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Particulated articular cartilage for symptomatic chondral defects of the knee

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Abstract The treatment of focal cartilage defects in the knee remains a challenging clinical problem. One relatively new unique treatment option is particulated articular cartilage, which includes autograft and off-the-shelf allogeneic juvenile grafts. The use of particulated cartilage has the advantage of being a single-stage procedure. In the case of autograft, it is cost efficient, while in the juvenile allograft form, it may have increased proliferative and restorative potentials. Laboratory and clinical data are limited for particulated cartilage grafts; however, there are promising histologic and clinical outcomes. This review provides a summary of the indications, surgical technique, and most up-to-date research on particulated cartilage for the repair of symptomatic chondral defects in the knee.

Keywords Juvenile cartilage · Cartilage repair · Particulated cartilage · Tissue regeneration · Cartilage transplant

Introduction

Articular cartilage defects are a common source of pain and disability in the knee, with somewhere between 30,000 and 100,000 chondral procedures performed every year in the USA [1]. Orthopedic surgeons in the USA have a limited number of techniques at their disposal to address symptomatic cartilage defects, each with a unique set of limitations that continue to encourage research into novel therapies that combine clinical ease of use with proven efficacy [2].

Particulated articular cartilage grafts were born out of these research efforts. The first use of adult particulated articular cartilage was published in the German-language literature in 1983 [3]. Years later, scientists at DePuy Mitek® launched similar experiments in mouse, goat, and finally horse models [4, 5]. Mechanical mincing of cartilage into 1–2-mm pieces was the critical innovation for successful cartilage repair. Effectively, this allows chondrocytes to escape from their surrounding extracellular matrix, migrate to surrounding tissues, and form a new hyaline-like cartilage tissue matrix [4–6]. DePuy Mitek® created the proprietary cartilage autograft implantation system (CAIS) for clinical use based on these animal studies. The Food and Drug Administration (FDA) approved a prospective randomized pilot study comparing CAIS with microfracture [7]. With the promising results of the pilot study, DePuy Mitek® initiated a large multicenter pivotal randomized control study. Unfortunately, the enrollment of patients was slow and CAIS was eventually discontinued on the basis of cost and return on investment considerations.

During the time frame of preclinical CAIS work, scientists at Zimmer® were developing an engineered cartilage construct from cells obtained from infantile/juvenile donors. After a small successful equine series, it was released for clinical use as particulated juvenile articular cartilage allograft (PJAC) with the proprietary name of DeNovo [6, 8] (DeNovo NT, Zimmer, Warsaw, IN). Note that PJAC was immediately available for clinical use as opposed to CAIS® or engineered cartilage (DeNovo ET®) in light of the way the FDA oversees tissues: they do not regulate minimally manipulated human tissue allograft under 361 HCT/P regulation.

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The proposed advantages of DeNovo NT are the availability of unlimited graft material for large lesions and the more robust activity of juvenile chondrocytes as compared to adult chondrocytes [6, 8]. Gene expression profiles in juvenile chondrocytes are more favorable for cartilage repair than in adult chondrocytes [9]. Specifically, genes that direct cartilage growth and expansion are upregulated [9]. In addition, juvenile chondrocytes have increased metabolic activity, cell density, and proliferation rate [10, 11]. Cartilage explants for DeNovo NT are obtained from the femoral condyle of donors aged 0–13 years. Each package contains tissue from a single donor, with anywhere between 30 and 200 cubes of tissue. These cartilage fragments are viable for 45 days from the time of harvest, making it a fresh allograft. Each package is intended to cover defects up to 2.5 cm^2, so multiple packets can be necessary for larger lesions. We will refer generically to the technique as PJAC.

The object of this review is to describe the indications, surgical technique, pitfalls, and clinical outcomes data from the last 3 years pertaining to PJAC for symptomatic chondral defects of the knee.

