
McNickle et al[38]	137 human subjects in vivo case series	IV	Age	ACI	Lysholm	Age ($P < 0.021$) is independent predictor of Lysholm score	ACI is associated with patient age
Niemeyer et al[39]	74 human subjects in vivo prospective study	II	Age (mean, 47.8 vs 31)	ACI	IKDC, Lysholm	No statistical difference in outcome IKDC or Lysholm scores between two groups with mean ages 47.8 and 31	ACI treatment outcomes may not be associated with patient age

Evidence level is determined based on the Oxford Centre for Evidence-Based Medicine grading system.
IKDC, International Knee Documentation Committee score.

and articulating condyles likely create microenvironments where cartilage defects behave differently. Clinically, outcome measures have not isolated specific condyles to support biomechanical data to this point.

Defect location not only influences the biomechanics of the defect but also influences clinical outcomes. Lateral and medial femoral condyles likely behave differently based on both biomechanical and clinical studies.[14,28] This is because of the different geometry of the condyles and the articulating surface of the corresponding meniscus and tibial plateau. Furthermore, outcomes of certain restorative techniques are influenced by location. Microfracture seemed to be better at treating lesions in the femoral condyles than trochlear, tibial, or patellar lesions. This is secondary to the less robust repair tissue, composed primarily of fibrocartilage.[26,47–49] In contrast, OAT and ACI outcomes do not seem to be influenced greatly by lesion location. These guidelines could be incorporated in the treatment algorithm, which currently oversimplifies the construct of lesion location to 2 groups: patellofemoral and femoral condyles.

Mechanical alignment issues are important in treatment of both tibiofemoral and patellofemoral articulations. The evidence shows that malalignment of the knee (tibiofemoral or patellofemoral) should be corrected via unloading osteotomy along with repair of cartilage defects to ensure better treatment outcomes. This backs up the claims in the existing algorithm that concomitant surgery may be needed along with cartilage repair to ensure the proper knee alignment that would favor defect repair.

The evidence on the role of patient age in the outcome of cartilage treatments was inconclusive, despite the presence of multiple studies with prospective designs. It seemed that in general, those younger than 30 years old had more favorable outcomes than those older (in both MFx and ACI). This is supported by current systematic review evidence.[44] Although other comparisons of age show no difference in outcomes after ACI or OAT, these studies lack the methodological strength of the studies showing an effect of age, which have larger samples and include prospective and randomized trials. It is likely that age affects all procedures of the knee, reflecting the degenerative process and the declining healing potential that progress with age. However, it is possible that the influence of age may not have as much of an effect on OAT and ACI because of the improved mechanical properties of the repair tissue.

Patient sex and BMI both appeared to be associated with cartilage breakdown and treatment outcome, which may have important clinical implications. However, although compelling due to prospective design and reasonably large samples, the evidence on the effect of these factors on treatments is limited to 2 studies for either factor. Although sex is not extensively studied in association with treatment outcomes, the existing studies show that women have shown higher cartilage loss rates and risk of progression of cartilage defects than men.[16,50–52] The sex effect on cartilage warrants further investigation into what cartilage structural or biomechanical properties are behind this finding and how they affect outcomes. With obesity becoming an epidemic in both Western and non-Western societies, the understanding of how BMI affects specific cartilage treatment is paramount. Further research is needed in both these areas to understand how to maximize treatment alternatives based on sex and BMI.

Although the discussed evidence points to the importance of including more factors in the treatment algorithm, a clear set of guidelines in treatment selection based on these factors must be established. The evidence only gives a general logic of how these other factors (sex, BMI, defect intra-articular location) may be used as guidelines. These findings merely suggest the importance of considering these factors in an expanded treatment algorithm, but stronger evidence with more clinical prospective studies is needed to know which treatment is best for each set of conditions.

Limitations

The quality of the evidence summarized in this review is an important limitation to the findings. Although some of the evidence is based on RCTs (level I evidence) and prospective cohort studies (level II), there are also lower-level evidence designs included (case series, animal, and cadaver experiments). Moreover, the populations studied are heterogeneous, and the study outcomes are measured through various methods, limiting our ability to compare results and extrapolate data to general populations. Some of the outcome measures used in the studies may also face validity criticism. The only validated scores for treatment of knee chondral injury are KOOS, IKDC, and Lysholm scores.[53,54] Cincinnati and Tegner activity scores are validated for other procedures but not cartilage treatment.[55–57] In the included and reviewed studies, follow-up duration was highly variable, making it difficult to compare findings. Finally, some of the studies scrutinized do not discuss the direct effect of many or all of the specific factors of interest on cartilage lesion treatment. More research is needed to address the direct relationships between treatment outcomes and the patient-specific, knee-specific, and defect-specific factors in this systematic review.

