Management of Large Focal Chondral and Osteochondral Defects in the Knee

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Abstract

Large, focal articular cartilage defects of the knee (> 4 cm^2) can be a source of significant morbidity and often require surgical intervention. Patient- and lesion-specific factors must be identified when evaluating a patient with an articular cartilage defect. In the management of large cartilage defects, the two classically utilized cartilage restoration procedures are osteochondral allograft (OCA) transplantation and cell therapy, or autologous chondrocyte implantation (ACI). Alternative techniques that are available or currently in clinical trials include a hyaluronan-based scaffold plus bone marrow aspirate concentrate, a third-generation autologous chondrocyte implant, and an aragonite-based scaffold. In this review, we will focus on OCA and ACI as the mainstay in management of large chondral and osteochondral defects of the knee. We will discuss the techniques and associated clinical outcomes for each, while including a brief mention of alternative treatments. Overall, cartilage restoration techniques have yielded favorable clinical outcomes and can be successfully employed to treat these challenging large focal lesions.

Keywords

- large chondral defects
- cartilage injury
- autologous chondrocyte implantation
- osteochondral allograft transplant

Focal articular cartilage defects of the knee are relatively common in the general population and, in symptomatic patients, often need to be addressed surgically.[1] The presence of chondral defects in the knee lead to increased contact pressures on the adjacent articular cartilage, potentially resulting in early degenerative changes.[2,3] While there are many options for the management of smaller cartilage defects (less than 2–4 cm^2), including chondroplasty and debridement, marrow stimulation techniques (MSTs) such as microfracture and drilling, and osteochondral autograft transfer, among others, options are more limited when addressing larger cartilage defects (greater than 2–4 cm^2).

The two classically utilized surgical procedures to address large cartilage defects are osteochondral allograft (OCA) transplantation and chondrocyte cell therapy: autologous chondrocyte implantation (ACI)/Matrix-associated Autologous Chondrocyte Implantation (MACI). There are novel techniques on the horizon including another third-generation ACI (Novocart 3D), an acellular aragonite-based scaffold (Agili-C), and a hyaluronan (HA)-based scaffold plus bone marrow aspirate concentrate (BMAC), among others, used around the world. In this review, we will discuss the above techniques (►**Table 1**) and associated clinical outcomes (►**Table 2**) for the treatment of large chondral defects of the knee.

Evaluation and Preoperative Planning

When evaluating a patient with a large chondral defect, the treating surgeon must identify patient- and lesion-specific factors as they approach the knee joint as an "organ." A thorough history is essential. Specifically, did the cartilage defect come as the result of an acute traumatic injury or was

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Table 1 Treatment options for large chondral and osteochondral defects

Method	Size	Location
OCA	No size limits	Femoral condyles and patellofemoral joint
ACI (MACI and Novocart 3D)	No size limits	Tibiofemoral joint and patellofemoral joint
Aragonite-based scaffold (Agili-C)	Cumulative defect < 7 cm^2	Femoral condyles and trochlea
BMAC implantation	Defect < 10 cm^2	Femoral condyles and patellofemoral joint
PJAC (DeNovo)	Defect < 6 cm^2	Femoral condyles and patellofemoral joint
PACI	Defect < 4 cm^2	Femoral condyles and trochlea
AMIC	Defect < 4 cm^2	Femoral condyles and patellofemoral joint
CVOCA (Cartiform)	Defect < 4 cm^2	Femoral condyles and trochlea
Viable cartilage allograft (CartiMax, ProChondrix, Chondrofix)	Defect < 5 cm^2	Femoral condyles and patellofemoral joint

Abbreviations: ACI, autologous chondrocyte implantation; AMIC, autologous matrix-induced chondrogenesis; BMAC, bone marrow aspirate concentrate; CVOCA, cryopreserved viable osteochondral allograft; OCA, osteochondral allograft; PACI, particulated autologous cartilage implantation; PJAC, particulated juvenile allograft cartilage.

it of insidious onset; does the patient have swelling, mechanical symptoms, or a sensation of instability; what is the patient's level of demand or sport participation; have they had any prior surgeries to this knee; etc. Patient-specific factors such as age, body mass index (BMI), activity level, occupation and employment status, nicotine use status, and other comorbidities can play a role in cartilage restoration decision-making and must be noted.

Limb and joint-specific factors including mechanical axis malalignment, meniscal deficiency, and ligamentous instability must be taken into account and addressed prior to surgical management of large cartilage defects.[4] A thorough physical examination should be performed, including a dynamic muscular and gait assessment, evaluation of alignment and patella tracking, location of tenderness to palpation, presence of an effusion, and ligamentous stability to rule out the above concomitant pathologies.

In addition to a thorough history and focused physical examination, the standard imaging includes a series of plain radiographs on initial visit (weight-bearing anterior to posterior, posterior to anterior flexion, lateral, Merchant, and full-length standing mechanical axis alignment views) (►**Fig. 1**). Advanced imaging work-up should include knee magnetic resonance imaging (MRI) with designated cartilage sensitive sequences when available. MRI will provide a preliminary assessment of the size and location of the lesion, status of the underlying subchondral bone with proper sequencing (equivalent to T2 fat suppressed), and rule out concomitant meniscal or ligamentous pathology (►**Fig. 2**). MRI often underestimates the extent of the cartilage defect and, therefore, the utilization of a staging arthroscopy is often beneficial to directly visualize and measure the cartilage defect, assess for underlying subchondral bone, and evaluate the entirety of the knee including the menisci and overall status of the cartilage.[5–7] It is important to measure the size of the defect after debridement and be sure not to underestimate the size. Computed tomography exams should be used selectively to evaluate and quantify osseous involvement, while more commonly it is combined with arthrogram, which allows thin-section mapping of the chondral lesions.

Surgery should be reserved for symptomatic patients that have failed nonoperative measures. Nonoperative treatment should focus on optimization of BMI, core-to-floor rehabilitation, activity modification, use of medications and injections as indicated, and trial of an unloader brace if tibiofemoral malalignment is present. Surgical treatment of cartilage injuries often involves a staging arthroscopy followed by insurance preauthorization and finally the definitive procedure. The use of a staging arthroscopy is also critical in the revision setting when the patient has had a prior cartilage restoration procedure. Concomitant treatment of comorbidities is performed during the staging or definitive intervention. These procedures often require prolonged and specific rehabilitation programs to optimize outcome. Therefore, the surgeon must clearly set expectations of the postoperative plan in addition to the surgery. It is imperative that the patient express understanding prior to proceeding (as unrealistic expectations can never be met).

The considerations above as well as the indications for each procedure below should help to guide the surgeon and patient in the selection of the appropriate procedure.

