Biological Enhancement of Meniscus Repair and Replacement

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Abstract: When a meniscus injury occurs, it is generally accepted that preserving the meniscus is important for life-long joint preservation. Traditional suture repair of the meniscus has good results; however, the healing potential of meniscus tissue remains as a biological challenge because it is not a completely vascularized structure. For this reason, investigators have continued to search for adjuncts to improve clinical results. Mechanical adjuncts, local factor enhancement, scaffolds, gene therapy, and cell therapy have all been examined as options for improvement of biology and structure. This study reviews the basic science and clinical application of these modalities and provides an assessment of techniques on the horizon.

Key Words: meniscus repair, meniscus regeneration, biological enhancement, meniscus scaffolds, cell therapy

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The menisci are important structures for knee stability, articular load, and cartilage health. Injury to the meniscus alters the normal anatomy and biomechanics with significant consequence. Radiographic signs of degeneration have been well documented in long-term studies after meniscectomy.[1–3] Consequently, clinical management of meniscus injury favors repair when possible. There are multiple techniques available for meniscus repair, and meniscus repair has a reported success rate between 59% and 100%.[2,4–13] However, as success is constantly being evaluated and critiqued, mechanisms to enhance biology and improve outcomes are evolving.

Healing is divided into 3 phases: inflammation, repair, and remodeling. These phases are dependent on the delivery of cells and mediators of healing as well as the removal of injured tissue. Arrival of blood products and an associated fibrin clot is important for healing. During the healing process, a clot provides structure for the repair processes. In addition, important signaling molecules, such as fibronectin and platelet-derived growth factor (PDGF), are contained within the platelets of the initial clot and provide chemotactic and mitogenic stimuli for the repair process.[14–16] When exposed to these normal mediators of healing, meniscus fibrochondrocytes are capable of proliferation and extracellular matrix synthesis.[16] However, the vascularity of the meniscus varies upon location, and thus, healing potential varies accordingly. The outer periphery of the meniscus has an organized vasculature that arises from the capsule and penetrates about one quarter of the meniscus.[17] This vascularity provides for good healing potential in the outer peripheral 25% of the meniscus via formation of a fibrovascular scar.[18] The peripheral supply tapers to an avascular internal section with little or no potential for healing.[18] Anatomically the meniscus is typically divided into an outer peripheral one-third with excellent-to-good healing potential, a middle one-third with moderate healing potential, and an inner central one-third with poor healing potential.

MECHANICAL ENHANCEMENT OF HEALING

In addition to mechanics of acceptable tissue repair, techniques have also evolved to enhance the biological potential for healing. The longest established techniques have aimed at increasing the blood supply available to the meniscus. The simplest forms of increasing the blood supply involve making conduits from the inner center avascular regions to the peripheral vascular regions. Most methods use a needle, blade, or trephine to make a conduit from the most central portion of the meniscus to the outer periphery. In a canine model to study the microvasculature and healing potential, Arnoczky and Warren[18] showed healing potential in the central regions by making vascular access channels. A similar canine model resulted in improved healing with trephination combined with immobilization.[19] Clinical application of vascular access channels has been reported as good to excellent in 90% of incomplete tears in a retrospective study.[20] The reported method involved removing a core of peripheral tissue to allow vascular access to the central tissue.[20]

A next theoretic step by some authors to improve vascular presence was to create a larger vascular access channel and implant a porous structure. The first attempts to implement this idea used open procedures. In a canine model, two thirds of longitudinal tears in the avascular region treated with this method healed partially or completely.[21] However, their method requires removal of a significant portion of peripheral meniscus; insufficient integration of the polymer with the meniscus occurred in some cases.[21] Large access channels can damage the integrity of the circumferential fibers, which are important for hoop stress integrity. No clinical studies using this method have been reported. However, further progression of this idea has led to the development of a bioabsorbable, porous implant that can be placed arthroscopically. The Bioduct (Schwartz Biomedical Company, Fort Wayne, IN) is a cylindrical device composed of poly-L-lactic acid. Implantation in a canine model has shown a 71% healing rate of avascular tears.[22] There are no published clinical reports to support the use of this device.

