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Operative Techniques in
Orthopaedics

Long-Term Outcomes of Chondrocyte-Based Cartilage Repair

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Autologous chondrocyte transplantation introduced cell therapy in the treatment of a pathologic condition in the locomotors stem, particularly in cartilage repair. The use of biomaterials as scaffolds for transplantation assured cell delivery and supported cell behavior toward the chondrocytic phenotype to provide a chondrogenic potential to regenerate articular cartilage. Furthermore, it allowed developing improved surgical techniques to address more challenging damage with a less-invasive approach by more efficient fixation methods. Overall, a successful cell transplantation can be expected in 75%-80% of patients younger than 40 years and in isolated cartilage defects. However, ultimate goals of tissue engineering are to regenerate the articular cartilage to normal and provide a sustainable long-term joint surface and to avoid deterioration of an initial cartilage defect to osteoarthritis and progressive joint damage. Now 20 years after the first publication, the newly developed techniques have to prove whether they are able to produce sufficient long-term outcomes. Studies with follow-up periods of approximately 5 years or longer are presented and analyzed in the context of sustainability for joint function and whether the promise of healing cartilage has come true at last.

Oper Tech Orthop 24:48-53

KEYWORDS cartilage repair, tissue engineering, autologous chondrocyte transplantation, biomaterials, long-term outcomes

From Autologous Chondrocyte Implantation to Matrix-Associated Autologous Chondrocyte Transplantation

The development of the autologous chondrocyte implantation (ACI) was a huge step forward in the treatment of articular cartilage defects.[1] The treatment was developed because current techniques at that time were not able to treat the entire spectrum of lesions, especially larger defects.[2] The original ACI technique used the injection of a suspension of cultured chondrocytes into a chondral defect underneath a sutured periosteal patch. Periosteum was used because it was thought to have a chondrogenic potential, and it contains pluripotential mesenchymal stem cells with the potential to form cartilage.[3] Recently, Minas reported results of 210 patients after 10 years of follow-up with a success rate and excellent or good patient satisfaction in about 75% of patients. The results were stratified based on the severity of the defect to simple, complex, and salvage cases, best results were observed in complex cases with more than an 80% success rate. Failures occurred mostly within the first 2 years mostly owing to insufficient biological regeneration or progressive joint disease, supporting the sustainability of improved healing response owing to cell application. Although the technique demonstrated good results,[4-7] there are several limitations that are given as follows: it requires complex surgery including the need for the sutured periosteum to seal the defect to avoid cell leakage, furthermore the requirement is to harvest a fitting for a periosteal patch, and the procedure results in a high rate of adverse events such as hypertrophy and adhesions.[8] Those limitations were addressed with the usage of a bioabsorbable collagen membrane instead of the periosteal patch (ACI-C). The procedure with the

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http://dx.doi.org/10.1053/j.oto.2013.12.002
1048-6666/

membrane allows much faster and easier surgery and demonstrated similar clinical improvement with a lower incidence of hypertrophy of the graft.[9-11]

The injection of cultured chondrocytes in suspension raised concerns regarding the uneven distribution of chondrocytes and the possibility of cell leakage.[12] Those shortcomings led to the innovation of the third-generation cell therapies, so-called matrix-associated autologous chondrocyte transplantation (MACT), where biodegradable scaffolds are seeded with chondrocytes. Approximately 15 years ago, the technique using precultured cell–augmented biomaterials was introduced into clinical practice.

Different MACT Products

Since the introduction of MACT, several biomaterials were introduced to serve as a scaffold for transplantation of autologous cultured cells. However, it has to be reported that none of these products is currently approved by the Food and Drug Administration and is therefore not available in the United States, except in trials in the certification process. Currently in Europe, 2 procedures are certified for use in the European Union (Tigenix, MACI—Sanofi Biosurgery) and more are in the process of certification by the European Medicines Agency. In the following article, we describe products that demonstrate follow-up for more than 4 years.

