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Narrative Review—CME

Treatment of Knee Meniscus Pathology: Rehabilitation, Surgery, and Orthobiologics

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Abstract

The meniscal tear treatment paradigm traditionally begins with conservative measures such as physical therapy and referral for operative management for persistent or mechanical symptoms. As a result, the partial meniscectomy is performed more than any other orthopedic procedure in the United States. This treatment paradigm has shifted because recent literature has supported the attempt to preserve or repair the meniscus whenever possible given its importance for the structural integrity of the knee joint and the risk of early osteoarthritis associated after meniscus excision. Choosing an appropriate management strategy depends on multiple factors such as patient demographics and location of the tear. Physical therapy remains a first-line treatment for knee pain secondary to meniscus tear and should be pursued in the setting of acute and chronic knee pain. Furthermore, there is a growing amount of evidence showing that elderly patients with complex meniscus tears in the setting of degenerative arthritis should not undergo arthroscopic surgery. Direct meniscus repair remains an option in ideal patients who are young, healthy, and have tears near the more vascular periphery of the meniscus but it is not suitable for all patients. Use of orthobiologics such as platelet-rich plasma and mesenchymal stem cells have shown promise in augmenting surgical repairs or as standalone treatments, although research for their use in meniscal tear management is limited.

Introduction

The menisci are fibrocartilaginous structures that contribute to static weight bearing, distributing compressive forces during joint movement, joint lubrication, joint stabilization, and proprioception [1-3]. Meniscal tears are a commonly occurring musculoskeletal injury across all age and functional groups [4-7], with incidental radiographic pathologic changes occurring in the asymptomatic population [8]. The mean annual incidence has been estimated to be as high as 60-70 per 100 000 knee injuries based on previous reviews [9]. The rate is higher in those older than 40 years and in men vs women [4] and in the medial meniscus compared with the lateral meniscus [5]. The incidence also has been found to be higher in active populations such as military members, in whom the meniscus tear incidence rate was determined to be 8.27 per 1000 person-years (10 times higher than any documented civilian study) [6]. Acute meniscal tears also occur at higher frequencies during athletic events, reportedly as high as 5.1 per 100 000 athlete exposures in high school-age athletes [7].

Considering the vital importance of the menisci to normal knee function, treatment paradigms have evolved greatly from when they were perceived to be inconsequential and functionless structures [10]. It was not until 1977 that the partial meniscectomy began to be recognized as superior to total meniscectomy surgery [11]. More recently, the paradigm has further evolved with the knowledge that partial meniscectomy has no greater benefit than conservative management of degenerative meniscal tears [12]. Conservative management continues to be a mainstay of treatment after knee injuries and meniscal repair techniques continue to evolve to preserve meniscal tissue whenever possible. There also has been growing interest in the use of orthobiologics, such as platelet-rich plasma (PRP) and mesenchymal stem cells (MSCs), to enhance the potential healing effects of

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articular and meniscal tissue. Recognizing differences in presentation is integral to choosing the optimal treatment strategy. In this article, we review meniscus anatomy, classification of meniscal tears, meniscal healing potential, and clinical presentation and provide an updated review of current and evolving treatment options for meniscal tears.

Anatomy of Knee Menisci

The knee menisci are crescent-shaped wedges of fibrocartilage situated between the femoral condyles and the tibial plateaus [13,14] (Figure 1). The outer edges of the menisci are convex with attachments to the joint capsule and the inner edges taper to a concave free edge [15]. The medial meniscus is C-shaped and covers approximately 60% of the medial compartment. The posterior horn of the medial meniscus has a firm attachment to the intercondylar area of the tibia near the posterior cruciate ligament and the anterior horn inserts into the anterior intercondylar area with fibers intermingling with the anterior cruciate ligament (ACL) [16,17] and the transverse ligament in 64% of dissections [16]. In addition to its capsular attachment, the medial meniscus shares fibers with the medial collateral ligament [18]. The lateral meniscus is more circular than the medial meniscus and has been reported to cover as much as 80% of the lateral compartment surface. The anterior horn inserts into the anterior intercondylar area with its fibers also blending with the ACL. The posterior horn has a more variable insertion but will typically insert anterior to the posterior horn of the medial meniscus through the ligament of Wrisberg, the ligament of Humphry, and from fascia covering the popliteus muscle [13,16,19].

The menisci are composed primarily of water (72%) with the remaining 28% primarily composed of collagens, glycosaminoglycans, DNA, and glycoproteins [20,21]. The proportion of these components is dependent on multiple factors, including age, injuries, and pathology [21,22]. The collagen is predominantly type I, with small quantities of types II, III, and V [23]. The peripheral and deep arrangement of collagen is primarily circumferential, with radially arranged fibers being more common medially and superficially [19,24] (Figure 2). This arrangement is important in counteracting the compressive forces exerted by the tibia and femur, which are radially directed by converting them to traction forces and transmitting the forces circumferentially to their strong anterior and posterior horn attachments in the tibia by "hoop strain" [24-26]. Proteoglycans are hydrophilic molecules that contribute to the large water content and shock absorption properties of the meniscus through the time-dependent exudation of water from the extracellular matrix [21,23,27].

In the mature meniscus, the morphologic type of cells vary based on location, with no uniform classification accepted in the literature. Nakata et al [28] identified 3 distinguishable cell types that included elongated fibroblast-like cells, polygonal cells, and small round chondrocyte-like cells. The outer portion of the meniscus has been shown in histologic studies to contain a larger proportion of fibroblast-like cells, whereas the inner avascular portion of the meniscus contains more rounded cells that behave similar to chondrocytes such as in the articular cartilage [29,30] (Figure 3). The extracellular matrix surrounding the fibroblast-like cells in the outer portion of the meniscus contains mostly type I cartilage in contrast to the inner portion of the meniscus, which is mostly composed of type II collagen and aggrecan in an extracellular matrix similar to the hyaline cartilage composition [31]. The third cell type, found in the superficial zone of the meniscus, has an intermediate morphology between fibrochondrocyte and fibroblast [29] and it has been postulated that these cells might have progenitor properties that initiate wound healing [32].

The main vascular supply to the menisci originates from the inferior and superior medial and lateral geniculate vessels arising from the popliteal artery. These vessels form a peri-meniscal capillary plexus within the

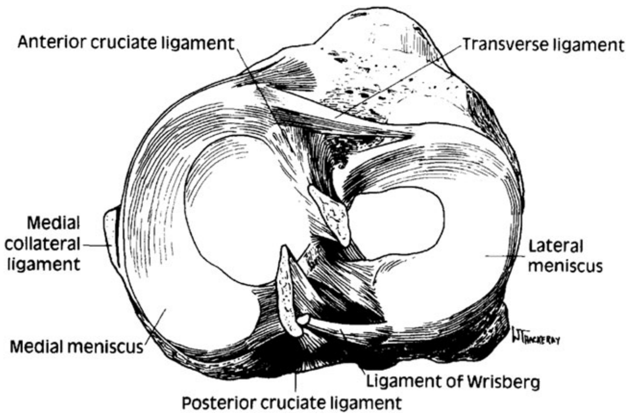

Figure 1. Drawing of the tibial plateau showing the shape and attachments of the medial and lateral menisci. Reproduced, with permission of Elsevier, from Caldwell GL, Allen AA, Fu FH. Functional anatomy and biomechanics of the meniscus. Oper Tech Sports Med 1994;2:152-163 [14].

