

Particulated Articular Cartilage: CAIS and DeNovo NT

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Abstract

Cartilage Autograft Implantation System (CAIS; DePuy/Mitek, Raynham, MA) and DeNovo Natural Tissue (NT; ISTO, St. Louis, MO) are novel treatment options for focal articular cartilage defects in the knee. These methods involve the implantation of particulated articular cartilage from either autograft or juvenile allograft donor, respectively. In the laboratory and in animal models, both CAIS and DeNovo NT have demonstrated the ability of the transplanted cartilage cells to “escape” from the extracellular matrix, migrate, multiply, and form a new hyaline-like cartilage tissue matrix that integrates with the surrounding host tissue. In clinical practice, the technique for both CAIS and DeNovo NT is straightforward, requiring only a single surgery to affect cartilage repair. Clinical experience is limited, with short-term studies demonstrating both procedures to be safe, feasible, and effective, with improvements in subjective patient scores, and with magnetic resonance imaging evidence of good defect fill. While these treatment options appear promising, prospective randomized controlled studies are necessary to refine the indications and contraindications for both CAIS and DeNovo NT.

Keywords

- ▶ particulated cartilage allograft
- ▶ Cartilage Autograft Implantation System
- ▶ DeNovo Natural Tissue

Articular cartilage lesions are a common cause of knee symptoms.^{1,2} The ultimate goal of surgical intervention is to restore the patient's comfort and function while the secondary goal is to prevent or delay osteoarthritis.^{3–5} As with other tissues, articular cartilage form follows function and recent studies suggest that improved clinical results correlate with better cartilage restoration constructs.⁶ Current surgical treatment options for symptomatic cartilage lesions include debridement/lavage, marrow stimulation, osteochondral autograft implantation, fresh osteochondral allograft implantation, and autologous chondrocyte implantation (ACI).^{7–12} More recently, minced cartilage autograft (Cartilage Autograft Implantation System [CAIS; DePuy/Mitek, Raynham, MA]) and particulated juvenile cartilage allograft (DeNovo Natural Tissue [NT]; ISTO, St. Louis, MO) options have been reported.^{3,13}

One repair strategy is to use a bioactive component (i.e., cells or growth factors) that drives the biological process and a

matrix (biomaterial that serves as a carrier or scaffold) that provides architectural support and facilitates the integration of the repaired tissue with the contiguous tissue.³ Current treatment options have unique advantages and disadvantages. Autograft osteochondral plugs provide a living osteochondral unit, but are limited to smaller lesions ranging from 1 to 2.5 cm².^{14,15} Marrow stimulation is easy to perform, but may also be limited with regard to the extent of durable hyaline-like cartilage formation, lesion size, and long-term sustained clinical gains.^{15,16} ACI was the first cultured chondrocyte-based therapies, but has variable long-term benefits when compared with microfracture and is technically tedious. Today, it is indicated for second line treatment, especially for those patients with larger chondral defects.^{8,17,18} Similar to ACI, other cultured chondrocyte techniques (e.g., ChondroCelect; DePuy/Mitek, Raynham, MA) have promising midterm results.^{6,16} Second and third generation cultured chondrocyte techniques culture the

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chondrocytes on a matrix, which improves the technical aspects, yet the results are similar to first generation and still require two-staged surgical procedures for harvest and implantation. Until recently, allograft treatment options have been limited to osteochondral grafts, as graft incorporation to host tissue was only possible at the bone level. The biologic requirement of transplant bone remodeling/incorporation to host bone at the basilar bone layer remains a challenge and availability is limited.^{1,2} In light of these limitations, ongoing research continues to search for cartilage restoration techniques that form durable tissue, are technically easier for the surgeon to perform and are less disruptive to patients' lives during the recovery phase.

