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Review Article

The Effect of Stem Cells on Meniscus Tear Injuries

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Abstract

The Meniscus injuries are associated with pain, swelling, impairment in function and activity levels as well as early osteoarthritis of the knee joint. The prevalence of meniscal tear injuries is close to 12% to 14%, with an occurrence of 60-70 cases per 100,000 individuals. There are about 850,000 cases per year and the global annual cost is estimated at $4 billion. Professional and amateur athletes demonstrate meniscus tear rates between 1.58-2.98 injuries per 10,000 athletic exposures. Sports with the highest rates of athletes affected by meniscus tear injuries include: football, soccer, basketball, wrestling, and rugby. Meniscus tear surgeries may lead to potential side effects or medical complications. The effectiveness of stem cells for meniscus injuries in animal and human subjects is something that researchers have investigated. Often preferred mesenchymal stem cells are the source for procedures seen in orthopedics as they change into many types of tissues including: cartilage, bone, muscle, bone, and fat. The use of stem cells in transplantation has shown an improved rate of healing, enhanced tissue quality, sustained functional gains, and improved outcomes in clinic. Researchers think the use of stem cells may offer other options for people with an orthopedic injury including meniscus tears decreasing recovery time, improving function, and decreasing degenerative osteoarthritis.

Key words: Meniscus injury; Stem cells; Treatment; Tissue engineering; Orthopedic.

Abbreviations: ACL-Anterior Cruciate Ligament; AE-Athletic Exposure; APM-Arthroscopic Partial Meniscectomy; ASC-Adipose Stem Cell; BMI-Body Mass Index; BMMSC-Bone Marrow Derived Mesenchymal Stem Cell; ECM-Extracellular Matrix; hIGF-1-human Insulin-like Growth Factor 1; ISAKOS-International Society of Arthroscopy Knee surgery and Orthopedic Sports medicine; MAT-Meniscal Allograft Transplantation; MLB-Major League Baseball; MRI-Magnetic Resonance Imaging; MSC-Mesenchymal Stem Cells; NBA-National Basketball Association; NSAID-Non-Steroidal Anti-Inflammatory Drug; OA-Osteoarthritis; OARSI-Osteoarthritis Research Society International; PT-Physical Therapy; ROM-Range Of Motion; RTP-Return To Play; TEC-Tissue Engineered Construct.

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Introduction

The knee meniscus is a fibrocartilaginous and semicircular structure that serves many important jobs in the function of a normal knee which includes stabilization of the knee, load transmission, and shock absorption [1,2]. Meniscus is derived from a Greek work known as meniskos which means “crescent”, a diminutive of the word mene, which means “moon” [3]. Meniscus injuries are associated with pain, swelling, impairment in function and activity levels as well as early osteoarthritis of the knee joint [4]. All populations are at risk for meniscal tears when an external force is exerted on the knee causing a twist in the knee. Meniscus tears are estimated to occur in approximately 60-70 cases per 100,000 individuals. The estimated number of cases per year is around 850,000 and a global annual cost is estimated at $4 billion [5]. Acute trauma-related tears are more common in an athletic population and are particularly prevalent in pivoting and contact sports in young individuals. Degenerative tears that are asymptomatic typically are more common in older adults. Not every tear requires treatment or symptomatic. Meniscus tears are starting to become easier to recognize with the advancement of magnetic resonance imaging (MRI). In a study of 18-to 39-year-old patients, asymptomatic meniscus tears were shown to have a prevalence of 5.6%. In the 50-to 90-year-old population, meniscus tears were shown to have a prevalence of 31%. The peak onset of degenerative meniscus tears in men ranges between 41 to 50 years and in females between 61 to 70 years [1,5,6]. Over a 10-year span of time, meniscus repair, meniscectomy, and nonoperative treatment led to rates of osteoarthritis at 53.0%, 99.3%, and 95.1% respectively [7]. Berthiaume and colleagues evaluated 32 patients between 40 and 80 years who fulfilled the criteria for diagnosis of knee osteoarthritis set forth by the American College of Rheumatology. All patients underwent MRI and 24 patients (75%) had little to moderate or severe damage in the meniscus. Acute knee pain exacerbation or knee trauma were not reported by these patients [8]. Several factors that can affect meniscal tear rates include: sex, anatomical and physiological differences within the knee, body mass index (BMI), occupations, concomitant injuries, and participation in contact sports. The incidence of meniscal tears is 2.5 times higher for men than women. People with a discoid meniscus, biconcave tibial plateau, and ligamentous laxity show an increased risk of meniscal tears. There is an 86% increase in incidence of meniscal tears in patients with anterior cruciate ligament injuries (ACL). Individuals who have a high BMI are more at risk for meniscal tears. Occupations that require lifting and carrying weights, squatting, and stair climbing have a greater risk for meniscal tears. Athletes participating in contact sports and other related activities demonstrate higher incidence of meniscal tears [6,9].