Osteochondral Allograft Transplantation

OCA transplantation has a long history as a cartilage restoration technique. Current fresh-stored OCA transplantation is a means of introducing mature viable hyaline cartilage and the underlying dead subchondral bone into a cartilage defect.[8] Therefore, OCA is often preferred in the presence of concomitant osseous pathology including posttraumatic injury, subchondral cysts, avascular necrosis, osteochondritis dissecans, and prior failed marrow stimulation or cell-based repair. OCA grafts are aneural, avascular, and are considered immunoprivileged as the viable chondrocytes are protected from the host immune surveillance by the surrounding matrix (however, residual cellular debris within the bone may elicit a variable low-grade response that does not necessitate immunosuppression).[9] The osseous portion of the graft functions as a structural scaffold to provide physical support and serve as an osteoconductive platform to promote an ingrowth of host cells and vasculature.[10] OCA can best be thought of as a composite graft of bone and cartilage with a viable hyaline cartilage portion atop a nonviable osseous scaffold.[9] Additionally, OCAs are quite

Table 2 Summary of clinical results presented in this manuscript for the treatment of large chondral defects (> 4 cm^2)

Study authors	Year	Graft	*N*	Age (y)	Follow-up	Defect size	Defect location (%)	Reoperation	Clinical outcomes (postop)	Other results
Briggs et al[23]	2015	OCA	61	32.9 (15.7–67.8)	3.64 y	9.6 cm^2	MFC 47.5 LFC 24.6 PF 8.2 Trochlea 4.9 Patella 8.2 Tibia 3.2	29.5% reop 18% fail	IKDC 80.4 KS-F 89.7 KOOS-Pain 88.2 KOOS-Symp 84.9 KOOS-ADL 91.9 KOOS-Sport 81.1 KOOS-QoL 65.5	Survivorship 89.5% (5 y) and 74.7% (10 y); 86.4% “satisfied” or “extremely satisfied”
Krych et al[24]	2012	OCA	43	32.9 (18–49)	2.5 y	7.25 cm^2	MFC 40 LFC 40 Trochlea 2 Multifocal 18	1 MUA	ADL 82.82 IKDC 79.29 Marx 8.35	Preinjury RTS 34/43 (79%); Time to RTS 9.6 mo (± 3.0)
Nielsen et al[25]	2017	OCA	149	31.2 (± 11.5)	6 y	8.2 cm^2	Condyle 60 Trochlea 14 Patella 8 Tibia 1 Multifocal 17	25.5% reop 9.4% fail	71% “Very good” to “excellent” IKDC 74.5 KS-F 90.9	75.2% RTS at some level; 91% “satisfied”
Shaha et al[31]	2013	OCA	38	29.83 (± 5.3)	3.89 y	5.02 cm^2	MFC 65.8 LFC 34.2	1 patient had revision ACL recon	SANE 58.7 KOOS-Pain 61.6 KOOS-Symp 47.4 KOOS-ADL 71.69 KOOS-Sport 35.5 KOOS-QoL 33.3	28.9% Return to full duty; 42.1% unable to return to any duty due to knee
Gracitelli et al[34]	2015	OCA (Primary)	46	27.5 (± 11.8)	7.8 y	8.2 cm^2	MFC 66 LFC 26 Trochlea 6 Patella 2	24% reop 11% fail	IKDC 78.2 KS-F 89.5 KOOS-Pain 89.9 KOOS-Symp 87.8 KOOS-ADL 94.5 KOOS-Sport 72.7 KOOS-QoL 69.5	Survivorship 87.4%; 87% “satisfied” or “extremely satisfied”
Gracitelli et al[34]	2015	OCA (Revision)	46	26.2 (± 10.4)	11.3 y	8.0 cm^2	MFC 61 LFC 31 Trochlea 2 Patella 2	44% reop 15% fail	IKDC 78.8 KS-F 91.9 KOOS-Pain 82.1 KOOS-Symp 79.8 KOOS-ADL 87.1 KOOS-Sport 70.7 KOOS-QoL 64.6	Survivorship 86%; 97% “satisfied” or “extremely satisfied”
Brittberg et al[46]	2018	MACI	65	35 (18–54)	5 y	5.1 cm^2	MFC 74 LFC 20 Trochlea 6	10.8% reop 1.5% fail	IKDC 68.5 KOOS-Pain 82.2 KOOS-Fxn 61.9 KOOS-Symp 80.9 KOOS-ADL 86.4 KOOS-QoL 59.8	MACI greater clinical improvement than MFx
Marlovits et al[49]	2012	MACI	21	35.2 (20.1–47.8)	5 y	5.1 cm^2	MFC 54 LFC 17 Patella 29	4.8% reop 4.8% fail	IKDC 74.3 Tegner-Lysholm 4.3	MOCART improved (52.9–75.8); MRI: 83% complete filling, 82% integration
Gobbi et al[67]	2015	MACI	19	43.1 (± 5.81)	59.7 mo	7.12 cm^2	Patella 36.8 Trochlea 26.3 Multifocal 36.8	26.3% reop	IKDC 75.7 KOOS-Pain 80.7 KOOS-Symp 81.1	Trochlea lesions had better clinical outcomes than patella; 76% complete filling MRI

(*Continued*)

Table 2 (*Continued*)

Study authors	Year	Graft	*N*	Age (y)	Follow-up	Defect size	Defect location (%)	Reoperation	Clinical outcomes (postop)	Other results
									KOOS-ADL 82.2 KOOS-Sport 68.8 KOOS-QoL 76.1 Tegner 5.3 VAS 0.8	
Vijayan et al[54]	2012	MACI "Sandwich"	14	23.6 (16–40)	5.2 y	7.2 cm^2	MFC 71.4 LFC 28.6	7% fail	Cincinnati 82.8 VAS 1.7	85.7% good to excellent outcomes; 71% RTS
Zak et al[55]	2014	Novocart 3D	23	30.8 (22–46)	24 mo	4.1 cm^2	MFC 30.4 LFC 17.4 Trochlea 8.7 Patella 34.8 Multifocal 8.7	0% reop 0% fail	IKDC 69.8 Noyes 77.5 KOOS-Pain 86.5 KOOS-Symp 65.0 KOOS-ADL 91.5 KOOS-Sport 54.5 KOOS-QoL 51.6 Tegner 4.4 VAS 1.8	Significant improvement in clinical outcomes with 100% survivorship and no reoperations at 2 years; MOCART 73.2
Gobbi et al[67]	2015	HA + BMAC	18	45.5 (± 7.55)	54.2 mo	5.54 cm^2	Patella 33.3 Trochlea 11.1 Multifocal 55.6	33.3% reop	IKDC 82.5 KOOS-Pain 93.5 KOOS-Symp 90.6 KOOS-ADL 92.1 KOOS-Sport 79.7 KOOS-QoL 84.0 Tegner 6.1 VAS 0.3	No difference between trochlea and patella; 81% complete filling MRI

Abbreviations: ADL, activities of daily living; BMAC, bone marrow aspirate concentrate; HA, hyaluronic acid; IKDC, International Knee Documentation Committee; KOOS, Knee Injury and Osteoarthritis Outcome Score; KS-F, Knee Society Function score; LFC, lateral femoral condyle; MACI, Matrix Autologous Chondrocyte Implantation; Marx, Marx Activity Rating Scale; MFC, medial femoral condyle; MFx, microfracture; MRI, magnetic resonance imaging; MUA, manipulation under anesthesia; OCA, osteochondral allograft transplantation; PF, patellofemoral (bipolar); QoL, quality of life; RTS, return to sport; VAS, Visual Analogue Scale.