The concept that cartilage could be transplanted without its underlying bony component and heal would be considered heretical even a few years ago by most cartilage surgeons. However, the potential safety and efficacy of both CAIS and DeNovo NT are challenging this paradigm. As in many aspects of science, the key to advances is "seeing" what has been there all along. While the phenomenon of hyaline cartilage repair using particulated articular cartilage is relatively new to the English speaking literature, a thorough literature review reveals a published report by Albrecht et al in the German literature dating back to 1983.¹⁹ Their work showed that cartilage autograft implantation without bone can lead to cartilage defect healing if the cartilage is cut into small pieces. Most scientists in the English speaking world were unaware of this article until recently, after US-based scientists noted the production of new chondrocyte and matrix formation adjacent to minced cartilage fragments. Researchers Ed Lu and Francois Binette began a series of experiments to investigate these findings. What followed was a rapid progression from in-vitro experiments to the mouse, goat, and finally horse model.^{20,21} All these studies together demonstrated that autograft cartilage, when mechanically minced into cubes of 1 to 2 mm, could affect cartilage repair.^{19,21} In essence, chondrocytes in the cartilage pieces could "escape" from the extracellular matrix, migrate, multiply, and form a new hyaline-like cartilage tissue matrix that would integrate with the surrounding host tissue. In addition, unlike cultured chondrocytes that take on a spindle-shaped morphology during culture, the chondrocytes from the minced cartilage retained the standard chondrocyte spheroid shape.²¹

These preclinical data were compelling enough for the Food and Drug Administration (FDA) to approve a proof of concept and safety pilot study of what the sponsor referred to as CAIS.³ The clinical outcomes are now published at 2 years and an extension follow-up study is complete to 4 years postoperative with publication to follow. Based on a parallel European study, the technique received a CE (Conformité Européenne) mark and is available through a limited release in Europe. In the United States, the FDA has approved a pivotal study of the technique, which began recruiting patients in 2010 and will enroll over 300 patients for a randomized prospective comparison of CAIS to MFX (microfracture) (i.e., CAIS is not available for general use in the United States. Use is limited to study patients).

In another laboratory, scientist Dr. Jian Q. Yao noted these early preclinical reports and decided to evaluate similar studies using particulated juvenile cartilage allograft (DeNovo NT; distributed by Zimmer, Warsaw, IN) in place of autograft.^{1,2} This alternative approach was based on two factors: (1) allograft allows conceptually no limit to the amount of harvested tissue and (2) juvenile cartilage has the potential of more robust cellular activity than older cartilage tissue.^{13,22-25} Yao demonstrated that new extracellular matrix can be formed from juvenile cartilage cubes in an explant culture study.¹ In addition, he demonstrated that particulated juvenile articular cartilage xenografts healed chondral defects on the trochlea of horse knee joint.¹ Given the momentum from these positive results, the FDA now considers DeNovo NT as a minimally manipulated human tissue allograft, regulated as a 361 HCT/P product similar to fresh osteochondral allograft and bone-tendon-bone allograft. It is available for use in clinical applications without an IDE (investigational device exemption) study and, to date, over 2200 patients have received this product.² During this same market release, the sponsor supported a prospective study of 25 patients in a multicenter study with preliminary results reported that compliment a case report in the literature.^{2,26}

Indications/Contraindications

The indications for CAIS and DeNovo NT are evolving. In general, they mirror the selection criteria for other cell-based cartilage procedures. On the basis of limited clinical trials, these products are indicated for treatment of symptomatic articular cartilage defects in patients from age 18 to 55. Prior to treatment, same day arthroscopic evaluation should confirm a cartilage lesion that is at least International Cartilage Repair Society (ICRS) grade 3 or higher. After peripheral cartilage debridement, lesion size should range from 1 to 5 cm². As with the treatment of all cartilage defects, careful attention must be paid to meniscal status, and to restoring, or maintaining knee alignment, and stability. Potential contraindications to CAIS or DeNovo NT include bipolar lesion > ICRS grade 2, significant underlying subchondral bony edema, or osteochondritis dissecans lesion with >6 mm subchondral bone loss, as the two last scenarios may require an osteochondral allograft or alternative techniques.

