Preservation of Knee Articular Cartilage

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Abstract: Hyaline articular cartilage is critical for the normal functioning of the knee joint. Untreated focal cartilage defects have the potential to rapidly progress to diffuse osteoarthritis. Over the last several decades, a variety of interventions aiming at preserving articular cartilage and preventing osteoarthritis have been investigated. Reparative cartilage procedures, such as microfracture, penetrate the subchondral bone plate in effort to fill focal cartilage defects with marrow elements and stimulate fibrocartilaginous repair. In contrast, restorative cartilage procedures aim to replace the defective articular surface with autologous or allogeneic hyaline cartilage. This review focuses on the preservation of articular cartilage, and discusses the current reparative and restorative surgical techniques available for treating focal cartilage defects.

Key Words: cartilage, arthroscopy, ACI, MACI, OAT, OCA, transplant, microfracture, osteoarthritis

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Articular cartilage is critical for the normal functioning of the knee joint. Over time, chondral damage may potentially progress to diffuse osteoarthritis (OA), which is estimated to be present in 38% to 47% of the population over the age of 60 in the United States.[1,2] OA by definition is irreversible, making OA prevention and articular surface preservation a critical topic of investigation.

Although each therapy has its own general indications, no clear unified algorithm exists for surgical decision making when treating articular cartilage defects. In addition, long-term outcomes between these techniques are still frequently debated. This review focuses on the current field of cartilage repair and restoration, and discusses the progression of the current surgical techniques available for treating focal cartilage defects (Fig. 1).

WHERE WE WERE 25 YEARS AGO

Over the last several decades, a variety of interventions aiming at preserving articular cartilage and preventing OA have been investigated. Reparative cartilage procedures, such as microfracture and other marrow stimulation techniques, penetrate the subchondral bone plate in effort to fill focal cartilage defects with marrow elements and stimulate fibrocartilaginous repair. The first marrow stimulation technique involved open Kirschner wire drilling of subchondral bone and damaged articular cartilage.[3] These less refined open techniques were quickly replaced with less invasive arthroscopic techniques, including microfracture. The microfracture technique was popularized in the late 1990s by Steadman, and is still considered by some experts as a first-line treatment for isolated cartilage defects.[3] Although short-term clinical outcomes were favorable, the highest level of evidence evaluating the comparative effectiveness of microfracture is mostly from select randomized control trials.[3,4] The limitations found at mid-term and long-term follow-up necessitated the implementation of current techniques and augmentations.

In contrast, restorative autologous procedures, such as osteochondral autograft transplantation (OAT), aim to replace the defective articular surface with the patient's own hyaline cartilage. The groundwork for OAT was laid by Campanacci et al[5] in 1985, who performed free patellar grafts to replace resected femoral and tibial condyles in 19 cancer patients with bony involvement. Campanacci et al[5] found complete relief of pain in over half of the patients, and over 70% of the patients having >90 degrees range of motion. Yamashita and colleagues used a similar concept to treat 2 patients with osteochondritis dissecans. After taking the graft from an area of the medial femoral condyle "which in extension was in contact with neither patella nor meniscus," he found that he was able to restore full range of motion.[6] Thus, the method of using non–weight-bearing surfaces was born and began to include other non–weight-bearing portions of the femur for years to come.

Use of the first generation of autologous chondrocyte implantation (ACI) can be traced back to the mid-1990s.[7] The 2-stage autologous chondrocyte-based therapy originally utilized a periosteal cover with several different methods of fixation through an arthrotomy.[7] Since then, ACI has evolved to include 3 generations of techniques. Each of these generations of ACI have sought to enhance chondrocyte induction, conduction, as well as organization within the articular defect.

