

# Biologic Enhancement of Meniscus Repair

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## KEYWORDS

- Platelet-rich plasma • Blood clot • Fibrin clot • Biologic
- Meniscus • Meniscal repair • PRP

The first meniscal repair was described by Annandale in 1885.<sup>1</sup> In addition to the patients' reported 1-month stay in the hospital, many other changes have occurred in the techniques of meniscal repair since that time.<sup>1</sup> Most repairs are performed arthroscopically, with a variety of suture techniques ranging from inside-out, outside-in, to all-inside. Regardless of the technique utilized, vertical suture placement is one of the cornerstones of meniscal repair. Meniscal repair techniques are discussed elsewhere in this *Clinics in Sports Medicine* issue and will not be further discussed herein.

Since the 1980s, biologic enhancement of meniscal repair has been reported. Initially, fibrin clot was used to augment meniscal repairs in avascular zones of injury. Recently, the use of platelet-rich plasma (PRP) to enhance spinal fusions, as well as tendon and ligament repair, has been carried over to studies involving its use in meniscal repair. Furthermore, basic science and animal studies have involved tissue engineering and the local delivery of growth factors in the enhancement of meniscal repair. This article discusses the use of biologic products to enhance meniscal repair.

## FUNCTION

Although Annandale described the first meniscal repair in 1885, and Fairbank first described degenerative changes that occurred after meniscectomy in 1948, removal of part or all of the meniscus was the treatment of choice until the 1960s and 1970s.<sup>2,3</sup> Since then, it has been understood that the meniscus plays an important anatomic function in knee kinematics.

One important function of the meniscus is to transmit compressive loads. Biomechanical studies have found that it is responsible for transmitting 50% of body weight load in extension and up to 85% in 90° of flexion.<sup>4,5</sup> Thus, debridement of even part

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of the meniscus can result in decreased contact area, which can then result in increased contact pressures.

Another function of the meniscus is to act as a shock absorber during gait. Biomechanical studies have found that normal knees have a 20% higher shock-absorbing capacity than knees treated with meniscectomy.<sup>6</sup>

Although definitive studies are lacking, it has been suggested that by increasing the congruity between the femoral and tibial condyles, the meniscus helps maintain articular lubrication.<sup>2</sup> Also, type I and type II nerve endings observed in the anterior and posterior horns of the meniscus suggest that it may also play a role in proprioception.<sup>7,8</sup>

## ANATOMY

The menisci are semicircular fibrocartilage disks positioned between the femur and the tibia. The medial meniscus is larger than the lateral meniscus in anterior-to-posterior diameter; it is approximately 3.5 cm long. It is thicker posteriorly than anteriorly. The medial meniscus has several points of fixation. Anteriorly, it is attached to the tibia in the intercondylar fossa, just anterior to the footprint of the anterior cruciate ligament. Its posterior insertion point is between the posterior insertion of the lateral collateral ligament and the footprint of the posterior cruciate ligament. Along the periphery, the medial meniscus is strongly attached to tibia through the coronary ligament as well as to a thickening of the medial joint capsule referred to as *the deep medial collateral ligament*.

The lateral meniscus, however, is more circular and covers almost 75% of the articular surface of the more convex lateral tibial plateau. Its anterior insertion point on the tibia is slightly posterior to the footprint of the anterior cruciate ligament. Its posterior insertion point is anterior to the insertion of both the medial meniscus and posterior cruciate ligament. The tibia has strong posterior attachments to the femur, referred to as *the ligament of Humphry*, which runs anterior to the posterior cruciate ligament, as well as the ligament of Wrisberg. Also, the popliteal hiatus is an area unique to the lateral meniscus. This is the area in which the popliteal tendon runs through the knee joint interrupting the lateral meniscus attachment to the joint capsule. This in part contributes to the fact that the lateral meniscus is more mobile than the medial meniscus.<sup>2</sup>