Surgical Technique

CAIS

Standard arthroscopic portals are established and the lesion (s) are evaluated to confirm size, location, and appropriateness for treatment. If CAIS is indicated, hyaline cartilage is then harvested arthroscopically from a low load-bearing surface (i.e., lateral wall of the intercondylar notch or trochlear margin with an amount similar to that harvested for ACL, roughly 200 mg) using a unique device that minces the cartilage into 1 to 2 mm pieces. After harvest, the device (DePuy Mitek, Raynham, MA) uniformly disperses the minced cartilage onto a biodegradable scaffold. (The CAIS scaffold

implant consists of an absorbable copolymer foam of 35% polycaprolactone and 65% polyglycolic acid, reinforced with a polydioxanone [PDO mesh] [Advanced Technologies and Regenerative Medicine, Raynham, MA]. The polymer foam is designed to keep the tissue fragments in place and serves as a three-dimensional scaffold for cartilage matrix generation. The reinforcing PDO mesh enables the foam to have adequate mechanical strength during implant handling. The fragments are then secured to this scaffold using a commercially available fibrin sealant (Tisseel, Baxter, IL). A mini-arthrotomy is performed, and the defect is identified and prepared similar to the technique used for ACI, whereby vertical lesion walls are created and the damaged cartilage is removed to the level of the subchondral bone using a ring curette. If bleeding is noted, hemostasis is achieved using epinephrine soaked sponges and/or punctuated amounts of fibrin glue. An arthroscopic ruler is used to measure width, length, and depth of the prepared lesion. Subsequently, a template sizes the area of the lesion. Sterile paper or foil is used to make a template of the cartilage defect and used to cut the minced cartilage/scaffold construct to the appropriate size. The trimmed CAIS

scaffold implant is transferred to the defect with the cartilage fragments facing the subchondral bone and affixed with two or more biodegradable staple anchors (prototype, Advanced Technologies and Regenerative Medicine), which consist of PDO straps and tip (Advanced Technologies and Regenerative Medicine).

DeNovo NT

After confirmatory arthroscopy, a limited medial or lateral arthrotomy is performed to fully visualize the lesion(s) as show in ►**Fig. 1A**. The defect is outlined with a scalpel to create a shoulder (vertical peripheral wall) of normal or nearly normal host articular cartilage. The cartilage within the outlined area is removed carefully with a curette to the vertical wall of the host cartilage shoulder and the base of the defect (►**Fig. 1B**). The base is cleared of all cartilage tissue including the calcified layer without entering into the subchondral bone. No marrow stimulation procedure is performed. Hemostasis, without a tourniquet, is achieved with epinephrine soaked cottonoids and fibrin glue. After measuring the defect dimensions and recording the visual findings