As the field of cartilage restoration grew, experts soon learned that fresh allograft tissue contained an ample concentration of viable chondrocytes, and could be useful for restoring the articular surface.[8–12] Approximately 30 years ago, the first fresh osteochondral allograft (OCA) transplant program was implemented. Since then, recent advancements in availability, procurement, processing, and storage of allografts have enhanced the popularity, availability, and clinical validity of OCA use in treatment of large chondral and osteochondral lesions.[13]

WHERE WE ARE TODAY

Marrow Stimulation/Microfracture

Marrow stimulation techniques involve the perforation of subchondral bone for the release of marrow elements,

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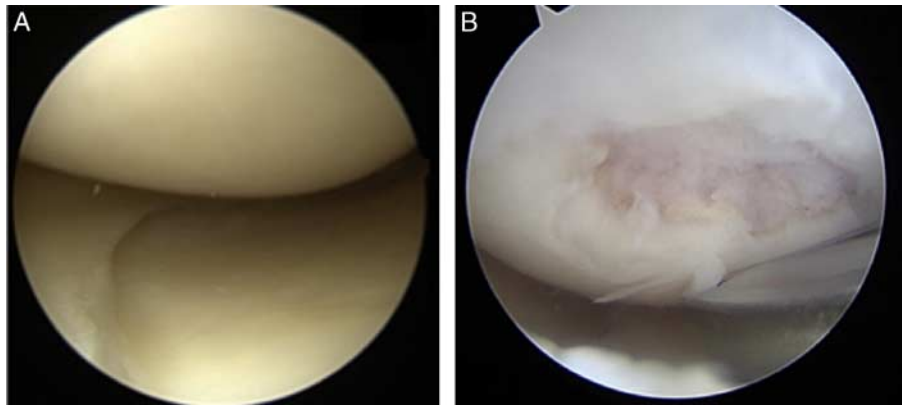

FIGURE 1. Articular cartilage. A, Arthroscopic images of healthy, normal knee cartilage of the femur (superior) and tibia (inferior) with normal meniscus visible. B, International Cartilage Restoration Society (ICRS) grade IV focal chondral defect of the femoral condyle.

including mesenchymal stem cells (MSCs) and growth factors, into the articular defect (Fig. 2).[14] The released MSCs may subsequently differentiate into fibrochondrocytes facilitating the formation and stabilization of a fibrocartilage clot. The marrow element clot eventually remodels to replace the damaged native cartilage with "cartilage-like" fibrocartilage. In comparison with native hyaline cartilage, fibrocartilage collagen deposition, and orientation is suboptimal, and thus has less capacity to resist sheering forces.[15]

Marrow stimulation is currently recommended for primary repair of symptomatic, known outerbridge grade III to IV focal articular cartilage defects. Marrow stimulation is generally reserved for smaller (<2 to $3\,cm^2$) defects, and should be avoided in the treatment of diffuse damage, large ($>4\,cm^2$) defects, bipolar articular cartilage lesions, or when subchondral bone damage is suspected on preoperative magnetic resonance imaging (MRI). Before surgery, patients should have failed the nonsurgical standard of care (injections, bracing, and physical therapy). Other relative contraindications to marrow stimulation include severe OA, malignancy, systemic inflammatory diseases, asymptomatic patients, low-grade lesions, high body mass index (BMI), and patients who lack the ability to comply with a strict postoperative rehabilitation protocol.

Although microfracture is still a popular iteration of marrow stimulation, many leaders in the field question the technique's sustainability.[4,16] Unquestionably, the early clinical outcomes of microfracture have been proven positive; however, a loss of benefit has been described after ~2 years. In a systematic review by Mithoefer et al[17] 3122 microfracture procedures yielded average knee function scores significantly above the preoperative level over the first 24 months with a short-term clinical improvement rate of 75% to 100% overall. After 24 months, however, 47% to 80% of microfracture patients reported subjective decline in functional outcomes. The regression of positive outcomes at long-term follow-up have been corroborated by several authors, raising concerns of the technique's validity.[16,18–20] Long-term outcomes have been negatively correlated with increased age, larger defects ($>2.5\,cm^2$), and increased BMI ($BMI > 30\,kg/m^2$).[4] Furthermore, several authors have reported suboptimal outcomes in highly active and athletic patients.[21–23] In particular, microfracture may be correlated with decreased minutes per game, decreased player efficiency rating, points per game, and most importantly, diminished return to sport (21% did not RTS) in National Basketball Association players.[22,23] The causal factor thought to be hindering marrow stimulation is the nature of the fibrocartilage clot it produces. Fibrocartilage has a different composition of collagen than native hyaline cartilage, which makes it less durable and more prone to wearing out over time.[4]

