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Augmentation techniques for isolated meniscal tears

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Abstract Meniscal tears are relatively common injuries sustained by athletes and non-athletes alike and have far reaching functional and financial implications. Studies have clearly demonstrated the important biomechanical role played by the meniscus. Long-term follow-up studies of post-menisectomy patients show a predisposition toward the development of degenerative arthritic changes. As such, substantial efforts have been made by researchers and clinicians to understand the cellular and molecular basis of meniscal healing. Proinflammatory cytokines have been shown to have a catabolic effect on meniscal healing. In vitro and some limited in vivo studies have shown a proliferative and anabolic response to various growth factors. Surgical techniques that have been developed to stimulate a healing response include mechanical abrasion, fibrin clot application, growth factor application, and attempts at meniscal neovascularization. This article discusses various augmentation techniques for meniscal repair and reviews the current literature with regard to fibrin clot, platelet rich plasma, proinflammatory cytokines, and application of growth factors.

Keywords Meniscus · Platelet rich plasma · Repair · Augmentation

Introduction

Injuries to the knee meniscus have functional and financial implications. Swenson and colleagues [1] identified more than 5000 knee injuries among high school athletes, of which 23 % included meniscal injury. Other studies have shown similarly high incidence of approximately 70 cases per 100,000 persons [2–4]. The C-shaped fibrocartilaginous structure serves an important functional role in knee kinematics, including static stability [5], transmission of load and contact forces [6], shock absorption [7], and improvement of femorotibial congruity [8].

Menisectomy alters joint biomechanics [9, 10] and potentiates the risk of developing degenerative changes [11]. More recently, Wroble et al [12] looked at the long term clinical findings (average 21 years follow-up) in 39 patients treated with total menisectomy as adolescents. They reported the presence of pain, stiffness, effusions, and instability in 71 %, 68 %, 54 %, and 41 % respectively. The majority of patients self rated their knee as unsatisfactory. Other authors have found similarly unsatisfactory results [13–16]. Walker [10] showed that the medial and lateral menisci bear 40 % and 70 % of the tibiofemoral load, respectively. Furthermore, Lee and colleagues [9] used a cadaveric model to show that increasing menisectomy leads to increased tibiofemoral contact pressures. Specifically, they found that the more peripheral zone of the medial meniscus contributes more to increasing contact area and decreasing the contact stresses than the more central zone and thus peak contact stresses increase with increasing amount of resection.

Treatment strategies for meniscal tears have emphasized restoration of normal anatomy and biomechanical relationships through meniscal preservation whenever possible. Tear type, location, and chronicity affect decision making when considering repair vs resection. Non-degenerated, longitudinally oriented tears that are less than 3 cm in length, which occur within the peripheral zone, are amenable to repair. Very large or chronic, degenerated tears tend not to heal. Furthermore, tear morphologies such as flaps, cleavage, and radial tears are irreparable and better treated with menisectomy. Objective evaluation of healing using imaging studies or direct arthroscopic inspection have reported complete

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healing in 60 %–70 %, partial healing in 15 %–20 %, and failure of healing in 15 %–20 %. Anterior cruciate ligament (ACL) reconstruction should accompany meniscal repair in the ACL deficient knee, to improve mechanical stability [17]. Meniscus healing is reported to be higher in the setting of concomitant ACL reconstruction, which is believed to be due to the hemarthrosis from drilling bone tunnels.

The avascular nature of the meniscus poses the most significant challenge to repair. Arnoczky and Warren [18] showed that only the peripheral 10 %–30 % of the meniscus is vascularized. Limited blood supply is a critical obstacle to healing. As such, researchers and clinicians are working to find effective meniscal repair augmentation techniques. These efforts include the use of growth factors, stem cells, platelet rich plasma (PRP), introduction of a fibrin clot, and the use of mechanical stimulus. This article reviews the current state of augmentation techniques for meniscal repair.