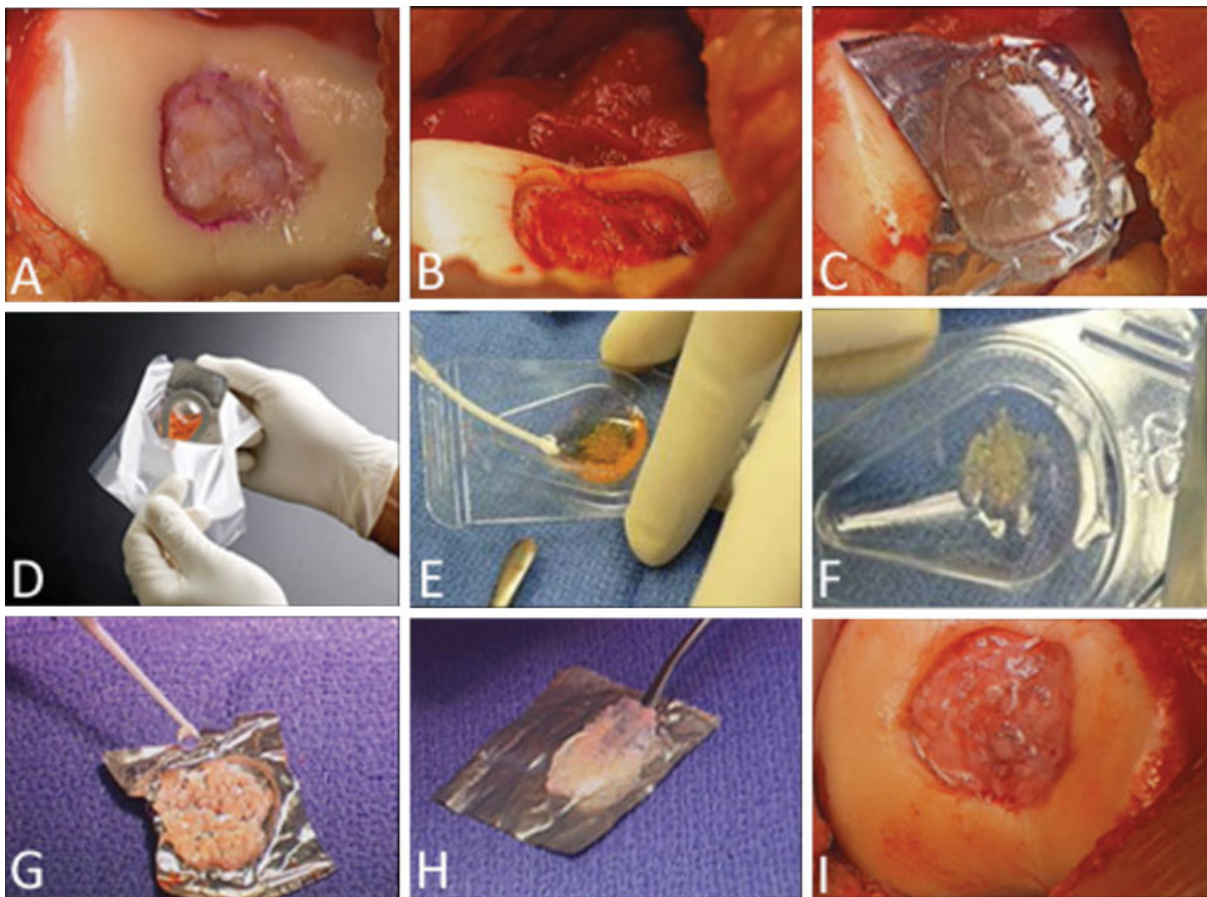


Figure 1 Surgical technique for DeNovo NT. (A) The defect is identified and a curette is used to clear the base of the defect (B). (C) A thin aluminum sterile foil is pressed into the defect to create a 3-dimensional mold. The DeNovo NT is shipped in a temperature-controlled package (D). The nutrient preserving medium (E, F) is aspirated. The cells are then transferred to the foil mold approximately 1 mm apart (G). Fibrin glue is then added and the cells are allowed to cure (G). At this time the construct is lifted in one piece (H). Fibrin glue is added to the base of the defect and the cartilage construct is then placed in the defect and sealed with fibrin glue and allowed to cure for 10 minutes. The cartilage construct is recessed relative to the surrounding cartilage (I). (Reprinted with permission from Farr J, Yao JQ. Chondral defect repair with particulated juvenile cartilage allograft. *Cartilage* 2011;2(4):346–353.)

with photographs, a thin aluminum sterile foil is pressed into the defect to create a three-dimensional mold, as a complete replica of the defect (►Fig. 1C). Once formed, the foil mold is removed from the defect and placed on the back table of the operating room. Using the measured defect dimensions, the defect surface area was calculated. One package of DeNovo NT graft is used for each 2.5 cm² defect. Larger defects require proportionally more packages of DeNovo NT graft.