ACI

ACI involves the induction of hyaline-like cartilage by the implantation of harvested and subsequently cultured autologous chondrocytes.[7] ACI is a plausible primary intervention for cartilage restoration in select patients.[24] Ideally, ACI candidates have large full-thickness surface chondral defects ($>4\,cm^2$) with no prior history of cartilage

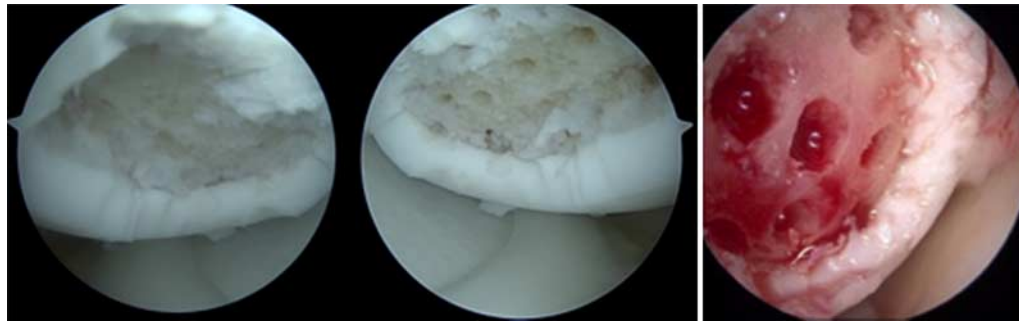

FIGURE 2. Microfracture surgery: arthroscopic images of a femoral condyle focal chondral defect after preparation, after subchondral perforation, and marrow elements egressing from the defect treated with microfracture surgery.

procedures, a short duration of preoperative symptoms, and minimal subchondral bone involvement.[7,25]

All ACI procedures are performed in 2 stages. The first is the arthroscopic harvest of chondral samples, typically performed at the initial diagnostic arthroscopy. These chondrocytes are cultured, expanded, and amplified in vitro. The chondrocyte biopsy is typically taken from the non–weight-bearing surface of the superolateral edge of the lateral femoral condyle, the superomedial edge of the medial femoral condyle, or the intercondylar notch.[25] Approximately 3 to 8 weeks later, the cultured cells are implanted into the prepared focal defect site via an arthrotomy or all-arthroscopic technique (Fig. 3).[7] Currently, 3 generations of ACI exist.[7] In first-generation ACI, culture expanded chondrocytes are transplanted and covered with a periosteal patch fixed with suture and fibrin glue. Second-generation ACI suspends the chondrocytes within a type I/III collagen membrane. In third-generation ACI or matrix-associated ACI (MACI), chondrocytes are implanted into a chondroinductive extracellular matrix scaffold which is fixated into the defect at the time of surgery. The MACI technique allows direct insertion of the chondrocyte-seeded matrix into the defect site and replaces suture fixation with fibrin glue. The simpler technique and fixation process may decrease operation time and exposure needed for implantation.[26]

New MACI techniques have allowed for the improved outcomes and durability when compared with prior generations of ACI. The associated matrix enhances organization and induction of chondrocytes for treating larger articular cartilage defects. This finding was supported by Brittberg et al[27] who demonstrated that MACI resulted in clinically and statistically significant improved subjective outcomes at 5 years compared with microfracture for the treatment of defects $\geq 3\,cm^2$. Moreover, defects treated with MACI display an improved histologic and radiologic quality in repair tissue quality, ultimately reducing of the overall complication rate of ACI.[28]

ACI has demonstrated significant improvements in treating large-sized ($>4\,cm^2$) full-thickness focal cartilage lesions at short-term and mid-term follow-up, as well as long-term outcomes. A systematic review by DiBartola et al[29] evaluated ACI in 155 adolescent patients at a mean follow-up of 52.3 months and mean defect size of $5.3\,cm^2$. These authors reported improvement in all subjective clinical outcome measures with a short duration of preoperative symptoms being the only variable correlated with improved outcomes. Importantly, Demange et al[30] have been able to demonstrate a survivorship of 71% at 10 years with improved function in 75% of patients. Other studies have reported sustained positive outcomes of ACI up to 20 years postoperatively with 92% of patients reporting satisfaction with the procedure.[31,32] Furthermore, a systematic review of high-level evidence suggests superior outcomes of ACI in comparison with microfracture, especially for treatment of larger size defects.[7] Although these authors report positive outcomes of ACI, no consensus exists on ACI when compared with OAT.

