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 β 1, 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 portion of the medial meniscus and subsequently filled with autologous 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- β 1 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- β 1 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- β 1, 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 TGF- 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 metalloproteinases) 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.

References

Papers of particular interest, published recently, have been highlighted as:

- Of importance

1. Swenson DM, Collins CL, Best TM, Flanigan DC, Fields SK, Comstock RD. Epidemiology of knee injuries among US high school athletes, 2005/06–2010/11. *Med Sci Sports Exerc.* 2013;45(3):462–9.
2. Hede A, Jensen DB, Blyme P, Sonne-Holm S. Epidemiology of meniscal lesions in the knee. 1215 open operations in Copenhagen 1982–84. *Acta Orthop Scand.* 1990;61:435–7.
3. Majewski M, Susanne H, Klaus S. Epidemiology of athletic knee injuries: a 10-year study. *Knee.* 2006;13:184–8.
4. Nielsen AB, Yde J. Epidemiology of acute knee injuries: a prospective hospital investigation. *J Trauma.* 1991;31:1644–8.
5. Shoemaker SC, Markolf KL. The role of the meniscus in the anterior-posterior stability of the loaded anterior cruciate-deficient knee: effects of partial vs total excision. *J Bone Joint Surg Am.* 1986;68:71–9.
6. Radin EL, de Lamotte F, Maquet P. Role of the menisci in the distribution of stress in the knee. *Clin Orthop Relat Res.* 1984;185(185):290–4.
7. Voloshin AS, Wosk J. Shock absorption of meniscectomized and painful knees: a comparative in vivo study. *J Biomed Eng.* 1983;5:157–61.
8. Greis PE, Bardana DD, Holmstrom MC, Burks RT. Meniscal injury: I. basic science and evaluation. *J Am Acad Orthop Surg.* 2002;10:168–76.
9. Lee SJ, Aadalen KJ, Malaviya P, et al. Tibiofemoral contact mechanics after serial medial meniscectomies in the human cadaveric knee. *Am J Sports Med.* 2006;34:1334–44.
10. Walker EA, Davis D, Mosher TJ. Rapidly progressive osteoarthritis: biomechanical considerations. *Magn Reson Imag Clin N Am.* 2011;19:283–94.
11. Fairbank TJ. Knee joint changes after meniscectomy. *J Bone Joint Surg Br.* 1948;30B:664–70.
12. Wroble RR, Henderson RC, Campion ER, el-Khoury GY, Albright JP. Meniscectomy in children and adolescents. A long-term follow-up study. *Clin Orthop Relat Res.* 1992;279(279):180–9.

13. Jorgensen U, Sonne-Holm S, Lauridsen F, Rosenkint A. Long-term follow-up of meniscectomy in athletes. A prospective longitudinal study. *J Bone Joint Surg Br.* 1987;69:80–3.
14. Roos H, Lauren M, Adalberth T, Roos EM, Jonsson K, Lohmander LS. Knee osteoarthritis after meniscectomy: prevalence of radiographic changes after 21 years, compared with matched controls. *Arthritis Rheum.* 1998;41:687–93.
15. Englund M, Roos EM, Lohmander LS. Impact of type of meniscal tear on radiographic and symptomatic knee osteoarthritis: a 16-year follow-up of meniscectomy with matched controls. *Arthritis Rheum.* 2003;48:2178–87.
16. Englund M, Lohmander LS. Risk factors for symptomatic knee osteoarthritis 15 to 22 years after meniscectomy. *Arthritis Rheum.* 2004;50:2811–9.
17. Nepple JJ, Dunn WR, Wright RW. Meniscal repair outcomes at greater than 5 years: a systematic literature review and meta-analysis. *J Bone Joint Surg Am.* 2012;94:2222–7.
18. Arnoczky SP, Warren RF. Microvasculature of the human meniscus. *Am J Sports Med.* 1982;10:90–5.
19. Zhang Z, Arnold JA, Williams T, McCann B. Repairs by trephination and suturing of longitudinal injuries in the avascular area of the meniscus in goats. *Am J Sports Med.* 1995;23:35–41.
20. Zhang ZN, Tu KY, Xu YK, Zhang WM, Liu ZT, Ou SH. Treatment of longitudinal injuries in avascular area of meniscus in dogs by trephination. *Arthroscopy.* 1988;4:151–9.