Indications/contraindications

While PJAC is a fresh chondral allograft, it shares similar indications to autologous chondrocyte implantation and matrix-induced chondrocyte implantation, and should be treated as a cell-based therapy in the surgical decision-making process [2, 6]. PJAC is indicated for the treatment of symptomatic chondral defects of the patellofemoral or tibiofemoral compartments in patients typically less than 55. However, physiologic age and the knee environment (status of remaining cartilage) is the true driver behind the decision to pursue non-arthroplasty treatment of a chondral defect [2]. PJAC should only be considered for lesions that are at least grade 3 or higher on the International Cartilage Repair Society (ICRS) scale (i.e., involving more than 50 % of the cartilage depth). While not clearly defined, most experts agree that lesion size after debridement should be between 1 and 6 cm^2 [6]. Finally, for optimal results, the patient's body mass index (BMI) should be below 35 kg/m^2.

The classic contraindications to PJAC include ICRS grade 1 or 2 lesions, extensive subchondral bone edema, uncorrected ligamentous instability, malalignment or meniscal deficiency, and osteochondritis dissecans lesions with >6 mm of subchondral bone loss (unless concomitant bone grafting) [6]. Relative contraindications are bipolar lesions that could shear against each other (may be protected with biologic patch to obviate this potential) or bone marrow lesions (noting that they may be concomitantly addressed). In addition, the understanding of the role of lesion containment and subchondral integrity status is still evolving. While the most stringent criteria for PJAC exclude uncontained lesions or lesions with subchondral bone insufficiency, the authors have had successful clinical results using collagen I/III membranes and suture anchors to contain grafts and using a "sandwich" technique of bone grafting followed by PJAC in the setting of focal, non-structural subchondral insufficiency.

Surgical technique

The authors' preferred surgical technique is shown in Fig. 1. The first step in surgical management should always be a diagnostic arthroscopy to look for concomitant pathology or lesion characteristics that would contraindicate the use of PJAC [6]. While arthroscopic application of PJAC has been described in the talus [12], we prefer an open technique through a small arthrotomy [6]. A lateral parapatellar arthrotomy is used for lesions of the patella, trochlea, and lateral femoral condyle, while a vastus-sparing medial parapatellar arthrotomy is used for defects of the medial femoral condyle [6]. If concomitant tibial tubercle osteotomy or meniscal allograft transplantation is planned, a single midline longitudinal incision can be used, and full-thickness skin flaps elevated to expose the medial or lateral retinaculum as necessary.

The chondral defect is then prepared using standard principles of cell therapy. The edges of the defect are delineated with a #15 scalpel, with the goal of creating stable, vertical peripheral walls [6]. The base of the defect is then cleared of diseased cartilage using ring curettes, taking care to completely remove the calcified cartilage layer without violating the subchondral bone. We recommended deflating the tourniquet at this stage to ensure that no significant bleeding is occurring in the base of the lesion, as this could dislodge the cartilage graft. If the subchondral bone is entered and bleeding is encountered, this can easily be controlled with epinephrine-soaked cottonoids and the application of fibrin glue under digital pressure to the base of the lesion [6].

The PJAC graft can be prepared either directly in the defect or on the back table using a mold technique [6]. If the graft will be prepared directly in the chondral defect, the patient's knee should be carefully positioned to place the defect base as close to horizontal as possible, minimizing the risk of graft displacement during application. This is most easily achieved in patellar and trochlear defects, using a combination of operative table Trendelenburg and hip flexion. Excess media is aspirated from the package using the flexible plastic portion of a shielded intravenous catheter. The minced cartilage pieces are then applied directly to the base of the defect. They should be spaced every 1–2 mm as a monolayer, and should sit approximately 1 mm below the surrounding shoulders of intact cartilage. Creating a graft that is proud may lead to increased compressive and shear loads on the graft, and may