The DeNovo NT graft, in a specially formulated nutrient preservation medium, is shipped in an aseptic temperature controlled packaging (►Fig. 1D). The medium is aspirated (►Fig. 1E) and the particulated cartilage pieces are transferred to the foil mold and distributed ~1 to 2 mm apart (potentially less separation depending upon the ratio between the implanted tissue volume and the surface area of the defect) (►Fig. 1F). Fibrin glue is then added to the cartilage pieces until the foil mold was filled to within ~1 mm of its full depth (►Fig. 1G). The glue is allowed to cure (typically 3 to 10 minutes). At that point, the fibrin glue/cartilage tissue construct is gently separated and then lifted from the foil in one piece (►Fig. 1H). Fresh fibrin glue is applied at the base of the patient's cartilage lesion and the fibrin glue/particulated cartilage construct is pressed into the defect and the glue allowed to cure (►Fig. 1I). As an alternative to the Zimmer/ISTO technique, some surgeons are directly applying the particulated cartilage into the defect and gluing it in situ.²⁶ It is imperative that the fibrin glue cartilage tissue construct is thinner (average 1 mm) than the surrounding cartilage shoulders (average 2 to 3 mm), to minimize the potential for shear or direct compressive load.

Rehabilitation Protocol

In general, the rehabilitation program focuses initially on protection of the cartilage repair process and then progresses toward controlled loading, increased range of motion, and progressive muscle strengthening.³ Patients receive a different rehabilitation protocol depending on whether they had a lesion in the patellofemoral compartment or the tibiofemoral compartment. Immediately after surgery, all patients receive a hinged knee brace locked in extension. Patients with a lesion on the femoral condyle are made nonweight bearing for the first 2 weeks and are advanced to partial weight bearing with an unlocked brace from week 2 through 6. Patients with a trochlear lesion are allowed to bear weight as tolerated immediately with the brace locked in extension. Regardless of lesion location, the brace is removed each day for continuous passive motion during the first 4 weeks, which is progressively increased (as tolerated) during the subsequent 3 weeks. Muscle strength is maintained using isometric quadriceps sets, straight leg raises, and isometric contraction of the hamstrings, hip abductors, and hip adductors. When tolerated, patients use a stationary bike without resistance to maintain passive range of motion. Patients return to low load activity levels at week 6 to 8 and progress in activity as strength and comfort permitted.

Clinical Results

CAIS

There is only one study in the clinical literature reporting outcomes of single-stage CAIS for symptomatic knee cartilage defects.³ The goal of this FDA approved study was to establish the safety of CAIS and to test whether CAIS improves quality of life by using standardized outcomes assessment tools. A total of 29 patients was randomized with the intent to treat with either MFX or CAIS. Patients were followed at predetermined time points for 2 years using several standardized outcomes assessment tools (Short Form-36 [SF-36], International Knee Documentation Committee [IKDC], Knee Injury and Osteoarthritis Outcome Score [KOOS]). Magnetic resonance imaging (MRI) was performed at baseline, 3 weeks, and 6, 12, and 24 months.

Lesion size and ICRS grade were similar in both groups. General outcome measures (e.g., physical component score of the SF-36) indicated an overall improvement in both groups, and no differences in the number of adverse effects were noted in comparisons between the CAIS and MFX groups. The IKDC score of the CAIS group was significantly higher compared with the MFX group at both 12 and 24 months. Select subdomains (4/5) in the KOOS instrument were significantly different at 12 and 18 months, and all subdomains (Symptoms and Stiffness, Pain, Activities of Daily Living, Sports and Recreation, Knee-related Quality of Life) were significantly increased at 24 months in CAIS versus MFX. These significant improvements were maintained at 24 months in both IKDC and KOOS.

Qualitative analysis of the imaging data did not note differences between the 2 groups in fill of the graft bed, tissue integration, or presence of subchondral cysts. Patients treated with MFX had a significantly higher incidence of intralesional osteophyte formation (54 and 70% of total number of lesions treated) at 6 and 12 months when compared with CAIS (8 and 25% of total number of lesions treated).