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In addition to enhancing vascularity as described above, increasing the synovial attachment to the meniscus is also a method that can increase the blood supply. One simple way to achieve this enhancement is by roughening the borders of the synovium and meniscus adjacent to the repair. This technique is referred to as synovial abrasion. In animal studies, this method resulted in increased healing in middle one-third meniscus repairs but no increase in healing with central one-third tears.[23,24] Clinical experience with this method, limited to one case-control study, has shown a decrease in failure rate from 22% to 9% after the authors began adding synovial abrasion to their meniscus repairs.[25] A slightly more complex method is to suture a vascularized pedicle of synovium into a meniscus repair. This method has been shown to increase the potential for healing the avascular segment when used to augment repair in animal models.[19,26] However, similar to vascular access channel methods, this technique also requires an open procedure with one study advocating prolonged immobilization.[19] As such, it has not found a role in modern arthroscopic management of meniscus repairs. It has shown promise as an adjunct for allograft meniscus transplants with faster revascularization in an animal model.[27]

LOCAL GROWTH FACTOR ENHANCEMENT

In addition to increasing the natural blood supply to the repaired meniscus, other techniques have been developed to deliver mediators of healing to the meniscus repair site. Growth factors have proven effective for enhancement of meniscus tissue regeneration in vivo and in vitro.[28–30] However, growth factors are not commercially available for clinical use with the exception of bone morphogenetic proteins, which in isolation have not been studied specifically for meniscus repair. When tissue injury occurs, the coagulation cascade activates platelets and forms a fibrin clot. Activated platelets have been found to produce neovascularization and initiate collagen synthesis.[14] The mechanism of these processes involves the release of growth factors. One of these growth factors is PDGF, which has chemotactic and mitogenic effects on fibroblasts and endothelial cells and a proliferative effect for collagen synthesis from fibroblasts.[14] Similarly, fibrin and fibrin degradation products act as a chemokine for leukocytes. In conjunction, platelets and the fibrin clot initiate a healing response after injury. This mechanism is the basis for the use of fibrin clots and platelet-rich plasma (PRP) as adjuncts to meniscus repair.

Animal studies using fibrin clot have mixed results. An initial study in dogs involved making 2-mm holes in the avascular region of the meniscus and filling the defects with fibrin clot. Defects filled with fibrin clot healed with the formation of fibrocartilage.[31] Another animal study examined fibrin clot to enhance repair of avascular meniscus tears in a goat model. This study found a poor healing rate of 17% with fibrin clot alone compared with an improved healing rate of 87% when repair was combined with synovial abrasion.[24] Regardless of the equivocal animal results, fibrin clots have yielded positive results in clinical practice. Henning et al[32] retrospectively reviewed results of arthroscopic meniscus repairs and found a 41% failure rate without the use of fibrin clot and an 8% failure rate when fibrin clot was used. Similarly van Trommel reported a case series of 5 patients who underwent repair of posterolateral meniscus tears adjacent to the popliteus tendon with second-look arthroscopy and long-term magnetic resonance imaging indicating healing.[33] However, a randomized prospective study at 2 years showed that fibrin clot as an adjunct to repair produced inferior results when compared with trephination and repair.[34]

PRP is a documented source for growth factors including PDGF, transforming growth factor-β, platelet-derived epidermal growth factor, vascular endothelial growth factor, insulin-like growth factor-1, fibroblastic growth factor, and endothelial cell growth factor.[35–37] For meniscus repair, the theoretical advantage of using PRP as an adjunct has in vitro and in vivo support from a single study.[38] In this study, cultured meniscus fibrochondrocytes in the presence of PRP in vitro demonstrated cell proliferation and extracellular matrix synthesis, notably synthesis of glycosaminoglycan. For the in vivo arm, gelatin hydrogel (GH) was used to make scaffolds for a slow controlled release of PRP. GH scaffolds were engineered for release of growth factors at an average of 2 weeks. Comparison included punch-biopsy defects in the avascular section of rabbit menisci. Defects were filled with GH alone, GH with PRP, or GH with platelet poor plasma. The GH eluted from the defects over a period of 4 weeks, and final histological results showed improved fill with fibrocartilage in PRP specimens. The investigators felt that the GH vehicle played an important role in the success of their study, noting the short half-life of growth factors and the quick secretion of growth factors from activated platelets in vivo.[38] In a similar study comparing the effects of PRP with additional modalities, no improvement was noted.[39] In that study, the PRP was placed on a hyaluronan-collagen composite scaffold made with a leaching technique involving 70% hyaluronan-ester and 30% gelatin. The resultant scaffold was similar to the vehicle used in the previous described study[38]; however, it was not synthesized with time release in mind. The notion that elution of PRP slowly is necessary for its adjunctive use is a potential explanation of the varied results. To date, there are no clinical data available on the performance of PRP as an adjunct for meniscus repair in humans.