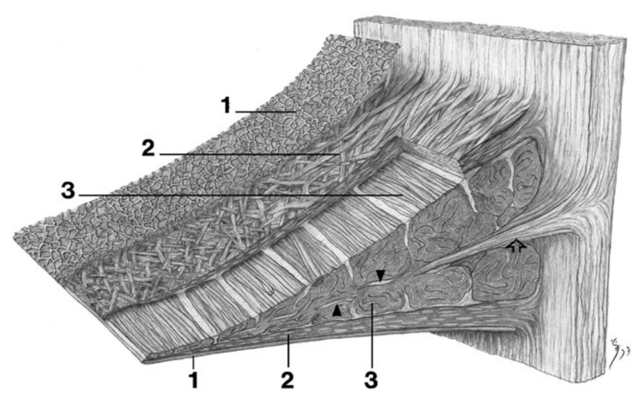

Figure 2. Synoptic drawing showing 3 distinct layers of the meniscus by scanning electron microscopy: (1) superficial network, (2) lamellar layer, and (3) central main layer. Reproduced, with permission of Elsevier, from Petersen W, Tillmann B. Collagenous fibril texture of the human knee joint menisci. Anat Embryol (Berl) 1998;197:317-324 [24].

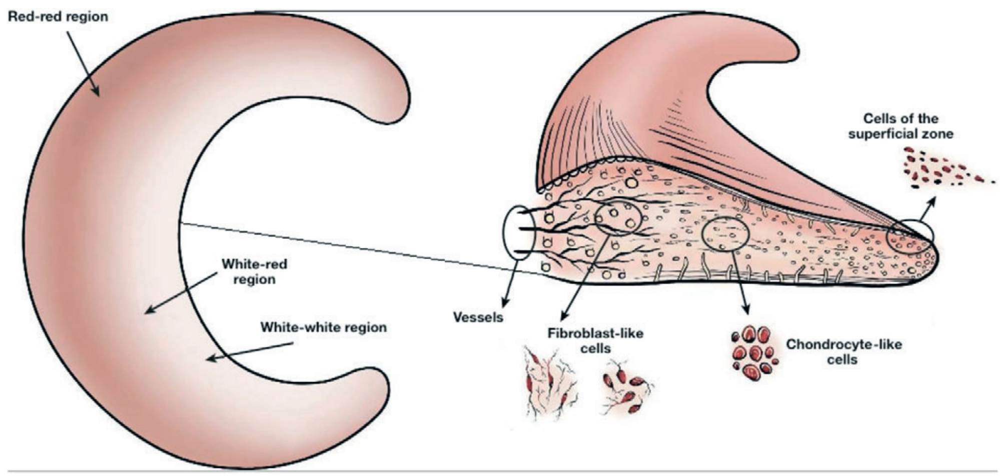

Figure 3. (Left) Regional variations in vascularization showing the red-red region, white-red region, and white-white region. (Right) Variations in cell phenotypes in the meniscus relative to vascularity. Reproduced, with permission of Elsevier, from Makris EA, Hadidi P, Athanasiou KA. The knee meniscus: structure–function, pathophysiology, current repair techniques, and prospects for regeneration. Biomaterials 2011;32:7411-7431 [30].

synovial and capsular tissue that supplies the peripheral border of the meniscus (Figure 4). The peripheral 10%-30% of the medial meniscus border and 10%-25% of the lateral meniscus border are well vascularized, with the remainder of the meniscus receiving nourishment from synovial fluid [19,33,34]. This has led to meniscus zones being described in a radial direction as red-red, red-white, and white-white based on vascularity.

Clinical Presentation, Classification, and Healing Potential

Acute meniscal tears often present with recognizable symptoms after a twisting knee injury. Most acute tears occur during sporting events [35], with cutting and pivoting sports requiring knee flexion at high activity levels generating the highest risk for meniscal injury [36]. Patients will often report a twisting knee injury with an associated snapping sound followed by sharp localized pain. They also might report delayed knee swelling and exacerbation of pain on deep knee bending and twisting. Mechanical locking of the knee can occur in the setting of flap or bucket-handle-type tears [35]. In the chronic setting, patients might complain of knee pain associated with intermittent swelling and mechanical symptoms [35]. Risk factors for nontraumatic, degenerative meniscal injury include age older than 60 years, male gender, and work-related kneeling, squatting, or climbing [37].

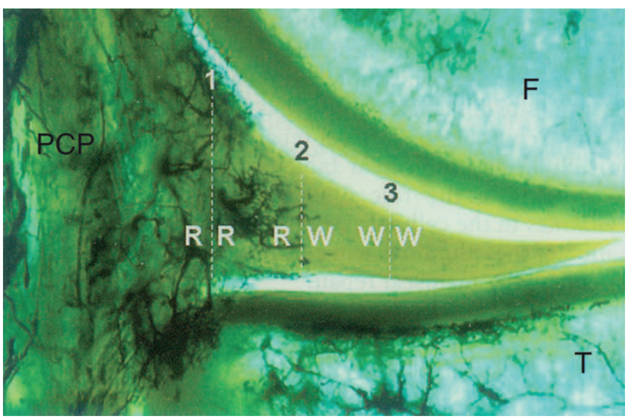

Figure 4. Frontal section of the medial compartment of the knee displaying branching radial vessels from the peri-meniscal capillary plexus (PCP), femur (F), and tibia (T). Also labeled are the (1) red-red (RR), (2) red-white (RW), and (3) white-white (WW) zones. Reproduced, with permission of Elsevier, from Miller RH, Azar FM. Knee injuries. In: Azar FM, Canale ST, Beaty JH, Campbell WC, eds. Campbell's Operative Orthopaedics. 13th ed. Philadelphia, PA: Elsevier, 2017, 2121-2297 [19]. Originally from Arnoczky SP, Warren RF, Spivak JM. Meniscal repair using an exogenous fibrin clot. An experimental study in dogs. J Bone Joint Surg Am 1988;70:1209-1217 [33].