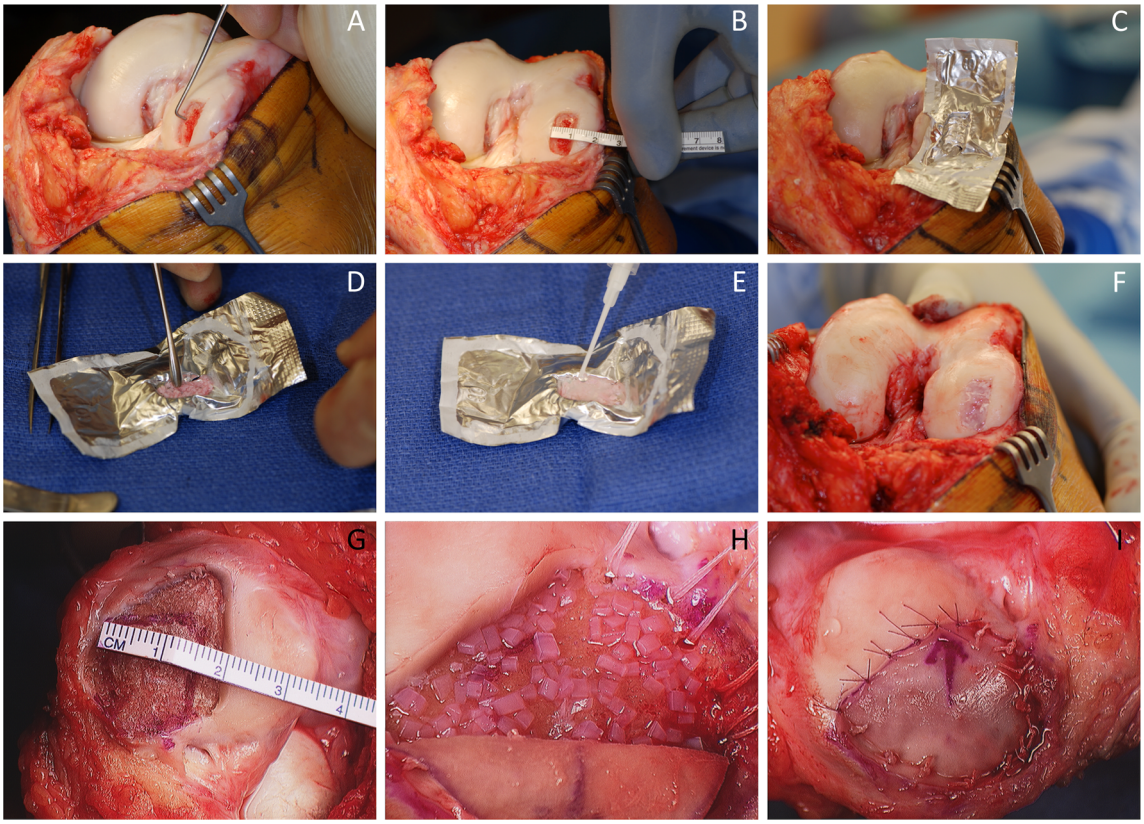

Fig. 1 Surgical Technique. Joint access is obtained with a parapatellar arthrotomy after completion of diagnostic arthroscopy. The chondral defect is then debrided to a bleeding base, taking care to create stable vertical edges (**a**). The defect is then sized using a flexible ruler (**b**). A thin sheet of sterile foil is then pressed into the defect to create a negative mold (**c**). On the back table, the particulated cartilage fragments are placed as a monolayer into the mold, spacing them every 1–2 mm (**d**). Fibrin glue is then used to fill the mold, making sure to keep the glue 1 mm recessed from the highest point of the mold (**e**). Once the pre-shaped implant is stable, a layer of fibrin glue is applied to the base of the defect, the implant is inserted, and a final layer of fibrin glue is used to secure the graft (**f**). For large defects that will be subject to high shear forces (such as the large patellar defect shown in (**g**)), particulated cartilage can be applied directly to the bed of the defect (**h**), fixed with fibrin glue, then covered with a collagen I/III membrane, which is sewn in using standard techniques from autologous chondrocyte implantation (**i**)

compromise graft stability post-operatively [6]. The minced cartilage is then covered with fibrin glue and allowed to set for 3–10 min. The knee is then taken through a range of motion to confirm implant stability under direct visualization.

If the surgeon chooses to prepare the graft on the back table, a thin piece of sterile foil is pressed into the defect to create a concave mold. The minced cartilage is then placed into the mold using the same technique as above, paying careful attention to spacing of the cartilage pieces. Fibrin glue is applied into the mold so that it rests 1 mm below the top of the mold. Once the pre-shaped implant is stable, a layer of fibrin glue is applied to the base of the defect, the implant is inserted, and a final layer of fibrin glue is used to secure the graft [6]. Implant stability with passive knee range of motion should be confirmed. Vigorous irrigation should be avoided after graft implantation. The arthrotomy is closed using absorbable #1 braided suture and standard skin closure is performed.