Matrix-Assisted Chondrocyte Implantation

The matrix-assisted chondrocyte implantation (MACI) was initially performed with a collagen membrane, which is a bilayer membrane with a rough side, where the cells are seeded, and a more smooth side that serves as a barrier surface toward the articular cavity.[13] Russlies et al[13] demonstrated in an in vitro study that cell numbers showed a 93% recovery of seeded cells and immunohistologic examination revealed positive staining for type II collagen in some areas.

As typical for the MACT procedure, MACI requires a 2-step procedure. In the first step, an arthroscopy is performed to harvest a cartilage biopsy from a non–weight-bearing area of the joint, containing approximately 200-400 mg of healthy cartilage. The biopsies are prepared in the laboratory so that the chondrocytes are isolated from the biopsy specimen by enzymatic digestion and subsequently expanded in cell cultures for approximately 4 weeks. Afterwards the cells are seeded on the rough side of the collagen matrix (eg, Chondro-Gide [Geistlich Biomaterials, Wolhusen, Switzerland]) and cultured with autologous serum for 3 days. The transplant is implanted in a second surgical step by either a miniarthrotomy or arthroscopy. For a successful transplantation, the defect must be prepared and carefully debrided to remove all fissured and undermined cartilage including the calcified layer, but care should be taken to preserve the subchondral plate as much as possible. The defect size is then template with sterile paper and the implant is cut to exactly fit the defect. The matrix is placed into the defect with the cell-loaded side facing the subchondral bone. The implant can be fixed with fibrin glue or by sutures or combination of both.

Behrens et al[14] described the first transplantation in 1999 using Chondro-Gide. The first midterm results were also published by Behrens et al in a group of 11 patients 5 years after surgery reporting that 8 of 11 patients rated the function of their knee as much better or better than before.[15] Ebert et al[16] documented the results of 41 patients (53 grafts) with clinical assessment and magnetic resonance imaging (MRI) measurements of 35 patients (46 grafts) 5 years after surgery. The results demonstrated a significant improvement in the Knee injury and Osteoarthritis Outcome Score (KOOS). MRI measurement depicted a complete filling of 67% of MACI grafts, whereas 89% showed a good to excellent filling. Most patients (98%) were satisfied with relief of pain, 86% with their improvements to perform normal daily tasks, and 73% with their ability to participate in sport. A further study by Macmull et al[17] compared ACI-C ($n = 25$) with MACI ($n = 23$) in patients with a proven retropatellar defect who had at least 1 failed marrow-stimulating procedure. The authors concluded that at an average follow-up of 40.3 months, the MACI technique demonstrated better results (57% vs 40% with excellent and good results). Marlovits et al[18] followed up with 21 patients prospectively for up to 5 years. The study cohort was clinically assessed using the KOOS, the Tegner-Lysholm score, the International Knee Documentation Committee (IKDC) Subjective Knee Form, and the modified Cincinnati score. The quality of the repair tissue was assessed by MRI using the magnetic resonance observation of cartilage repair tissue (MOCART) score.[19,20] Treatment failure occurred in 2 patients (9.5%). The clinical scores demonstrated a significant improvement at all points of time. Similarly, there was significant improvement in the MOCART score from baseline (52.9 ± 12.5) to the fifth year (75.8 ± 18.0). Overall, the collagen membrane was able to sufficiently replace the periosteal flap and provide long-term improved outcomes with less complication owing to periosteal problems like hypertrophy or graft delamination. However, differences between preculturing the collagen membrane and the use of the unseeded collagen matrix with cell suspension cannot yet be definitely determined. The stable fixation of the sutured collagen membrane allows usage of MACI techniques in more challenging locations of the knee like the patellafemoral joint.

Hyalograft C

HYAFF-11-S (Fidia, Anika Therapeutics), the hyaluronan-based scaffold of Hyalograft C, is a hyaluronan polymer created by total esterification with benzyl alcohol. It consists of a network of 20-μm thick fibers with interstices of different sizes.[21] The polymer is completely dissolved after approximately 4 months.[22] The surgical technique is similar to the one described earlier. Opposed to MACI, Hyalograft C is a softer biomaterial and is not stable enough for sufficient suturing. However, owing to the homogenous material characteristic, the even cell distribution can be applied on both sides to the defect ground, and a contained defect fixation is not necessary owing to the sticky properties to the rough bone surface. As in