Minced Articular Cartilage—Basic Science, Surgical Technique, and Clinical Application

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Abstract: Minced articular cartilage procedures are attractive surgical approaches for repairing articular cartilage, as they are 1-staged, autologous, and inserted on a carrier that can potentially be placed arthroscopically. The principle of mincing the autologous donor cartilage is to create a larger surface area for cartilage expansion. Placement on a scaffold carrier allows for a chondro-inductive and chondro-conductive milieu. Early animal and preclinical models have demonstrated hyaline-like tissue repair. Further work needs to be conducted in this promising approach.

Key Words: minced articular cartilage, cartilage autograft implantation system, DeNovo natural tissue grafting

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Articular cartilage is a thin layer of highly specialized connective tissue that permits smooth, nearly frictionless movement and load-bearing force distribution throughout joints. Although these properties confer excellent durability to cartilage, this tissue is vulnerable to acute injuries. It is also subject to damage from acute or chronic inflammatory conditions.[1–4] Articular cartilage is avascular, aneural, alymphatic, and contains a single-cell type—the chondrocyte. Its lack of vascularity, high extracellular matrix to cell ratio, and lack of local progenitor cells leads to its limited capacity to heal injuries.[5]

Cartilage defects are characterized according to the depth and linear size.[6,7] Partial thickness defects resemble clefts and fissures and do not heal spontaneously. This failure is thought to be secondary to the lack of subchondral bone penetration, and therefore do not have access to the progenitor cells of the bone marrow.[8] However, full-thickness defects breach the zone of calcified cartilage, and may even penetrate into subchondral bone, thus gaining access to the mesenchymal stem cells. Most authors theorize that autogenous progenitor cells cannot be delivered to the site of injury without direct penetration of the bone. Although unlikely, it is possible that synovium derived stem cells may contribute to cartilage repair. The repair process elicited in full-thickness defects results in the formation of fibrocartilage.[9] This repair tissue is a poor substitute for articular cartilage and, with time and intrinsically altered load distribution, there can be marked degeneration of the fibrocartilage and the surrounding articular cartilage.[10–12] Moreover, flaps of articular cartilage may become elevated and/or detach, leading to synovial lining irritation, recurrent effusions, and mechanical symptoms.[13]

Each year it is estimated that chondral lesions affect up to 900,000 individuals in the United States resulting in over 200,000 surgical procedures annually.[14] Noninvasive attempts to treat cartilage defects, such as intra-articular steroid injections, viscosupplements, physical therapy and activity modifications, attempt to ameliorate the symptoms but do not produce cartilage repair. Currently, there are a variety of surgical approaches to repair cartilage defects: microfracture and abrasion arthroplasty via bone marrow stimulation; autologous osteochondral graft transplantation from a nearby articular surface area; and the use of allograft donor cartilage. Autologous chondrocyte implantation (ACI) is one of the preferred cell-based cartilage resurfacing technique[15]; in addition, osteochondral allograft offers a sound reconstructive option.

As previously discussed, fibrocartilage cannot withstand the demands of articular cartilage over a long period of time. Successful treatment with this technique requires optimal patient and defect selection and yielding good, short-term results that are not sustainable.[16] Osteochondral autograft transplantation is a promising treatment that uses osteochondral plugs from nonweight-bearing areas. The disadvantages of this technique include donor-site morbidity, technical difficulty in matching the joint contour, defect-size limitations, residual gaps between plugs, and the risk of cartilage and bone collapse. Allogeneic grafting is a possible solution to the above limitations of autograft transplantation with added shortcomings: graft availability, technical difficulty, cost, and possible disease transmission.[13]

Finally, ACI, a first-generation option for cell-based treatment of chondral defects is a 2-staged procedure, technically difficult, expensive, and has a high reoperation rate. Because of the inherent difficulties in first-generation

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techniques, recent research is focusing on tissue-engineered hyaline-like cartilage.[17]

The advancement of cartilage tissue engineering allows for significant gains in the treatment of cartilage defects. This technology is promising for a number of reasons: numerous tissue sources can provide adequate numbers of chondrocytes, chondrocytes can expand and lay down extracellular matrix onto the temporary structure it creates, and the materials used can be both chondro-conductive and chondro-inductive. Tissue engineering assists the surgeon to solve the basic science limitations of obtaining a suitable number of progenitor cells or regenerating chondrocytes and creates an artificial environment that will allow these cells to construct an in-vivo hyaline-like extracellular matrix with properties and durability similar to hyaline cartilage.[18–20]