Mechanical stimulus

Adjunctive surgical techniques have been developed to promote neovascularization in the setting of meniscus tears to stimulate a healing response. Theoretically, trephination produces vascular channels to help redirect blood flow from an area of vascularity to a less vascular zone [19, 20]. Abrasion of the adjacent synovium can be used to stimulate a healing response. Ritchie et al [21] showed superior performance of mechanical abrasion compared with fibrin clot application in their goat model. Other authors have demonstrated, in limited cohort studies, a positive impact of trephination and/or rasping of the parameniscal synovium [22]. Zhang et al [19] reported that the addition of trephination to a sutured meniscal repair in their goat model promotes healing, even in avascular areas as evidenced by measured DNA synthesis and tissue ingrowth. In their clinical study, Fox and colleagues [22] reported good to excellent results in 90 % of patients that they treated with arthroscopic trephination in the setting of incomplete meniscal tears. One concern with trephination is compromise of meniscal collagen fiber integrity. Others have described additional techniques for augmentation of meniscal repair including bone marrow stimulation through arthroscopic microfracture [23] and synovial abrasion [24, 25]. Clinical evidence supporting the efficacy of such techniques, however, is limited.

Ochi et al [26] investigated the effect of synovial rasping on production of interleukin-1-α, transforming-growth-factor β1, platelet-derived growth factor, and proliferating cell nuclear antigen in a rabbit model using immunohistochemical staining. They found that these factors were increased following rasping when compared with control and postulated their importance in neovascularization.

Fibrin clot

Fibrin clot is made up of fibrin and platelets. The alpha granules and dense granules in platelets contain numerous cytokines and other bioactive factors. The application of fibrin clot in the setting of meniscal repair is intended to serve as a scaffold for repair and to stimulate a reparative process in the avascular zone [27]. Arnoczky and Warren [27] used a dog model to evaluate the mitogenic and chemotactic properties of an exogenous fibrin clot on meniscal healing. A 2-m-diameter defect was created in the avascular potion of the medial meniscus and subsequently filled with autologus fibrin clot. They noted morphological healing of the experimental meniscal tears and absence of such a response in the control animals. Henning and colleagues [28] reported a significantly decreased rate of failure of meniscus repair in those treated with exogenous fibrin clot compared with those treated without (41 % vs 8 %).

Peripheral tears are reported to be amenable to repair with fibrin clot augmentation. Van Trommel et al [29] reported their results in patients with primary repair of a radial tear of the posterolateral meniscus treated with fibrin clot augmentation. Peripheral healing was confirmed in all patients during second look arthroscopy (5 of 5) in short-term follow-up and maintained at 71 months in all patients (3 of 3) evaluated with MRI. In a more recent small series of patients with complete radial tears treated with exogenous fibrin clot a 92 % healing rate (11 of 12) was noted on follow-up MRI at 30 months postoperatively [30]. Seven of the 12 patients had second-look arthroscopies that confirmed healing in 6 of 7 patients.

Results from exogenous fibrin clot augmentation in the setting of central, avascular zone, meniscal tears are less promising. Ritchie et al [21] looked at central medial meniscus tears in a goat model and found that repair with fibrin clot augmentation was less effective than repair with parameniscal synovial abrasion (17 % compared with 87.5 %, respectively). Furthermore, the authors looked at a third group of goats with simulations of peripheral tears, which were repaired primarily (without augmentation) and all healed. This study highlights 2 points: (1) the central avascular zone heals differently (if at all) than the peripheral vascular zones; and (2) synovial tissue stimulation may aid in meniscal healing.

Cell biology and meniscal healing: cytokines and growth factors

Several cytokines and growth factors have been investigated with regard to their ability to stimulate cell proliferation. Webber et al [31] used meniscal fibrochondrocyte from New Zealand white rabbits to demonstrate a dose-dependent

proliferative response in cell cultures to fibroblast growth factor (FGF) and human platelet lysate. With this in mind, other investigators have sought to elucidate the role of various cytokines and growth factors in healing [32, 33].