There have been many proposed classification systems to describe meniscal tears without an established standard. However, meniscal tears are generally classified by pattern, location, and thickness as determined at magnetic resonance imaging (MRI) or arthroscopy [38,39] (Figure 5). Tear types include vertical (longitudinal or radial), horizontal, and complex [9,19,40,41]. Vertical longitudinal tears result in disruption of the superficial radial collagen fibers in line with the circumferential fibers. With large tears, the inner meniscus can displace into the intercondylar notch, resulting in a commonly described "bucket-handle" tear [19,41]. Longitudinal tears also are more commonly associated with trauma [42] and typically occur in the red-white and white-white zones of the meniscus [43]. Horizontal tears involve separation of the meniscus into 2 layers while leaving circumferential fibers intact and are frequently asymptomatic. Radial tears occur more commonly in the lateral meniscus compared with the medial meniscus and involve circumferential fibers with consequent disruption of hoop stresses. When oblique in pattern, radial tears can result in flaps that might cause mechanical symptoms [19]. Complex, or degenerative, tears typically involve multiple tear configurations [44] and are the most common

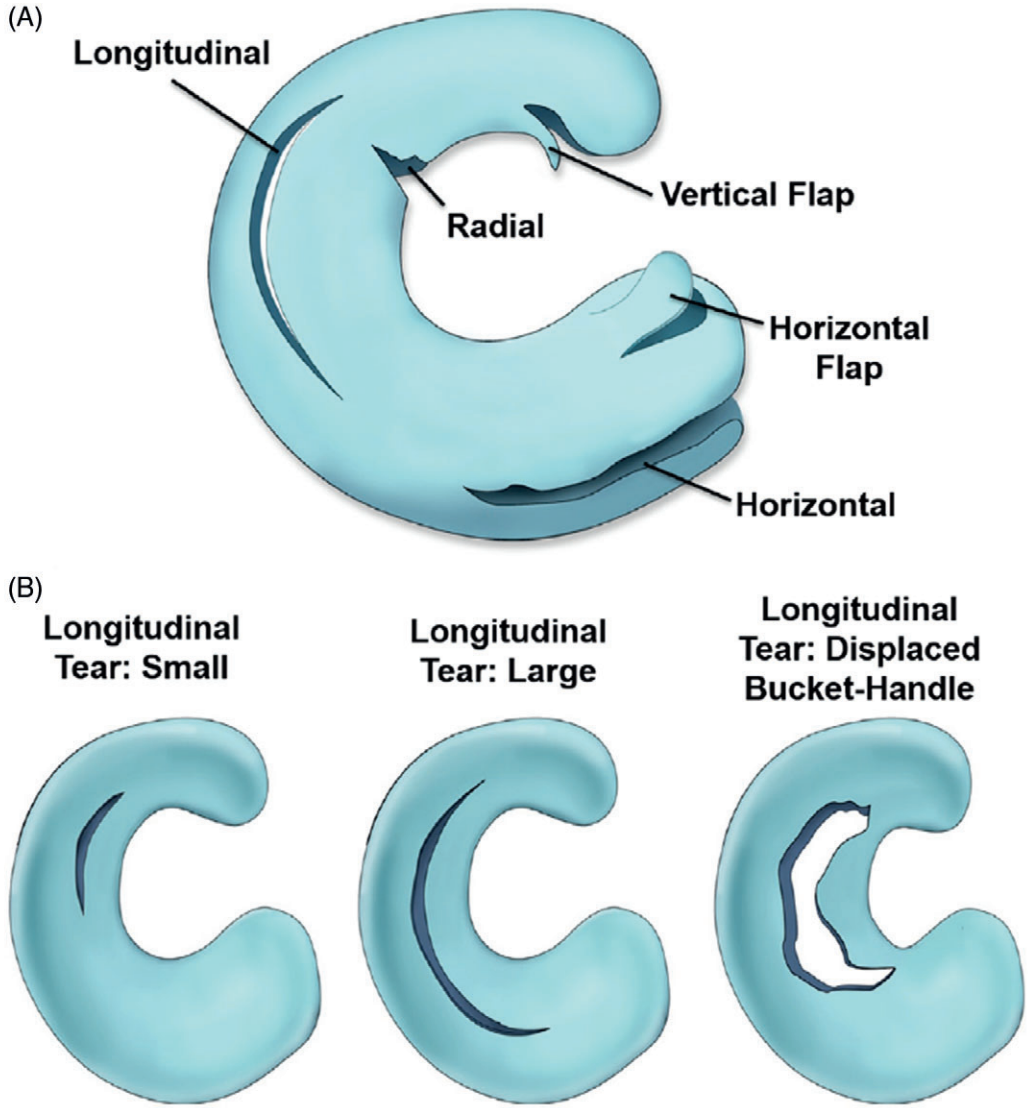

Figure 5. Illustration of proposed arthroscopic meniscal tear classification system by the International Society of Arthroscopy, Knee Surgery and Orthopaedic Sports Medicine Knee Committee. Reproduced, with permission of Elsevier, from Wadhwa V, Omar H, Coyner K, Khazzam M, Robertson W, Chhabra A. ISAKOS classification of meniscal tears—Illustration on 2D and 3D isotropic spin echo MR imaging. Eur J Radiol 2016;85:15-24 [39].

meniscal lesion, with peak incidence at 41-50 years of age in men and 61-70 years of age in women [9]. Degenerative and radial tear types also are associated with a significantly higher rate of articular cartilage change compared with longitudinal tears [8,45,46].

The success of meniscal healing can vary based on the patient's age, length of time since injury, and tear type [47–50]. It has been well established that peripheral meniscal tears can successfully heal spontaneously or after intervention [47,51–54], although a poor intrinsic healing response has been noted when the tear site is within the inner two-thirds of meniscal tissue, outside the red-red zone [55].

Pathologic studies have shown that migration of perimeniscal tissue and synovial cells over the surface of the meniscus to the tear site is vital in the healing response within the vascular zone [51,53,56]. However, this spontaneous healing response fails in the avascular portion of the meniscus [57–59], indicating that those cells are intrinsically incapable of mounting a sufficient repair response [33]. Mesiha et al [8] found that in patients older than 40 years, there were lower intrinsic cellularity in the meniscus and decreased peri-meniscal response after a tear, which would likely contribute to the poor healing response seen in other clinical studies. Notably, they also found that there was no proliferative fibroblastic or angiogenic response to injury of the meniscus. Compared with other soft tissue healing, meniscal tears also lack a fibrin clot or bridging structure to stabilize the tear site owing to the presence of fibrinolytic enzymes in synovial fluid [60].

Another challenge to effective meniscal healing is the inflammatory environment present in the synovial fluid in the setting of acute or chronic meniscal tears [61,62]. Interleukin (IL)-1β and tumor necrosis factor-α are generally acknowledged as primary inflammatory mediators associated with cartilage degeneration, bone changes, and synovial inflammation in the setting of osteoarthritis [63] and their presence has suppressed meniscal repair in vitro [64]. Increased levels of proinflammatory cytokines IL-6, IL-8, and tumor necrosis factor-α also have been shown to persist 3 months after meniscal tear [62]. And an increase of IL-6 and tumor necrosis factor-α 18 years after meniscectomy correlates with radiographic progression of osteoarthritis [61]. Furthermore, the presence of degradative enzymes such as metalloproteinases and aggrecanases can contribute to meniscal degradation through proteoglycan and collagen degradation [65]. Modifying this proinflammatory environment in the synovial fluid can mitigate the inhibitory effects of proinflammatory cytokines [66].

Despite these challenges, studies have shown that various anabolic growth factors, such as transforming growth factor-β, insulin-like growth factor-1, fibroblast growth factor, and vascular endothelial growth factor, can benefit angiogenesis, chondrogenesis, and cell survival in the setting of meniscal tears [67]. The induction of these growth factors in regenerative meniscal repair techniques continues to be a promising focus of ongoing research.