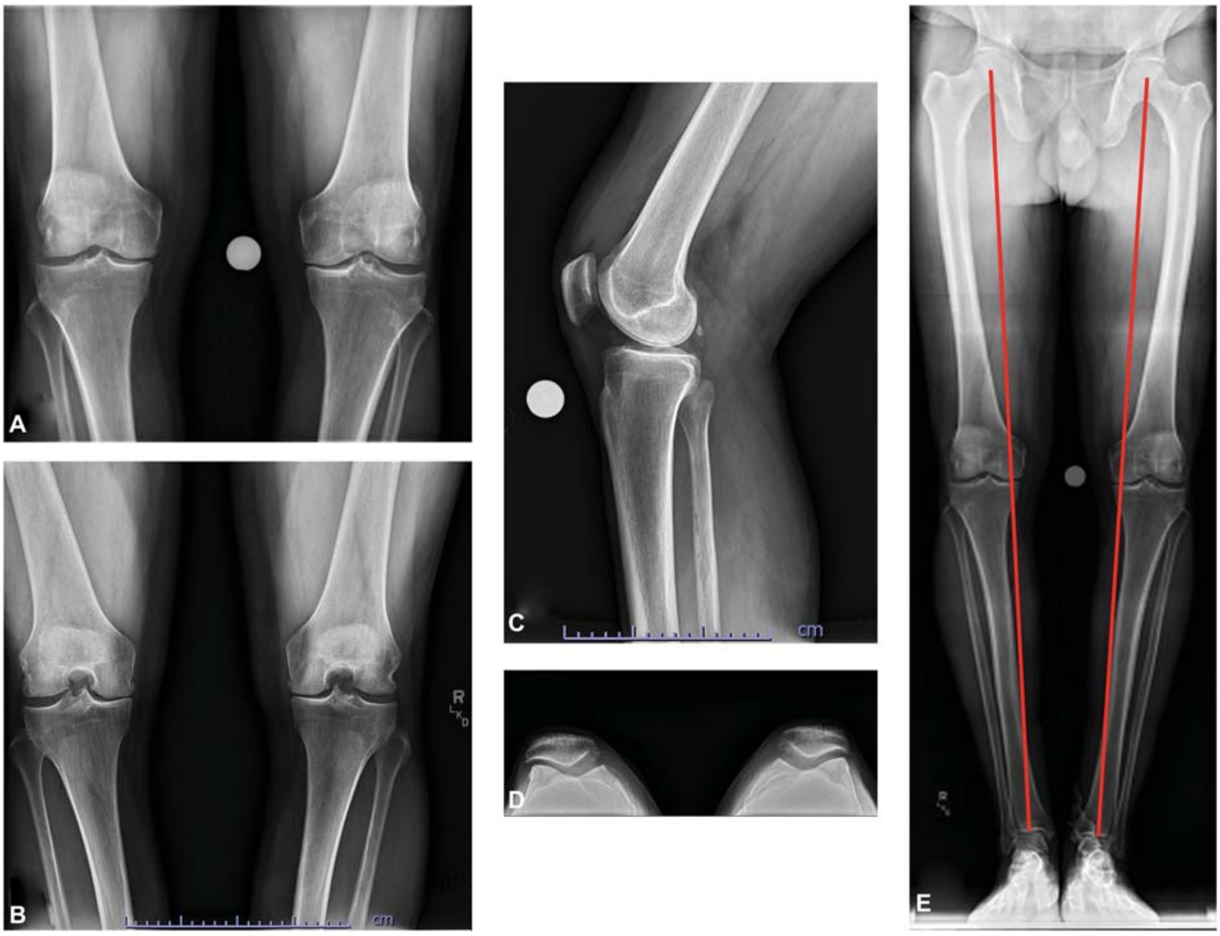

Fig. 1 Standard knee radiograph series including (**A**) weight-bearing AP, (**B**) PA flexion, (**C**) lateral, (**D**) Merchant, and (**E**) standing hip to ankle alignment view with the mechanical axis indicated by the red line. AP, anterior to posterior; PA, posterior to anterior.

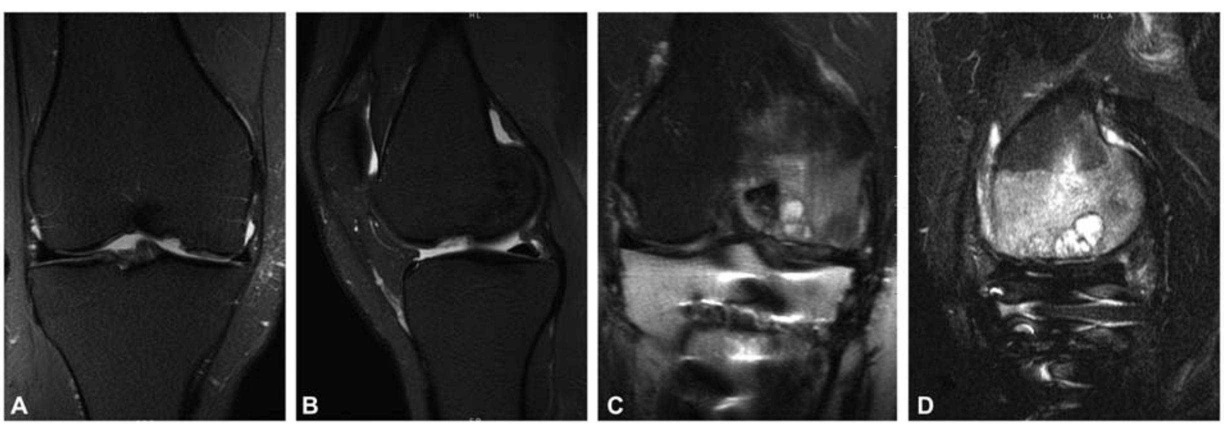

Fig. 2 Magnetic resonance imaging of the knee from two different patients with medial femoral condyle cartilage defects. On the left (**A** and **B**) is an isolated cartilage defect without surrounding bony edema; on the right (**C** and **D**) is a large cartilage defect with underlying subchondral bone cystic changes and extensive bony edema.

versatile, with the availability of bulk allografts and shell allografts depending on the size, depth, and location of the defect.