The extracellular matrix of the meniscus is composed of water and collagen, primarily type I collagen (almost 90%), but types II, III, V, and VI had been identified as well, as well as proteoglycan. Collagen fibers are lined up circumferentially along the middle length of the meniscus and act to transmit load across the knee joint. A smaller portion of collagen fibers are lined radially within the substance of the meniscus to potentially resist the longitudinal splitting of the meniscus under compressive forces.<sup>2,9</sup>

## VASCULARITY

The vascular supply to the various portions of the meniscus forms the basis of treatment options. The meniscus is a relatively avascular structure. The lateral and medial geniculate arteries give rise to the perimeniscal capillary plexus (PCP). This plexus surrounds the periphery of the meniscus providing blood mostly to the outer third of the meniscus, with the central portion of the meniscus receiving progressively less blood supply. Anatomic studies have shown that this arborization of blood vessels penetrates only approximately 10% to 30% the width of the medial meniscus and 10% to 25% of the lateral meniscus. A vascular synovial membrane covers the area surrounding the femoral and tibial articular attachments of the meniscus.<sup>2,10</sup> As

such, meniscal tears have been described based on their location within the meniscus relative to the periphery and thus the vascular supply. Meniscal tears are said to fall within the red-red, or most vascular peripheral third; red-white, or middle third; and white-white, or avascular central third. When considering whether a meniscal tear is repairable, the location of a meniscal tear relative to the periphery is just as, if not more, important than the type of meniscal tear itself.

Of note, in addition to the central portion of the meniscus, the area of the popliteal hiatus in the lateral meniscus has also been described as an avascular area.<sup>2</sup>

## HEALING

Understanding how the meniscus naturally heals tears is the key to both the development and the application of biological enhancement of meniscal repairs today. The most important fact to recall is that the basis of vascularity of the meniscus comes from the PCP. When a tear occurs in the peripheral third, a fibrin clot forms, which is rich in inflammatory cells. The PCP grows rapidly over the fibrin conduit, as well as into the fibrous scar, while contributing undifferentiated mesenchymal cells. Studies have found that tears within the vascular peripheral zone are completely healed by a fibrovascular scar by 10 weeks.<sup>11</sup>

In general, many factors have been described to play important roles in the healing pathway, including insulinlike growth factor-1 (IGF-1), vascular endothelial growth factor (VEGF), transforming growth factor beta (TGF- $\beta$ ), platelet-derived growth factor (PDGF) and basic fibroblast growth factor (bFGF).<sup>11</sup> Multiple basic science studies focus on growth factors' effects more specifically on meniscal cells and the processes involved in healing a meniscal tear. Interleukin-1 and epidermal growth factor have been shown to stimulate meniscal cell migration, whereas bone morphogenic proteins-2 and IGF-1 have been shown to stimulate fibrochondrocyte migration from the middle to avascular zone.<sup>12</sup> Webber and coworkers<sup>13</sup> have suggested in their literature that fibroblastic growth factor and human platelet lysate have been found to stimulate the proliferation of meniscal cells. Thus, meniscal repair is based on available vascular supply to supply healing factors. This is the basis for biological enhancement of meniscal repair in avascular areas of the meniscus.

## INDICATIONS FOR MENISCAL REPAIR

When a patient presents with knee pain, one should begin with a focused history and physical examination. Specialty tests, such as the McMurray test and Apley grind test, can suggest meniscal pathology, but the most specific physical examination sign suggesting meniscal pathology, as shown by Weinstabl and colleagues al<sup>14</sup>, is joint line tenderness in an acutely injured knee. Typical symptoms include pain with deep flexion or twisting, or mechanical symptoms such as an inability to fully extend the knee or the knee locking in certain positions. Imaging studies should begin with radiographs, which include weight-bearing flexion views to identify concomitant osteoarthritis. The most currently effective further imaging study should be a magnetic resonant image. Meniscal tears are treated when they are painful to patients, have failed conservative management, and interfere with daily activities.<sup>14,15</sup>