Although tissue engineering can provide important solutions to the cartilage defect treatment dilemma, treatment must be amenable to economic realities, the Food and Drug Administration (FDA) approval process, and surgical delivery. The optimal product for chondral repair should have optimized chondrocytes, both in number and ability to form a new matrix; a conductive and/or inductive scaffold delivery mechanism capable of withstanding the in vivo stressful mechanical environment; and the ability to deliver growth factors to the regenerating tissue. It should also consist of a single-stage ''minimally invasive'' procedure, be cost-effective, have a high-success rate, and have few complications.[5]

Minced cartilage repair is a treatment that parallels the theory of ACI, but by providing autologous chondrocytes within their surrounding matrix, seeded on a scaffold, it incorporates the key factors mentioned for successful tissue engineering. As such, it is considered a second-generation technique providing viable chondrocytes, a mechanically sound conductive and/or inductive scaffold for delivery, and the ability to deliver growth factors to the regenerating tissue.[21] Moreover, it is a single-staged minimally invasive procedure that does not require costly in vitro cell expansion, and has a less cumbersome FDA approval process.

The principle of minced cartilage techniques is to accomplish hyaline-like chondral repair through using ''minced'' pieces of autologous hyaline cartilage often supplemented with a scaffold delivery system. Mincing a small amount of tissue creates enough chondrocytes to treat a relatively large defect. Specifically, this technique only requires one-tenth of the amount of cartilage that originally filled the defect (a 2 cm^2 defect would require $\sim$0.65 cm^2 of autologous cartilage).[22] By applying minced cartilage techniques, the same amount of donor tissue used in ACI (200 to 300 mg) can be used to treat a 10 cm^2 lesion. The scaffold allows for even distribution of the chondrocytes to expand within the defect providing structural and mechanical protection.[22] The first of 2 technologies being developed for clinical use is the cartilage autograft implantation system (CAIS) procedure by DePuy Mitek (Raynham, MA). The CAIS procedure requires the use of 2 single use items (CAIS harvester and disperser) and 2 implantable devices (CAIS scaffold implant and staples). The harvester consists of a stainless steel tube with a foot pedal-controlled cutting/grater tip distally that is connected to a trigger retraction system to allow engagement with the cartilage. The CAIS disperser, with the aid of surgical vacuum, directs the minced cartilage mixed with irrigation fluids onto the scaffold located in a bottom compartment of the disperser. The CAIS scaffold implant is a resorbable copolymer foam of 35% polycaprolactone (PCL), and 65% polyglycolic acid (PGA), and is reinforced with a polydioxanone (PDS) mesh. This is fastened with CAIS staples (resorbable PDS U-shaped strap) (Figs. 1–3).

Once the inclusion criteria for CAIS are satisfied, the cartilage can then be harvested arthroscopically from healthy, nonweight-bearing areas (the lateral femoral trochlea, medial femoral trochlea, sulcus terminalis, or intercondylar notch). A minimum of 200 mg of tissue is required from approximately two 13 $\times$ 5 mm harvest sites. This tissue is then minced and dispersed onto the scaffold. The surgeon visually confirms even distribution of the minced chondral tissue. After removing the tissue/scaffold from the device, a fibrin sealant mechanically stabilizes the cartilage fragments to the scaffold. Through a mini-arthrotomy, the defect site is debrided to stable vertical walls without disrupting the subchondral bone. Using a slightly oversized template of the defect, the scaffold should be trimmed accordingly. The tissue/scaffold is then stapled securely into the defect site with resorbable staples.

This technique has been the subject of several studies ranging from in vitro analysis to clinical trials. Minced human and bovine cartilage have been shown to synthesize uniform extracellular matrix at 6 weeks when loaded onto PGA/PLA nonwoven felt or PGA/PCL foam reinforced with PDS.[22] This same cartilage, when implanted into severe combined immunodeficient mice for 4 weeks showed proteoglycan content near chondrocyte-like cells to be more intense than the cultured fragments alone. From these studies, 2 other important points were noticed: there is an inverse relationship

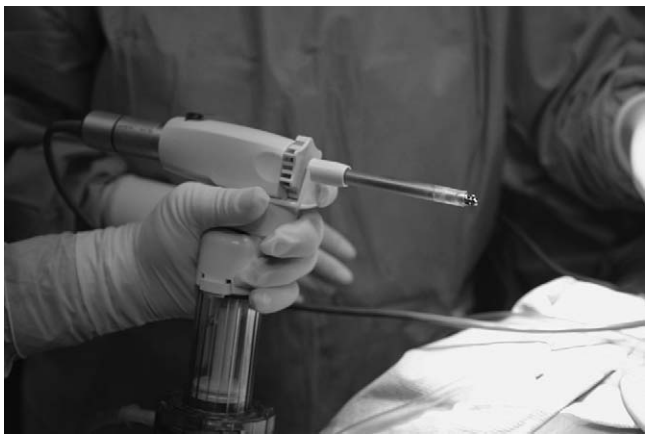

FIGURE 1. Cartilage autograft implantation system harvester.