Despite the positive findings that support ACI, complications and limitations still exist. There are significant technical challenges associated with the periosteal harvest and suturing of the periosteal flap in first-generation ACI.[26] First-generation periosteal grafts have also been strongly associated with hypertrophic tissue growth, resulting in reoperation rates reaching as high as 50%.[25,33] Patellofemoral ACI has been shown to be at particularly high risk for this complication. In addition, MRI graft hypertrophy and repair tissue signal after ACI have been strongly correlated with clinical outcomes.[34] Implant hypertrophy results in joint stiffness and often requires revision procedures.[33] Graft hypertrophy remains the most common complication associated with both second-generation and third-generation ACI. MACI has reported an overall graft hypertrophy rate of ~5%.[26] However, use of an absorbable collagen membrane with second-generation ACI has demonstrated a decrease in graft hypertrophy and a reduction in reoperation rate up to 80%.[35]

As previously mentioned, ACI should be reserved for treating patients with no prior history of cartilage procedures, especially microfracture. Microfracture and other marrow stimulation techniques disrupt the subchondral bone plate and may be "bridge burning" techniques for future ACI. Pestka et al[36] examined failure rates of ACI after failed microfracture compared with ACI as a first-line treatment. ACI after failed microfracture has significantly greater failure rates as well as lower subjective outcomes than first-line ACI at 48 months follow-up. Prior microfracture is also associated with an increased risk of osteophyte formation after ACI, which can result in higher rates of reoperation.[30]

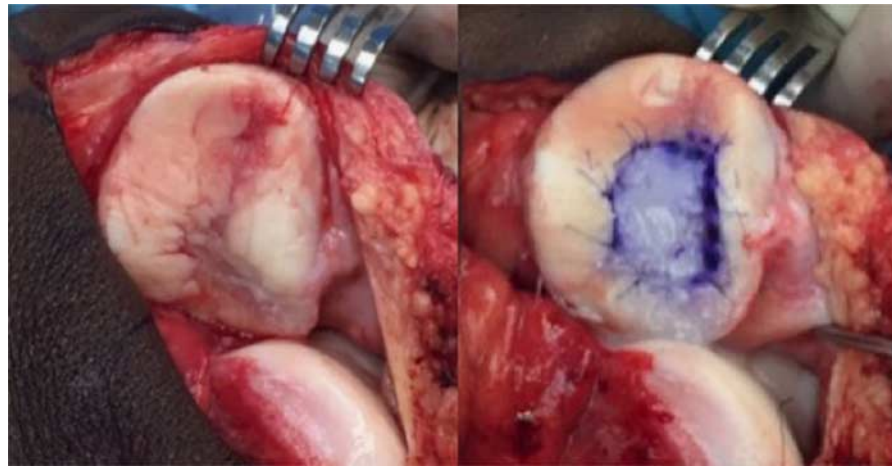

FIGURE 3. Autologous chondrocyte implantation. Intraoperative photographs of a chondral defect of the right patella in which the cartilage defect is treated with autologous chondrocyte implantation.

OAT

OAT provides the ability to immediately restore focal articular defects with non–weight-bearing portions of the host knee. As it involves the transfer of the articular chondral surface, deep and middle subchondral bone, and cancellous bone from the host, OAT can repair defects that extend well past the chondral surface or that have underlying cystic changes in the bone. Depending on the defect size, one or multiple smaller plugs (known as mosaicplasty) of osteochondral tissue are transferred from non–weight-bearing areas (which include the intercondylar notch or the region of the medial and lateral condyles proximal to the sulcus terminalis) to the site of chondral loss.[37] Ideal candidates for OAT are those with: high physical demands, unipolar lesions of the patella, trochlea, or femoral condyle no $>2.5\,cm^2$, neutral alignment, and normal BMI.[37]