CONCLUSIONS

Choice of the appropriate repair or restoration technique for focal cartilage defects in the knee is multifactorial. A treatment algorithm should consider already commonly used factors such as defect size, location, knee alignment, and patient demand. However, patient sex and BMI should also be considered in this algorithm. Patient age was not significantly associated with clinical outcome.

REFERENCES

1. Widuchowski W, Widuchowski J, Trzaska T. Articular cartilage defects: study of 25,124 knee arthroscopies. *Knee*. 2007;14:177–182.
2. Hjelle K, Solheim E, Strand T, et al. Articular cartilage defects in 1,000 knee arthroscopies. *Arthroscopy*. 2002;18:730–734.
3. Alford JW, Cole BJ. Cartilage restoration, part 1: basic science, historical perspective, patient evaluation, and treatment options. *Am J Sports Med.* 2005;33:295–306.
4. Browne JE, Branch TP. Surgical alternatives for treatment of articular cartilage lesions. *J Am Acad Orthop Surg.* 2000;8:180–189.
5. Flanigan DC, Harris JD, Trinh TQ, et al. Prevalence of chondral defects in athletes' knees: a systematic review. *Med Sci Sports Exerc.* 2010;42:1795–1801.

6. Minas T. The role of cartilage repair techniques, including chondrocyte transplantation, in focal chondral knee damage. *Instr Course Lect.* 1999; 48:629–643.
7. Minas T, Nehrer S. Current concepts in the treatment of articular cartilage defects. *Orthopedics*. 1997;20:525–538.
8. Alford JW, Cole BJ. Cartilage restoration, part 2: techniques, outcomes, and future directions. *Am J Sports Med.* 2005;33:443–460.
9. Gomoll AH, Farr J, Gillogly SD, et al. Surgical management of articular cartilage defects of the knee. *Instr Course Lect.* 2011;60:461–483.
10. Salzmann GM, Niemeyer P, Steinwachs M, et al. Cartilage repair approach and treatment characteristics across the knee joint: a European survey. *Arch Orthop Trauma Surg.* 2011;131:283–291.
11. Cain EL, Clancy WG. Treatment algorithm for osteochondral injuries of the knee. *Clin Sports Med.* 2001;20:321–342.
12. Farr J, Cole B, Dhawan A, et al. Clinical cartilage restoration: evolution and overview. *Clin Orthop Relat Res.* 2011;469:2696–2705.
13. Bekkers JE, Inklaar M, Saris DB. Treatment selection in articular cartilage lesions of the knee: a systematic review. *Am J Sports Med.* 2009;37 (suppl 1):148S–155S.
14. de Windt TS, Bekkers JE, Creemers LB, et al. Patient profiling in cartilage regeneration: prognostic factors determining success of treatment for cartilage defects. *Am J Sports Med.* 2009;37(suppl 1):58S–62S.
15. Mithoefer K, Williams RJ 3rd, Warren RF, et al. The microfracture technique for the treatment of articular cartilage lesions in the knee. A prospective cohort study. *J Bone Joint Surg Am.* 2005;87:1911–1920.
16. Hanna FS, Teichtahl AJ, Wluka AE, et al. Women have increased rates of cartilage loss and progression of cartilage defects at the knee than men: a gender study of adults without clinical knee osteoarthritis. *Menopause*. 2009;16:666–670.
17. Obremskey WT, Pappas N, Attallah-Wasif E, et al. Level of evidence in orthopaedic journals. *J Bone Joint Surg Am.* 2005;87:2632–2638.
18. Micheli LJ, Browne JE, Erggelet C, et al. Autologous chondrocyte implantation of the knee: multicenter experience and minimum 3-year follow-up. *Clin J Sport Med.* 2001;11:223–228.
19. Rose T, Craatz S, Hepp P, et al. The autologous osteochondral transplantation of the knee: clinical results, radiographic findings and histological aspects. *Arch Orthop Trauma Surg.* 2005;125:628–637.
20. Brown TD, Pope DF, Hale JE, et al. Effects of osteochondral defect size on cartilage contact stress. *J Orthop Res.* 1991;9:559–567.
