Current Concepts Review

Restoration of Articular Cartilage

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- Novel (i.e., quantitative and semiquantitative) cartilage imaging techniques can evaluate cartilage composition to augment information obtained from traditional magnetic resonance imaging sequences that detail morphology.
- A well-defined role for drugs leading to chondroprotection has not yet been determined.
- Shortcomings of bone marrow stimulation include limited production of hyaline repair tissue, unpredictable repair cartilage volume, and a negative impact on later cellular transplantation if required.
- The role of biological augments, such as cellular concentrates or platelet-rich plasma, remains undefined. When their use is reported in the literature, it is important that their process of production and characterization be detailed.
- Rehabilitation programs, incorporating controlled exercise and progressive partial weight-bearing, are an important part of cartilage repair surgery and should be detailed in reports on operative techniques applied.
- Malalignment, meniscal injury, and ligament deficiency should be corrected in a staged or concomitant fashion to reduce the overall likelihood of mechanical failure in cartilage repair surgery.

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Articular cartilage has limited intrinsic capacity for repair[1,2]. For symptomatic defects refractory to nonoperative management, operative intervention can provide both pain relief and functional improvement[3,4]. However, practicing evidence-based surgery for the management of chondral defects can be difficult. This is in part due to the heterogeneity in conditions and patients included in studies in the literature as well as regional variation in treatment options approved for use in the clinical setting. Regardless of the intervention proposed, a comprehensive understanding of a patient's specific goals, in addition to a discussion of evidence-based management options, is required in all cases[5]. Furthermore, in addition to an understanding of the specifics of individual procedures or techniques described for replacing lost articular cartilage, an appreciation of cartilage imaging, the management of concomitant joint injury, and appropriate rehabilitation is an important part of this process[6,7].

Cartilage Imaging

Magnetic resonance imaging (MRI) offers a powerful method of noninvasive evaluation of chondral lesions and repair procedures[8,9]. While the use of quantitative computed tomography (CT) imaging of cartilage for evaluation of glycosaminoglycan (reflective of cartilage matrix and morphology) may have a role, given its wide availability, ionizing radiation is best avoided where possible. Standard MRI using a cartilage-sensitive sequence

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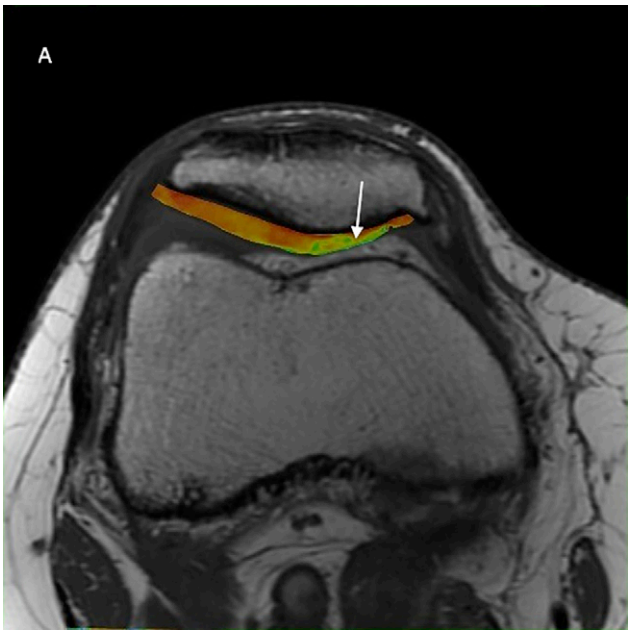

Fig. 1-A

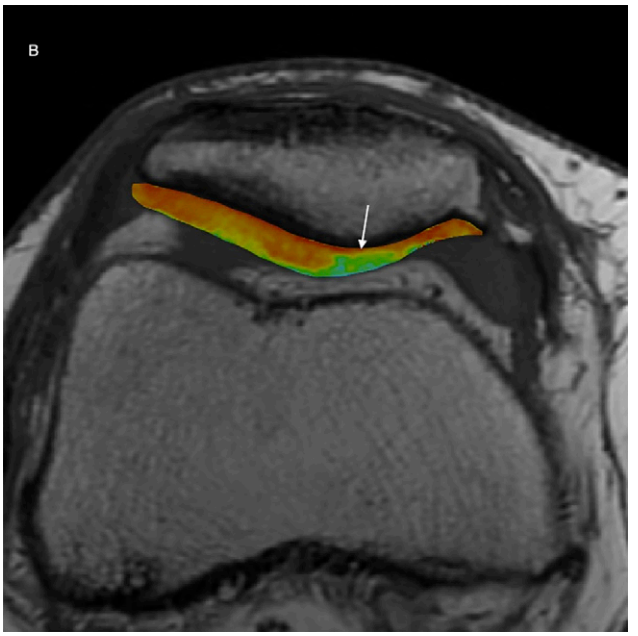

Fig. 1-B

Figs. 1-A and 1-B Magnetic resonance images of T2 mapping. **Fig. 1-A** Preoperative T2 map in a patient with a chondral defect (arrow) on the medial facet of the patella. **Fig. 1-B** Twelve months after implantation of juvenile-derived minced articular cartilage allograft, the area of the implant (arrow) demonstrates partial T2 stratification of the tissue that is indicative of incomplete tissue maturation. Although immature, there is flush integration to the native articular cartilage and evidence of good defect filling.

(e.g., spoiled gradient-recalled echo or fast spin echo) can show cartilage fissuring, delamination, and focal loss as verified by arthroscopy[9,10]. Quantitative and semiquantitative cartilage imaging techniques are now available and include dGEMRIC (delayed gadolinium-enhanced MRI of cartilage), sodium-23 imaging, T1rho, T2*, and T2 mapping techniques[11]. In comparison with traditional MRI, which emphasizes morphology, these additional techniques help to evaluate cartilage composition. In broad terms, dGEMRIC, sodium, and T1rho are sensitive to proteoglycan content, while measurement of T2 or T2* relaxation times are sensitive to collagen architecture, specifically collagen orientation. Given that dGEMRIC requires the administration of intravenous gadolinium with a period of exercise to disperse the contrast material followed by a delay period, the use of T1rho and T2 relaxation mapping technique is often preferred[12]. T1rho is effective in detecting early cartilage degeneration and determining progress in cartilage repair following intervention[13-17].