If the surgeon is concerned about shear forces on the graft, or the lesion is uncontained, a commercially available collagen I/III membrane can be sutured using 6-0 absorbable braided suture to the surrounding cartilage shoulders, or using suture anchors for an uncontained lesion. The technique of membrane application is identical to that used in autologous chondrocyte implantation [13].

In the setting of osteochondritis dissecans defects, there can be focal, non-structural insufficiency of the subchondral bone. In these cases, the bony bed is debrided to a healthy margin and drilled using a smooth K-wire to allow egress of marrow contents. Cancellous autograft bone is then impacted into the base of the defect until it is flush with the surrounding subchondral plate. Standard PJAC grafting is then performed.

Post-operative rehabilitation

All patients are placed in a hinged knee brace locked in extension at the completion of surgery. Distinct rehabilitation protocols are then recommended based on whether the graft was placed in the patellofemoral or tibiofemoral compartment [6].

For patellofemoral grafts, full weight bearing in extension is allowed immediately if no concomitant osteotomy was

performed. If a tibial tubercle osteotomy was performed, patients are non-weight bearing for 2 weeks and partial weight bearing from 2 to 4 weeks. The hinged knee brace should be locked in extension for 1 week during weight bearing, and can then be unlocked and worn during daytime only from 1–4 weeks. The brace can then be discontinued. A continuous passive motion machine (CPM) is used out of the brace for 6 h daily starting from 0° to 30°, with the goal of reaching 90° at 2 weeks, and near full motion at 6 to 8 weeks. The CPM can then be discontinued. Quadriceps sets, straight leg rises in the brace, calf pumps and leg hangs to 45° are encouraged immediately after surgery. At 2 weeks, patellofemoral and tibiofemoral mobilizations are started, in addition to side-lying hip and core strengthening. Gait training and closed chain strengthening can start at 8 weeks, and patients can progress to elliptical, swimming, and biking as tolerated after 12 weeks. Return to full activities is anticipated around 8 months.

For tibiofemoral grafts, patients are limited in weight bearing for 2 weeks for small lesions, and 6 weeks for larger lesions. The hinged knee brace is worn locked in extension for 2 weeks and then discontinued. CPM is initiated immediately from 0° to 40° then progressed 5° to 10° daily as tolerated, with the goal of achieving full range of motion at 6 to 8 weeks. Quadriceps sets, straight leg rises in the brace, calf pumps, and passive leg hangs to 90° are encouraged immediately after surgery. Gait training and closed chain strengthening can start at 8 weeks, and patients can progress to elliptical, biking, and swimming as tolerated after 12 weeks. Return to full activities is anticipated around 8 months.

Laboratory research

Much like the clinical literature, few studies have been performed in the last 3 years in the laboratory. Perhaps the most clinically relevant study is one performed in a rabbit model comparing the efficacy of adult autologous, juvenile allogeneic, and combined adult/juvenile particulated cartilage grafts for the restoration of trochlear defects [14]. While only six to nine animals were treated with each method, the authors show early evidence that combined autologous and juvenile allogeneic transplants may provide higher quality cartilage repair tissue based on macroscopic, microscopic, and immunohistochemistry grading scales [14].

The other primary focus of laboratory research has been the development of a composite scaffold for the delivery of autologous particulated cartilage [15–17]. The authors demonstrated in a rabbit model that chondral defects of the knee could be effectively treated with autologous particulated cartilage delivered in a composite scaffold made of hyaluronic acid felt, fibrin glue, and platelet rich plasma [16]. These results were then replicated in a goal model [17]. However, they have not shown superiority of this technique to simple transplantation of autologous particulated cartilage in fibrin glue. In a subsequent in vitro study using human cell cultures, the same group showed that outgrowth of human chondrocytes from the same composite scaffold was age-dependent (younger cartilage was more likely to proliferate), and that outgrowth could be promoted using two growth factors: transforming growth factor β1 (TGF-β1) and granulocyte colony stimulating factor (G-CSF) [15].

Clinical outcomes

At the time of publication of our prior review on particulated articular cartilage [6], only two case series [8, 18] totaling five patients were available to document the outcomes of the procedure. In the last 3 years, several new studies have added to our understanding of this emerging technique [19, 20•, 21, 22•, 23, 24, 25•].