21. Guettler JH, Demetropoulos CK, Yang KH, et al. Osteochondral defects in the human knee: influence of defect size on cartilage rim stress and load redistribution to surrounding cartilage. *Am J Sports Med.* 2004;32: 1451–1458.
22. Nelson BH, Anderson DD, Brand RA, et al. Effect of osteochondral defects on articular cartilage. Contact pressures studied in dog knees. *Acta Orthop Scand.* 1988;59:574–579.
23. Guettler JH, Demetropoulos CK, Yang KH, et al. Dynamic evaluation of contact pressure and the effects of graft harvest with subsequent lateral release at osteochondral donor sites in the knee. *Arthroscopy.* 2005;21: 715–720.
24. Papaioannou G, Demetropoulos CK, King YH. Predicting the effects of knee focal articular surface injury with a patient-specific finite element model. *Knee*. 2010;17:61–68.
25. Qiu YS, Shahgaldi BF, Revell WJ, et al. Observations of subchondral plate advancement during osteochondral repair: a histomorphometric and mechanical study in the rabbit femoral condyle. *Osteoarthritis Cartilage.* 2003;11:810–820.
26. Gudas R, Kalesinskas RJ, Kimtys V, et al. A prospective randomized clinical study of mosaic osteochondral autologous transplantation versus microfracture for the treatment of osteochondral defects in the knee joint in young athletes. *Arthroscopy*. 2005;21:1066–7105.
27. Knutsen G, Engebretsen L, Ludvigsen TC, et al. Autologous chondrocyte implantation compared with microfracture in the knee. A randomized trial. *J Bone Joint Surg Am.* 2004;86-A:455–464.
28. Flanigan DC, Harris JD, Brockmeier PM, et al. The effects of lesion size and location on subchondral bone contact in experimental knee articular cartilage defects in a bovine model. *Arthroscopy*. 2010;26: 1655–1661.
29. Karataglis D, Green MA, Learmonth DJ. Autologous osteochondral transplantation for the treatment of chondral defects of the knee. *Knee*. 2006;13:32–35.
30. Biswal S, Hastie T, Andriacchi TP, et al. Risk factors for progressive cartilage loss in the knee: a longitudinal magnetic resonance imaging study in forty-three patients. *Arthritis Rheum.* 2002;46:2884–2892.
31. Mandelbaum B, Browne JE, Fu F, et al. Treatment outcomes of autologous chondrocyte implantation for full-thickness articular cartilage defects of the trochlea. *Am J Sports Med.* 2007;35:915–921.
32. Kreuz PC, Steinwachs MR, Erggelet C, et al. Results after microfracture of full-thickness chondral defects in different compartments in the knee. *Osteoarthritis Cartilage.* 2006;14:1119–1125.
33. Jackson DW, Lalor PA, Aberman HM, et al. Spontaneous repair of full-thickness defects of articular cartilage in a goat model. A preliminary study. *J Bone Joint Surg Am.* 2001;83-A:53–64.
34. Pascual-Garrido C, Slabaugh MA, L'Heureux DR, et al. Recommendations and treatment outcomes for patellofemoral articular cartilage defects with autologous chondrocyte implantation: prospective evaluation at average 4-year follow-up. *Am J Sports Med.* 2009;37(suppl 1): 33S–41S.
35. Parker DA, Beatty KT, Giuffre B, et al. Articular cartilage changes in patients with osteoarthritis after osteotomy. *Am J Sports Med.* 2011;39: 1039–1045.
36. Gigante A, Enea D, Greco F, et al. Distal realignment and patellar autologous chondrocyte implantation: mid-term results in a selected population. *Knee Surg Sports Traumatol Arthrosc.* 2009;17:2–10.
37. Mina C, Garrett WE Jr, Pietrobon R, et al. High tibial osteotomy for unloading osteochondral defects in the medial compartment of the knee. *Am J Sports Med.* 2008;36:949–955.
38. McNickle AG, L'Heureux DR, Yanke AB, et al. Outcomes of autologous chondrocyte implantation in a diverse patient population. *Am J Sports Med.* 2009;37:1344–1350.