FIGURE 2. Cartilage autograft implantation system scaffold seeded with the minced cartilage and prepared for implantation.

between cartilage fragment size and amount of outgrowth (smaller size, more chondral growth) and the highest level of cellular activity (bromodeoxyuridine incorporation) is localized at the minced cartilage edge.

These studies were followed by large animal studies including a goat model where 7 mm trochlear defects were treated in 3 different manners: empty, scaffold alone, and scaffold with minced autologous cartilage fragments.[22] Whereas all the treatments generated tissue in the defect, the scaffold with minced fragments produced whiter tissue, had better congruency, stained more intensely for proteoglycans, demonstrated zonal structure, and had a higher collagen type II to type I ratio. As the fragments with scaffold produced much better results than scaffold alone, it is thought that the contribution from synovial fluid, surrounding chondrocytes, and bone fissures is minimal in this setting.

FIGURE 3. Intraoperative picture of cartilage autograft implantation system scaffold implanted in the cartilage defect.

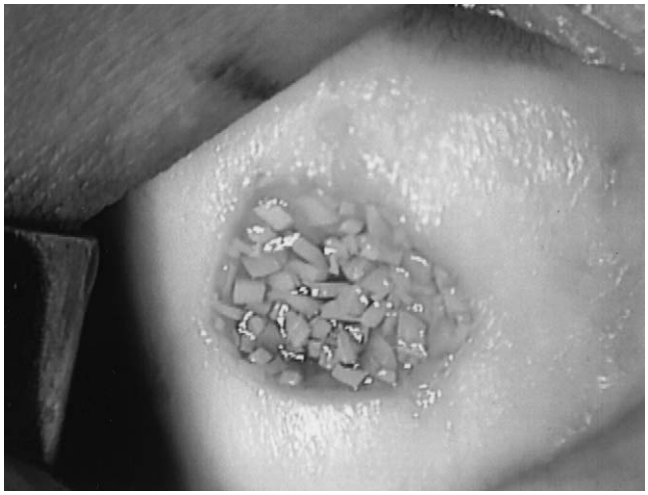

FIGURE 4. Intraoperative picture of DeNovo NT in cartilage defect; courtesy of Kevin Bonner, MD, Virginia Beach, VA.

As studies such as these demonstrated that scaffolds are beneficial, Frisbie et al[23] looked at the effects of different scaffold materials on the growth of minced cartilage fragments: PGA/PCL foam reinforced with PDS mesh, porcine-derived scaffold—small intestine submucosa and nonwoven Panacryl. At 4 months, the highest quality tissue was consistently seen in fragments on PDS reinforced foam. In a similar horse model using porcine small intestine submucosa scaffold, CAIS and showed improved arthroscopic, gross, and histologic progression toward hyaline-like tissue at 12 months.[24] Though these procedures produced similar tissue, the CAIS group had decreased pain, increased exercise tolerance, and was a single-stage surgical procedure.

Anecdotally, the authors experience with clinical trials of CAIS suggests that the hyaline-like tissue produced by minced cartilage techniques may be superior to that formed after microfracture. Though this is promising, the technology is still in its infancy and no long term or randomized human studies have been concluded.

DeNovo NT Graft (''Natural Tissue Graft,'' Zimmer Inc, Warsaw, IN/ISTO Technologies Inc, St Louis, MO) is a similar application for cartilage regeneration and repair. DeNovo NT consists of cartilage tissue pieces obtained from juvenile allograft donor joints (Fig. 4). The cartilage is manually minced under aseptic conditions and no enzymatic digestion or biologic manipulation is performed. Because of the minimal manipulation of the tissue, Denovo NT graft is classified as a 361 hTC/P product, such does not require FDA premarketing approval. ISTO, which is the processor company of

Denovo NT follows Good Tissue Practice in processing Denovo NT. Mincing the allograft tissue helps with cell migration from the extracellular matrix and helps with fixation. Thus, it is available on the market and over 70 cases have been performed. Clinical and basic studies are currently underway.

During surgical implantation, the minced cartilage tissue is mixed in a fibrin glue adhesive. The living cartilage tissue pieces are mixed intraoperatively with fibrin and the cartilage-fibrin construct is then implanted into the defect with an additional thin fibrin adhesive layer applied to the defect.

CONCLUSIONS

Minced articular cartilage procedures are attractive as they are 1-stage, consist of natural chondral tissue, and are inserted on a carrier that can potentially be placed with arthroscopic techniques. Early animal and preclinical models have demonstrated hyaline-like tissue. The scaffold and sealant have been shown to be important for viability. Further clinical and basic science data regarding minced chondral procedures is necessary.