21. Ritchie JR, Miller MD, Bents RT, Smith DK. Meniscal repair in the goat model. The use of healing adjuncts on central tears and the role of magnetic resonance arthrography in repair evaluation. *Am J Sports Med.* 1998;26:278–84.
22. Fox JM, Rintz KG, Ferrel RD. Trephination of incomplete meniscal tears. *Arthroscopy.* 1993;9:451–5.
23. Freedman KB, Nho SJ, Cole BJ. Marrow stimulating technique to augment meniscus repair. *Arthroscopy.* 2003;19:794–8.
24. Tetik O, Kocabey Y, Johnson DL. Synovial abrasion for isolated, partial thickness, undersurface, medial meniscus tears. *Orthopedics.* 2002;25:675–8.
25. Okuda K, Ochi M, Shu N, Uchio Y. Meniscal rasping for repair of meniscal tear in the avascular zone. *Arthroscopy.* 1999;15:281–6.
26. Ochi M, Uchio Y, Okuda K, Shu N, Yamaguchi H, Sakai Y. Expression of cytokines after meniscal rasping to promote meniscal healing. *Arthroscopy.* 2001;17:724–31.
27. Arnoczky SP, Warren RF, Spivak JM. Meniscal repair using an exogenous fibrin clot: an experimental study in dogs. *J Bone Joint Surg Am.* 1988;70:1209–17.
28. Henning CE, Lynch MA, Yearout KM, Vequist SW, Stallbaumer RJ, Decker KA. Arthroscopic meniscal repair using an exogenous fibrin clot. *Clin Orthop Relat Res.* 1990;252(252):64–72.
29. van Trommel MF, Simonian PT, Potter HG, Wickiewicz TL. Arthroscopic meniscal repair with fibrin clot of complete radial tears of the lateral meniscus in the avascular zone. *Arthroscopy.* 1998;14:360–5.
30. Ra HJ, Ha JK, Jang SH, Lee DW, Kim JG. Arthroscopic inside-out repair of complete radial tears of the meniscus with a fibrin clot. *Knee Surg Sports Traumatol Arthrosc.* 2012. doi:10.1007/s00167-012-2191-3
31. Webber RJ, Harris MG, Hough Jr AJ. Cell culture of rabbit meniscal fibrochondrocytes: proliferative and synthetic response to growth factors and ascorbate. *J Orthop Res.* 1985;3:36–42.
32. Hennerbichler A, Moutos FT, Hennerbichler D, Weinberg JB, Guilak F. Interleukin-1 and tumor necrosis factor alpha inhibit repair of the porcine meniscus in vitro. *Osteoarthritis Cartil.* 2007;15:1053–60.
33. McNulty AL, Estes BT, Wilusz RE, Weinberg JB, Guilak F. Dynamic loading enhances integrative meniscal repair in the presence of interleukin-1. *Osteoarthritis Cartil.* 2010;18:830–8.
34. McNulty AL, Moutos FT, Weinberg JB, Guilak F. Enhanced integrative repair of the porcine meniscus in vitro by inhibition of interleukin-1 or tumor necrosis factor alpha. *Arthritis Rheum.* 2007;56:3033–42.
35. McNulty AL, Weinberg JB, Guilak F. Inhibition of matrix metalloproteinases enhances in vitro repair of the meniscus. *Clin Orthop Relat Res.* 2009;467:1557–67.
36. Cao M, Stefanovic-Racic M, Georgescu HI, Miller LA, Evans CH. Generation of nitric oxide by lapine meniscal cells and its effect on matrix metabolism: stimulation of collagen production by arginine. *J Orthop Res.* 1998;16:104–11.
37. Wilusz RE, Weinberg JB, Guilak F, McNulty AL. Inhibition of integrative repair of the meniscus following acute exposure to interleukin-1 in vitro. *J Orthop Res.* 2008;26:504–12.
38. Hulth A, Johnell O, Miyazono K, Lindberg L, Heinegard D, Heldin CH. Effect of transforming growth factor- β and platelet-derived growth factor-BB on articular cartilage in rats. *J Orthop Res.* 1996;14:547–53.
39. Finesmith TH, Broadley KN, Davidson JM. Fibroblasts from wounds of different stages of repair vary in their ability to contract a collagen gel in response to growth factors. *J Cell Physiol.* 1990;144:99–107.
40. Letson AK, Dahnert LE. The effect of combinations of growth factors on ligament healing. *Clin Orthop Relat Res.* 1994;308(308):207–12.