Rehabilitation and Conservative Management

Initial nonoperative management of meniscal tears is dependent on clinical presentation and is typically reserved for patients who do not have severely restricted range of motion, locking, or instability of the afflicted knee. Those deemed good candidates for conservative management after an acute knee injury should be initially managed with rest, ice, compression, and elevation of the injured knee. Offloading also might be required for comfort, although patients can progress to full weight bearing when tolerated [35]. Thereafter, physical therapy can aid in a gradual resolution of symptoms over 6 weeks [11]. A therapeutic program should focus early on controlling and managing swelling while maintaining knee range of motion. The program should later incorporate quadriceps and hamstring strengthening, eventually progressing to dynamic proprioceptive training. Conditioning can be maintained with use of an exercise bike and walking and eventually progress to running and other sport-specific exercises [68]. Factors that can favor success with conservative treatment include ability to bear weight, minimal swelling, delayed onset of symptoms after injury, and minimally restricted range of motion [68].

Detailed therapeutic regimens designed for nonoperative management of meniscal tears have not been well studied in the literature, with a noted lack of randomized controlled trials comparing physical therapy with time and rest. However, there is an abundance of literature validating the success of strengthening and aerobic conditioning programs in managing knee pain and improving general function in the setting of knee osteoarthritis [69,70]. Stensrud et al [71] developed a 12-week strength training and neuromuscular rehabilitation regimen for managing knee pain with concurrent MRI-diagnosed degenerative meniscal tears that was extrapolated from programs successfully used to manage knee osteoarthritis. This neuromuscular regimen aimed to improve the position of the trunk and lower limbs relative to one another and incorporate dynamic lower extremity strengthening through the use of single-leg exercises on varying surfaces and plyometrics. In a series of 20 patients, they documented clinically meaningful improvement in Knee Injury and Osteoarthritis Outcome Score (KOOS) quality-of-life and pain subscales in 16 patients and improved measurable quadriceps strength in all patients at the end of the program. Results were sustained or improved at 1 year and no patients underwent surgery [71]. Similar results were seen in conservative management groups of 4 randomized controlled trials [72–75] comparing arthroscopic partial meniscectomy (APM) with physical therapy or an exercise program for management of knee pain secondary to meniscal tears (Table 1). In all 4 studies, patients met minimum clinically important changes in reported outcomes at short-term and long-term follow-up but such changes were less apparent when only a home exercise program was used [72]. Furthermore, physical therapy has been shown to improve hamstring strength and quadriceps endurance parameters after partial meniscectomy [76].

APM—Superior to Conservative Management in the Degenerative Meniscal Tear?

The surgical treatment of meniscal tears is often recommended to patients with mechanical symptoms, such as catching and locking, or to treat symptoms of pain if conservative management fails. The most frequently used treatment is APM. APM is the most common orthopedic procedure, with more than 700 000 cases annually in the United States and estimated direct medical costs over $4 billion per year [77,78]. Randomized control studies have shown that APM and physical therapy after meniscal tears result in significant functional improvement and decreased pain compared with baseline; however, no randomized trial effectively supports the notion APM is superior to nonsurgical management of degenerative meniscal tears (Table 2). Moreover, a clinical practice guideline recently published in the *British Journal of Medicine* strongly recommends “against the use of arthroscopy in nearly all patients with degenerative knee disease” and even recommends “using number of arthroscopies performed in patients with degenerative knee disease as an indicator of quality care” [12]. Nevertheless, APM is frequently used in middle-aged and older patients [79,80] who might have concomitant degenerative changes in the menisci and/or osteoarthritis [81].

Table 1
Outcomes in conservative management groups in randomized controlled trials evaluating the efficacy of arthroscopic partial meniscectomy

Study	Study Type	Control Group Patients, n; Intervention	Outcome Measures	Subscale	Change from Baseline	Minimum Clinically Important Change
Katz et al 2013 [73]	multicenter RCT	169; physical therapy then exercise program	WOMAC-pf		18.5 (15.6-21.5), 22.8 (19.8-25.8)	8 [14]
			KOOS pain (6 and 12 mo)		21.3 (18.4-24.2), 27.3 (24.1-30.4)	8-10 [30]
Yim et al 2013 [75]	single-center RCT	52; physical therapy then exercise program	Lysholm Knee Scoring Scale		15.2, 17.1, 18.9, 19.1	10 [75]
			VAS (3, 6, 12, and 24 mo)		−2.2, −2.8, −3.1, −3.2	1.99 [14]
Gauffin et al 2014 [72]	Single-center RCT	75; home exercise program only; 68 after crossover	KOOS* (3 and 12 mo)	pain	12.9 (8.0-17.7), 16.6 (10.6-22.6)	8-10 [30]
				symptoms	9.5 (5.4-13.7), 15.0 (9.8-20.0)	8-10 [30]
				activity of daily living	8.5 (4.3-12.7), 11.7 (6.5-16.9)	8-10 [30]
				sports and recreation	14.5 (8.5-20.6), 21.1 (13.4-28.8)	8-10 [30]
				quality of life	12.9 (7.4-18.5), 21.9 (15.4-28.4)	8-10 [30]
Kise et al 2016 [74]	multicenter RCT	70; physical therapy, then exercise program	KOOS4 (12 mo)		25.3 (21.6-29.0)	8-10 [30]

RCT = randomized controlled trial; WOMAC-pf = Western Ontario and McMaster Universities Osteoarthritis Index with physical function subscale score; KOOS = Knee Injury and Osteoarthritis Outcome Score; VAS = visual analog scale; $KOOS_4$ = aggregated Knee Injury and Osteoarthritis Outcome Score omitting activity of daily living subscale.
*Results from "as treated" analysis.

The Finnish Degenerative Meniscal Lesion Study (FIDELITY) trial was a double-blinded, sham-controlled trial involving 146 patients 35-65 years old with nontraumatic degenerative meniscal tears and no evidence of osteoarthritis. In this study, the mean improvement at 12 months was measured by the Lysholm Knee Scoring Scale (LKSS) score (21.7 points in partial meniscectomy group vs 23.3 points in sham surgery group) and the Western Ontario Meniscal Evaluation Tool (WOMET) score (24.6 in partial meniscectomy group vs 27.1 in sham surgery group), which showed no significant difference in improvements in patients undergoing partial meniscectomy compared with sham surgery despite adequate power [82]. Furthermore, a 2-year follow-up study was recently published showing that the mean improvement at 24 months was measured by the LKSS score (23.1 points in partial meniscectomy group vs 26.3 points in sham surgery group) and the WOMET score (27.3 in partial meniscectomy group vs 31.6 in sham surgery group) and continued to show a statistically insignificant difference. The investigators concluded that the results supported the notion that APM provided no significant benefit over placebo surgeries in patients with degenerative meniscal tear and no knee osteoarthritis [83].