OCA utilizes fresh-stored cadaver bone and cartilage. Fresh-stored grafts maximize the viability of the chondrocytes and matrix of the hyaline cartilage. Frozen or processed grafts are thought to damage the viability of the living cartilage and therefore fresh-stored grafts are preferred. Several logistical hurdles of OCA have been overcome as commercial availability of fresh-stored OCAs has increased the accessibility of the grafts and have made their utilization more common.[11] One of the large hurdles was that grafts had to be harvested fresh and transplanted in a timely fashion as cell viability and viable cell density decreases with increased time between harvest and implantation.[11–13] Previous studies have demonstrated chondrocyte viability up to 28 days prior to implantation, although shorter storage times are associated with greater viability.[12,13] A recent study examining the clinical relevance of OCA storage time found that prolonged storage of up to 28 days is safe and effective with no significant difference in 5-year graft survivorship or patient-reported pain, function, and satisfaction.[14]

Surgical Indications

Given its composite nature, OCA can be utilized for a wide range of chondral and osteochondral pathology. Indications for OCA range from small to large chondral defects, especially when there is underlying osseous involvement at the location of the chondral defect. Along the same line, OCA is frequently utilized in revision situations where the lesion may be larger in size and/or involve the subchondral bone. While fresh precut OCA can be utilized in small defects (up to 2 cm^2), other lower cost and single-stage options including osteochondral autograft may be preferable. Therefore, OCA is typically reserved for medium to larger chondral defects ($> 2\,cm^2$), especially when osseous pathology is present. Additionally, OCA is preferred to osteochondral autograft in the patellofemoral joint as OCA can provide better matching of the contour and cartilage thickness while avoiding donor site morbidity.[15] When considering OCA transplantation, preoperative radiographs with sizing markers and/or advanced imaging can aid in the matching process. Surgeons work with the tissue bank to identify an appropriately sized donor match; an acceptable match is $\pm$ 2 to 3 mm.[9] The larger the defect, the more difficult it is to find a suitable match.[16]

Surgical Technique

An initial staging arthroscopy is often utilized to assess and debride the defect. The size of the defect should be measured after the debridement and slightly overestimated to ensure adequate size of the allograft. At the time of the definitive procedure, if not performed earlier, arthroscopy may be performed to address other potential intra-articular pathologies (e.g., a meniscus tear). An appropriate arthrotomy is performed and the defect is visualized and sized with a cylindrical sizing guide ensuring that the guide is perpendicular to the articular surface. The size of the defect should then be compared with the available allograft prior to reaming to confirm that the available allograft matches the size and contour at the corresponding location. The perpendicular central guide pin is then inserted through the cylindrical sizing guide and the defect is cored under saline irrigation to a depth of approximately 6 to 8 mm using the cannulated counter bore reamer. The exact depth is measured with a ruler at the 3, 6, 9, and 12 o'clock positions.[17]

The allograft is then secured into the harvesting jig. The appropriately sized bushing is positioned perpendicular to the surface of the graft. The donor allograft is marked at the position that corresponds to the 12 o'clock position on the recipient site to ensure that the contours match. Using copious irrigation, the appropriate size coring reamer creates an OCA cylinder. The plug is then cut using a saw at the appropriate length that matches the previously measured recipient site depth. The osseous edges of the allograft are then gently beveled using a rongeur or rasp for smooth graft insertion. Pulse lavage is used to wash the allograft clear of any residual blood and marrow cells to minimize the risk of a host immune response.[18] The donor plug is then inserted into the recipient site by hand using a press-fit technique rarely followed by gentle tamping if necessary, minimizing any excess pressure placed on the hyaline cartilage matrix and living chondrocytes, thus avoiding potential chondrocyte death.[19] The graft should sit flush with the surrounding native cartilage and not be left proud[20] (►**Fig. 3**). If the allograft plug remains loose despite press-fit, it can be secured using absorbable helical nails or twin-pitched screws. If the defect is too large for a single plug, a stacked "snowman" or an overlapping "MasterCard" technique may be used.

Outcomes

OCA transplantation in the knee has positive long-term clinical outcomes in the current literature, including in more active, high-demand populations.[21–27] In their systematic review including 291 patients, Assenmacher et al found that OCA transplantation led to a significant improvement in clinical outcome scores and what they deemed to be good durability and a successful outcome in 75% of patients at a mean follow-up of over 12 years postoperatively.[21] While historically, OCA was often used for revision and salvage cartilage pathology cases, Briggs et al showed that OCA can be an effective primary treatment for chondral and osteochondral defects in the knee.[23]

Patients who undergo OCA have demonstrated a high rate of return to sports. Krych et al[24] reported an 88% return to sport rate with a return to preinjury level in 79% of patients after OCA, while others have demonstrated similar successful return to sport rates after OCA.[25,28–30] Despite the high rate of return to sports at some level after OCA, evaluation of return to a physically demanding occupation in the military population has demonstrated less promising results. Thomas et al reported only a 63.9% return to a level of activity that allowed for completion of military duties after OCA for medium to large defects in the knee.[27] Similarly, Shaha et al in a small case series of 38 OCA transplantations in a military population demonstrated a return to full duty of only 28.9%, while 42.1% were unable to return to military duties of any kind because of their operative knee.[31]

OCA transplantation has a successful track record in revision cartilage surgery.[32–34] In their series of 163 patients who underwent OCA in a revision setting after a failed prior cartilage procedure (MST, osteochondral autograft, or ACI), Gracitelli et al found an OCA graft survivorship of 82% at 10 years and 74.9% at 15 years.[33] In a comparison of primary OCA to OCA after previous marrow stimulation procedure, Gracitelli et al showed an 86% graft survivorship with 97% of patients satisfied or extremely satisfied in the revision group.[34]

Importantly, OCA has demonstrated excellent long-term survivorship. One recent systematic review including the results of 19 studies on OCA in over 1,000 patients found that the mean OCA graft survival rate was 86.7% at 5 years, 78.7%