Inflammatory cytokines appear to have a negative effect on meniscal healing. Hennerbichler et al [32] evaluated the role of such cytokines on healing of full thickness meniscal defects made in a porcine meniscal explant in vitro. Specimens were cultured in 1 of 3 conditions: (1) media alone, (2) media with interleukin-1 (IL-1), or (3) media with tumor necrosis factor alpha (TNF-α). They demonstrated with the use of confocal microscopy and mechanical testing that specimens cultured in media-only preparation demonstrated the capacity to heal. Specimens cultured in media containing TNF-α and IL-1, however, failed to show a similar response. As such, the authors suggest that pro-inflammatory cytokines such as these have an inhibitory effect on meniscal healing. IL-1 increases matrix metalloproteinase (MMP), nitric oxide, and other catabolic mediators and decreases the shear strength of meniscal tissue at the repair site in vitro [33]. Others have shown similar results [34–37]. McNulty et al [35] suggested that IL-1 stimulates the production of numerous metalloproteinases as evidence by their finding that a broad-spectrum MMP inhibitor applied in vitro had a positive effect on tissue repair whereas specific MMP blockade did not.

In contrast to the inhibitory effects of pro-inflammatory cytokines, a number of growth factors including fibroblast growth factor (FGF), platelet derived growth factor (PDGF), transforming growth factor beta (TGF-β), and insulin-like growth factor (IGF) have been shown to stimulate a healing response in articular cartilage [38], wound granulation [39], and ligament [40].

Tumia and colleagues presented a series of experiments in which they showed that meniscal cells from the inner avascular zone could be stimulated to proliferate when exposed to IGF [41], FGF [42], and PDGF-AB [43]. Platelet derived growth factor, in particular was shown to stimulate an 8-fold increase in cell proliferation and a 4-fold increase in matrix production in vitro [43]. More recently, Riera et al [44] investigated the role of TGF-β1 on meniscal repair. They used medial menisci isolated from skeletally mature pigs. Meniscal cells were then cultured from either the inner two-thirds or the peripheral one-third of the meniscus. A micro-wound healing assay using a meniscal cell monolayer was then used to assess cell migration and proliferation. Cells that were exposed to IL-1 and TNF-α demonstrated decreased cell proliferation, while those exposed to TGF-β1 exhibited increased cell proliferation.

While the application of various growth factors has shown substantial promise with regard to meniscal healing in vitro, its translation into clinical practice remains to be fully realized. Recently, several authors have sought to apply this science to an in vivo model [45, 46•, 47]. Narita and colleagues [46•] evaluated the impact of FGF-2 impregnated gelatin hydrogels on meniscal healing in a rabbit model. Horizontal tears were made in the medial meniscus of 64 skeletally mature rabbits. Histologic evaluation revealed significantly higher cell density and number of proliferating cells in the group treated with FGF impregnated gelatin hydrogels compared with controls.

Vascularity plays a very important role in meniscal healing. Therefore, growth factors that stimulate vascular proliferation may be important adjuvants for meniscal repair. The practical application of such factors in vivo has not yet been convincingly demonstrated. Kopf et al [48•] explored the ability of vascular endothelial growth factor (VEGF) to induce vascular proliferation and improve healing in vivo and found no significant improvement in meniscal healing. The authors used 18 sheep and created longitudinal tears in the avascular region, which were subsequently repaired with sutures with various coatings—uncoated, coated with VEGF and its carrier poly (D,L-lactide), and coated with carrier poly (D,L-lactide) alone. Macroscopic, microscopic, and molecular analysis failed to show improvement in healing parameters or an induction of meniscal angiogenesis.

Platelet rich plasma

Platelet rich plasma **(**PRP) is easily harvested by phlebotomy and processed by centrifuge resulting in an approximately 3- to 8-fold increase in platelet concentration relative to that of whole blood [49].

Platelets may be activated by a number of agents including, calcium chloride, thrombin, fibrin, or type-1 collagen. Activation of clotting achieves a gelatinous consistency that can be more accurately applied to a repair site [50] and, more importantly, leads to additional platelet aggregation, thrombin generation, fibrin formation, and release of a host of local growth factors including PDGF, TGF-β1, VEGF, and IFG-1 [49, 51, 52]. Specifically, the release of these growth factors can promote angiogenesis and stimulate the aggregation of reparative cells [53].