Indications for repair of meniscal tears are based on several factors, including tear type, location, how acute the tear is, activity level of the patient, patient age, and knee stability. With regard to tear type, the best indication is for unstable tears that are complete and nondegenerative and vertical longitudinal tears greater than 10 to 12 mm in length. Location of meniscal tears is also critical in determining the ability of the tear to heal based on the vascular supply of the meniscus as described above. Tears

in the peripheral third are most appropriate for repair because of the excellent blood supply. Repairs of the middle third, the red-white zone, can be attempted as long as they extend into the peripheral third, and central third meniscal tears are generally felt to have poor healing rates as discussed above. Patient-specific factors also play a role in determining if a meniscal tear is appropriate for repair. Active younger patients, in their second, third, or fourth decade of life, are felt to be excellent candidates. Patients also must be willing to undergo postoperative rehabilitation programs as well as adhere to postoperative weight-bearing and activity restrictions. General contraindications include patients older than 60 years, sedentary lifestyle, unwillingness to participate in postoperative rehabilitation programs or restrictions, or those medically unfit to undergo an operation. Furthermore, degenerative, chronic tears that are stable, less than 10 mm, or in the central third are also contraindicated for repair.<sup>16</sup>

## RESULTS

When evaluating meniscal repair results cited in the literature, it is important to consider 3 factors: criteria used to define a successful result, associated injuries, and finally duration of follow-up. Second-look arthroscopy, clinical examinations specific to meniscal symptoms, double-contrast arthrography, and, most recently, magnetic resonance imaging are commonly used to evaluate meniscal repair success. It is important to determine the presence of associated injuries, specifically, anterior cruciate ligament (ACL) rupture, because meniscal repairs associated with ACL tears are frequently more successful based on both the acuteness of injury as well as the presence of a hemarthrosis and associated healing environment the ACL tear creates. Finally, duration of follow-up should be at least 2 years, because shorter follow-up may overestimate success of repair.<sup>17</sup>

In general, meniscal repair rates are more successful for lateral versus medial meniscal tears, when tears are associated with ACL reconstruction, when the rim width is less than 3 mm (peripheral tears), and when tears are results of acute injuries, such as those less than 2 to 8 weeks.<sup>17</sup>

Although the general rule is that meniscal tears of the central third should not be repaired, there are several studies of this that show promise.<sup>2,18,19</sup> In one study by Rubman and colleagues,<sup>20</sup> 198 meniscal tears that initially extended into the avascular zone (rim >4 mm) were repaired and reviewed at least 2 years postoperatively. Seventy-one percent of the meniscal tears occurred in patients with associated ACL tears. Eighty percent were felt to be asymptomatic for tibiofemoral pain. A total of 91 patients overall were evaluated with follow-up arthroscopy, which showed that 25% were completely healed, 38% partially healed, and 36% did not heal. The authors concluded that meniscal tears into the avascular zone should be repaired because despite the 20% risk of recurrent tibiofemoral symptoms, and 36% overall failure rate on second-look arthroscopy, the benefits of a potentially functional meniscus far outweighed the risk of future degenerative joint arthritis.<sup>20</sup>

### ***Biological Enhancement***

Because most studies have found that peripheral meniscal tears heal more predictably than central avascular meniscal tears, most effort has been focused on enhancing the potential of healing central meniscal tears. First, mechanical techniques, such as rasping<sup>21</sup> and synovial abrasion,<sup>19</sup> were used with some degree of success in an effort to stimulate bleeding and a vascular pannus, which can migrate to the tear and aide in healing by providing inflammatory cells. Recently, biological enhancements, such as fibrin clot, PRP, and growth factors, have been studied, and their application in meniscal repair is discussed below.