To assess the collagen orientation and free water content of repair tissue, T2 mapping techniques can be used. Individual pixel T2 values may be demonstrated on a dynamic color map that is overlaid onto a grayscale morphologic image, producing a T2 map that shows a visual representation of water content and collagen fiber orientation (Fig. 1). T2 mapping demonstrates alterations in zonal stratification and areas of early osteoarthritis even before changes can be detected on traditional MRI sequences or radiographs[18]. The application of these various imaging techniques may be complementary.

Chondroprotection

Chondroprotection typically refers to the prevention or delay of progressive articular cartilage degeneration occurring through inflammatory, degenerative, and/or metabolic imbalances in the tissue. Disease-modifying osteoarthritis drugs attempt to manipulate chondrocyte metabolism and the pathways involved in cartilage matrix degradation[19,20]. Such drugs include P188 (Figs. 2-A, 2-B, and 2-C), anti-apoptotic agents, caspase inhibitors, glucosamine, risedronate, doxycycline, growth factors, platelet-rich plasma (PRP), cyclooxygenase inhibitors, and chondroitin sulfate[21-23]. Overall, however, results of published studies have been mixed, with little substantial clinical validation of the benefit of drugs used to date.

Mechanical factors also play a role in gradual cartilage loss and can therefore be a target for non-pharmacological forms of chondroprotection[19]. Altered mechanics affect the physiology and biochemistry of cartilage. Furthermore, when mechanical abnormalities are present to an advanced degree, the effect of a potentially chondroprotective drug on cartilage will only have a minor effect on the joint. Chondroprotection may therefore also require operative intervention, such as intra-articular fracture reduction, meniscal repair or replacement, corrective osteotomy, or ligament reconstruction, to enhance joint stability or improve kinematics and cartilage loading. Ongoing studies should provide further information on the benefits of chondroprotection. For example, the goal of the Early ARthritis THerapies (EARTH) multicenter clinical initiative is to evaluate acute interventions following severe joint injuries, such as anterior cruciate ligament (ACL) tears or

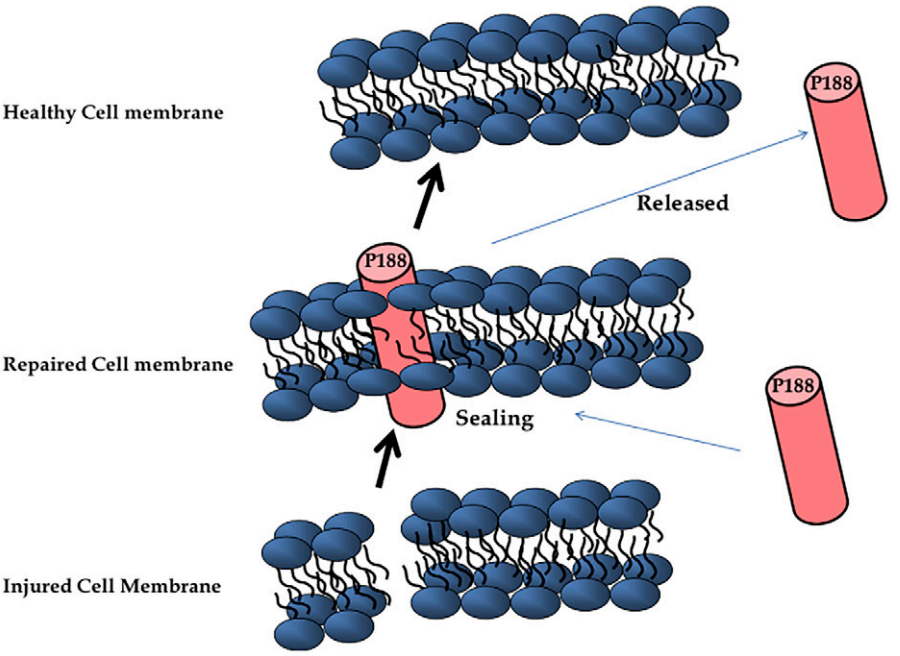

Fig. 2-A

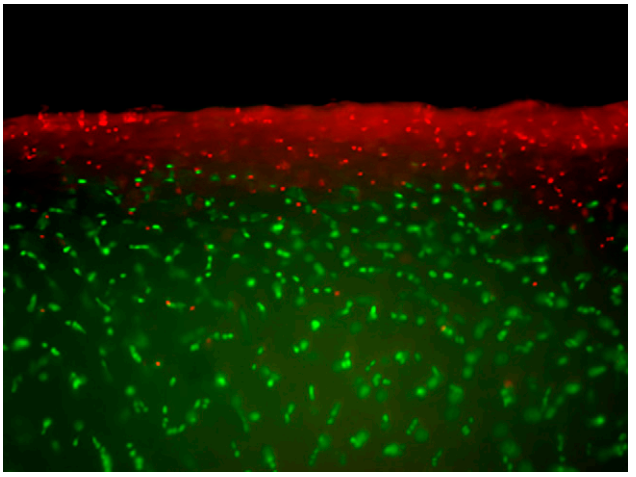

Fig. 2-B

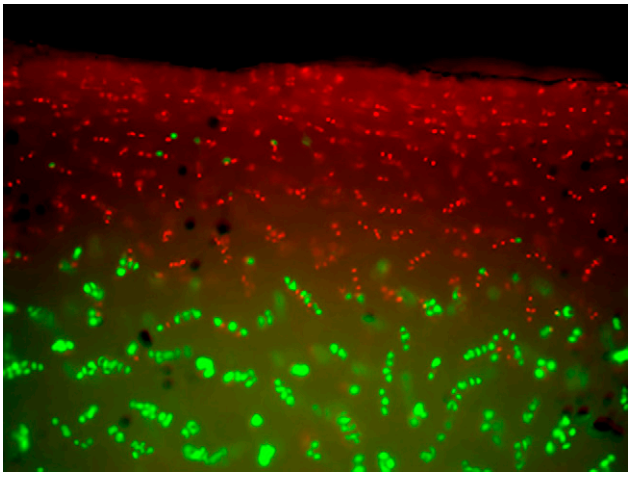

Fig. 2-C

Figs. 2-A, 2-B, and 2-C A disease-modifying osteoarthritis drug. **Fig. 2-A** P188, a chondroprotective drug, prevents cell death by sealing the plasma membrane and arresting the leakage of intracellular materials and influx of calcium ions from the damaged cells. It delays the progression of cell death and thus cartilage destruction in the area adjacent to the impacted regions[21]. (Reproduced, with permission of S. Chubinskaya, from: Lidder S, Chubinskaya S. Post-traumatic osteoarthritis: biologic approaches to treatment. In: Rothschild BM, editor. Principles of osteoarthritis–its definition, character, derivation and modality-related recognition. Rijeka, Croatia: InTech [intechopen.com]; 2012. p 233-60.) **Fig. 2-B** A live-dead assay showing impacted cartilage that was pretreated with P188 (red area indicates dead cells). **Fig. 2-C** Control live-dead assay (no treatment) showing a higher number of dead cells present (right).

intra-articular fractures, as strategies to delay or prevent the onset of posttraumatic osteoarthritis[24]. The underlying hypotheses are that joint injury initiates a series of events resulting in more rapid joint degeneration that culminates in early disabling osteoarthritis, and that early intervention prior to the development of irreversible changes may modify the disease course. Successful chondroprotective strategies will likely require input from many disciplines to further develop and validate quantitative imaging, biomechanical measures, and biomarkers of joint structure, composition, and function that predict the accelerated development of osteoarthritis. This input will play an important role in defining the benefit of both pharmacological and operative chondroprotective strategies, and the appropriate timing of intervention.