DeNovo NT

To date, there are only two clinical studies on the use of DeNovo NT for symptomatic cartilage lesions in the knee that are reported in the literature.^{2,26}

The first is a case report on the use of particulated juvenile cartilage tissue for a symptomatic full thickness patella cartilage defect.²⁶ At 2 year follow-up, the patient experienced substantial clinical improvement in both pain and function when evaluated with both the IKDC subjective evaluation and the KOOS outcome measures. MRI at final follow-up demonstrates fill of the defect with repair tissue, and near complete resolution of preoperative bony edema. ►Fig. 2 shows a preoperative MRI from a patient implanted with DeNovo NT and at 21 months postoperatively (►Fig. 3).

The second is an early interim report of patients that are a part of an on-going multicenter, prospective, single arm study of 25 subjects.² This study is designed to evaluate clinical outcomes such as IKDC, KOOS, and visual analog scale (VAS)



Figure 2 Preoperative magnetic resonance imaging demonstrating a full-thickness chondral defect of the patella with underlying bone edema and early subchondral cyst formation (indicated by the arrow). (Reprinted with permission from Bonner KF, Daner WD, and 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;23:109–113.)

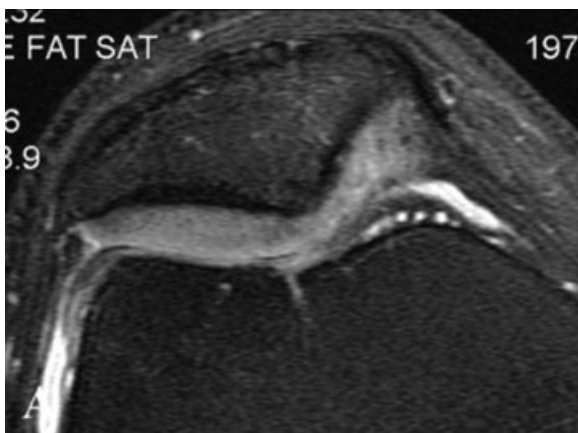


Figure 3 Postoperative magnetic resonance imaging at 21 months reveals near resolution of the bone edema and repair tissue within the previous defect site. (Reprinted with permission from Bonner KF, Daner WD, and Yao JQ. 2-year postoperative evaluation of a patient with a symptomatic full-thickness patellar cartilage defect repaired with particulated juvenile cartilage tissue. *J Knee Surg* 2010;23:109–113.)

scores, as well as extent and quality of repair with MRI and optional biopsies. To date, 25 patients with one or two chondral lesions on the femoral condyle or trochlea have been enrolled at three study sites. Four patients have completed 24 months follow-up and their outcomes have been recently reported in *Cartilage*.² Detailed results of all 25 patients will be reported once they have all reached the 2-year postoperative follow-up milestone.

Of the four patients with 2-year follow-up, three had nontraumatic cartilage lesions and one had a traumatic cartilage injury. The average age was 43 ± 5.4 years and body mass index was 27 ± 5.8 lb/in². The average lesion

size was 2.71 ± 1.2 cm². Two patients had isolated trochlea lesions, one had an isolated condyle lesion, and one had focal lesions of both the femoral condyle and trochlea. KOOS, IKDC, and VAS scores demonstrate clear improvements in all scores across the 24-month follow-up period. Most of these improvements, especially in KOOS and VAS, were achieved at the 12-month mark, and maintained throughout the study period. A representative patient MRI taken preoperative at 12 months and at 24 months is shown in **Fig. 4**. This demonstrates good defect fill at 24 months postoperative.