PRP has been investigated by a number of disciplines including oral and maxillofacial reconstruction [52], cardiology [54], podiatry [55], and ophthalmology in addition to orthopedics [56, 57]. Anitua et al [58] performed an in vitro analysis of cytokines and growth factor production in the presence of platelet-rich and platelet-poor preparations on tendon healing and found a significant difference favoring the platelet-rich clot. A number of animal studies have also shown a benefit of PRP [59, 60]. Level-1 evidence to support the clinical use of PRP, however, is equivocal at best. A number of randomized studies have reported limited

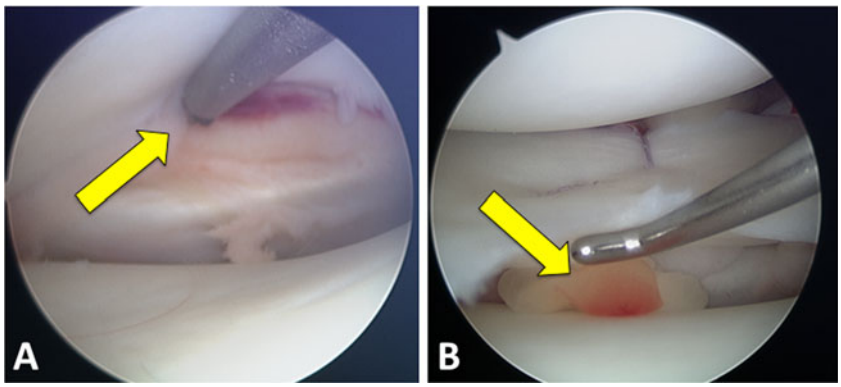

Fig. 1 Synovial abrasion (**A**) is used for meniscus repairs in all cases with a small round rasp (arrow). Platelet-rich fibrin matrix (**B**, arrow) is used for all isolated repairs in the setting of marginal vascularity, larger tears, or older patient age

or no clinical efficacy of PRP for pathologies including patellar tendon healing [61], lateral epicondylitis [62–64], Achilles tendinopathy [65, 66], plantar fasciitis [64, 67], and rotator cuff tears [68–71]. The major limitation of PRP is the significant variability between PRP produced from different individuals and using different commercial systems, with variation in platelet number, inclusion of white blood cells, and platelet activation.

There are no controlled studies evaluating PRP as an augment to meniscal repair. As such, the benefits remain theoretical and anecdotal [53, 72, 73]. Turnia and Johnstone [43] demonstrated in vitro that meniscal cells obtained from the inner avascular zone respond to PDGF-AB with induction of fibrochondrocyte proliferation and new matrix formation. Ishida and colleagues [74•] reported a positive mitogenic effect of PRP on monolayer meniscal cell cultures. They found increased fibrocartilage-related messenger RNA expression using real-time polymerase chain reaction in experimental cells treated with PRP. The investigators then evaluated PRP in vivo using a rabbit model in which a 1.5 mm diameter full-thickness defect was created in the inner avascular meniscal zone. Their experimental groups included PRP in a hydrogel delivery vehicle, platelet-poor plasma with hydrogel delivery, and hydrogel only as control. Histology and molecular evaluation suggested superior results in those treated with PRP.

Conclusions

The importance of the knee meniscus is clear. As such, there has been a shift in treatment strategy from resection to repair. The vascular anatomy, in particular, makes this structure particularly difficult to repair. A number of surgical techniques have thus been developed to augment repair. Fibrin clot may be a useful augment to meniscal healing, but it may be difficult to maintain localization of the clot without immobilizing the knee. Mechanical adjuvants such as rasping and trephination may stimulate neovascularization and a healing response, but may have detrimental structural effects on the meniscus with resultant impairment of biomechanical function. Application of growth factors remains an active area of research, but with limited translational data. Several studies have shown catabolic effects of IL-1 and TNF-α. Others have shown the positive proliferative effects of IGF, FGF, PDGF, and TFF-β in cell culture models. While an angiogenic factor such as vascular endothelial derived growth factor would seem to have the potential to augment healing, a recent study [48•] failed to show any significant impact on vascular induction or meniscal healing in a sheep meniscal tear model repaired with VEGF-coated sutures. One study reports molecular and histologic data that suggests a positive effect of PRP on meniscal healing in vitro and in vivo [74•]. There are, however, no large randomized trials that have reported the effects of PRP on meniscal healing in humans.