41. Tumia NS, Johnstone AJ. Regional regenerative potential of meniscal cartilage exposed to recombinant insulin-like growth factor-I in vitro. *J Bone Joint Surg Br.* 2004;86:1077–81.
42. Tumia NS, Johnstone AJ. Promoting the proliferative and synthetic activity of knee meniscal fibrochondrocytes using basic fibroblast growth factor in vitro. *Am J Sports Med.* 2004;32:915–20.
43. Tumia NS, Johnstone AJ. Platelet derived growth factor-AB enhances knee meniscal cell activity in vitro. *Knee.* 2009;16:73–6.
44. Riera KM, Rothfus NE, Wilusz RE, Weinberg JB, Guilak F, McNulty AL. Interleukin-1, tumor necrosis factor-alpha, and transforming growth factor- β 1 and integrative meniscal repair: influences on meniscal cell proliferation and migration. *Arthritis Res Ther.* 2011;13:R187.
45. Ionescu LC, Lee GC, Huang KL, Mauck RL. Growth factor supplementation improves native and engineered meniscus repair in vitro. *Acta Biomater.* 2012;8:3687–94.
46. • Narita A, Takahara M, Sato D, et al. Biodegradable gelatin hydrogels incorporating fibroblast growth factor 2 promote healing of horizontal tears in rabbit meniscus. *Arthroscopy.* 2012;28:255–63. *The authors 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, suggesting that FGF-2 may have a role in enhancement of meniscal healing.*
47. He W, Liu YJ, Wang ZG, Guo ZK, Wang MX, Wang N. Enhancement of meniscal repair in the avascular zone using connective tissue growth factor in a rabbit model. *Chin Med J.* 2011;124:3968–75.
48. • Kopf S, Birkenfeld F, Becker R, et al. Local treatment of meniscal lesions with vascular endothelial growth factor. *J Bone Joint Surg Am.* 2010;92:2682–91. *The authors used a sheep model (n=18) to investigate the role of vascular endothelial growth factor (VEGF) and its ability to induce vascular proliferation and improve healing in vivo. They found no significant improvement in meniscal healing. A longitudinal meniscal tear was made in the avascular region, which was subsequently repaired with sutures of various coating — 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.*

49. Eppley BL, Woodell JE, Higgins J. Platelet quantification and growth factor analysis from platelet-rich plasma: implications for wound healing. *Plast Reconstr Surg*. 2004;114:1502–8.
50. Hall MP, Band PA, Meislin RJ, Jazrawi LM, Cardone DA. Platelet-rich plasma: current concepts and application in sports medicine. *J Am Acad Orthop Surg*. 2009;17:602–8.
51. Anitua E, Andia I, Ardanza B, Nurden P, Nurden AT. Autologous platelets as a source of proteins for healing and tissue regeneration. *Thromb Haemost*. 2004;91:4–15.
52. Fufa D, Shealy B, Jacobson M, Kevy S, Murray MM. Activation of platelet-rich plasma using soluble type I collagen. *J Oral Maxillofac Surg*. 2008;66:684–90.
53. Scordino LE, Deberardino TM. Biologic enhancement of meniscus repair. *Clin Sports Med*. 2012;31:91–100.
54. Li XH, Zhou X, Zeng S, et al. Effects of intramyocardial injection of platelet-rich plasma on the healing process after myocardial infarction. *Coron Artery Dis*. 2008;19:363–70.
55. Slesaczeck T, Paetzold H, Nanning T, et al. Autologous derived, platelet-rich plasma gel in the treatment of nonhealing diabetic foot ulcer: a case report. *Ther Adv Endocrinol Metab*. 2012;3:75–8.
56. Kim KM, Shin YT, Kim HK. Effect of autologous platelet-rich plasma on persistent corneal epithelial defect after infectious keratitis. *Jpn J Ophthalmol*. 2012;56:544–50.
57. Kim JG, Lee YS, Bae TS, et al. Tibiofemoral contact mechanics following posterior root of medial meniscus tear, repair, meniscectomy, and allograft transplantation. *Knee Surg Sports Traumatol Arthrosc*. 2012. doi:10.1007/s00167-012-2182-4
58. Anitua E, Andia I, Sanchez M, et al. Autologous preparations rich in growth factors promote proliferation and induce VEGF and HGF production by human tendon cells in culture. *J Orthop Res*. 2005;23:281–6.