### ***Fibrin Clot***

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Beginning in the 1980s, the literature suggested the use of fibrin clot as an option to adjunct natural healing of meniscal repair. The idea is that by placing a fibrin clot in a stable lesion within the avascular zone of the meniscus, the fibrin clot will aid in healing in 2 ways. First, the fibrin clot will provide a chemotactic and mitogenic stimulus to the reparative process. Furthermore, the fibrin clot itself will serve as scaffolding over which fibrous tissue may form. In a landmark study by Arnoczky and coworkers,<sup>18</sup> avascular tears in the menisci of 6 dogs were surgically created and repaired with the use of a fibrin clot. At 1-, 3-, and 6-month intervals, the menisci were grossly and histologically monitored to check healing status. By 6 months, all of the menisci repaired with fibrin clot were healed grossly and histologically with tissue that resembled mature fibrocartilage, although it did not look like the adjacent uninjured meniscal tissue. Furthermore, the control samples of avascular meniscal tears treated without fibrin clots showed no growth, and in 3 of the 6 samples, only a small film of tissue filled less than 2% of the defect. The key to this technique is not in bringing a direct vascular supply to a previously avascular area, but instead to bring the factors found within a hematoma, which normally forms when there is an injury but cannot form in an avascular meniscal tear. By applying the fibrin clot and the healing factors contained within it, the avascular meniscal repairs have a more natural attempt to heal. In that way the indications for meniscal repair can be broadened, and a larger group of people can benefit from retaining meniscal tissue rather than depending on a meniscectomy.<sup>18</sup>

In a study by Henning and colleagues,<sup>19</sup> 153 meniscal tears were repaired with 1 to 2 mL of exogenous fibrin clot. Eight percent of tears were treated in isolation, whereas 92% had association with ACL tear repair. Isolated tears without exogenous clot had a failure rate of 41% compared with 8% when treated with fibrin clot, showing some promise for this treatment option.<sup>19</sup>