Arthroscopic management of the defect is contingent upon its location and size, as well as the surgeon's experience and ability to obtain perpendicular access.[37] The defect is first measured with a sizer to determine the number and size of the autografts. The donor tissue is then gathered by positioning the harvesting tool perpendicular to the cartilage surface, impacting to a depth of 12 to 15 mm, and removing the intact plug.[37] Motorized shavers, curettes, and/or the corresponding core harvester are used to obtain stable vertical margins at the recipient site to maximize congruency in plug placement. As chondrocytes can be damaged during impaction, it is imperative to gently impact the plug in a press-fit manner and ensure it is flush with the native surrounding cartilage.[38,39]

Success with OAT has mainly been seen in small to mid-sized chondral defects. In order to minimize the risk of donor site morbidity and allow for the donor surface to reconstitute, harvest plugs should be limited to 3 to $4\,cm^2$.[39] Good clinical results have been achieved with lesion sizes between 2 and $4\,cm^2$,[40] while Braun et al[41] reporting good clinical results for lesions $>4\,cm^2$ at 5.5 years postoperatively. Although osteochondral lesions as large as $8\,cm^2$ have been treated by this technique, lesions with $<2\,cm^2$ are associated with superior outcomes.[42]

Although OAT shows promise for the treatment of young active patients with small chondral lesions, more investigation needs to be undertaken to evaluate its long-term efficacy.[43] A systematic review by Lynch et al[44] demonstrated significant improvements in 607 patients, with return to sport as early as 6 months after surgery, and superior results for lesions $<2\,cm^2$. Similarly, Pareek et al[42] performed a systematic review of 10 studies with a total of 610 patients at a mean 10.2-year follow-up, and found significantly improved IKDC and Lysholm scores. Although outcomes were improved in 72% of patients, there was a reoperation rate of 19%.[42] A meta-analysis by Riboh and colleagues compared clinical outcome scores and reoperation rates among OAT, MFX, and second-generation ACI at 2, 5, and 10 years. It was found that reoperation rates in patients with OAT were higher than those with second-generation ACI and lower than those with MFX.[43] Clinical scores were not statistically significant at 2 years, and were not measured at 5 and 10 years.[43] Unfortunately, the technically demanding nature of the procedure, correlation of increased defect size and age with failure, and risk of donor site morbidity limits the use of isolated OAT to a small subset of patients—those with small unipolar lesions, neutral alignment, and a normal BMI.[42,45]

OCA Transplantation

OCA can restore articular cartilage while also addressing associated subchondral bony damage (Fig. 4).[13] Primary indications for OCA are full-thickness chondral or osteochondral defects $>3\,cm^2$. OCA can be implemented in the presence of deep subchondral bone damage, osteochondritis dissecans, as well as posttraumatic focal lesions.[12,46–53] OCA is also useful for remediation of failed cartilage repair procedures, particularly following microfracture, ACI, or OAT.[54–57] Relative contraindications include patients with early OA, inflammatory arthropathies, avascular necrosis, BMI > 30, and those over 45 years of age.[56,58,59] In addition, it is essential to address any concomitant pathology associated with the defect such as instability, malalignment, and/or meniscal deficiency to optimize long-term outcomes.[49,56,57,60–62]

Overall, OCA has shown a high clinical success rate in improving subjection outcomes, function, and mobility.[19,56] Long-term investigations report successful improvement in subjective outcomes in 75% of OCA patients after 12.3 years, and 85% graft survival rate after 10 years..[47,56,63,64] At a minimum of 5-year follow-up, the reoperation rate of primary OCA was found to be 37% with previous ipsilateral knee surgery associated with a higher risk of reoperation.[65] A recent review of literature by Pisanu et al[56] demonstrated that outcomes positively correlated with young age, unipolar lesions, posttraumatic lesions, and a short duration of symptoms.[49,51,61,66–71] Notably, OCA has been successful in treating highly active patients. Krych et al[69] reported a 80% return to play in professional athletes at a mean 2.5-year follow-up. In addition, at a minimum 2-year follow-up, patients self-identifying as athletes had an 81.8% rate of RTS, with increasing BMI correlated with failure to RTS.[72]