Authors preferred technique

The authors preferred technique for meniscus repair is an all-inside approach for smaller tears (<15 mm in length) that are located in the vascular zone of the meniscus. The typical repairable meniscus tear is a vertical longitudinal tear in the peripheral vascular region of the meniscus. We have typically used the Fast-fix 360 (Smith & Nephew Memphis, TN). An inside-out suture technique with a small accessory posterior incision is preferred for tears that are larger or that have complex morphology, as this technique allows more accurate placement of sutures on both the femoral and tibial sides of the meniscus. The inside-out technique is also used if tissue quality is questionable or there is marginal vascularity at the tear site, as there is concern that the larger needle required for currently available all-inside implants may compromise meniscus integrity. An outside-in technique is used for repair of more anterior tears, as it is difficult to place sutures perpendicular to the tear via standard anterior portals. A radially oriented tear is repaired using multiple depth sutures placed in a “purse string” fashion. Root avulsion tears are repaired by passing grasping sutures through

the avulsed posterior horn using an arthroscopic suture passing device, and then shuttling these sutures through a bone tunnel that is drilled using a standard ACL vector guide. The sutures are then tied over the front of the tibia using a button or other cortical fixation device.

We currently use synovial abrasion for all meniscus repairs. There is often a fibrinous material that coats the tear site, and this should be removed to allow healing. Synovial abrasion is done using a small round rasp (Fig. 1A). Augmentation using a platelet-rich fibrin matrix (PRFM) is done for all isolated repairs, especially in the setting of marginal vascularity (a tear at the red-white junction), larger tears, or an older patient (Fig. 1B). A suture is passed across the repair site using an outside-in technique with an 18 gauge spinal needle. Alternatively, this can be done using the inside-out approach if that technique is being used for the repair. The PRFM material is then attached to this suture, and then the suture is used to shuttle the material into the joint. This is done through an 8.25 mm diameter cannula that has the diaphragm removed. PRFM augmentation is not typically used in the setting of concomitant ACL reconstruction.

We are currently evaluating a technique to suture a collagen membrane over the meniscus repair site and then injecting concentrated bone marrow-derived cells on this membrane. Preliminary results using this technique have been recently reported [75].

Future of meniscus biology augmentation techniques

The basic paradigm for connective tissue repair is that optimal healing requires 3 factors: (1) a mechanical scaffold for cell adherence and to support new tissue formation, (2) the appropriate cell type and number to initiate healing and new matrix synthesis, and (3) signals (cytokines) to stimulate the cells to allow optimal differentiation of the cells and to stimulate expression of matrix genes. Fibrin clots and PRP materials primarily provide "signals" via platelet-derived cytokines.

As discussed above, at this time there is little data demonstrating a positive effect of PRP on meniscus healing in patients. A fundamental limitation in the current PRP literature is the tremendous variability in the different commercially-available PRP formulations. As further information becomes available about the cytokines that have a positive (anabolic growth factors) or negative (pro-inflammatory mediators, matrix metaloproteinases) effect on meniscus biology, there is optimism that techniques will be developed to "customize" PRP by isolating the desired cytokines and/or removing unwanted factors.

Futures progress in meniscus healing may come from attention to the other 2 aspects of the paradigm (cells and scaffolds). Improved methods to isolate and concentrate mesenchymal stem cells from autologous sources such as bone marrow or adipose tissue, or the identification of an effective allogeneic cell source, will allow further evaluation of the role of cell-based techniques to augment healing. Finally, the development of novel scaffold materials and techniques to implant such materials will aid our efforts to affect the local biologic environment of the healing meniscus.

Conflict of interest SA Taylor declares no conflicts of interest. SA Rodeo: Consultant for Smith and Nephew; declares no conflicts of interest.

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