The highest quality data available come from a prospective, multicenter single-arm study reporting the clinical, radiographic, and histological outcomes at 2 years after particulated juvenile articular cartilage grafting [22•]. The authors report their results on 29 lesions (18 femoral condyle, 11 trochlea) in 25 patients. These patients were predominantly male (72 %), young (mean age 37 years), and of normal weight (mean BMI 25.6). All patients had ICRS grade 3 or 4 defects. Mean defect size was 2.7 cm^2. Significant improvements were seen at all time points from 3 to 24 months in International Knee Documentation Committee (IKDC) subjective, visual analog pain and all knee injury and osteoarthritis outcome score (KOOS) subcategory scores. Progressive filling of the defects was seen on MRI, from 43 % at 3 months to 109 % at 24 months. T2 cartilage signal grading on MRI also showed a growing percentage of the graft having signal identical to intact cartilage (up to 40 % at 24 months). Eleven of the 25 patients agreed to an elective diagnostic arthroscopy at 2 years, and biopsies were available from eight of these patients. Nine of the 11 grafts were graded >9 (nearly normal) on the ICRS repair scale. One graft had partially delaminated (~10 %) in a patient with effusion and pain, and one graft had completely delaminated in an asymptomatic patient. The majority of grafts that were biopsied showed a well-integrated mixture of hyaline and fibrocartilage in varying ratios. Cartilage fibrillation and chondrocyte necrosis were typically low. Adverse effects were well documented, and were commensurate in frequency and nature with those reported for similar cartilage restoration procedures [22•]. The most common adverse effects were a joint effusion and stiffness.

A retrospective case series of 15 patients undergoing PJAC grafting for ICRS grade 4 chondral defects of the patella was published in 2013 [25•]. MRI and functional outcome scores (KOOS, IKDC subjective, Visual analog pain, Tegner, and Kujala) were collected at a mean follow-up of 28 months. The patients were young (mean age 26.4 years) and evenly

distributed between men (53 %) and women (47 %). Mean defect size was 2.4 cm^2. Normal or nearly normal cartilage repair tissue was seen on MRI in 73 % of patients, while three patients had mild graft hypertrophy, and two had severe graft hypertrophy requiring surgical debridement. Mean defect fill on MRI was 89 %. Good to excellent functional outcome scores were reported; however, there were no baseline scores available for comparison.

A similar retrospective case series was published in 2014 [20•]. Thirteen patients undergoing PJAC grafting of high-grade chondral defects of the patella were retrospectively reviewed. The patients were younger than in other studies (mean age 22.4 years) and predominantly female (77 %). Mean defect size was 2.3 cm^2. Six patients underwent concomitant tibial tubercle osteotomy. Unfortunately, mean follow-up was only 8 months. Significant improvement was seen in the KOOS global score; however, no significant differences were seen in any of the KOOS sub-scores or the WOMAC scores. No re-operations were documented.

The histological appearance of PJAC at 3 years was reported in a study of a single patient [24]. PJAC grafting was performed concomitantly with a high tibial osteotomy in a 44-year-old woman with a large (7.9 cm^2) uncontained full-thickness defect of the medial femoral condyle with significant subchondral edema, medial meniscal deficiency, and varus malalignment. The patient failed this treatment rapidly, and subsequently had an osteochondral autograft plug and then a unicompartmental arthroplasty. A biopsy of the PJAC graft at the time of arthroplasty (3 years after index procedure) showed a heterogeneous mix of poor quality hyaline and fibrocartilage. This study is likely not a fair assessment of PJAC, however, given the inhospitable knee in which it was implanted.

While this review focuses on the use of PJAC in the knee, simultaneous advances in its use in the ankle have been described. Several authors have now documented successful arthroscopic implantation of PJAC into talar lesions [12, 19, 23]. This technique may prove useful in other constrained joints such as the elbow or hip. The clinical results for talar lesions have been reported in a single retrospective case series of 24 ankles in 23 patients (12 male, 11 female) [21]. Mean patient age was 35 years and mean defect size was 1.2 cm^2. Patients were followed for an average of 16 months. Good to excellent functional outcome scores were reported, though no baseline scores were available for comparison. A single re-operation was performed for a partial graft delamination.