39. Niemeyer P, Kostler W, Salzmann GM, et al. Autologous chondrocyte implantation for treatment of focal cartilage defects in patients age 40 years and older: a matched-pair analysis with 2-year follow-up. *Am J Sports Med.* 2010;38:2410–2416.
40. Teichtahl AJ, Wang Y, Wluka AE, et al. The longitudinal relationship between body composition and patella cartilage in healthy adults. *Obesity (Silver Spring)*. 2008;16:421–427.
41. Gille J, Schuseil E, Wimmer J, et al. Mid-term results of Autologous Matrix-Induced Chondrogenesis for treatment of focal cartilage defects in the knee. *Knee Surg Sports Traumatol Arthrosc.* 2010;18:1456–1464.
42. Burr DB, Radin EL. Microfractures and microcracks in subchondral bone: are they relevant to osteoarthrosis? *Rheum Dis Clin North Am.* 2003;29:675–685.
43. Patel AA, Donegan D, Albert T. The 36-item short form. *J Am Acad Orthop Surg.* 2007;15:126–134.
44. Harris JD, Brophy RH, Siston RA, et al. Treatment of chondral defects in the athlete's knee. *Arthroscopy*. 2010;26:841–852.
45. Trinh TQ, Harris JD, Flanigan DC. Surgical management of juvenile osteochondritis dissecans of the knee [published online ahead of print]. *Knee Surg Sports Traumatol Arthrosc.* 2012;20:2419–29.
46. Harris JD, Siston RA, Pan X, et al. Autologous chondrocyte implantation: a systematic review. *J Bone Joint Surg Am.* 2010;92:2220–2233.
47. Krych AJ, Harnly HW, Rodeo SA, et al. Activity levels are higher after osteochondral autograft transfer mosaicplasty than after microfracture for articular cartilage defects of the knee: a retrospective comparative study. *J Bone Joint Surg Am.* 2012;94:971–978.
48. Nehrer S, Spector M, Minas T. Histologic analysis of tissue after failed cartilage repair procedures. *Clin Orthop Relat Res.* 1999:149–162.
49. Oneto JM, Ellermann J, LaPrade RF. Longitudinal evaluation of cartilage repair tissue after microfracture using T2-mapping: a case report with arthroscopic and MRI correlation. *Knee Surg Sports Traumatol Arthrosc.* 2010;18:1545–1550.
50. Brennan SL, Cicuttini FM, Shortreed S, et al. Women lose patella cartilage at a faster rate than men: a 4.5-year cohort study of subjects with knee OA. *Maturitas*. 2010;67:270–274.
51. Karsdal MA, Byrjalsen I, Bay-Jensen AC, et al. Biochemical markers identify influences on bone and cartilage degradation in osteoarthritis–the effect of sex, Kellgren-Lawrence (KL) score, body mass index (BMI), oral salmon calcitonin (sCT) treatment and diurnal variation. *BMC Musculoskelet Disord.* 2010;11:125.
52. Cicuttini F, Wluka A, Wang Y, et al. The determinants of change in patella cartilage volume in osteoarthritic knees. *J Rheumatol.* 2002;29: 2615–2619.

53. Bekkers JE, de Windt TS, Raijmakers NJ, et al. Validation of the Knee Injury and Osteoarthritis Outcome Score (KOOS) for the treatment of focal cartilage lesions. *Osteoarthritis Cartilage.* 2009;17: 1434–1439.
54. Wang D, Jones MH, Khair MM, et al. Patient-reported outcome measures for the knee. *J Knee Surg.* 2010;23:137–151.
55. Barber-Westin SD, Noyes FR, McCloskey JW. Rigorous statistical reliability, validity, and responsiveness testing of the Cincinnati knee rating system in 350 subjects with uninjured, injured, or anterior cruciate ligament-reconstructed knees. *Am J Sports Med.* 1999;27: 402–416.
56. Briggs KK, Kocher MS, Rodkey WG, et al. Reliability, validity, and responsiveness of the Lysholm knee score and Tegner activity scale for patients with meniscal injury of the knee. *J Bone Joint Surg Am.* 2006;88:698–705.
57. Crawford K, Briggs KK, Rodkey WG, et al. Reliability, validity, and responsiveness of the IKDC score for meniscus injuries of the knee. *Arthroscopy*. 2007;23:839–844.