The Meniscal Repair in Osteoarthritis Research (METEOR) trial was a large multicenter randomized control trial involving 351 patients older than 45 years with degenerative meniscus tears and evidence of mild to moderate osteoarthritis and compared the results of partial meniscectomy plus postoperative physical therapy with standardized physical therapy regimen alone using the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) physical function score. At 6 months, patients who underwent partial meniscectomy had a WOMAC score improvement of 20.9 points compared with 18.5-point improvement in the conservative treatment group. Comparing the operative with the nonoperative treatment showed the results were not significant. Similarly, the comparison between the 2 groups at 12 months was not significant. Also noted was that 30% of patients in the physical therapy group crossed over to the APM group in the first 6 months and had similar WOMAC scores to the APM group, indicating that they were at no disadvantage by prolonged conservative management before undergoing APM [73].

Several meta-analyses examining randomized controlled APM trials have not demonstrated long-term benefit for pain relief or functional improvement in patients with degenerative meniscal tears [84-87]. One recent study by van de Graaf et al [87] observed the results of APM in 5 randomized controlled trials [73,75,82,88-90], which included 1477 patients. Similar to the other meta-analyses, results of this study showed only small significant differences in LKSS, WOMAC, and KOOS scores during short-term (6-month) follow-up and no difference at 12-month follow-up compared with conservative treatment [87]. In addition, there was no significant difference in pain scores using the KOOS pain subscale and the visual analog scale (VAS) between the groups. Furthermore, a common theme identified in these meta-analyses is a high risk of bias in most included randomized trials owing to lack of blinding to surgical intervention. It has been

Table 2
Recent randomized controlled trials evaluating the efficacy of arthroscopic partial meniscectomy

Study	Study Type	Blinding	Osteoarthritis Grading	Control Group Patients, n; Intervention	Treatment Group Patients, n; Intervention	Outcome Measures	Results
Herrlin et al 2013 [88]	single-center RCT	none	Ahlback criteria grade 0-1	49; exercise program	47; APM and exercise	KOOS at 60 mo, Lysholm Knee Scoring Scale, Tegner Activity Scale, VAS scores at 24 and 60 mo	no statistically significant difference between groups
Katz et al 2013 [73]	multicenter RCT	none	Kellgren-Lawrence grade 0-3	169; physical therapy then exercise program	161; APM	WOMAC-pf, KOOS pain score, SF-36 physical activity scores at 6 and 12 mo	no statistically significant difference between groups
Sihovenen et al 2013 [82]	multicenter RCT	participant and assessor	Kellgren-Lawrence grade 0-1	76; sham arthroscopic surgery	70; APM	Lysholm Knee Scoring Scale, WOMET, VAS at 12 mo	no statistically significant difference between groups
Yim et al 2013 [75]	single-center RCT	none	Kellgren-Lawrence grade 0-1	52; physical therapy, then exercise program	50; APM	Lysholm Knee Scoring Scale, VAS, patient satisfaction, Tegner Activity Scale scores at 3, 6, 12, and 24 mo	no statistically significant difference between groups
Gauffin et al 2014 [72]	single-center RCT	none	Ahlback criteria grade 0, Kellgren-Lawrence grade 0-2 (93% 0-1)	75; exercise program; 68 after crossover	75; APM; 82 after crossover	KOOS, EQ5D (includes VAS), PAS, symptom satisfaction at 3 and 12 mo	significant intention-to-treat difference in KOOS Pain score at 3 mo (11.6, 4.7-18.5, *P* = .001) and 12 mo (10.6, 3.4-17.7, *P* = .004); other results showed no statistically significant difference
Kise et al 2016 [74]	multicenter RCT	assessor only	Kellgren-Lawrence grade 0-3	70; exercise program	70; APM	KOOS, SF-36 physical, mental, and performance tests, lower extremity strength at 3, 6, and 12 mo	significant increase in thigh strength in exercise group at 3 mo; other results showed no statistically significant difference

RCT = randomized controlled trial; APM = arthroscopic partial meniscectomy; KOOS = Knee Injury and Osteoarthritis Outcome Score; VAS = visual analog scale; WOMAC-pf = Western Ontario and McMaster Universities Osteoarthritis Index physical function subscale score; SF-36 = Medical Outcomes Study 36-Item Short-Form Health Survey; WOMET = Western Ontario Meniscal Evaluation Tool; EQ5D = EuroQol Quality of Life Measure; PAS = Physical Activity Scale.

suggested that the bias created from a perceived lack of intervention in patients assigned to exercise-only groups could result in crossing over from physical therapy to APM after failed conservative management [83]. These crossover rates can be as high as 21%-30% at 6-14 months [72,73,91]. Patients who crossed over eventually obtained outcomes similar to the APM group [73], which could support the notion that APM remains an option after failed conservative management. However, the placebo effect of having received a requested surgical intervention also can lead to a bias regarding patients' subjective postoperative pain and functional status [83].

One study by Gauffin et al [72] in 2014 compared APM with a 3-month home exercise program taught by physiotherapists in middle-aged patients with confirmed meniscal tears and "meniscal symptoms." They found significant differences in KOOS pain score at 12 months in the exercise and APM groups, with a between-group change supporting the APM group of 10.6 (confidence interval 3.4-17.7, *P* = .004). However, this study included only patients with an Ahlback radiologic osteoarthritis grade of 0, corresponding to no radiographic sign of osteoarthritis [92]. This is an important distinction because degenerative meniscal tears are commonly found in the setting of osteoarthritis regardless of active meniscal symptoms [81,93]. Because arthroscopic surgery for the management of osteoarthritis has been well established as ineffective, including when performing concurrent debridement of torn meniscal tissue [94,95], it can be inferred that performing APM for degenerative meniscal tears in the setting of osteoarthritis will lead to minimal long-term improvement in pain and function.

Previous studies regarding APM in the setting of degenerative meniscal tears not only found a lack of long-term functional outcome and pain but also noted increased future risk of osteoarthritis [96-98]. Factors contributing to this risk included the amount of meniscal tissue resected [99], compartment involved, tear orientation, pre-existing chondral damage, ACL insufficiency, knee alignment, body habitus, age older than 40 years, and activity level [100]. This trend also was seen in elite athletes, with a mean age of just 22.8 years, who had imaging of the knee performed at the National Football League combine because of a history of knee surgery. The rate of osteoarthritis was highest in athletes who had previous partial meniscectomy, noted to be 27% in this young, athletic population [101]. Furthermore, Rongen et al [102] reported that the hazard ratio for receiving a total knee replacement was 3.0 in patients who previously had APM compared with a risk-matched cohort who did not undergo APM.

Direct Meniscal Repair

Attempts to preserve the meniscus have increased in popularity because of its functional importance to the knee and risk of long-term osteoarthritis associated with meniscectomy. Not all meniscal tears are repairable. Typical guidelines based on previous literature [103–105] used to identify patients who will have a successful surgical repair include age younger than 40 years, acute tears, vertical tears, red-red zone tears, no mechanical misalignment, and tears longer than 1 cm but shorter than 4 cm [106]. Peripheral tears in the red-red zone are more amenable to repair because they are closest to the peri-meniscal capillary plexus [103,105]. Failure rates have been shown to be as high as 70% at second-look arthroscopy after inside-out repair of radial and oblique tears that did not extend into the red-red zone [107]. Horizontal tears also have been traditionally considered poor candidates for repair [105], although new techniques have shown similar outcomes to other tear patterns [108]. Repair techniques can be augmented through the use of fibrin clot or techniques such as trephination or rasping. If direct repair is not possible, then meniscal allograft transplantation (MAT) and scaffolding also might be options.