Finally, there has been a renewed interest in the use of particulated autologous cartilage, despite the withdrawal of DePuy's® CAIS® [26•]. In a small prospective cohort of eight patients, osteochondritis dissecans lesions of the knee were treated with "autologous dual-tissue transplantation" [26•]. The bony defect was first packed with morselized cancellous bone from the proximal tibia, and the cartilage defected then filled with particulated autologous cartilage from the non-weight bearing portion of the trochlea embedded in fibrin glue. Mean patient age was 32 years and the mean defect size was 3.1 cm^2. At 1 year, the authors reported significant improvements in IKDC subjective, KOOS, and Tegner scores. Furthermore, magnetic resonance observation of cartilage repair tissue (MOCART) scores improved significantly, and 80 % bony filling of the osseous defects was noted. This offers promising evidence for a simple and cost-effective technique to address osteochondral defects of the knee, and lends support to the "sandwich" technique of bone grafting followed by application of particulated cartilage, whether it is autologous or allogeneic juvenile tissue.

Pitfalls and complications

While PJAC is technically simple, it is the decision-making to indicate the procedure that remains the most challenging and risk-fraught. Though significant additions to the literature have been made in the last 3 years, it remains sparse and cannot support conclusive indications and contraindications to PJAC.

Nonetheless, based on the results available, certain inferences can be made. First, the reports of successful PJAC in the knee include relatively small lesions (<3 cm^2 on average) [22•, 25•]. While traditionally indicated up to 5 cm^2, the outcomes of PJAC in larger defects (3–5 cm^2) are still poorly documented. In contrast, defect location does not have a clear effect on outcomes. Successful results have been described in the patella [20•, 25•], trochlea [22•], and femoral condyles [22•]. Finally, while there are no clear differences between outcomes of patellofemoral PJAC performed with or without a simultaneous unloading tibial tubercle osteotomy, this should be followed closely in light of the superior results in most chondrocyte implantation studies when tibial tubercle surgery is added [20•, 22•, 25•].

Another challenging question is whether PJAC should truly be used as a single-stage procedure for symptomatic chondral defects. While treating a chondral defect with PJAC at the index procedure is conceptually appealing, there is emerging evidence that simple debridement may be sufficient to provide durable pain relief in a large portion of these patients. An ongoing study at our institution has shown that 75 % of patients undergoing a biopsy for planned autologous chondrocyte implantation (ACI) elect not to proceed with the graft, the most common reason being complete symptomatic relief. Thus, there may still be a role for chondral debridement with the creation of stable vertical walls prior to considering more expensive treatments such as PJAC. A formal cost-effectiveness analysis would be required, however, to determine the optimal strategy.

Intra-operative pitfalls include graft displacement during fibrin glue setting from inadequate patient positioning,

overfilling of the defect (the graft should sit 1 mm recessed), and inadequate defect preparation according to standard principles of cartilage repair. In addition, failure to address concomitant ligamentous laxity, meniscal deficiency, subchondral bone insufficiency, or malalignment can contribute to failure of PJAC.

The post-operative complications of PJAC are similar to those of other cell-based therapies including ACI and matrix-carried ACI (MACI) [27]. The most commonly reported adverse effects are a joint effusion and stiffness. The most common causes for re-operation are graft hypertrophy and graft delamination.

Future directions

Many important questions about the use of PJAC in the knee remain unanswered. The primary objective of future studies should be to investigate the comparative efficacy and safety of PJAC in comparison to ACI (in the USA) or MACI (in Europe) in head-to-head randomized studies. Without evidence of clinical equivalence or superiority to ACI/MACI, PJAC is unlikely to become widely adopted. More focused research objectives could be reached using a prospective multicenter registry, such as offered by the new Surgical Outcomes System sponsored by the Arthroscopy Association of North America (Arthrex, Naples, FL). Indeed, approximately 1000 PJAC implantations are done each year in the USA [6], but the clinical data from these patients are essentially lost. If captured, even partially, this information could help answer the questions required for sound decision-making: (1) what are the effects of defect size, location, and depth on outcomes? 2) what is the effect of lesion containment on outcomes? 3) can simultaneous subchondral bone grafting and PJAC achieve similar results as simple PJAC? and 4) what is the importance/necessity of performing concomitant unloading osteotomies with PJAC?