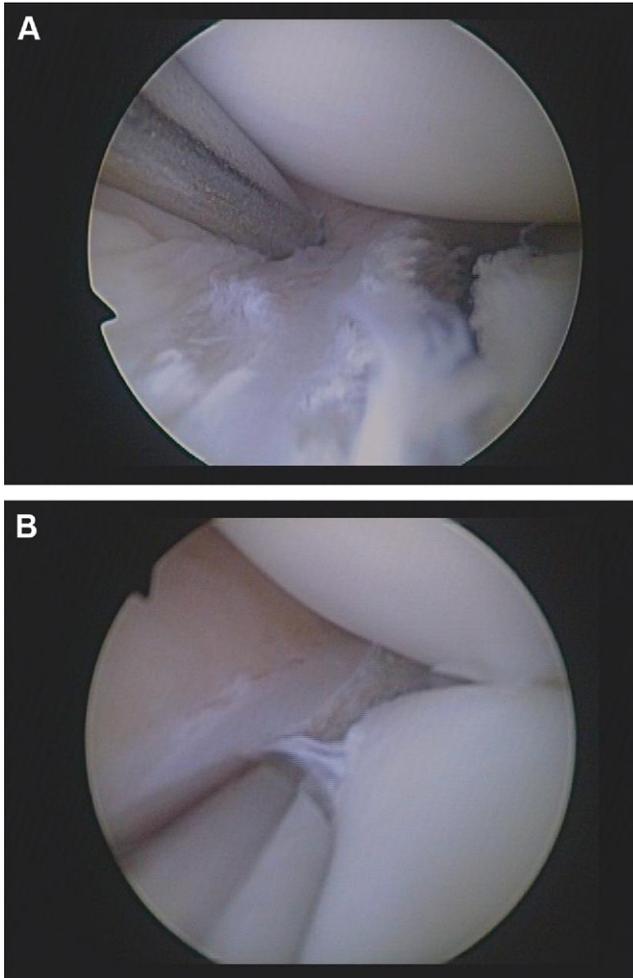
### ***Platelet-rich Plasma***

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PRP is a sample of autologous blood that has been prepared until it has concentrations of platelets that are above baseline values. Higher levels of platelets are desired because studies suggest that growth factors released by platelets recruit reparative cells and may augment soft-tissue repair. PDGF, VEGF, transforming growth factor B1 TGF- $\beta$ , FGF, and epidermal growth factor have all been found in platelets while hepatocyte growth factor and IGF-1 are found in plasma. These growth factors are important in soft tissue healing, as they induce angiogenesis, stimulate cell replication and differentiation, potentiate other growth factors, and help regulate fibrosis and myocyte regeneration.<sup>22</sup> These growth factors are found in varying concentrations depending on which of the many preparation systems on the market is used.

Preparation of PRP begins as a centrifuge or filter is used to separate the sample of anticoagulated blood into red blood cells, leukocytes, and platelets. The plasma is further concentrated in platelet-rich and platelet-poor portions. Often, the isolated PRP is mixed with an activating agent, such as calcium chloride or thrombin, which creates a putty or gel-like clot, which can then be sutured at the surgical site. These activating agents are used to initiate platelet activation, allowing growth factor release and clot formation at the area of PRP application.<sup>23</sup> As seen in **Fig. 1**, the process of PRP application in meniscal repair includes preparation of the meniscal tear, injection of the PRP gel or putty into the crux of the tear, and repair of meniscus by preferred technique. (See video online for full demonstration of meniscal repair with PRP.)

There are various preparation kits used to create PRP, and each kit results in different proportions of growth factors, activating agent, leukocyte concentration,



**Fig. 1.** PRP application to meniscal tear. (A) A longitudinal full-thickness meniscal tear is visualized through the arthroscope. (B) The meniscal tear has been repaired with edges debrided to a smooth area for repair. The PRP is being injected arthroscopically. The meniscus is then repaired by surgeon preference with PRP within the tear edges.

autologous blood volume, PRP volume, and final platelet amount. Initially, PRP was shown to be clinically effective when the platelet concentration was 4 times that of normal but in further studies has been shown to be effective in lower concentrations. Because of the qualitative and quantitative differences based on preparation kit used to create each lot of PRP, results found in the literature cannot be generalized to all preparation systems.<sup>23</sup>

Before discussing the research that supports PRP use in meniscal tears, it is important to review PRP use in tendon and ligament pathologies—the initial building blocks of why PRP could help in meniscal repair. Basic science studies have found that tendons treated in vivo with PRP showed increased expression of vital reparative growth hormones including VEGF, TGF- $\beta$ , PDGF compared with those treated with

platelet-poor plasma.<sup>24,25</sup> Animal studies have also suggested benefits to PRP use in tendon repair. Murine models with patellar tendon repair enhanced by PRP have shown increased forces to failure, larger tendon callus, and increased tenocyte proliferation.<sup>26,27</sup> Pig ACL reconstruction models enhanced with PRP have shown higher loads to failure, and rabbit patellar tendon repair models have suggested PRP use shows gains in the earlier stages of healing, which appear to level off approximately 4 weeks into the healing process.<sup>28–30</sup> Clinical studies have mainly focused on chronic tendinopathy, such as for lateral epicondylitis and noninsertional Achilles tendonopathy, that has not responded to conservative management. These studies have shown promising results compared with those of placebo (Geaney LE, Arciero RA, DeBerardino TM, et al. The effects of PRP on tendon and ligament: basic science and clinical application. CORR, submitted for publication).<sup>31–33</sup> In the largest randomized, control trial for the use of PRP to treat noninsertional Achilles tendinopathy, no difference was found between the use of PRP and placebo and stretching alone. It has been suggested that these results could be in part because an indication of failure of conservative treatment was not used in the DeVos study.<sup>34</sup>

Thus, basic science and animal studies as well as smaller clinical trials show promising results for PRP in tendon healing, whereas the largest randomized, controlled trial is not as supportive of the use of PRP in tendon healing. The important factors contained in PRP, which show results suggestive of benefit in tendon healing, could also help in the healing process of meniscal repairs in the avascular zone.