59. Aspenberg P, Virchenko O. Platelet concentrate injection improves Achilles tendon repair in rats. *Acta Orthop Scand*. 2004;75:93–9.
60. Lyras DN, Kazakos K, Verettas D, et al. The effect of platelet-rich plasma gel in the early phase of patellar tendon healing. *Arch Orthop Trauma Surg*. 2009;129:1577–82.
61. de Almeida AM, Demange MK, Sobrado MF, Rodrigues MB, Pedrinelli A, Hernandez AJ. Patellar tendon healing with platelet-rich plasma: a prospective randomized controlled trial. *Am J Sports Med*. 2012;40:1282–8.
62. Krogh TP, Bartels EM, Ellingsen T, et al. Comparative effectiveness of injection therapies in lateral epicondylitis: a systematic review and network meta-analysis of randomized controlled trials. *Am J Sports Med*. 2012. doi:10.1177/0363546512458237
63. Thanasis C, Papadimitriou G, Charalambidis C, Paraskevopoulos I, Papanikolaou A. Platelet-rich plasma vs autologous whole blood for the treatment of chronic lateral elbow epicondylitis: a randomized controlled clinical trial. *Am J Sports Med*. 2011;39:2130–4.
64. Peerbooms JC, Sluimer J, Bruijn DJ, Gosens T. Positive effect of an autologous platelet concentrate in lateral epicondylitis in a double-blind randomized controlled trial: platelet-rich plasma vs corticosteroid injection with a 1-year follow-up. *Am J Sports Med*. 2010;38:255–62.
65. de Jonge S, de Vos RJ, Weir A, et al. One-year follow-up of platelet-rich plasma treatment in chronic Achilles tendinopathy: a double-blind randomized placebo-controlled trial. *Am J Sports Med*. 2011;39:1623–9.
66. de Vos RJ, Weir A, van Schie HT, et al. Platelet-rich plasma injection for chronic Achilles tendinopathy: a randomized controlled trial. *JAMA*. 2010;303:144–9.
67. Peerbooms JC, van Laar W, Faber F, Schuller HM, van der Hoeven H, Gosens T. Use of platelet rich plasma to treat plantar fasciitis: design of a multi-center randomized controlled trial. *BMC Musculoskelet Disord*. 2010;11:69.
68. Rodeo SA, Delos D, Williams RJ, Adler RS, Pearle A, Warren RF. The effect of platelet-rich fibrin matrix on rotator cuff tendon healing: a prospective, randomized clinical study. *Am J Sports Med*. 2012;40:1234–41.
69. Randelli P, Arrigoni P, Ragone V, Aliprandi A, Cabitza P. Platelet rich plasma in arthroscopic rotator cuff repair: a prospective RCT study, 2-year follow-up. *J Shoulder Elbow Surg*. 2011;20:518–28.
70. Jo CH, Kim JE, Yoon KS, et al. Does platelet-rich plasma accelerate recovery after rotator cuff repair? A prospective cohort study. *Am J Sports Med*. 2011;39:2082–90.
71. Castricini R, Longo UG, De Benedetto M, et al. Platelet-rich plasma augmentation for arthroscopic rotator cuff repair: a randomized controlled trial. *Am J Sports Med*. 2011;39:258–65.
72. Delos D, Rodeo SA. Enhancing meniscal repair through biology: platelet-rich plasma as an alternative strategy. *Instr Course Lect*. 2011;60:453–60.
73. Wei LC, Gao SG, Xu M, Jiang W, Tian J, Lei GH. A novel hypothesis: the application of platelet-rich plasma can promote the clinical healing of white-white meniscal tears. *Med Sci Mon*. 2012;18:HY47–50.
74. • Ishida K, Kuroda R, Miwa M, et al. The regenerative effects of platelet-rich plasma on meniscal cells in vitro and its in vivo application with biodegradable gelatin hydrogel. *Tissue Eng*. 2007;13:1103–12. *The authors found mitogenic effects of PRP on monolayer meniscal cell cultures such as increased fibrocartilage-related messenger RNA expression using real-time polymerase chain reaction. They 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.*
75. Piontek T, Cierniewska-Gorzela K, Szulc A, Slomczykowski M, Jakob R. All-arthroscopic technique of biological meniscal tear therapy with collagen matrix. *Pol Orthop Traumatol*. 2012;77:39–45.