Conclusions

Significant additions to the literature supporting PJAC for symptomatic chondral defects of the knee have become available in the last 3 years. The treatment offers promise for small to medium sized chondral defects in physiologically young patients. Successful outcomes have been reported in the femoral condyles, trochlea, and patella, with no clear influence of location on results. In spite of these promising early data, the comparative efficacy and safety of PJAC as compared to accepted cell-based procedures remains unknown. Evidence-based indications cannot be generated from the available literature, and progressively more challenging cases including those with loss of containment or subchondral bone insufficiency are being tackled with PJAC. Further studies are necessary to provide robust clinical practice guidelines, and in the interim, surgeons should follow the time-tested principles of cell-based cartilage repair to achieve satisfactory outcomes with PJAC.

Compliance with Ethics Guidelines

Conflict of Interest Dr. Jonathan Riboh declares that he has no competing interests.

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References

Papers of particular interest, published recently, have been highlighted as:
- Of importance

1. Montgomery SR, Foster BD, Ngo SS, Terrell RD, Wang JC, Petrigliano FA, et al. Trends in the surgical treatment of articular cartilage defects of the knee in the United States. Knee Surg Sports Traumatol Arthrosc. 2014;22(9):2070–5.
2. Moran CJ, Pascual-Garrido C, Chubinskaya S, Potter HG, Warren RF, Cole BJ, et al. Restoration of articular cartilage. J Bone Joint Surg Am. 2014;96(4):336–44.
3. Albrecht F, Roessner A, Zimmermann E. Closure of osteochondral lesions using chondral fragments and fibrin adhesive. Arch Orthop Trauma Surg. 1983;101(3):213–7.
4. Frisbie DD, Lu Y, Kawcak CE, DiCarlo EF, Binette F, McIlwraith CW. In vivo evaluation of autologous cartilage fragment-loaded scaffolds implanted into equine articular defects and compared with autologous chondrocyte implantation. Am J Sports Med. 2009;37 Suppl 1:71S–80S.
5. Lu Y, Dhanaraj S, Wang Z, Bradley DM, Bowman SM, Cole BJ, et al. Minced cartilage without cell culture serves as an effective intraoperative cell source for cartilage repair. J Orthop Res. 2006;24(6):1261–70.
6. Farr J, Cole BJ, Sherman S, Karas V. Particulated articular cartilage: CAIS and DeNovo NT. J Knee Surg. 2012;25(1):23–9.
7. Cole BJ, Farr J, Winalski CS, Hosea T, Richmond J, Mandelbaum B, et al. 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;39(6):1170–9.
8. Farr J, Yao JQ. Chondral defect repair with particulated juvenile cartilage allograft. Cartilage. 2011;2(4):346–53.
9. Adkisson HD, Martin JA, Amendola RL, Milliman C, Mauch KA, Katwal AB, et al. The potential of human allogeneic juvenile