There is a wide variety of direct repair techniques involving the use of sutures to stabilize the torn meniscus and these techniques can be very successful if used in the optimal patient. Direct repair techniques can be stratified based on open vs arthroscopic technique and the direction of suture placement (eg, outside-in, inside-out, and all-inside). The inside-out technique is considered the "gold standard" for meniscal repair, although all-inside techniques continue to evolve [109]. Overall, research comparing meniscectomy with meniscal repair is limited as demonstrated in a recent meta-analysis that identified only 7 eligible studies to review, only 1 of which was a randomized prospective trial [110]. Three studies showed significantly improved LKSS scores in the repair group and 4 studies reported less activity loss in the repair group using Tegner Activity scores [110]. One retrospective study comparing 10-year outcomes of 32 patients with a mean age of 33 years who underwent APM vs meniscal repair showed significantly higher KOOS scores in pain, activity of daily living, and sports and recreation subscales in the meniscal repair group. It also showed significantly lower grade of osteoarthritis, with a median Kellgren-Lawrence osteoarthritis grade of 0 (vs 2 for APM group) [111]. In addition to the increased functional outcome and decreased complications in meniscal repair vs partial meniscectomy, the financial burden of partial meniscectomy is much greater than that of meniscal repair. In a cost analysis done in 2016 by Feeley et al [112], it was estimated that patients who receive meniscal repair vs APM would save more than $2000 over the course of treatment. In addition, a change of 10% of APMs to meniscal repairs would equate to an estimated health care savings of $43 million annually to payers. Although direct meniscal repair has been shown to have an increased rate of failure compared with partial meniscectomy (relative risk 4.37), the overall financial savings and increased quality-adjusted life years make it a dominant treatment strategy for most patients with reparable tears to decrease risk of osteoarthritis and decrease financial burden.

Despite the use of optimal patients, meniscal repair failure rate at more than 5 years remains 22.3%-24.3% [113], which encourages the use of augmentation techniques. Interestingly, meniscal tears in the setting of ACL tears exhibit improved outcomes compared with meniscus tears alone [103,114,115], leading to the conclusion that intra-articular blood and marrow release created by the ACL tunnel might be augmenting meniscal healing. In a similar fashion, trephination and rasping are 2 techniques used to induce vascular growth and healing, especially in the red-white and white-white regions. These techniques involve the creation of vascular access channels from the peripheral vascular rich areas to the central avascular regions of the menisci. Trephination is performed by puncturing the meniscus and extending the inner rim and substance of the tear into the capsule [116]. It has been shown that direct meniscal repair augmented with trephination has a significantly decreased risk of failure compared with direct suturing alone [117]. In a study by Zhang and Arnold [117], 28 patients received suturing only and 36 received sutures plus trephination. At 78-month follow-up, 6% of patients with trephination plus sutures had symptomatic re-tear compared with 25% of patients with sutures only ($P < .01$). Furthermore, 27 of 30 patients in another case series with vertical and longitudinal meniscal tears who underwent trephination procedures without direct meniscal repair showed a significant increase in LKSS score and satisfactory subjective return to function [116].

Although typically performed arthroscopically, trephination also can be performed under sonographic guidance given its accuracy in safely performing intrameniscal injections [118]. Similar to trephination, rasping techniques use abrasion from the peri-meniscal synovium toward the avascular region of the menisci to stimulate growth factor release and healing. Uchio et al [55] found rasping techniques induced complete healing in 71% of patients with full- and partial-thickness lateral and medial meniscal tears. Notably, the extent of healing was affected by the length of the original lesion and the distance to the joint capsule. Potential drawbacks of the trephination and rasping techniques are the possible damage the procedures cause to the meniscus and effects on biomechanical properties, thus increasing risks for self-collapse, channel closure, and delayed healing [119].

Exogenous fibrin, in the form of powder, glue, or clots, has been used in the operating room since 1909 to promote hemostasis and accelerate postoperative healing [120]. It also has been used to augment meniscal repairs through the activation of platelets and promoting the release of platelet-derived growth factors, interleukins, angiogenesis factors, and endothelial growth factors [120]. In 2013, Ra et al [121] reported full healing of complete radial tears in 12 patients after direct suturing augmented by fibrin clot. At 2-year follow-up all patients had significant improvement in LKSS score and International Knee Documentation Committee (IKDC) knee score. Although the use of fibrin clot to augment direct repair of meniscal tears is promising, there are currently no level I studies on fibrin clot augmentation and additional research is needed to demonstrate its efficacy in treating meniscal tears.

Meniscal allograft transplantation is a promising surgical treatment option for relatively young patients with knee pain after total meniscectomy who are not candidates for knee arthroplasty [122]. Nevertheless, current literature is limited because of different available allograft preservation and surgical techniques, resulting in high variability in outcomes [123]. Meniscal allograft transplantation also has limited use in the setting of osteoarthritis and typically requires concurrent surgical procedures to correct malalignment or instability of the knee joint. Furthermore, patients are typically limited in their ability to return to high-impact sports [122]. A recent review of 39 studies [122] concluded that, despite the difficult comparison secondary to large variability, meniscal allograft transplantation can result in significant relief of pain and improvement in function in a large percentage of patients, with longstanding improvement in approximately 70% of patients. All included studies were limited by a lack of controlled comparison. Reported transplant failure and reoperation rates also vary considerably, averaging 18.7% and 31.3%, respectively [123]. Meniscal allograft transplantation also is not considered curative in the long term because 15-year failure rates were reported to be as high as 81% [124].

Meniscal scaffolding involves the use of collagen meniscal implants or polymer scaffolds to manage knee pain after partial or total meniscectomy and help prevent the progression of joint degeneration. In addition, it avoids the need for tissue banks or complex sizing procedures such as in meniscal allograft transplantation [125]. The 2 scaffolds currently available for commercial use are the Collagen Meniscal Implant (CMI, Ivy Sports Medicine, Gräfelfing, Germany) and the Actifit polyurethane scaffold (Actifit, Orteq Ltd, London, UK). The CMI is made of type I collagen from an Achilles tendon and is suitable for use in patients who have had more than 50% of their meniscus resected, allowing for meniscal tissue to grow into the implant [126]. In like manner, the Actifit allows for tissue ingrowth but is meant to slowly degrade over a 5-year period [127]. Long-term prospective cohort studies have shown statically significant improvements in VAS, IKDC, and Tegner index scores at 10 years compared with partial meniscectomy alone [125]. However, the current literature supporting the use of meniscal scaffolding is limited because of the few available independent studies [123] but remains a promising option for patients with large meniscal lesions.