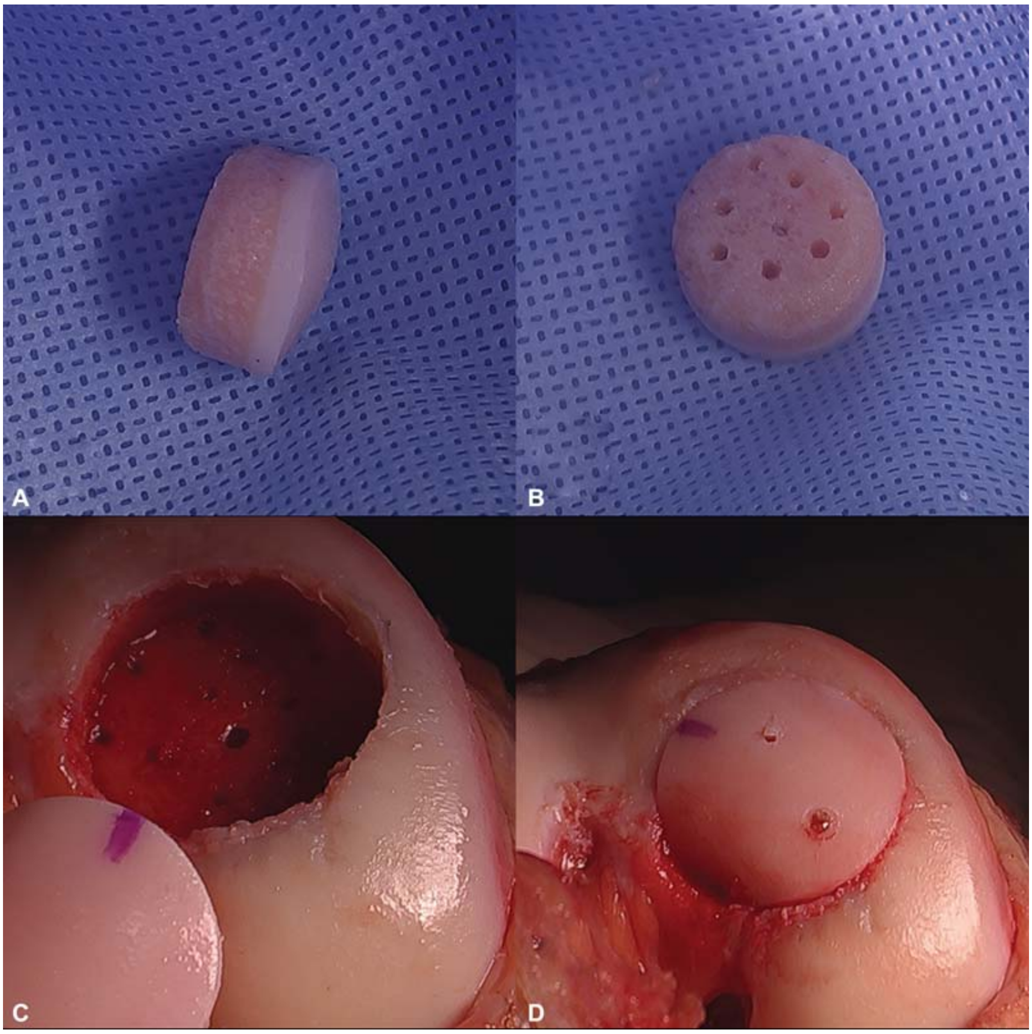

Fig. 3 Clinical photographs of a prepared osteochondral allograft plug with the (**A**) tapered edges of the bone and (**B**) the subchondral bone drilled. The plug is appropriately sized based on the (**C**) prepared defect and then (**D**) inserted into the defect.

at 10 years, 72.8% at 15 years, and 67.5% at 20 years.[35] However, very large defects that require multiple plugs using the "snowman technique" have demonstrated significantly inferior clinical outcomes, higher reoperation rates, and a greater rate of failure than isolated, single-plug OCA.[36]

Autologous Chondrocyte Implantation

ACI is a well-studied technique that is effective for cartilage defects of many sizes and is especially utilized in the treatment of large chondral defects. The ACI technique involves tissue engineering of harvested autograft articular chondrocytes, which are grown in culture and implanted into the cartilage defect during a second procedure. ACI has gone through multiple generations and is currently on its third generation: MACI. First generation ACI utilized an autologous periosteal patch harvested from the proximal tibia to span the cartilage defect and cover the cultured chondrocytes. With the common complication of graft hypertrophy often requiring reoperation, the periosteal patch fell out of favor. In the second generation of ACI, the periosteal patch was replaced with a porcine type I/III collagen membrane, which has demonstrated less graft hypertrophy, a good safety profile, and cost-effectiveness compared with autologous periosteal patch.[37,38] In the United States, this second generation of ACI has been replaced by the third generation: MACI. MACI is unique from the other two generations of ACI in that the chondrocytes are adhered directly to a porcine membrane, which is then used to be implanted into the cartilage defect. MACI is the first tissue-engineered autologous scaffold that has been U.S. Food and Drug Administration (FDA) approved in the United States. According to the FDA Web site, MACI is indicated for the repair of symptomatic, single, or multiple full-thickness cartilage defects of the knee with or without bone involvement in adults.[39] The benefits of MACI compared with earlier generations of ACI are the ease of technique (described below), uniform cell distribution, the potential for an accelerated rehabilitation timeline, and the ability to treat previously difficult to reach tibial defects.

Surgical Indications

ACI is a versatile cartilage restoration technique that can be utilized in a range of cartilage defects including various shapes, sizes, and locations; however, due to relatively positive results using more cost-effective techniques in smaller defects, ACI is typically reserved for large, full-thickness cartilage defects (> 3–4 cm^2) or in the revision setting when other restoration modalities have failed. Current FDA approval is for use only in the knee. Major indications for MACI include the patellofemoral joint, multifocal defects, tibial defects, or, as mentioned above, as an option for large solitary defects of the femoral condyles.[40,41] The application of MACI to other joints or to bipolar defects are FDA off-label indications. Contraindications include the presence of established osteoarthritis with greater than 50% joint space narrowing, obesity with a BMI greater than 35, and inflammatory arthritis. As in any cartilage restoration procedure, other articular pathologies including ligamentous instability, mechanical axis malalignment, and meniscal deficiency should be addressed either in a staged or concurrent fashion. Additionally, ACI is best suited with a solid osseous base where the subchondral bone is largely intact. However, the "sandwich" technique can be effectively utilized to simultaneously bone graft the defect while implanting the autologous chondrocytes in larger osteochondral defects.[42,43]

Surgical Technique

An initial staging arthroscopy is performed to assess and debride the defect and harvest the chondral biopsy. For MACI, approximately 200 to 300 mg of articular cartilage is required for the harvest and is often taken from the intercondylar notch and can be stored for up to 5 years. The cell expansion process takes approximately 3 to 4 weeks allowing the cells to reach 15 to 20 million. Cells are uniformly seeded onto the membrane just prior to shipping. Cell viability is reported at the time of implantation.