chondrocytes for restoration of articular cartilage. Am J Sports Med. 2010;38(7):1324–33.
10. Adkisson, H. D.; Gillis, M. P.; Davis, E. C.; Maloney, W.; and Hruska, K. A.: In vitro generation of scaffold independent neocartilage. Clin Orthop Relat Res, (391 Suppl): S280-94, 2001.
11. Bonasia DE, Martin JA, Marmotti A, Amendola RL, Buckwalter JA, Rossi R, et al. Cocultures of adult and juvenile chondrocytes compared with adult and juvenile chondral fragments: in vitro matrix production. Am J Sports Med. 2011;39(11):2355–61.
12. Kruse DL, Ng A, Paden M, Stone PA. Arthroscopic De Novo NT((R)) juvenile allograft cartilage implantation in the talus: a case presentation. J Foot Ankle Surg. 2012;51(2):218–21.
13. Gomoll AH, Probst C, Farr J, Cole BJ, Minas T. Use of a type I/III bilayer collagen membrane decreases reoperation rates for symptomatic hypertrophy after autologous chondrocyte implantation. Am J Sports Med. 2009;37 Suppl 1:20S–3S.
14. Bonasia, D. E.; Martin, J. A.; Marmotti, A.; Kurriger, G. L.; Lehman, A. D.; Rossi, R.; and Amendola, A.: The use of autologous adult, allogenic juvenile, and combined juvenile-adult cartilage fragments for the repair of chondral defects. Knee Surg Sports Traumatol Arthrosc, 2015
15. Marmotti A, Bonasia DE, Bruzzone M, Rossi R, Castoldi F, Collo G, et al. Human cartilage fragments in a composite scaffold for single-stage cartilage repair: an in vitro study of the chondrocyte migration and the influence of TGF-beta1 and G-CSF. Knee Surg Sports Traumatol Arthrosc. 2013;21(8):1819–33.
16. Marmotti A, Bruzzone M, Bonasia DE, Castoldi F, Rossi R, Piras L, et al. One-step osteochondral repair with cartilage fragments in a composite scaffold. Knee Surg Sports Traumatol Arthrosc. 2012;20(12):2590–601.
17. Marmotti A, Bruzzone M, Bonasia DE, Castoldi F, Von Degerfeld MM, Bignardi C, et al. Autologous cartilage fragments in a composite scaffold for one stage osteochondral repair in a goat model. Eur Cell Mater. 2013;26:15–31. **discussion 31–2**.
18. Bonner KF, Daner W, Yao JQ. 2-year postoperative evaluation of a patient with a symptomatic full-thickness patellar cartilage defect repaired with particulated juvenile cartilage tissue. J Knee Surg. 2010;23(2):109–14.
19. Adams Jr SB, Demetracopoulos CA, Parekh SG, Easley ME, Robbins J. Arthroscopic particulated juvenile cartilage allograft transplantation for the treatment of osteochondral lesions of the talus. Arthrosc Tech. 2014;3(4):e533–7.
20.• Buckwalter JA, Bowman GN, Albright JP, Wolf BR, Bollier M. Clinical outcomes of patellar chondral lesions treated with juvenile particulated cartilage allografts. Iowa Orthop J. 2014;34:44–9. **A retrospective review of 13 patients undergoing PJAC grafting of high-grade chondral defects of the patella**.
21. Coetzee JC, Giza E, Schon LC, Berlet GC, Neufeld S, Stone RM, et al. Treatment of osteochondral lesions of the talus with particulated juvenile cartilage. Foot Ankle Int. 2013;34(9):1205–11.
22.• Farr J, Tabet SK, Margerrison E, Cole BJ. Clinical, radiographic, and histological outcomes after cartilage repair with particulated juvenile articular cartilage: a 2-year prospective study. Am J Sports Med. 2014;42(6):1417–25. **A prospective, multi-center single-arm study reporting the clinical, radiographic and histological outcomes at 2 years after particulated juvenile articular cartilage grafting**.
23. Giza E, Delman C, Coetzee JC, Schon LC. Arthroscopic treatment of talus osteochondral lesions with particulated juvenile allograft cartilage. Foot Ankle Int. 2014;35(10):1087–94.
24. Stevens HY, Shockley BE, Willett NJ, Lin AS, Raji Y, Guldberg RE, et al. Particulated juvenile articular cartilage implantation in the knee: a 3-year EPIC-microCT and histological examination. Cartilage. 2014;5(2):74–7.
25.• Tompkins M, Hamann JC, Diduch DR, Bonner KF, Hart JM, Gwathmey FW, et al. Preliminary results of a novel single-stage cartilage restoration technique: particulated juvenile articular cartilage allograft for chondral defects of the patella. Arthroscopy. 2013;29(10):1661–70. **A retrospective case series of 15 patients undergoing PJAC grafting for ICRS grade 4 chondral defects of the patella**.
26.• Christensen BB, Foldager CB, Jensen J, Lind M. Autologous dual-tissue transplantation for osteochondral repair: early clinical and radiological results. Cartilage. 2015;6(3):166–73. **A prospective cohort of 8 patients with osteochondritis dissecans lesions of the knee treated with "autologous dual-tissue transplantation"**.
27. Williams Iii RJ, Brophy RH. Cartilage repair procedures: clinical approach and decision making. Instr Course Lect. 2008;57:553–61.