Addressing the Treatment Gap—Orthobiologics

Because certain orthopedic surgeries have failed to demonstrate significant benefit in relieving pain or restoring function after a musculoskeletal injury, patients have begun to explore novel treatments to improve their conditions. Orthobiologics can be defined as substances used with a therapeutic goal of enhancing or aiding the body's ability to repair or regenerate musculoskeletal tissue. Research on stem cell and cell-based therapies has greatly evolved during the past 2 decades, as has research on orthobiologic applications. We believe there is a distinct treatment gap in patients with degenerative meniscal tears, who have not responded to conservative management, and who are not candidates for direct meniscal repair. These patients eventually might be offered APM because of a perceived lack of available treatment options. Such patients would benefit most from innovative treatments for meniscal tears, such as the use of PRP, MSCs, or micro-fragmented adipose tissue (MFAT).

Platelet-rich Plasma

The use of PRP as a therapeutic technique to manage musculoskeletal injuries continues to increase in popularity and indications [128], with strong evidence for its use in knee osteoarthritis [129,130]. Nevertheless, current evidence for the use of PRP in treatment of meniscal tears is limited but encouraging. Platelets are known to release biomolecules and more than 1500 different proteins, including growth factors, cytokines, and chemokines, are contained in the platelet releasate [131]. These products have a myriad of roles, including recruitment, proliferation, and maturation of cells, to facilitate regeneration of the tendon, ligament, muscle, bone, and cartilage [131]. Multiple anabolic growth factors have important roles in healing after a lesion of the meniscus, with greater effect in the avascular zone of the meniscus because of its inherently poor ability to heal [132]. These include vascular endothelial growth factor-A, insulin-like growth factor-1, transforming growth factor-β1, platelet-derived growth factor-B, and IL-1β [67,133]. PRP represents an autologous source of these and other growth factors that could improve repair and regeneration of medial meniscal lesions [132]. Moreover, PRP has been shown to inhibit the negative inflammatory-mediated effects of osteoarthritis on chondrocytes [134].

Ishida et al [135] examined in vitro monolayer Lapine meniscal cell cultures in a rabbit model to assess the proliferation, extracellular matrix synthesis, and mRNA expression that occurred after exposure to a PRP product. A gelatin hydrogel scaffold was used as drug delivery for growth factors secreted by PRP to enhance healing of meniscal defects. The meniscal lesions showed a significant increase in fibrochondrocytes, DNA synthesis, extracellular matrix synthesis, and greater mRNA expression of biglycan and decorin meniscal cells compared with platelet-poor plasma and controls [135]. Their findings suggested that the combination of hydrogel and PRP supports meniscal cell proliferation and synthesis of a glycosaminoglycan-rich extracellular matrix.

Intrameniscal injections of PRP have the ability to attenuate pain associated with meniscal lesions and augment direct meniscal repair. Blanke et al [136] conducted a study involving 10 recreational athletes with grade 2 intra-substance meniscal lesions. These 10 patients underwent percutaneous intrameniscal injections of PRP and were followed up 6 months after the procedure. The average pain numeric rating scale score (11 points) significantly improved from 6.7 to 4.5 6 months after treatment (P = .027). In addition, 6 of the 10 patients reported an increase in sports activity compared with their activity levels before injections. Moreover, a recent case report described the efficacy of PRP in a patient with a grade 3a medial meniscus tear. These patients were followed for 30 months after treatment and reported significant improvement in pain symptoms from baseline (VAS score = 70 mm; Global Rating of Change [GROC] score not available; KOOS score = 39) to 30 months (VAS score = 40 mm; GROC score = 5; and KOOS score = 63.1) [137]. More recently, a double-blinded randomized controlled trial was performed using PRP to augment direct meniscal repair of vertical longitudinal tears. These tears were longer than 10 mm and in the red-white zone of the meniscus; red-zone tears were excluded. The primary outcome of meniscus healing as determined by second-look arthroscopy or 1.5-T MRI showed 85% healing in the PRP group vs 47% in the saline control (P = .048). The PRP group also showed significant differences in IKDC, WOMAC, and all 5 KOOS subscale scores compared with control [138].

Mesenchymal Stem Cells

MSCs are a subset of stem cells that have been isolated from bone marrow (BM) [139], periosteum, trabecular bone, adipose tissue [140,141], skeletal muscle, and deciduous teeth [142]. These cells have generated considerable interest in their clinical applications to regenerative medicine because of their ability to participate in a number of cellular processes, including tissue homeostasis, remodeling, and repair [143,144]. It has been proposed that MSCs in adult tissues represent reservoirs of reparative cells that are ready to differentiate in response to wound repair signals and disease states [143]. MSCs were first isolated from BM in the late 1960s [145] and subsequent studies have found these multipotent cells can form other cell types such as adipocytes, osteoblasts, and chondrocytes. Human adipose-derived stem cells (ASCs) have more recently been recognized and possess the ability to differentiate into adipocytes, osteoblasts, and chondrocytes [146,147]. Recent studies have shown that ASCs are not only easier to isolate from the body than BM-derived MSCs but also appear in higher concentrations [141]. Here, we elucidate the various roles of BM-derived MSCs and ASCs in the repair of meniscal tears.

Studies have reported successful repair of meniscal punch defects in the avascular zone with a MSC-biomaterial combination on a hyaluronan-collagen base. Zellner et al [148] created a circular 2-mm punch meniscal defect in the avascular zone of rabbit meniscus, which was then left empty or treated with biodegradable hyaluronan-collagen composite matrices. These defects were loaded with PRP, BM, BM-derived MSCs pre-cultured in chondrogenic medium for 2 weeks, or BM-derived MSCs without any pre-culture. Defects that were left empty or treated without cells showed muted growth, whereas uncultured MSC-loaded scaffolds showed defect filling with meniscus-like tissue. Although limited in use owing to the animal model, MSCs appeared to be able to stimulate the growth of meniscus-like tissue [148].

There is early high-level evidence for use of BM-derived MSCs in management of knee pain after partial meniscectomy. A randomized, double-blinded, controlled study was conducted by Vangsness et al [149] involving 55 patients who underwent a partial medial meniscectomy followed by an injection 7-10 days later. They were randomly assigned to treatment with 50 million (group A) or 150 million (group B) BM-derived allogenic MSCs suspended in a sodium hyaluronate suspension compared with suspension alone (group C). Twenty-four percent of patients in group A and 6% of patients in group B showed a significant meniscal volume gain at quantitative MRI (threshold defined as 15%) after 1 year. No patients in group C met the threshold of gaining significant meniscal volume. In addition, this study found that high doses of allogeneic MSCs could be safely injected into the knee joint without ectopic tissue formation. VAS pain scores and LKSS scores showed significant and sustained improvements in all groups up to 2 years. There were no significant intergroup differences except for significant decreases in pain in patients with evidence of osteoarthritis changes of the knee at baseline compared with control [149]. More recently, a prospective case study examined the use of MSCs in augmenting direct meniscal repair in a series of 5 patients. BM-derived MSCs placed in a collagen scaffold were arthroscopically implanted into a meniscal tear before suture repair. The patients were followed for 24 months and showed clinical improvements on the Tegner-Lysholm score and the IKDC score at 24 months. However, 2 of the patients eventually pursued partial meniscectomy because of re-tear vs non-healing of the meniscal tear [150].