Basic science research has suggested that PRP significantly enhances meniscal repair. For example, Ishida and coworkers,<sup>35</sup> in a study performed in Japan, suggested that PRP enhances meniscal tissue regeneration both in vitro and in vivo. They studied mRNA expression of extracellular matrix proteins produced by meniscal cells cultured with PRP compared with meniscal cells without PRP. Significantly higher amounts of mRNA were expressed when cultured with PRP. Even more impressively, in vivo, they showed that full-thickness meniscal tears created in the avascular region of rabbits and treated with PRP delivered by gelatin hydrogel (GH) histologically showed better meniscal repair than those treated with GH and platelet-poor plasma, or GH alone.<sup>35</sup>

There are no large, randomized controlled trials investigating the use of PRP for meniscal repair in human avascular meniscal tears. These studies should be done in future research to contribute to our understanding of the use of PRP in the enhancement of meniscal repair and the expansion of indications for repair.

### ***Tissue Engineering***

Cell-based therapy involves growing autologous articular chondrocytes, seeding them to a scaffold, and incorporating this in the repair of meniscal tears. In a study based on a porcine model, this technique resulted in the gross and histologic healing of all specimens. This was in comparison with no repairs seen in the control group, which included 1 meniscal tear repaired with a scaffold alone, 1 with a repair alone, and 1 with no repair at all. Similarly, another porcine-based study showed 100% healing rate with the use of autologous and allogenic chondrocytes seeded on a bioabsorbable mesh and used to treat avascular meniscal tears. This was in comparison with no healing in the control group.<sup>16,36,37</sup> Another idea that has been tested in animal studies is the genetic modification of meniscal and mesenchymal stem cells. These cells were modified to produce TGF- $\beta$ 1, seeded to a scaffold then incorporated in the repair of an avascular meniscal tear in the bovine model. The results showed increased levels of proteoglycan and collagen production as well as histologic

evidence of healing.<sup>16,38,39</sup> As these technologies develop, future studies will guide our use of these treatment options in the future.

### **Growth Factors**

The theory of delivering much-needed growth factors to avascular areas of the meniscus is dependent on a good carrier to deliver the growth factors. Because of the short half-life associated with growth factors, it appears that injecting a one-time dose of growth factors would likely be inefficient. Ideally, the scaffold would be a porous, biodegradable material, which could slowly elute growth factors at an effective concentration but would degrade over time as to not interfere with the regenerative process.<sup>40,41</sup> Basic science studies have shown promise for the use of growth factors to stimulate meniscal cells to aid repair of avascular zone meniscal tears. Tumia and colleagues<sup>42</sup> extracted sheep meniscal fibrochondrocytes from the peripheral, middle, and central third of the meniscus, then cultured the cells in fetal calf serum with or without basic FGF and monitored the response of DNA and protein synthesis. The study showed that even cells from the avascular zone responded to bFGF by showing the potential to replicate and produce extracellular matrix.<sup>42</sup>

### **SUMMARY**

The biologic enhancement of meniscal repairs is focused on the delivery of factors that help to create a healing environment despite the lack of natural delivery of these factors in the avascular zone of the meniscus. The use of fibrin clot, PRP, tissue engineering, and local delivery of growth factors are all potential biologic enhancements used in the repair of meniscal tears in the avascular zone of the meniscus. By expanding successful meniscal repair into the avascular zone of the meniscus, many more patients could benefit from this procedure. Larger, randomized studies with human subjects need to be performed to show the potential benefit of these treatment options. Follow-up should be for at least 2 years and can help answer the question whether meniscal repair truly results in the theoretical advantage of avoiding meniscectomy and the associated increased degenerative arthritis that may result.

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