The second stage of MACI is performed via limited arthrotomy. The bed and edges of the defect are meticulously prepared, removing all degenerative tissue to create a stable rim and debride the zone of calcified cartilage to the subchondral bone layer[44] (►**Fig. 4A**). If the debridement of the subchondral bone is too aggressive, excessive bleeding may occur, which should be avoided. The depth of the defect is evaluated, and with defects deeper than 8 mm, the "sandwich" technique can be utilized.

The patch is removed from its container and placed rough (cell) side up (determined by a notch in the lower left corner of the graft). The graft is sized to fit the defect by using a precontoured guide. Alternatively, the graft can be cut to fit any shape using glove paper or foil as a template. The bony bed of the defect is then irrigated and meticulous hemostasis is obtained with the tourniquet deflated. A thin layer of fibrin glue is placed at the base of the defect. The implant is then laid into the defect, ensuring that the cell side is down toward the bone and that the implant is entirely contained within the prepared defect (►**Fig. 4B**). Another layer of fibrin glue is placed on the edges of the membrane and held in place by gentle thumb pressure for 3 to 5 minutes while the fibrin glue dries. If the defect is very large and uncontained, additional fixation can be achieved using small absorbable sutures to secure the implant to the adjacent native cartilage.

Outcomes

ACI has demonstrated promising outcomes in the literature, especially in large cartilage defects. In the Superiority of MACI Implant to Microfracture Treatment (SUMMIT) randomized controlled clinical trial, MACI demonstrated significantly better clinical outcomes in treating large cartilage defects (> 3 cm^2) than microfracture with a similar safety profile.[45] Their study reported improved 2-year functional and pain Knee Injury and Osteoarthritis Outcome Score (KOOS) following MACI for grade IV chondral lesions (average size 4.8 cm^2) compared with microfracture (KOOS function: microfracture 12.6 to 48.7, MACI 14.9 to 60.9; KOOS pain: microfracture 35.5 to 70.9, MACI 37.0 to 82.5). At 5-year follow-up, this greater improvement in clinical outcome scores with MACI over microfracture in large lesions remained statistically significant.[46] In a recent meta-analysis of randomized controlled trials, Gou et al found a significant benefit in activities of daily living, quality of life, and pain relief after ACI compared with microfracture.[47] However, they found no difference in the International Knee Documentation Committee (IKDC), Lysholm, or overall KOOS between ACI and microfracture.

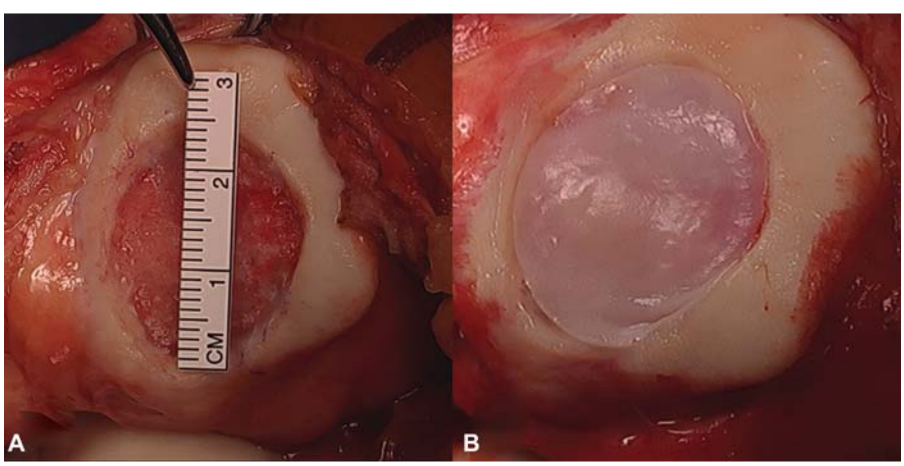

Fig. 4 Clinical photographs of a chondral defect in the patella (**A**) after preparation and (**B**) with the MACI implant cut to size and implanted into the defect. MACI, Matrix-associated Autologous Chondrocyte Implantation.

Ebert et al demonstrated high rates of patient satisfaction and improved clinical and radiographic results for isolated tibiofemoral chondral lesions at 5 years after arthroscopic MACI.[48] In another MACI study with 5-year follow-up, Marlovits et al showed a significant improvement in KOOS in 90.5% (19/21) of patients as well as in Magnetic Resonance Observation of Cartilage Repair Tissue (MOCART) scores with complete filling in 83% and complete integration in 82% of patients, despite bony edema on MRI persisting in up to 50% of patients.[49] Aldrian et al showed that significant improvements from baseline in IKDC, Noyes sports activity rating, and KOOS quality of life and pain scores were maintained in patients 10 years postoperatively following MACI for single or multifocal lesions; however, all scores showed some level of deterioration beyond 5 years postoperatively.[50] In this study, the average MOCART score at 10 years was 70.4, with complete defect filling seen in 73.9% of cases while residual subchondral edema was present in over 85% of cases.

The patellofemoral joint typically poses a difficult challenge in cartilage restoration due to the high contact pressures and the unique contours of the articular cartilage surface. Nevertheless, utilization of MACI to address cartilage defects in the patellofemoral joint has demonstrated comparable positive results to the tibiofemoral joint, when concomitant pathologies such as maltracking/malalignment, soft tissue deficiency, and instability are properly addressed.[51]

Samsudin and Kamarul performed a review of the multiple generations of ACI and did not demonstrate superiority of one generation over the others; however, their results suggested that ACI may be most appropriate for patients with larger defects or those who have failed other cartilage restoration procedures.[52] The importance of a preserved subchondral bone in ACI was confirmed in the systematic review by Lamplot et al, which demonstrated inferior outcomes in ACI after a failed cartilage procedure compared with primary ACI, especially when the index procedure compromises the subchondral bone as in MSTs.[53]

However, MACI has still been shown to produce good results in the treatment of large osteochondral lesions with significant depth of bony involvement (> 8 mm).[42,43,54] For these large bony lesions, a "sandwich" technique can be performed utilizing a bilayer collagen membrane, where impaction bone grafting of the lesions is first performed followed by application of a dual-stacked MACI implant.

Alternative Techniques and Treatments on the Horizon

There are numerous emerging techniques for cartilage restoration, many of which are not yet FDA approved and remain experimental in the United States. A few of the techniques that have demonstrated promise in the treatment of large cartilage defects include a different third-generation autologous chondrocyte implant (Novocart 3D), an aragonite-based scaffold (Agili-C), and a HA-based scaffold plus BMAC.