SCAFFOLDS

When repair is not possible, replacing damaged or removed meniscus with a graft is an option. Ideally, intrinsic cells and mediators of healing incorporate into the graft, which acts as a template and provides for matrix synthesis and cellular infiltration, ultimately producing a regenerated and remodeled meniscus. Current options for clinicians include allografts, collagen-based scaffolds, and synthetic scaffolds. Allografts have the longest clinical application and are indicated in cases of complete meniscectomy, whereas collagen-based and synthetic scaffolds require intact anterior and posterior horn attachments and an intact rim over the entire circumference of the involved meniscus.

Long-term outcomes studies for allograft transplant report 10-year survival rates from 50% to 70%.[40–43] Established risk factors for failure include malalignment and degenerative cartilage.[44–46] Variable factors include implantation technique, graft-processing technique, and storage technique. Although cadaveric biomechanical studies have shown that bone-plug fixation is stronger than soft tissue fixation at the time of implantation, outcomes and survival studies have not shown a clinical superiority in the

long term.[47–52] The biological and mechanical effects of graft preparation and storage techniques are not completely understood. Available options include fresh grafts, deep-frozen, freeze-dried, and cryopreserved allografts. Animal and human retrieval studies have shown that meniscus allografts do not completely incorporate or remodel in vivo, and immune response occurs dependent on graft selection and host individuality.[45,53–55] Although theoretical advantage exists from the decreased immunogenic potential of an acellular graft, it is unclear whether host cells from the synovium or recipient cells from the graft are best suited for population and maintenance of the graft.[42,51,56] Although population of a scaffold with host cells that can incorporate and become metabolically active has theoretical advantage, the role of donor cells within transplanted material is unclear. A study of viable human grafts has shown maintenance of donor DNA as long as 64 months after transplantation, suggesting that retained donor cells can survive and function for extended periods of time.[57] Alternatively, DNA probes in a goat study of transplanted meniscus showed no remaining donor DNA at 4 weeks.[58] Although advances have been made to develop acellular allografts that retain structure and function,[42,51,56,59] further animal studies are needed to determine which cell line best serves to seed acellular scaffolds.

In cases of partial meniscectomy, a collagen-based scaffold (Menaflex or Collagen Meniscus Implant or CMI, ReGen Biologics, Hackensack, NJ) is an option (Fig. 1). The Collagen Meniscus Implant, not approved for use in the United States at this time, has shown good clinical outcomes at 5 and 10 years with superiority when compared with partial meniscectomy.[28,60–65] In a multicenter study reported by Rodkey et al involving 311 patients followed for 5 years, implant of CMI was compared with partial meniscectomy in a randomized trial involving 2 patient subgroups, those who had previous meniscectomy before implantation surgery (chronic arm) and those with concurrent first partial meniscectomy and implantation surgery (acute arm).[61] In the chronic arm, fewer nonprotocol reoperations were performed on patients who received a CMI in comparison with controls who underwent partial meniscectomy. In addition, patients with prior meniscectomy who underwent CMI regained more of their previously lost activity as measured by Tegner Index when compared with control patients. No differences were detected in the acute arm. At 1 year, 141 of these patients underwent second-look arthroscopy with a measured and documented significant increase in meniscus tissue compared with controls, and there was evidence of a meniscus-like matrix and integration upon histological evaluation (Fig. 2).[61]