Bone Marrow Stimulation and Biological Augmentation of Microfracture

Bone marrow stimulation and microfracture techniques, which encourage the formation of fibrocartilage from host subchondral bone marrow cells, have been well described[3,4]. A recent systematic review of twenty-eight studies with >3000 patients found that knee function was consistently improved in the first twenty-four months after microfracture in the patients studied[25]. After two years, knee function scores remained above preoperative levels but declined; only 67% to 85% of patients continued to report improvement in the two to five-year time frame. It was also noted that shortcomings of the microfracture technique included limited production of hyaline cartilage, unpredictable repair cartilage volume, and higher failure rates for cell transplantation surgery following failed prior microfracture compared with patients in whom similar cellular treatments were used as first-line options[25]. As with many cartilage repair studies, the systematic review was limited by the quality of the studies available in the literature. These studies were affected by patient heterogeneity and study design; most studies failed to differentiate between femorotibial and patellofemoral lesions, and many also failed to exclude patients undergoing concomitant meniscal or ligamentous procedures.

There is growing evidence that modification or augmentation of microfracture may improve the quality of the repair tissue formed and ultimately the clinical outcome for patients[26-28]. Techniques to facilitate the availability of cells (i.e., stem cells) and/or availability of individual growth factors (i.e., PRP), from either endogenous or exogenous sources, with or without additional scaffold material, has a potential benefit that may be better defined through high-quality clinical studies[29-31]. For example, in an equine model, delivery of bone marrow aspirate concentrate to augment microfracture resulted in healing of acute full-thickness cartilage defects that was superior to that after microfracture alone[29]. Randomized controlled clinical studies are required to evaluate the potential of such options in patients. However, it is important that clinical studies utilizing such technology are performed with the level of rigor required for the U.S. Food and Drug Administration. Biological products must be clearly defined. For example, cell-concentrating techniques differ in the makeup of the final product depending on the individual system used. Furthermore, the final product can differ between patients and even between different time points in the same patient. It is important, therefore, that all cellular concentrates or related products that are used as biological augments in cartilage repair are fully characterized. If this can be done, biological augmentation of microfracture may represent an important step toward an applicable point-of-care or off-the-shelf solution that is low in cost. At the present time, it is believed that marrow stimulation techniques are best reserved as a first-line option for isolated defects of <2.5 cm^2 on the femoral condyles. Biologic augmentation techniques may broaden these indications and improve long-term outcomes.

Cell-Based Options

Cell-based options attempt to repair hyaline cartilage defects with chondrocyte or stem cell implantation. Autologous chondrocyte implantation has had good clinical results (patient satisfaction and clinical examination) at a mean of thirteen years after implantation[32]. Some studies have shown that prior bone-marrow stimulation and opposing chondral lesions lead to a higher risk of failure, while others have demonstrated satisfactory outcomes in both these patient groups and also patients affected by early osteoarthritis, patellofemoral defects, osteochondral lesions, and osteochondritis dissecans[33-36]. Periosteal patch hypertrophy was a concern in first-generation autologous chondrocyte implantation but has been reduced by the use of a type-I/III collagen membrane. Ultimately, however, it remains an issue that autologous chondrocyte implantation requires two separate operative procedures with an intervening period of cell culture. This creates substantial cost and inconvenience at a clinical level, in addition to a propensity for chondrocytes to dedifferentiate toward a fibroblastic phenotype during culture. Characterized chondrocyte implantation has been developed in an effort to select cells with a stable chondrocyte phenotype, but further studies are required to verify the clinical benefits of this approach[37,38]. However, a recent study evaluating fifty-one participants treated with characterized chondrocyte implantation and sixty-one treated with microfracture, all of whom were undergoing operative intervention at less than three years after symptom onset, found that characterized chondrocyte implantation obtained significantly and clinically better results than microfracture ($p = 0.026$) and that delayed treatment resulted in less predictable outcomes for characterized chondrocyte implantation[38]. These data suggest that early intervention with cell transplantation (rather than reserving it as a second-line option for failed bone-marrow stimulation) may increase the likelihood of a good outcome[38].

Matrix-assisted autologous chondrocyte implantation and related techniques are second-generation forms of cell implantation that provide a three-dimensional structure for cell adhesion, proliferation, and matrix production[39]. Cultured autologous chondrocytes are seeded onto the surface of a biodegradable type-I/III collagen membrane or similar scaffold. Implantation may be performed through minimal exposure or even arthroscopic techniques. Although current literature suggests that procedures using three-dimensional scaffolds are safe, both matrix-assisted autologous chondrocyte implantation and alternative cell-scaffold techniques are still only available for use outside the U.S. because of variations in their regional regulation. In addition to the growing use of scaffolds to augment chondrocyte transplantation (differentiated cells), there is ongoing interest in applying alternative (undifferentiated) cell sources. For example, some data exist to support a role for mesenchymal stem cells derived from bone marrow, synovium, or other sources to produce sufficient autologous or allogeneic cells suitable for use in a single-stage operative intervention[40-42]. While there are limited clinical data available, phase-I and phase-II clinical trials are underway. Finally, as data to support cell transplantation

continue to grow, current literature suggests that chondrocyte or other cells may be best reserved as a second-line option behind microfracture for lesions of <2.5 cm^2 and as a primary option for larger defects. The ease of use of matrix or scaffold-cell techniques may be preferable in countries where they are currently approved.