OCA can also be an effective treatment when used with concomitant procedures or to revise a prior failed intervention. A recent comparative study by Saltzman et al[73] detailing the influence of full-thickness chondral defects on meniscal allograft transplantation (MAT) reported no significant difference in subjective outcomes, survival, or complication rates between patients who underwent (MAT) in isolation versus patients who underwent MAT with concomitant OCA. When investigating OCA as a revision procedure, Gracitelli et al[75] reported 86% and 87.4% 10-year survival rates in patients undergoing OCA transplant after failed microfracture and primary OCA transplant, respectively.[74] These authors also reported patient feedback as "satisfied" or "extremely satisfied" in 97% of patients where OCA was used to revise a prior cartilage procedure.[75]

WHERE WE WILL BE IN THE FUTURE

Recently, new advancements have sought to enhance microfracture's fibrocartilaginous repair durability by improved techniques or augmentation. Complete removal of the calcified cartilage layer has been demonstrated to result in improved clot stability and repair quality.[76,77] Moreover, exogenous cartilage matrixes can be fixated over the perforated subchondral bone and act as a scaffold for the released MSC and growth factors allowing enhanced stability and organization. The early basic science and clinical trials investigating collagen scaffold augmentations have shown promising results and improved repair.[15,78] In addition, biological augmentation of microfracture has resulted in mixed yet promising outcomes. However, there remains a paucity of clinical trials and most data are from animal models.[79–82] Bone marrow aspiration concentrate (BMAC)

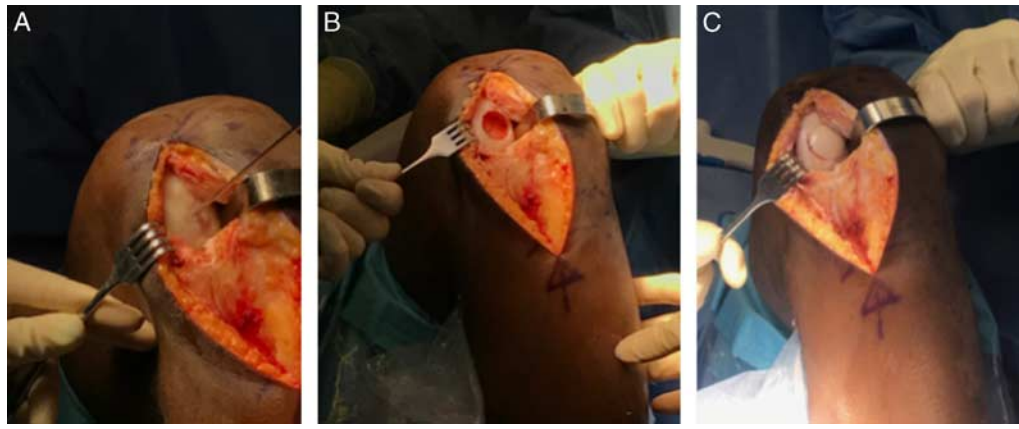

FIGURE 4. Osteochondral allograft. A, Intraoperative photograph of a left knee medial femoral condyle focal chondral defect with guide pin inserted. B, Photograph of the left knee medial femoral condyle after reaming to excise the chondral defect. C, The allograft osteochondral plug implanted to reconstruct the articular surface.

has the ability to improve fibrocartilage filling and organization with increases type II cartilage deposition more similar to native cartilage.[81]

The use of biologics has also been investigated in order to optimize osteochondral incorporation. Successful animal models have shown a use for biologics as an adjunct for patients undergoing OAT or mosaicplasty. Altan and colleagues investigated the use of platelet-rich plasma (PRP) in mosaicplasty in rabbits by injecting a PRP solution in the defect before fixation as well as in the joint after closure. At 3 weeks postoperatively, improved integration at the graft interface was seen in the group that received the adjunctive PRP compared with control defects treated with isolated OAT.[83] In a separate study, Maruyama et al[84] used a rabbit model to investigate the effect of PRP injections andplatelet-rich fibrin clots placed into the graft site before OAT. At 3 weeks the platelet-rich fibrin group demonstrated macroscopically healed compared with the control and PRP group.