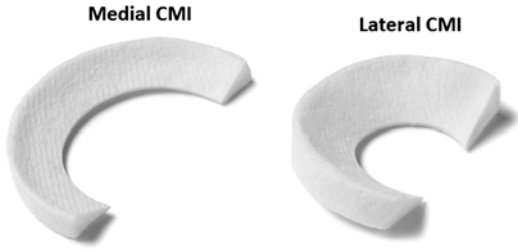

FIGURE 1. The Collagen Meniscus Implants (CMI) as they appear before implantation. There are separate medial and lateral implants.

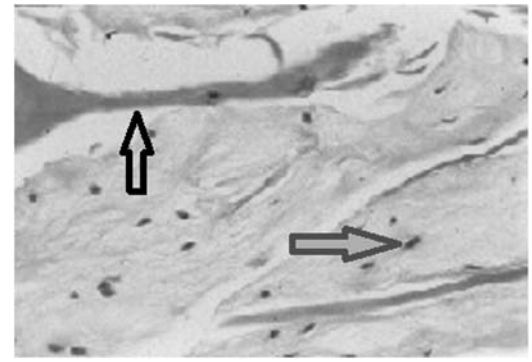

FIGURE 2. The Collagen Meniscus Implants (CMI) was progressively invaded and replaced by cells similar to meniscus fibrochondrocytes (horizontal colored arrow) with production of new meniscus-like matrix. Some implant remnants (CMI) are noted by the open vertical up arrow. Original magnification, 100×.

In addition to the 5-year study with the CMI, 2 studies are available at 10 years.[60,65] Monllau et al[60] reported on a case series of 25 patients; similar to the previously discussed 5-year study, these 25 patients included a chronic arm and an acute arm. Lysholm scores improved from 59.9 preoperatively to 87.5 at final follow-up for all patients. In addition, mean pain scores on visual analog scale improved by 3.5 points at the final follow-up, and magnetic resonance imaging analysis with Genovese scores found 64% of cases as nearly normal and 21% of cases as normal. Implant failure was noted in 8%. In a case-control trial, Zaffagnini et al[65] compared CMI implantation with partial meniscectomy alone and found improved pain, activity level, and radiological outcomes at a minimum of 10 years when compared with partial meniscectomy alone.

A porcine small intestinal submucosa-based scaffold (Restore Orthobiologic Implant; DePuy, Warsaw, IN) has been tested in animals for partial meniscus replacement. When studied in a canine model, initial encouraging results in clinical outcomes and post-sacrifice morphologic and histologic results were reported when compared with partial meniscectomy alone.[66,67] To date, no clinical studies have been reported.

In addition to biological grafts, synthetic implants have also been investigated. Biomechanical analysis has shown that degradable synthetic porous scaffolds can improve contact mechanics after implantation[68] and provide a scaffold which can be replaced with repair tissue after time.[69–71] For this tissue regeneration to occur, cell population and extracellular matrix production is required. Implant design has been directed by animal studies optimizing pore number, pore size, and interpore connectivity with compressibility, in-growth, and degradation time (Fig. 3).[72–74] Studies in dogs have shown success based on postimplantation infiltration and tissue regeneration.[69,70] However, biomechanical testing results have varied. Encouraging results have included a compression-stress curve similar in shape but differing in magnitude to that of native meniscus in one study and frictional coefficients which approach those of native meniscus in another.[69,75] Histological examination has been promising with abundant type II collagen and proteoglycans suggestive of cartilage-like repair tissue.[70] Early clinical data at 12 months have also been encouraging with 1 synthetic scaffold, not approved