Third-Generation Autologous Chondrocyte Implant: Novocart 3D

Novocart 3D (Aesculap Biologics, LLC, Breinigsville, PA) is a third-generation ACI product that is not yet approved by the FDA in the United States, but is currently in phase 3 clinical trials. Novocart 3D utilizes a collagen-chondroitin sulfate biphasic scaffold membrane, compared with MACI, which utilizes a type I/III porcine collagen matrix. Additionally, Novocart 3D is fixed into the defect in a similar manner as earlier ACI generations using absorbable sutures or small bioresorbable pins. In a case series by Zak et al on the treatment of large focal chondral and osteochondral defects in the knee with Novocart 3D, the authors reported significant improvement in clinical outcome scores and follow-up MRI results at 2 years postoperatively[55] (►Fig. 5). One major complication with the early generation ACI procedures was graft hypertrophy. Niethammer et al examined the incidence of graft hypertrophy 2 years after Novocart 3D implantation and found a significantly higher incidence of graft hypertrophy in the patients who had an acute injury or osteochondritis dissecans lesion.[56] Their group has also demonstrated a graft maturation time of at least 1 year and an improvement in clinical outcomes despite persistent bone marrow edema at 3 years postoperatively.[57,58] In a more recent follow-up study by Niethammer et al, they found graft maturation to be completed at 2 years and reported a 22% rate of graft hypertrophy, although this did not correspond to reduced cartilage quality at 4 years postoperatively.[59] In a study comparing primary Novocart 3D to Novocart 3D for revision after failed MST in large cartilage defects (mean 5.4 cm^2), Müller et al demonstrated significantly improved clinical outcome scores in both groups, although with significantly

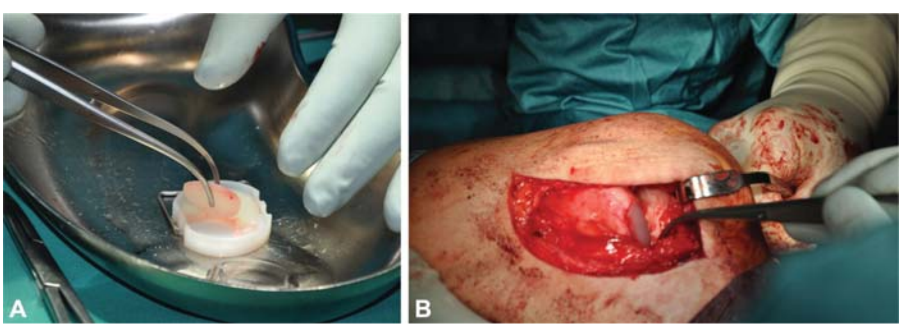

Fig. 5 Clinical photographs of the Novocart 3D scaffold (A) being prepared and (B) after implantation. (© 2014. Reprinted with permission of SAGE Publications, Inc. from Zak L, Albrecht C, Wondrasch B, et al. Results 2 years after matrix-associated autologous chondrocyte transplantation using the Novocart 3D scaffold: An analysis of clinical and radiological data. Am J Sports Med. 2014;42(7):1618–1627.)

Fig. 6 Tapered aragonite-based Agili-C implant. Image Courtesy: Kon et al. 2016.[63]

better outcomes in the primary group.[60] There were no revision surgeries in the primary Novocart 3D group, while the revision group had a 30% reoperation rate.

Aragonite-Based Scaffold: Agili-C

Another technique on the horizon for the treatment of large cartilage defects that is not yet approved for clinical use in the United States is an aragonite-based scaffold known as Agili-C (CartiHeal, Kfar Saba, Israel). Aragonite, which is composed of inorganic calcium carbonate, is the mineral that makes up the endoskeleton of coral. Agili-C is a cell-free, porous, biocompatible, and resorbable biphasic aragonite scaffold (►**Fig. 6**). Previous animal studies have shown promising results with a resorption of the implant that was replaced by trabecular bone and a regeneration of overlying hyaline cartilage.[61,62] An early human clinical trial in medium-sized defects (mean 2.5 cm^2) showed a significant improvement in clinical outcomes with no reoperations at 1-year postoperative follow-up.[63] Finally, in an ex vivo model, Chubinskaya et al demonstrated the potential for chondrocytes in culture to migrate to the Agili-C implant and contribute to the creation of an extracellular matrix made up of type II collagen and aggrecan with progenitor-like cells on the surface of the implant. Together, these studies demonstrate the potential of Agili-C as an effective cartilage restoration technique that can be performed in a single stage.[64] Agili-C is currently in the process of enrolling for an FDA Investigational Device Exemption clinical study. This phase III clinical study is a prospective, multicenter, open-label, randomized controlled trial of Agili-C versus the surgical standard of care (microfracture or debridement) for the treatment of cartilage lesions of the knee.[65] Interim analysis has yielded favorable results demonstrating sufficient safety and efficacy that future enrollments have been suspended due to anticipated success.[66]

BMAC with Hyaluronan Scaffold

BMAC on a HA-based scaffold has demonstrated promising results in the management of large cartilage lesions. In a study comparing a HA-based scaffold plus BMAC to MACI for large patellofemoral cartilage defects, Gobbi et al found a significant improvement in clinical outcomes from baseline in both groups with no significant difference between groups at a minimum follow-up of 3 years postoperatively[67] (►**Fig. 7**). MRI showed complete fill of the defect in 81% of the BMAC patients with hyaline-like qualities on histological analysis. Another study by Gobbi et al examining BMAC on an HA scaffold for large cartilage lesions (mean 8.5 cm^2), demonstrated significant improvements in clinical outcomes scores (KOOS, Tegner, and IKDC) in patients older and younger than 45 years of age with complete filling of the defect on MRI in the vast majority of patients (80% > 45 years, 71% < 45 years), and again hyaline-like tissue on histological analysis.[68] Additionally, treatment of full-thickness cartilage defects with BMAC on a HA scaffold in a single-stage repair demonstrates significantly better clinical outcomes and durability compared with microfracture at 5-year follow-up.[69]

Other Single-Stage Options

Particulated juvenile allograft cartilage (PJAC), known commercially as DeNovo NT (Zimmer Biomet, Warsaw, IN), is a minced allograft juvenile hyaline cartilage that can be used for defects of varying shapes and sizes. These immature chondrocytes have demonstrated increased proliferative activity, cell density, and metabolic activity compared with adult chondrocytes.[70,71] A single packet of PJAC covers approximately 2.0 to 2.5 cm^2, so for larger defects, multiple packets would be required. While no long-term clinical data are currently available for PJAC in the human knee, short-term results in the patella, trochlea, and femoral condyle have demonstrated promising outcomes in mostly small and medium-sized defects. Patients who underwent PJAC demonstrated significantly improved clinical outcomes including pain and function, MRI demonstrating good fill of the defect with normal appearing articular cartilage, and histological analysis showing a combination of hyaline and fibrocartilage.[72–74]