Chondral and Osteochondral Grafts

Minced cartilage autograft and particulated juvenile cartilage allograft have now also been reported as grafts for chondral repair[43,44]. Both techniques demonstrate that transplanted cartilage cells migrate from the extracellular matrix, proliferate, and form a new hyaline-like cartilage tissue matrix that integrates with the surrounding host tissue. The techniques for minced or particulated grafts are relatively straightforward and have the benefit of requiring just one surgical procedure. Short-term (two-year) studies have demonstrated the procedures to be safe and effective, with improvements in subjective patient scores and MRI evidence of defect fill[43,44]. Clinical experience is limited, however, and given the long-standing belief that integration requires osseous contact, the long-term survival and integration of the graft with host tissue should be monitored closely.

Osteochondral autograft plugs and mosaicplasty (smaller osteochondral autograft plugs) provide a complete, living osteochondral unit and are attractive because of the integrative properties of autogenous bone compared with cartilage alone[45]. Harvest site morbidity remains a concern, but studies have shown good to excellent outcomes at up to five years following surgery[45]. Limitations of osteochondral autograft studies include small sample sizes and retrospective design, but they do offer an important option in smaller lesions (<3 cm^2) extending into the subchondral region. Fresh osteochondral allografts are a suitable treatment option for larger chondral defects, especially when there are related abnormalities of underlying bone[46]. The literature demonstrates their efficacy both in the form of primary intervention and for salvage of failed prior attempts. Good long-term survivorship of 82% at ten years, 74% at fifteen years, and 66% at twenty years has recently been reported for 122 patients (129 knees) who underwent osteochondral allograft transplantation of the femoral condyle[47]. Poorer results were found for older patients, bipolar and patellofemoral lesions, and corticosteroid-induced osteonecrosis. In all cases, it is recommended that allografts contain the least amount of bone possible to minimize the risk of osseous collapse or insufficiency fractures resulting from incomplete osseous incorporation due to the slow process of creeping substitution.

The production of off-the-shelf natural or synthetic scaffolds, with suitable cells included, remains attractive. Overcoming the regulatory process for approval of osteochondral tissue-engineered products is not easy. It is estimated that it may cost up to $500 million to bring a new biological option to the market in the U.S. Acellular options, such as biphasic osteochondral scaffold plugs, have now been available for some time. However, recent studies on a biphasic plug have noted concerning findings with regard to both clinical outcomes and structural analysis, with the finding of fibrous repair tissue and foreign-body giant cells at the defect site at the time of revision surgery[48]. In contrast with these findings, another study with MRI at later time points has suggested that integration of these scaffolds may improve following a period of greater than one year or more[49].

Randomized Controlled Trials

Comparative outcomes between cartilage repair techniques are difficult to interpret because of heterogeneity between and within study groups. There are also concerns relating to potential conflicts of interest or bias in the literature. While it is impossible to review all comparative data in the present report, some studies may provide useful information for decision making (Table I[50-57]). For example, Krych et al. showed that athletic activity levels are higher after osteochondral autograft transfer mosaicplasty than after microfracture for articular cartilage defects of the knee[45]. Bentley et al. reported a controlled randomized study of 100 patients with ten-year follow-up comparing autologous chondrocyte implantation with osteochondral autograft transfer for the treatment of large chondral lesions (>2 cm^2)[50]. Patients treated with autologous chondrocyte implantation did significantly better and had a lower rate of failed repair (17% versus 55%; $p < 0.001$). Interestingly, the pattern of failure was different for the two groups. The group that had autologous chondrocyte implantation showed a low steady failure rate across the ten years, while the mosaicplasty group remained relatively satisfactory for the first two years, and then experienced a steep failure rate over the next two years with a suggestion of leveling out thereafter[50]. Crawford et al. compared a tissue-engineered cartilage (autologous chondrocyte—three-dimensional matrix tissue implant) with microfracture for the treatment of similarly sized chondral lesions of the femoral condyle[51]. There were twenty-one patients in the implant group and nine in the microfracture group. At twenty-four months postoperatively, they reported better outcomes for the patients treated with the implant. They also found that 79% of the implant group responded to the treatment compared with 44% of the microfracture group. The study was limited by the size of the sample. Cole et al. compared minced autologous cartilage fragments with microfracture for the treatment of chondral lesions of the femoral condyle or trochlea[52]. At twenty-four months of follow-up, patients treated with the cartilage fragments did substantially better than those with microfracture. MRI did not find a significant difference between the groups. Other randomized controlled trial data from the past three years are shown in Table I[50-57]. Studies of this nature, but with longer follow-up data, will hopefully guide future care in the field.

Rehabilitation

There remains a relative lack of understanding of the optimal rehabilitation program for cartilage repair procedures[58-60]. Developing an evidence base for recommendations requires accurate reporting and use of well-defined protocols. Programs incorporating controlled exercise and progressive partial weight-bearing should be adhered to, given the increased

TABLE I Randomized Controlled Trials Comparing Different Cartilage Procedures in the Last Three Years

Year	Study	Group 1*	Group 2*	No.	Follow-up (yr)	Clinical Outcome*	Other Findings*
2012	Bentley et al.[50]	OATS	ACI	100	10	Cincinnati score significantly better in ACI group ($p = 0.02$)	15% failed in ACI group vs. 55% in OATS group
2012	Crawford et al.[51]	Cartilage implant	Microfracture	30	2	IKDC, KOOS, and VAS significantly better in implant group ($p = 0.0125$)	76% in cartilage implant group vs. 44% in microfracture group responded to procedure
2011	Cole et al.[52]	Fragmented cartilage transplant	Microfracture	29	2	IKDC and KOOS significantly better in fragmented cartilage transplant group ($p < 0.05$)	MRI did not find difference between groups
2010	Basad et al.[54]	MACI	Microfracture	60	2	MACI group did significantly better than microfracture group ($p = 0.005$ for Lysholm and $p = 0.04$ for Tegner)	
2010	Zeifang et al.[55]	MACI	ACI	21	2	No significant difference between groups	MOCART significantly better at 6 mo. for MACI group; no difference at 24 mo.
2010	Van Assche et al.[57]	CCI	Microfracture	67	2	No significant difference between groups	
2009	Gudas et al.[53]	OATS	Microfracture	50	4	OATS group did significantly better than microfracture group ($p < 0.05$)	Children with osteochondral lesions
2009	Saris et al.[56]	CCI	Microfracture	85	3	CCI group did significantly better than microfracture group ($p = 0.048$)	83% in CCI group vs. 62% in microfracture group responded to procedure