Implantation of minced or particulated cartilage is a novel technique currently being investigated for the treatment of articular defects. Both autologous and allogeneic particulated cartilage transplant systems exist. Allogeneic systems may be particularly useful due to the limited immunogenic response, and the increased shelf-life.[85,86] The cartilage autograft implantation system (CAIS) procedure involves harvesting of cartilage from a non–weight-bearing surface of the joint. The autologous minced cartilage pieces are integrated onto a scaffold, which is then fixated into the defect site.[86] By contrast, the DeNovo NT Graft (Zimmer Inc., Warsaw, IN) system utilizes particulated cartilage allograft from juvenile (below 13-y old) donors.[87] Mid-term and long-term clinical outcomes supporting the use of particulated minced cartilage are currently unavailable, but early outcomes have demonstrated promising results.[85–88] In a prospective study, Farr et al[89] reported on 25 patients receiving Denovo NT, and found favorable more hyaline-like defect filling on immunohistochemistry. In addition, it has been reported that Denovo NT has resulted in a mean fill of 89% on MRI. Cole et al[88] compared CAIS with microfracture in 29 patients with a minimum 2-year follow-up. The CAIS cohort demonstrated significantly higher subjective outcomes as well as a lower risk of intralesional osteophyte formation compared with the microfracture group.[88] Despite promising early trials, the long-term efficacy of this technology remains to be seen. Further high-level clinical trials are required to better examine the viability of these techniques.

Cryopreserved OCA equivalent implants, such as Cartiform, are also being investigated. Cartiform is composed of allograft chondrocytes, growth factors, and extracellular matrix. Similar to OCA, the implant allows for regenerative treatment of full-thickness cartilage defects. The cryopreserved nature of the implant imparts an increased shelf-life critical to increasing wide availability of allografts. In addition, the perforated implant scaffold can be shaped to anatomically match the defect. Few positive clinical trials currently exist,[90] but early animal studies are optimistic.[91] Research is also being performed on the development of scaffold-free constructs from cultured synovial MSCs. With their ability for chondrogenic differentiation and ease of harvest, these constructs have already been used to treat chondral lesions in porcine models.[92,93] From 2013 to 2016, Ando et al[94] treated 5 patients with full-thickness chondral lesions of the knee (ranging from 1.5 to 3.0 cm^2) in a 2-stage procedure: the first for arthroscopic evaluation and synovial biopsy for culture, and the second for implantation of the scaffold after culturing for 3 weeks. It was found that patient reported outcomes for pain, sports activity, symptoms, and quality of life were significantly improved at 24 months post operatively.[94] In addition, second-look arthroscopy at 48 weeks demonstrated full coverage of the defect, and histologic similarity of the repair tissue to hyaline cartilage.[94] Although promising, future studies with a larger study size are needed to scrutinize the clinical reliability of these 2 types of cell-based constructs .

In the future, basic science research can elucidate methods to improve integration of graft bone at bone-graft interface of OCA patients. Specifically, injection of bone marrow aspirate concentrate at the time of surgery has the potential to serve as an adjunct to optimize the integration of the newly implanted tissue. Oladeji et al[95] reported significantly higher radiographic graft integration of OCA as well as significantly less graft sclerosis following BMAC augmentation. Biological injections such as PRP have also been used as a supplemental treatment postoperatively to encourage recruitment of anti-inflammatory cells at the site of incorporation. Stoker et al[96] compared isolated OCAs with those treated with BMAC or PRP and found both BMAC and PRP samples had significantly higher concentrations of

multiple osteogenic proteins than the control group. In addition, topographic studies of the transplant implantation site are attempting to elucidate the amount of mismatch OCAs from opposite condyles incurs.[97] These topographic studies may prove critical in expansion of the acceptable allograft pool for increased allograft availability.

CONCLUSIONS

In comparison with other areas of orthopedic surgery, cartilage reparation and restoration remains a relatively emerging field, and continues to rapidly evolve. New innovations and techniques are improving current surgical algorithms and interventions for treating articular cartilage defects. The prevention or delay of debilitating OA remains a pervasive goal. The aforementioned techniques are proven methods for preserving articular cartilage of the knee, and serve as an important foundation upon which orthopedic surgeons can continue to build.

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