Adipose-derived Stem Cells

ASCs are MSCs obtained from adipose tissue and have the capacity to differentiate into multiple cell lineages [146,147]. ASCs were first identified as MSCs in adipose tissue in 2001 and have since been studied as a cell source for tissue engineering and regenerative medicine. ASCs can be isolated from subcutaneous adipose tissue of the abdomen, thigh, and arm. Compared with BM, adipose tissue has been shown to yield more stem cells. One gram of aspirated adipose tissue yields approximately 500 times the amount of MSCs isolated from a gram of BM aspirate [151]. In similar fashion to MSCs, ASCs have shown the capability to secrete various growth factors including vascular endothelial growth factor and hepatocyte growth factor [141]. These 2 growth factors also promote neovascularization, a mechanism through which ASCs promote host tissue repair [152]. Previous studies have elucidated the benefit of ASCs to promote revascularization of ischemic mouse hind limbs through hepatocyte growth factor secretion [153] and repair of scarred myocardium [152,154], indicating that it could be of use in the avascular portion of the meniscus. Also, like MSCs, ASCs express markers, such as CD13, CD29, CD44, CD63, CD73, CD90, and CD105. They also are negative for hematopoietic antigens, such as CD14, CD31, CD45, and CD144 [155].

In vitro studies have demonstrated the regenerative potential of ASCs, including its differentiation into chondrogenic and osteogenic cells. Several studies have investigated clinical outcomes of ASCs injected into rabbit osteoarthritis models. After 16 and 20 weeks, rabbits receiving ASCs showed lower degrees of cartilage degeneration, osteophyte formation, and subchondral sclerosis than the non-ASC control group [156]. Van Pham et al [157] induced osteoarthritis in mice by needle disruption and pretreated the joint space with PRP. They concluded that PRP-pretreated ASCs improved healing of injured articular cartilage in murine models compared with that of untreated ASCs. Ude et al [158] compared ASCs and BM stem cells in a surgically induced sheep osteoarthritis model via ACL tear and medial meniscectomy and found that the proliferation rate of ASCs was significantly higher than that of BM stem cells. However, chondro-induced BM stem cells had significantly higher expression of chondrogenic-specific genes compared with those of chondrogenic ASCs. In addition, tracking dye (PKH26) fluorescence in the injected cells showed that they had populated the damaged area of cartilage.

There is a limited amount of literature describing the use of ASCs for the regeneration of the meniscus in humans. Pak et al [159] published a safety cohort report in which 91 patients with hip or knee pain and radiologic evidence of degenerative joint disease were treated with an intra-articular mixture of ASCs, PRP, and a hyaluronic acid scaffold. Patients showed significant improvements in pain at 3 months and complications were limited to localized pain and swelling or tenosynovitis. A subsequent review by the same group reported that 32 of patients who had evidence of meniscal tears also demonstrated significant improvements in pain and function [160]. They also reported on a 2014 case study in which a 32-year-old woman with a grade 2 medial meniscal tear in the posterior horn was injected with a similar combination of ASCs, PRP, hyaluronic acid, and calcium chloride, with 4 additional doses of PRP with calcium chloride and hyaluronic acid at days 3, 7, 14, and 28. Repeat MRI at 3 months showed near-complete repair of her torn meniscus and improvement in pain and function [141]. Although the results are positive, it is difficult to draw conclusions regarding the dosing, regimen, or effect of any one treatment used in these studies given their simultaneous use.

Micro-fragmented Adipose Tissue

There are different methods to process autologous adipose into MFAT with minimal manipulation and avoiding the use of enzymes [161–164]. Processed MFAT has been used as regenerative treatment for the management of musculoskeletal conditions such as knee osteoarthritis [165–167], shoulder pain secondary to osteoarthritis and rotator cuff tear [168], and osteochondral defects of the talus [169]. In addition, case reports have reported improvement in pain and function scores after intra-articular injection of MFAT in the setting of knee osteoarthritis and meniscal tear [170,171]. Furthermore, a case report has been presented on this use of this device in the successful treatment of a degenerative meniscal tear in a triathlete [172]. MFAT has been shown to have larger percentages of pericytes and human MSCs compared with unprocessed fat graft, possibly contributing to its regenerative potential [163].

U.S. Food and Drug Administration Considerations

In light of the growing interest of allogeneic stem cells for therapeutic use, several concerns have arisen regarding the safety, potential for contamination, and manipulation of these products. One concern raised by the U.S. Food and Drug Administration (FDA) is the concept of "manipulation," which refers to altering the inherent structural or biological nature or structure of the product [173]. For example, enzymatic dissociation of adipose tissue to isolate ASCs would be classified as "more than minimal manipulation" [174]. Concerns about these products focus on the potential for the risk of contamination when these products have been banked, transported, or processed in facilities with other cellular or tissue-based products [174]. Because of these public safety concerns, the FDA maintains its jurisdiction over the regulation of the production and marketing of any stem cell-based therapy involving the transplantation of human cells into patients. Most stem cell-based products are currently regulated under the Public Health Safety Act, Section 351, because they are considered biologic products, which is defined as cells or tissues that are "highly processed, used for other than their normal function, are combined with non-tissue components, or are used for metabolic purposes" [175].

A new device for processing and transfer of adipose tissue into MFAT has recently been approved by the FDA [176]. The process involves a closed, full-immersion, low-pressure cylindrical system designed to harvest, process, and transfer refined adipose tissue. Therefore, it qualifies as minimally manipulated under FDA guidelines because it uses mild mechanical forces to micro-fragment fat tissue and wash away any proinflammatory oil and blood residues without the use of enzymes, additives, or separation centrifugation while preserving the microarchitecture [177]. However, there is controversy regarding the qualification of this device and other MFAT harvesting techniques as "homologous use" in certain orthopedic applications [173]. At this time, there are ongoing studies accessing the efficacy of this system in the treatment of meniscal tears.

Conclusion

The menisci are important fibrocartilaginous structures with limited blood supply and capabilities of healing after injury. Conservative management combined with physical therapy remains a successful option for mitigating pain and functional deficits after a meniscal tear but does not directly address the meniscal tear. Historically, patients who have not responded to conservative management have been treated with APM; however, recent evidence has suggested that this surgery is no better than physical therapy or sham surgery and can result in increased joint loading and progression of degenerative arthritis. This results in not only a great monetary cost to the health care system but also functional limitations in patients. Direct meniscal repair and replacement techniques show promise but are limited in their applicability at this time. Recent research has shown that the use of regenerative treatments such as PRP, MSCs, or MFAT might stimulate healing of the meniscus and justify further research in their application alone or combined with procedures such as meniscal repair, replacement, or trephination.

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CME Question

According to this article, which of the following treatments for degenerative meniscal tears has been shown to increase future risk of osteoarthritis?

a. Physical Therapy
b. Arthroscopic Partial Meniscectomy
c. Platelet Rich Plasma Injections
d. Mesenchymal Stem Cell Injections

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