REFERENCES

1. Buckwalter JA, Mankin HJ. Articular cartilage repair and transplantation. *Arthritis Rheum*. 1998;41:1331–1342.
2. Buckwalter JA, Mankin HJ, Grodzinsky AJ. Articular cartilage and osteoarthritis. *Instr Course Lect*. 2005;54:465–480.
3. Jackson DW, Scheer MJ, Simon TM. Cartilage substitutes: overview of basic science and treatment options. *J Am Acad Orthop Surg*. 2001;9:37–52.
4. Mankin HJ. The response of articular cartilage to mechanical injury. *J Bone Joint Surg Am*. 1982;64:460–466.
5. Alford JW, Cole BJ. Cartilage restoration, part 1: basic science, historical perspective, patient evaluation, and treatment options. *Am J Sports Med*. 2005;33:295–306.
6. Brittberg M, Winalski CS. Evaluation of cartilage injuries and repair. *J Bone Joint Surg Am*. 2003;85-A(suppl 2):58–69.
7. Kleemann RU, Krocker D, Cedraro A, et al. Altered cartilage mechanics and histology in knee osteoarthritis: relation to clinical assessment (ICRS Grade). *Osteoarthritis Cartilage*. 2005;13:958–963.
8. Redman SN, Oldfield SF, Archer CW. Current strategies for articular cartilage repair. *Eur Cell Mater*. 2005;9:23–32.
9. Shapiro F, Koide S, Glimcher MJ. Cell origin and differentiation in the repair of full-thickness defects of articular cartilage. *J Bone Joint Surg Am*. 1993;75:532–553.
10. DePalma AF, McKeever CD, Subin DK. Process of repair of articular cartilage demonstrated by histology and autoradiography with tritiated thymidine. *Clin Orthop Relat Res*. 1966;48:229–242.
11. Mankin HJ. The reaction of articular cartilage to injury and osteoarthritis (first of two parts). *N Engl J Med*. 1974;291:1285–1292.
12. Nehrer S, Spector M, Minas T. Histologic analysis of tissue after failed cartilage repair procedures. *Clin Orthop Relat Res*. 1999;365: 149–162.
13. Detterline AJ, Goldberg S, Bach BR Jr, et al. Treatment options for articular cartilage defects of the knee. *Orthop Nurs*. 2005;24: 361–366; quiz 367–368.
14. Curl WW, Krome J, Gordon ES, et al. Cartilage injuries: a review of 31,516 knee arthroscopies. *Arthroscopy*. 1997;13:456–460.
15. Bentley G, Biant LC, Carrington RW, et al. A prospective, randomised comparison of autologous chondrocyte implantation versus mosaicplasty for osteochondral defects in the knee. *J Bone Joint Surg Br*. 2003;85:223–230.
16. Kreuz PC, Steinwachs MR, Erggelet C, et al. Results after microfracture of full-thickness chondral defects in different compartments in the knee. *Osteoarthritis Cartilage*. 2006;14:1119–1125.
17. Dragoo JL, Carlson G, McCormick F, et al. Healing full-thickness cartilage defects using adipose-derived stem cells. *Tissue Eng*. 2007; 13:1615–1621.
18. Cancedda R, Dozin B, Giannoni P, et al. Tissue engineering and cell therapy of cartilage and bone. *Matrix Biol*. 2003;22:81–91.
19. Elisseeff J. Injectable cartilage tissue engineering. *Exp Opin Biol Ther*. 2004;4:1849–1859.
20. Salgado AJ, Oliveira JT, Pedro AJ, et al. Adult stem cells in bone and cartilage tissue engineering. *Curr Stem Cell Res Ther*. 2006;1: 345–364.
21. Ahmed TA, Dare EV, Hincke M. Fibrin: a versatile scaffold for tissue engineering applications. *Tissue Eng Part B Rev*. 2008;14:199–215.
22. Lu Y, Dhanaraj S, Wang Z, et al. Minced cartilage without cell culture serves as an effective intraoperative cell source for cartilage repair. *J Orthop Res*. 2006;24:1261–1270.
23. Frisbie DD, Lu Y, Colhoun HA, et al. In vivo evaluation of a one step autologous cartilage resurfacing technique in a long term equine model. ORS. Edited, 2005.
24. McIlwraith CW, Frisbie DD, Lu Y, et al. In-vivo evaluation of a one-step autologous cartilage resurfacing technique (CAIS) compared to a modified ACI technique in a long-term equine model. ICRS. Edited, San Diego, 2006.