*OATS = osteochondral autologous transplantation. ACI = autologous chondrocyte implantation, CCI = characterized chondrocyte implantation, MOCART = magnetic resonance observation of cartilage repair tissue scoring system, IKDC = International Knee Documentation Committee, KOOS = Knee Injury and Osteoarthritis Outcome Score, VAS = visual analog scale, MACI = matrix-assisted autologous chondrocyte implantation, and MRI = magnetic resonance imaging.

awareness of the role of mechanobiology in tissue repair and regeneration[60]. While cellular therapies have traditionally been associated with more conservative protocols than microfracture, it has been shown that an accelerated, structured, matrix-assisted autologous chondrocyte implantation protocol over eight weeks (versus the traditional twelve weeks) is not only safe but also provides comparable, if not superior, clinical outcomes for patients throughout the postoperative timeline at up to five years postoperatively[59]. Well-defined accelerated programs may also be valid in other cartilage restoration strategies. It will be helpful to the field if ongoing and future studies and registries can record accurate and detailed rehabilitation data. Further information about the effect of mechanical load on chondrocyte biology will also be needed to provide objective evidence to guide rehabilitation prescription. This is a growing area of basic-science research, and improved communication and translation between bench and bedside will likely be of benefit to patients.

Patient characteristics are also important; expectations and focus may differ between the professional athlete and the weekend and/or recreational athlete. Mithoefer et al. noted that rehabilitation should take into consideration the biology of the cartilage repair technique, the characteristics of the cartilage defect being treated, and each athlete's sport-specific demands to optimize functional outcome[60]. Structural factors such as knee alignment and meniscal status should also be considered. Systematic, stepwise rehabilitation with criteria-based progression is recommended for an individualized rehabilitation of each athlete[60]. This is not only to achieve initial return to sport at the preinjury level but also to continue sports participation and reduce the risk for reinjury or joint degeneration.

Restoration of Mechanical Environment

While a visible injury to the articular surface is an obvious target for treatment, meniscal deficiency, malalignment, and instability should be identified and corrected in a staged or concomitant fashion to reduce the likelihood of mechanical failure of articular repair techniques. Injured or deficient menisci should be repaired or replaced when necessary. Meniscal allograft transplantation, the only form of meniscal replacement surgery available in the U.S., can yield fair to excellent results (in terms of symptom relief) at up to ten years following surgery[61]. However, current data suggest that it does not alter the natural history of the knee and that degenerative change continues[62]. Although not available in the U.S. at the present time, additional options for partial meniscal replacement are available in Europe and other regions. For example, a collagen meniscal implant has recently had favorable subjective outcomes at up to ten years as a partial meniscal replacement, while a biodegradable, polyurethane scaffold has now shown safety and good clinical efficacy two years after implantation[63-65]. As these or similar options are further developed, and possibly augmented with exogenous cells or growth factors to enhance scaffold-meniscus integration and matrix formation, their impact on the field of cartilage repair is likely to increase.

It has been noted that restoration of a neutral biomechanical environment may be the single most important factor

contributing to the success of any cartilage repair procedure[3,4]. Malalignment is most often corrected with medial opening-wedge high tibial osteotomy (varus malalignment) or a lateral opening-wedge distal femoral osteotomy (valgus malalignment). Alignment of the patella and patellofemoral tracking is also critically important when managing patellofemoral defects; it has been noted previously that it is often best to make minor adjustments to a number of sites rather than attempt to solve the problem by addressing only one issue[4]. Ligament deficiency is also of concern; it has recently been shown that all ACL tears are associated with transchondral fractures of varying severity, with progression in cartilage deterioration over time[16]. Alterations in normal knee kinematics shift loading from cartilage regions adapted for loading to regions less well suited for loading. Furthermore, delays in ACL reconstruction independently lead to increased risk of meniscal and articular cartilage injury, with a substantial percentage of injuries occurring very early in the ACL-deficient knee[66]. This problem provides a strong rationale for early intervention to provide stability in the ligament-deficient knee. As methods for detecting subclinical abnormalities in cartilage become increasingly robust, it is possible that the evidence for relationships among ACL-deficient or ACL-reconstructed states, low-grade cartilage injury, and progression of osteoarthritis will become clearer.

Clinical Planning

Patient and defect-specific variables are important factors when considering clinical intervention for chondral defects[3]. Understanding and addressing the concerns and goals specific to any given patient is critical to achieving a successful outcome from that patient's perspective. Knowledge of the specific marginal improvements that an individual procedure can provide can give the patient a reasonable expectation regarding his or her outcome and facilitates a properly informed consent process. Although chondral lesions are seen in >60% of knee arthroscopies, many patients are asymptomatic[1-4]. This group represents a growing dilemma, as these lesions may or may not progress to symptomatic and/or further degenerative change. In turn, early intervention may be warranted in high-risk subgroups if they can be identified[1-4]. At the present time, however, surgery for asymptomatic lesions does not represent the standard of care.

Cartilage surgery must focus on both restoration of organ level mechanics and address defect-specific variables, including defect location, number, size, depth, geometry, condition of subchondral bone and surrounding cartilage, and the degree of containment. The difficulty in this process was again recently demonstrated in a study highlighting the high variability in sizing of knee cartilage defects[67]. However, both organ and defect characteristics, in addition to patient age, body mass index, symptom type, occupation or family commitments, risk aversion to subsequent surgical procedures, response to previous treatments, and rehabilitation after previous surgical treatments, are all important preoperative considerations. While chronologic age is often cited as a relative indication or contraindication to cartilage repair, it is really physiologic age that determines the patient's eligibility for a non-arthroplasty solution. Typically, patients who become symptomatic after the fourth or fifth decade of life have concomitant chondral and subchondral disease in opposing articular surfaces that precludes a biologic treatment option. Furthermore, the results of partial and total knee arthroplasty, even in relatively young patients, are associated with more predictable outcomes.

Clinical Research and Registry Data

Despite the development of new cartilage repair procedures, the quality of the existing clinical evidence is limited[68]. The impact of comorbid pathology and related intervention is difficult to analyze reliably. The process is also affected by difficulties in enrollment, diverse methodology in surgery, outcome measures, outcome instruments, inadequate follow-up, strict government guidelines, varying regulatory environments, and the numerous inherent potential biases faced by investigators. However, the International Cartilage Repair Society (ICRS) noted that clinical trial databases of ongoing trials document a trend suggesting improved study designs and clinical evaluation methodology[69]. Detailed methodological recommendations and a consensus statement were developed by the same ICRS study group for the statistical study design, patient recruitment, control group considerations, study end point definition, documentation of results, use of validated patient-reported outcome instruments, and inclusion and exclusion criteria for the design and conduct of scientifically rigorous cartilage repair study protocols. Clinicians involved in cartilage repair and transplantation surgery should be aware of these guidelines and utilize cartilage registries so that high-quality data may be reported in an effort to facilitate evidence-based decision making in the future. ■

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References

1. Pearle AD, Warren RF, Rodeo SA. Basic science of articular cartilage and osteoarthritis. Clin Sports Med. 2005 Jan;24(1):1-12.