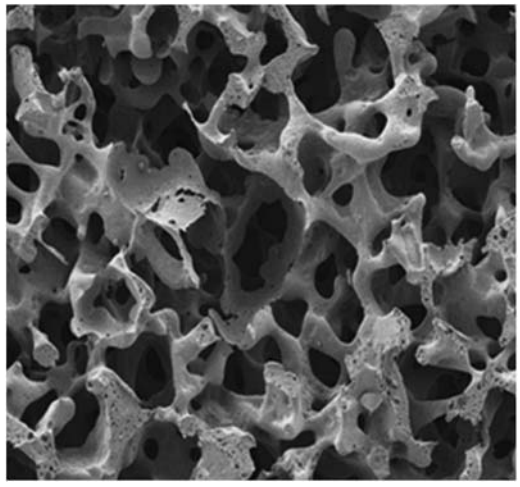

FIGURE 3. A scanning electron photomicrograph of the Actifit meniscus scaffold. It is a highly porous acellular scaffold made from polyurethane. Courtesy Dr E-L Heinrichs, Orteq Sports Medicine, London, UK.

for use in the United States at this time (Actifit, Orteq Sports Medicine, London, UK).[71] In a case series of 52 patients, 44 patients underwent second-look arthroscopy at 12 months. Forty-three of 44 patients had tissue integration with the scaffold and presence of viable tissue.[71] Of note, of the initial 52 patients, 3 were lost to follow-up, 2 discontinued study participation due to serious adverse events, 1 patient's scaffold was removed due to an infection, and 1 patient underwent conversion to a total knee arthroplasty.[71]

CELL THERAPY

Investigation into the use of scaffolds is complimented by interest in innate cell-seeding methods and how these processes may be augmented and/or manipulated. Stem cells have become an area of interest. Under inductive conditions, stem cells have the ability to differentiate into a given cell line, proliferate, integrate, and function. In animal studies, autologous marrow-derived mesenchymal stem cells (MSCs) have been evaluated with encouraging results.[39,76] Initial evaluations illustrated successful repair in avascular and vascular regions of meniscus in a rabbit model.[76] The investigators used cells that had been cultured in a chondrogenic medium and planted in sponge scaffolds made of hyaluronan-ester and gelatin. Repair tissue showed integration and meniscus-like fibrocartilage in 8 of 11 rabbits treated with MSCs and 2 of 11 rabbits treated with scaffolds alone. Follow-up evaluation sought to investigate whether growth factors in the media or cells themselves were the important factor for healing; marrow aspirate without processing was compared with unmanipulated MSCs and MSCs that had been precultured in a chondrogenic medium.[39] Marrow aspirate did not improve healing in comparison with controls. Precultured MSCs resulted in fibrocartilage-like repair tissue that was only partially integrated with native meniscus. The noncultured MSCs produced the best results with meniscus-like tissue that was fully integrated with surrounding tissue.[39] This study provides exciting data that suggest that MSCs can provide an important role as an adjunct for meniscus repair. It also raises the theory that minimally manipulated cell lines may prove more advantageous as opposed to precultured populations. MSC success with enhancement of meniscus repair parallels recent success with enhancement of cartilage regeneration in which an equine model demonstrated increased aggrecan content and tissue firmness.[77]

In addition to MSCs, additional cell lines that warrant further attention are adipose-derived stem cells and autologous peripheral blood progenitor cells. Both of these cell lines have also shown promise in cartilage repair studies.[78,79] A recent study of peripheral blood progenitor cells showed that these cells are similar to embryonic stem cells in that they express transcription factors specific to pluripotential cells, have proliferative potential, have the ability to differentiate into cells of all 3 embryologic cell lines, and are more immature than MSCs.[80] Further preclinical investigation is needed to determine which cell lines have the greatest potential for meniscus repair.

Challenges provided by meniscus repair are based on the limited blood supply and instances in which degenerative tissue provides little or no possibility for repair. Biological advances include scaffolds of various compositions that have yielded good clinical results and with documented evidence of improved healing. Meniscus allografts currently are the best option for complete meniscus loss, but the Collagen Meniscus Implant has the longest track record and by far the most clinical data for use after partial meniscectomy. PRP has had promising but mixed results in animal studies, but there are no clinical data for use of PRP in meniscus repairs at this point. Stem-cell therapy research has also yielded encouraging animal data, but further evaluations with preclinical and clinical studies are lacking. Further investigations will provide data to support which modalities are superior as we improve our treatment for this challenging clinical problem.

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