Discussion

CAIS and DeNovo NT are somewhat similar surgical procedures that involve the single stage implantation of minced articular cartilage using either autograft or juvenile allograft, respectively. Several in-vitro and in-vivo models demonstrate the unique ability of both particulated autograft and juvenile allograft chondrocytes to escape from the extracellular matrix, migrate, and form new hyaline-like cartilage tissue that integrates with the surrounding host cartilage.^{19–21} In short-term clinical studies, both procedures appear to be safe, feasible, and effective, with improvements in subjective patient scores and with MRI evidence of good defect fill.^{2,3,26}

There are several potential advantages to these techniques. Both CAIS and DeNovo NT do not require the violation of the subchondral bone, as is necessary for marrow stimulation procedures. These truly represent a “burn no bridge” procedure, unlike reports that prior marrow stimulation may compromise subsequent revision surgeries.²⁷ Similarly, these procedures avoid the need to surgically create an osteochondral defect as is necessary for osteochondral allograft transplantation. CAIS and DeNovo NT use a strategy of cartilage–cartilage healing in the defect bed. This may help to avoid problems of bony healing as seen in failed osteochondral allograft procedures, including lack of bone incorporation, necrosis, and avascular necrosis like collapse. Other potential advantages include: (1) the use of fibrin fixation, which eliminates problems relating to flap hypertrophy, as seen with other techniques²⁸; (2) CAIS and DeNovo NT are single stage procedures unlike techniques such as ACI; (3) DeNovo NT lacks any autogenous donor site morbidity; (4) the autograft tissue portion of CAIS is obviously without charge (as compared with cultured cells or allograft).

A disadvantage specific to CAIS is the potential for donor site morbidity at cell harvest. This risk is minimal and is, in theory, similar to the risk involved in ACI harvest. Potential disadvantages specific to DeNovo NT include the theoretical risk of disease transmission, and/or immunological rejection, that is inherent to any allograft procedure. The risk of disease transmission is extremely low in allograft procedures, due to stringent donor requirements by the FDA, and standard allograft screening tests to ensure tissue safety.² Thirty years of cumulative knowledge has similarly shown that immune rejection is an extremely rare phenomenon with osteochondral allograft transplantation. No