2. Moran CJ, Shannon FJ, Barry FP, O'Byrne JM, O'Brien T, Curtin W. Translation of science to surgery: linking emerging concepts in biological cartilage repair to surgical intervention. J Bone Joint Surg Br. 2010 Sep;92(9):1195-202.

3. Cole BJ, Pascual-Garrido C, Grumet RC. Surgical management of articular cartilage defects in the knee. J Bone Joint Surg Am. 2009 Jul;91(7):1778-90.

4. Gomoll AH, Farr J, Gillogly SD, Kercher J, Minas T. Surgical management of articular cartilage defects of the knee. J Bone Joint Surg Am. 2010 Oct 20;92(14):2470-90.

5. Moran CJ, Barry FP, Maher SA, Shannon FJ, Rodeo SA. Advancing regenerative surgery in orthopaedic sports medicine: the critical role of the surgeon. Am J Sports Med. 2012 Apr;40(4):934-44. Epub 2011 Nov 15.

6. Hayter C, Potter H. Magnetic resonance imaging of cartilage repair techniques. J Knee Surg. 2011 Dec;24(4):225-40.

7. Mithoefer K, Hambly K, Logerstedt D, Ricci M, Silvers H, Della Villa S. Current concepts for rehabilitation and return to sport after knee articular cartilage repair in the athlete. J Orthop Sports Phys Ther. 2012 Mar;42(3):254-73. Epub 2012 Feb 29.

8. Felson DT, Lynch J, Guermazi A, Roemer FW, Niu J, McAlindon T, Nevitt MC. Comparison of BLOKS and WORMS scoring systems part II. Longitudinal assessment of knee MRIs for osteoarthritis and suggested approach based on their performance: data from the Osteoarthritis Initiative. Osteoarthritis Cartilage. 2010 Nov;18(11):1402-7. Epub 2010 Sep 17.

9. Brown WE, Potter HG, Marx RG, Wickiewicz TL, Warren RF. Magnetic resonance imaging appearance of cartilage repair in the knee. Clin Orthop Relat Res. 2004 May;(422):214-23.

10. Marlovits S, Singer P, Zeller P, Mandl I, Haller J, Trattnig S. Magnetic resonance observation of cartilage repair tissue (MOCART) for the evaluation of autologous chondrocyte transplantation: determination of interobserver variability and correlation to clinical outcome after 2 years. Eur J Radiol. 2006 Jan;57(1):16-23. Epub 2005 Oct 3.

11. Potter HG, Chong R. Magnetic resonance imaging assessment of chondral lesions and repair. J Bone Joint Surg Am. 2009 Feb;91(Suppl 1):126-31.

12. Bashir A, Gray ML, Boutin RD, Burstein D. Glycosaminoglycan in articular cartilage: in vivo assessment with delayed Gd(DTPA)(2-)-enhanced MR imaging. Radiology. 1997 Nov;205(2):551-8.

13. Wheaton AJ, Casey FL, Gougoutas AJ, Dodge GR, Borthakur A, Lonner JH, Schumacher HR, Reddy R. Correlation of T1rho with fixed charge density in cartilage. J Magn Reson Imaging. 2004 Sep;20(3):519-25.

14. Carballido-Gamio J, Bauer JS, Stahl R, Lee KY, Krause S, Link TM, Majumdar S. Inter-subject comparison of MRI knee cartilage thickness. Med Image Anal. 2008 Apr;12(2):120-35. Epub 2007 Aug 31.

15. Keenan KE, Besier TF, Pauly JM, Han E, Rosenberg J, Smith RL, Delp SL, Beaupre GS, Gold GE. Prediction of glycosaminoglycan content in human cartilage by age, T1ρ and T2 MRI. Osteoarthritis Cartilage. 2011 Feb;19(2):171-9. Epub 2010 Nov 26.

16. Potter HG, Jain SK, Ma Y, Black BR, Fung S, Lyman S. Cartilage injury after acute, isolated anterior cruciate ligament tear: immediate and longitudinal effect with clinical/MRI follow-up. Am J Sports Med. 2012 Feb;40(2):276-85. Epub 2011 Sep 27.

17. Li X, Han ET, Ma CB, Link TM, Newitt DC, Majumdar S. In vivo 3T spiral imaging based multi-slice T(1rho) mapping of knee cartilage in osteoarthritis. Magn Reson Med. 2005 Oct;54(4):929-36.

18. Jazrawi LM, Alaia MJ, Chang G, Fitzgerald EF, Recht MP. Advances in magnetic resonance imaging of articular cartilage. J Am Acad Orthop Surg. 2011 Jul;19(7):420-9.

19. Felson DT, Kim YJ. The futility of current approaches to chondroprotection. Arthritis Rheum. 2007 May;56(5):1378-83.

20. Loeser RF, Goldring SR, Scanzello CR, Goldring MB. Osteoarthritis: a disease of the joint as an organ. Arthritis Rheum. 2012 Jun;64(6):1697-707. Epub 2012 Mar 5.

21. Pascual Garrido C, Hakimiyan AA, Rappoport L, Oegema TR, Wimmer MA, Chubinskaya S. Anti-apoptotic treatments prevent cartilage degradation after acute trauma to human ankle cartilage. Osteoarthritis Cartilage. 2009 Sep;17(9):1244-51. Epub 2009 Mar 24.

22. Anderson DD, Chubinskaya S, Guilak F, Martin JA, Oegema TR, Olson SA, Buckwalter JA. Post-traumatic osteoarthritis: improved understanding and opportunities for early intervention. J Orthop Res. 2011 Jun;29(6):802-9. Epub 2011 Feb 11.

23. Wildi LM, Raynauld JP, Martel-Pelletier J, Beaulieu A, Bessette L, Morin F, Abram F, Dorais M, Pelletier JP. Chondroitin sulphate reduces both cartilage volume loss and bone marrow lesions in knee osteoarthritis patients starting as early as 6 months after initiation of therapy: a randomised, double-blind, placebo-controlled pilot study using MRI. Ann Rheum Dis. 2011 Jun;70(6):982-9. Epub 2011 Mar 1.