A similar technique to PJAC that utilizes autologous cartilage is particulated autologous cartilage implantation (PACI). PACI uses the patient's own cartilage cells, which are harvested and reimplanted in a single procedure. This technique involves harvesting a small amount of autologous cartilage (200–300 mg), mincing it on the back table and then reimplanting it back into the cartilage defect and securing it into place with fibrin glue and a porcine type I/III collagen- or HA-based membrane. PACI has demonstrated favorable outcomes when compared with microfracture; however, there is no long-term clinical data available for the utilization of PACI in the knee.[75]

Autologous Matrix-Induced Chondrogenesis (AMIC) utilizes marrow stimulation with drilling or microfracture that

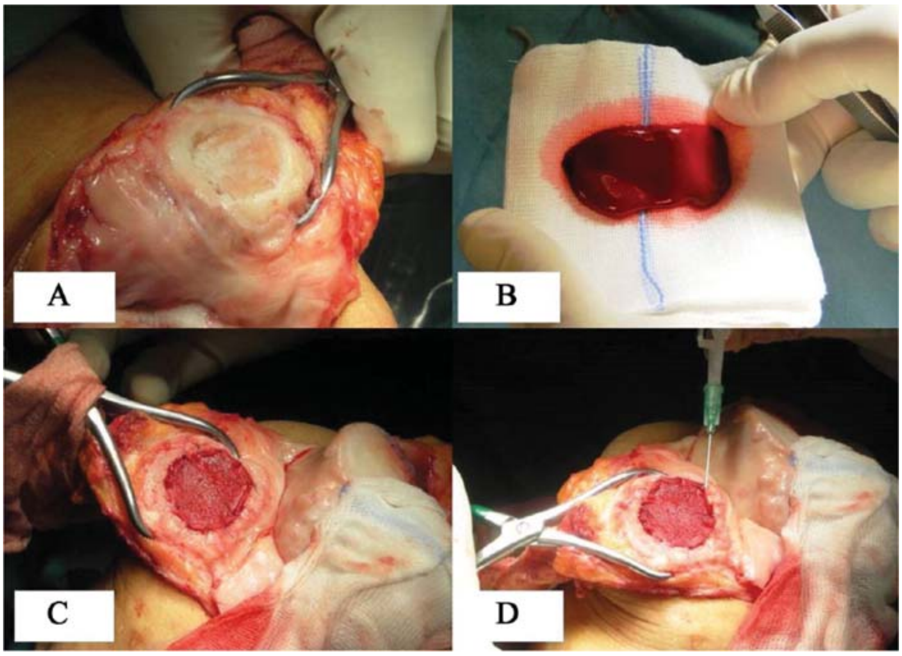

Fig. 7 BMAC implantation: (**A**) prepared bed of chondral defect in patella, (**B**) BMAC clot after activation, (**C**) clot inserted into bed of defect, and (**D**) scaffold stabilized with fibrin seal. (© 2015. Reprinted with permission of SAGE Publications, Inc. from Gobbi A, Chaurasia S, Karnatzikos G, Nakamura N. Matrix-induced autologous chondrocyte implantation versus multipotent stem cells for the treatment of large patellofemoral chondral lesions: a nonrandomized prospective trial. *Cartilage*. 2015;6(2):82–97.) BMAC, Bone Marrow Aspirate Concentrate.

is covered with a porcine type I/III collagen- or HA-based membrane fixed with fibrin glue. This membrane serves as a scaffold to which the marrow elements adhere, differentiate and grow, forming hyaline-like cartilage tissue. AMIC has demonstrated decreased pain and improved functional outcome scores postoperatively.[76–78] While the results of AMIC have been promising, current evidence is insufficient to recommend a specific range of defect sizes in the knee that can be treated with AMIC.

Another option is cryopreserved viable OCA (CVOCA) (Cartiform, Osiris Therapeutics, Inc, Columbia, MD), which contains full-thickness articular cartilage along with a thin layer of underlying subchondral bone. The structure of CVOCA allows for an intact native cartilage architecture with viable chondrocytes, chondrogenic growth factors, and extracellular matrix proteins to promote articular cartilage repair.[79] A small clinical case series of 3 patients demonstrated "satisfactory" results without adverse events at 2 years, but further research is needed.[80]

Other viable cartilage allografts include CartiMax (MTF Biologics, Edison, NJ) and ProChondrix (AlloSource, Centennial, CO), although no substantial clinical data are available. Additional technologies have been introduced to address the availability and matching issues surrounding fresh-stored OCA. One technology previously introduced as a single-stage cartilage restoration option to help solve the limited access to fresh OCA is a decellularized OCA (Chondrofix, Zimmer Biomet, Warsaw, IN). However, this product demonstrated high failure rates of up to 72% within the first 2 years, with higher failure rates associated with larger defects.[81,82]

Conclusion

Large, focal articular cartilage defects of the knee can be a source of significant morbidity for patients and often require surgical intervention. The treating surgeon must consider patient- and lesion-specific factors and plan to optimize concomitant limb- and joint-specific comorbidities. In the management of large cartilage defects, the two classically utilized cartilage restoration procedures with significant long-term data are OCA transplantation and ACI. Emerging techniques are either in clinical trial or currently available for use with limited supporting evidence. Comprehensive presurgical work-up often including staging arthroscopy is critical. Meticulous surgical technique and adherence to rehabilitation guidelines will maximize the chance of a favorable outcome. With appropriate surgical indications, cartilage restoration options for large focal defects have a proven track record with sustained subjective and objective improvement.

Conflict of Interest

S. L. S. reports personal fees from Joint Restoration Foundation, personal fees from Olympus, personal fees from Smith and Nephew, personal fees from Vericel, personal fees from Arthrex, personal fees from ConMed, personal fees from Flexion Therapeutics, personal fees from Vivorte, outside the submitted work.

J. F. reports other from Active Implants, personal fees from Aesculap/B.Braun, from American Journal of Orthopedics, personal fees and other from Arthrex, Inc., personal fees from Biopoly, LLC, personal fees from Cartiheal, other from Cartilage, personal fees from Cook Biotech, Inc.,

other from Episurf, personal fees from Exactech, other from Fidia Pharma, other from JRF Ortho, personal fees from MedShape, Inc., personal fees and other from Moximed, Inc., other from Novartis, personal fees and other from Organogenesis, personal fees from Ortho Regenerative Tech, Inc., personal fees from Regentis, personal fees and other from Samumed, Inc., personal fees and other from Springer, personal fees and other from Thieme Medical Publishers, Inc., personal fees and other from Vericel, other from ZimmerBiomet, personal fees from ZKR Orthopedics, Inc., outside the submitted work.

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