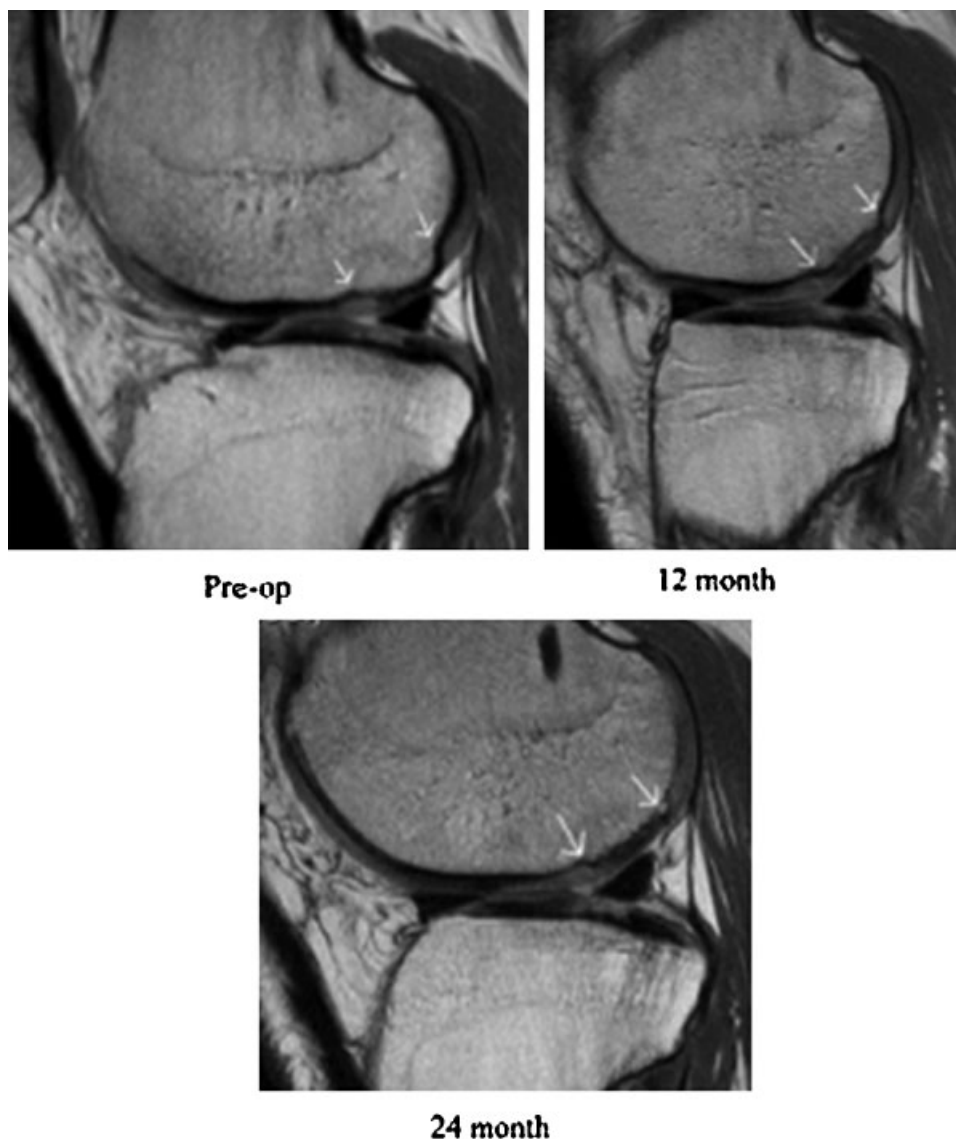


Figure 4 Note that the sagittal plane is not identical from one image to the next secondary to slight position differences of the knee in the MRI. The image plane that best demonstrated the lesion was chosen. (Reprinted with permission from Farr J, Yao JQ. Chondral defect repair with particulated juvenile cartilage allograft. *Cartilage* 2011;2(4):346–353.)

immune responses have been reported to the cartilage component of osteochondral allografts.² In addition, articular cartilage has been shown to be immune privileged, partly due to a lack of vascularity and the dense extracellular matrix of the tissue.²⁹

Other clinicians have tried to treat chondral defects of the knee with particulated chondral or osteochondral tissue from mature donors. In particular, Stone et al implanted a paste of autologous osteochondral tissue into defects concomitantly treated with microfracture.³⁰ While good clinical results were reported, several animal studies have shown that a combination bone and cartilage paste forms both bone and cartilage, whereas cartilage pieces alone formed cartilage.^{19,21,30} We believe that CAIS and DeNovo NT potentially may improve upon the paste grafting concept by using a homogenous cartilage-only approach, and by avoiding concomitant microfracture.

Despite the obvious limitations of short-term outcomes, the results of both CAIS and DeNovo NT compare favorably to other procedures for similar cartilage lesions. Cole et al demonstrated that CAIS is safe to use, with risks comparable to those of MFX. In that study, CAIS had consistent and progressive improvement during the 2nd year after surgery, when compared with the microfracture group.³ Similarly, the preliminary results of DeNovo NT compare favorably with 2-year postoperative KOOS pain scores for ACI and microfracture, and with IKDC subjective scores for ACI.^{8,16,31} Comparison of MRI results from CAIS and MFX patients suggests a difference in the biologic repair process. MRI from DeNovo NT patients also demonstrates good lesion fill at early follow-up.^{2,8,10,26} Future study will require sophisticated imaging or second look biopsies to determine whether the quality and quantity of hyaline-like fill correlates with subjective and objective clinical outcomes.

Conclusion

CAIS and DeNovo NT appear to be promising new treatment options for the young patient with a symptomatic focal chondral defect in the knee. Further study is needed before there are evidence-based recommendations. Prospective randomized controlled studies will certainly help to refine the indications and contraindications for both CAIS and DeNovo NT.

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