24. Chu CR, Beynnon BD, Buckwalter JA, Garrett WE Jr, Katz JN, Rodeo SA, Spindler KP, Stanton RA. Closing the gap between bench and bedside research for early arthritis therapies (EARTH): report from the AOSSM/NIH U-13 Post-Joint Injury Osteoarthritis Conference II. Am J Sports Med. 2011 Jul;39(7):1569-78.

25. Mithoefer K, McAdams T, Williams RJ, Kreuz PC, Mandelbaum BR. Clinical efficacy of the microfracture technique for articular cartilage repair in the knee: an evidence-based systematic analysis. Am J Sports Med. 2009 Oct;37(10):2053-63. Epub 2009 Feb 26.

26. Farr J, Cole B, Dhawan A, Kercher J, Sherman S. Clinical cartilage restoration: evolution and overview. Clin Orthop Relat Res. 2011 Oct;469(10):2696-705.

27. Chen H, Sun J, Hoemann CD, Lascau-Coman V, Ouyang W, McKee MD, Shive MS, Buschmann MD. Drilling and microfracture lead to different bone structure and necrosis during bone-marrow stimulation for cartilage repair. J Orthop Res. 2009 Nov;27(11):1432-8.

28. Strauss EJ, Barker JU, Kercher JS, Cole BJ, Mithoefer K. Augmentation strategies following the microfracture technique for repair of focal chondral defects. Cartilage. 2010 Mar;1(2):145-52.

29. Fortier LA, Potter HG, Rickey EJ, Schnabel LV, Foo LF, Chong LR, Stokol T, Cheetham J, Nixon AJ. Concentrated bone marrow aspirate improves full-thickness cartilage repair compared with microfracture in the equine model. J Bone Joint Surg Am. 2010 Aug 18;92(10):1927-37.

30. Fortier LA, Barker JU, Strauss EJ, McCarrel TM, Cole BJ. The role of growth factors in cartilage repair. Clin Orthop Relat Res. 2011 Oct;469(10):2706-15.

31. Fortier LA, Hackett CH, Cole BJ. The effects of platelet-rich plasma on cartilage: basic science and clinical application. Oper Tech Sports Med. 2011 Sep;19(3):154-9.

32. Peterson L, Vasiliadis HS, Brittberg M, Lindahl A. Autologous chondrocyte implantation: a long-term follow-up. Am J Sports Med. 2010 Jun;38(6):1117-24. Epub 2010 Feb 24.

33. Minas T, Gomoll AH, Rosenberger R, Royce RO, Bryant T. Increased failure rate of autologous chondrocyte implantation after previous treatment with marrow stimulation techniques. Am J Sports Med. 2009 May;37(5):902-8. Epub 2009 Mar 4.

34. Minas T, Gomoll AH, Solhpour S, Rosenberger R, Probst C, Bryant T. Autologous chondrocyte implantation for joint preservation in patients with early osteoarthritis. Clin Orthop Relat Res. 2010 Jan;468(1):147-57. Epub 2009 Aug 4.

35. Rosenberger RE, Gomoll AH, Bryant T, Minas T. Repair of large chondral defects of the knee with autologous chondrocyte implantation in patients 45 years or older. Am J Sports Med. 2008 Dec;36(12):2336-44. Epub 2008 Aug 25.

36. Pascual-Garrido C, Slabaugh MA, L'Heureux DR, Friel NA, Cole BJ. 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 Nov;37(Suppl 1):33S-41S. Epub 2009 Oct 27.

37. Dhollander AA, Verdonk PC, Lambrecht S, Verdonk R, Elewaut D, Verbruggen G, Almqvist KF. Short-term outcome of the second generation characterized chondrocyte implantation for the treatment of cartilage lesions in the knee. Knee Surg Sports Traumatol Arthrosc. 2012 Jun;20(6):1118-27. Epub 2011 Nov 8.

38. Vanlauwe J, Saris DB, Victor J, Almqvist KF, Bellemans J, Luyten FP; TIG/ACT/01/2000&EXT Study Group. Five-year outcome of characterized chondrocyte implantation versus microfracture for symptomatic cartilage defects of the knee: early treatment matters. Am J Sports Med. 2011 Dec;39(12):2566-74. Epub 2011 Sep 9.

39. Kon E, Filardo G, Di Martino A, Marcacci M. Marcacci M. ACI and MACI. J Knee Surg. 2012 Mar;25(1):17-22.

40. Haleem AM, Singergy AA, Sabry D, Atta HM, Rashed LA, Chu CR, El Shewy MT, Azzam A, Abdel Aziz MT. The Clinical Use of Human Culture-Expanded Autologous Bone Marrow Mesenchymal Stem Cells Transplanted on Platelet-Rich Fibrin Glue in the Treatment of Articular Cartilage Defects: A Pilot Study and Preliminary Results. Cartilage. 2010 Oct;1(4):253-61.

41. Fan J, Varshney RR, Ren L, Cai D, Wang DA. Synovium-derived mesenchymal stem cells: a new cell source for musculoskeletal regeneration. Tissue Eng Part B Rev. 2009 Mar;15(1):75-86.

42. Evans CH. Barriers to the clinical translation of orthopedic tissue engineering. Tissue Eng Part B Rev. 2011 Dec;17(6):437-41. Epub 2011 Aug 8.

43. Cole BJ, Farr J, Winalski CS, Hosea T, Richmond J, Mandelbaum B, De Deyne PG. Outcomes after a single-stage procedure for cell-based cartilage repair: a prospective clinical safety trial with 2-year follow-up. Am J Sports Med. 2011 Jun;39(6):1170-9. Epub 2011 Apr 1.

44. Farr J, Cole BJ, Sherman S, Karas V. Particulated articular cartilage: CAIS and DeNovo NT. J Knee Surg. 2012 Mar;25(1):23-9.

45. Krych AJ, Harnly HW, Rodeo SA, Williams RJ 3rd. 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 Jun 6;94(11):971-8.

46. Demange M, Gomoll AH. The use of osteochondral allografts in the management of cartilage defects. Curr Rev Musculoskelet Med. 2012 Sep;5(3):229-35.

47. Levy YD, Görtz S, Pulido PA, McCauley JC, Bugbee WD. Do fresh osteochondral allografts successfully treat femoral condyle lesions? Clin Orthop Relat Res. 2013 Jan;471(1):231-7.

48. Dhollander AA, Liekens K, Almqvist KF, Verdonk R, Lambrecht S, Elewaut D, Verbruggen G, Verdonk PC. A pilot study of the use of an osteochondral scaffold plug for cartilage repair in the knee and how to deal with early clinical failures. Arthroscopy. 2012 Feb;28(2):225-33. Epub 2011 Oct 20.

49. Bedi A, Foo LF, Williams RJ, Potter HG, Cartilage Study Group. The maturation of synthetic scaffolds for osteochondral donor sites of the knee: an MRI and T2-mapping analysis. Cartilage. 2010 Jan;1(1):20-8.

50. Bentley G, Biant LC, Vijayan S, Macmull S, Skinner JA, Carrington RW. Minimum ten-year results of a prospective randomised study of autologous chondrocyte implantation versus mosaicplasty for symptomatic articular cartilage lesions of the knee. J Bone Joint Surg Br. 2012 Apr;94(4):504-9.

51. Crawford DC, DeBerardino TM, Williams RJ 3rd. NeoCart, an autologous cartilage tissue implant, compared with microfracture for treatment of distal femoral cartilage lesions: an FDA phase-II prospective, randomized clinical trial after two years. J Bone Joint Surg Am. 2012 Jun 6;94(11):979-89.

52. Cole BJ, Farr J, Winalski CS, Hosea T, Richmond J, Mandelbaum B, De Deyne PG. Outcomes after a single-stage procedure for cell-based cartilage repair: a prospective clinical safety trial with 2-year follow-up. Am J Sports Med. 2011 Jun;39(6):1170-9. Epub 2011 Apr 1.

53. Gudas R, Simonaityte R, Cekanauskas E, Tamosiūnas R. A prospective, randomized clinical study of osteochondral autologous transplantation versus microfracture for the treatment of osteochondritis dissecans in the knee joint in children. J Pediatr Orthop. 2009 Oct-Nov;29(7):741-8.

54. Basad E, Ishaque B, Bachmann G, Stürz H, Steinmeyer J. Matrix-induced autologous chondrocyte implantation versus microfracture in the treatment of cartilage defects of the knee: a 2-year randomised study. Knee Surg Sports Traumatol Arthrosc. 2010 Apr;18(4):519-27.

55. Zeifang F, Oberle D, Nierhoff C, Richter W, Moradi B, Schmitt H. Autologous chondrocyte implantation using the original periosteum-cover technique versus matrix-associated autologous chondrocyte implantation: a randomized clinical trial. Am J Sports Med. 2010 May;38(5):924-33. Epub 2009 Dec 4.

56. Saris DB, Vanlauwe J, Victor J, Almqvist KF, Verdonk R, Bellemans J, Luyten FP; TIG/ACT/01/2000&EXT Study Group. Treatment of symptomatic cartilage defects of the knee: characterized chondrocyte implantation results in better clinical outcome at 36 months in a randomized trial compared to microfracture. Am J Sports Med. 2009 Nov;37(Suppl 1):10S-19S. Epub 2009 Oct 21.

57. Van Assche D, Staes F, Van Caspel D, Vanlauwe J, Bellemans J, Saris DB, Luyten FP. Autologous chondrocyte implantation versus microfracture for knee cartilage injury: a prospective randomized trial, with 2-year follow-up. Knee Surg Sports Traumatol Arthrosc. 2010 Apr;18(4):486-95. Epub 2009 Oct 10.

58. Nho SJ, Pensak MJ, Seigerman DA, Cole BJ. Rehabilitation after autologous chondrocyte implantation in athletes. Clin Sports Med. 2010 Apr;29(2):267-82, viii.

59. Ebert JR, Fallon M, Zheng MH, Wood DJ, Ackland TR. A randomized trial comparing accelerated and traditional approaches to postoperative weightbearing rehabilitation after matrix-induced autologous chondrocyte implantation: findings at 5 years. Am J Sports Med. 2012 Jul;40(7):1527-37. Epub 2012 Apr 26.

60. Mithoefer K, Hambly K, Logerstedt D, Ricci M, Silvers H, Della Villa S. Current concepts for rehabilitation and return to sport after knee articular cartilage repair in the athlete. J Orthop Sports Phys Ther. 2012 Mar;42(3):254-73. Epub 2012 Feb 29.

61. Cole BJ, Carter TR, Rodeo SA. Allograft meniscal transplantation: background, techniques, and results. Instr Course Lect. 2003;52:383-96.

62. van der Wal RJ, Thomassen BJ, van Arkel ER. Long-term clinical outcome of open meniscal allograft transplantation. Am J Sports Med. 2009 Nov;37(11):2134-9. Epub 2009 Jun 19.

63. Brophy RH, Matava MJ. Surgical options for meniscal replacement. J Am Acad Orthop Surg. 2012 May;20(5):265-72.

64. Monllau JC, Gelber PE, Abat F, Pelfort X, Abad R, Hinarejos P, Tey M. Outcome after partial medial meniscus substitution with the collagen meniscal implant at a minimum of 10 years' follow-up. Arthroscopy. 2011 Jul;27(7):933-43. Epub 2011 May 31.

65. Verdonk P, Beaufils P, Bellemans J, Djian P, Heinrichs EL, Huysse W, Laprell H, Siebold R, Verdonk R; Actifit Study Group. Successful treatment of painful irreparable partial meniscal defects with a polyurethane scaffold: two-year safety and clinical outcomes. Am J Sports Med. 2012 Apr;40(4):844-53. Epub 2012 Feb 9.

66. Murrell GA, Maddali S, Horovitz L, Oakley SP, Warren RF. The effects of time course after anterior cruciate ligament injury in correlation with meniscal and cartilage loss. Am J Sports Med. 2001 Jan-Feb;29(1):9-14.

67. Siston RA, Geier D, Bishop JY, Jones GL, Kaeding CC, Granger JF, Skaife T, May M, Flanigan DC. The high variability in sizing knee cartilage defects. J Bone Joint Surg Am. 2013 Jan 2;95(1):70-5.

68. Worthen J, Waterman BR, Davidson PA, Lubowitz JH. Limitations and sources of bias in clinical knee cartilage research. Arthroscopy. 2012 Sep;28(9):1315-25. Epub 2012 May 23.

69. Mithoefer K, Saris DBF, Farr J, Kon E, Zaslav K, Cole BJ, Ranstam J, Yao J, Shive M, Levine D, Dalemans W, Brittberg M. Guidelines for the design and conduct of clinical studies in knee articular cartilage repair: International Cartilage Repair Society recommendations based on current scientific evidence and standards of clinical care. Cartilage. 2011 Apr;2(2):100-21.