Surgical management is the most prevalent medical intervention for meniscal tears. Meniscal tear was first described in 1731. Annandale performed the first open meniscal tear repair using surgery in 1885. A variety of arthroscopic knee techniques were introduced in 1960 [4]. Until the 1970s the gold standard was seen as total meniscectomy for surgery related to tears in the meniscus. The limited understanding of important role of meniscus caused this. Recently, studies emphasized the importance of the meniscus

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as a structure that can bear weight and the absence could lead to osteoarthritis and instability in the knee. Orthopedic surgeons began to focus on options that promoted meniscal injury repair and preservation. Abrams and colleagues suggested that over the past five years preservation of the meniscus procedures have almost doubled. The change of approach has shown improved functional outcomes and shorter recovery times in meniscal treatment from resection to preservation. In 1989, the first article related to meniscus transplant was published. Current strategies to utilize stem cells and tissue engineering are beginning to show improved potential in repairing tissue and slowing joint damage in meniscal injuries [2,6,10,11].

Modifiable and nonmodifiable risk factors for meniscus injury	
Risk Factor	**Description**
Modifiable	
Activity level	Increased activity level for most tears; decreased activity level for MMPRT
BMI	BMI>25 kg/m^2
Nonmodifiable	
Age	Increased age; younger age may be protective, especially in cases of delayed ACL reconstruction
Gender	Men at increased risk; among gender-comparable sports, women may be at greater risk; women at risk of MMPRT
Anatomy	
PTS	PTS>13° may increase risk in ACL-deficient knees
MMS	MMS>3.5° may increase risk of ramp lesion in ACL deficiency
Biconcave medial tibial plateau	Biconcave plateau may increase risk of complex medial meniscus tears
Knee malalignment	<178° or >182°; higher risk of meniscal extrusion with valgus knees

Table 1: Outlines meniscus injury risk factors [9].

Anatomy and physiological function

Located between the femoral condyle and tibial plateau, the knee joint contains medial and lateral components. Medial and lateral are the two shapes of the menisci. These two menisci are hydrated tissue structures compartments of the lateral and medial side of the knee joint. These menisci are both fibrocartilaginous Various ligaments cross the meniscus and the meniscus and support stabilization of the knee joint [10,12].

Fundamental shape of medial and lateral meniscus is developed in between the eighth and tenth gestational weeks. The intermediate layer of mesenchymal tissue is condensed resulting in the menisci to form enclosing joint capsule attachments [3].

Approximately 35mm in diameter the medial meniscus is semicircular, and is broader posteriorly than it is anteriorly. Near the intercondylar fossa the tibia plateau is attached to the anterior horn in an anterior-

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to-anterior cruciate ligament [3]. Located between the lateral meniscus and posterior cruciate ligament, the posterior horn is attached to posterior intercondylar fossa of the tibia.

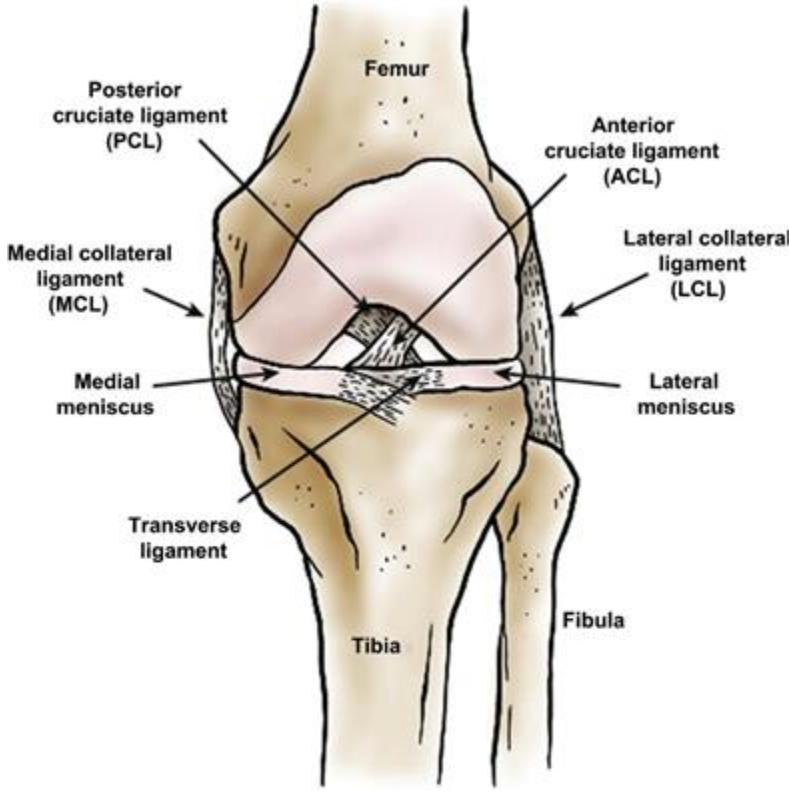

Figure 1: Outlines anatomy of the knee joint: anterior view [10].

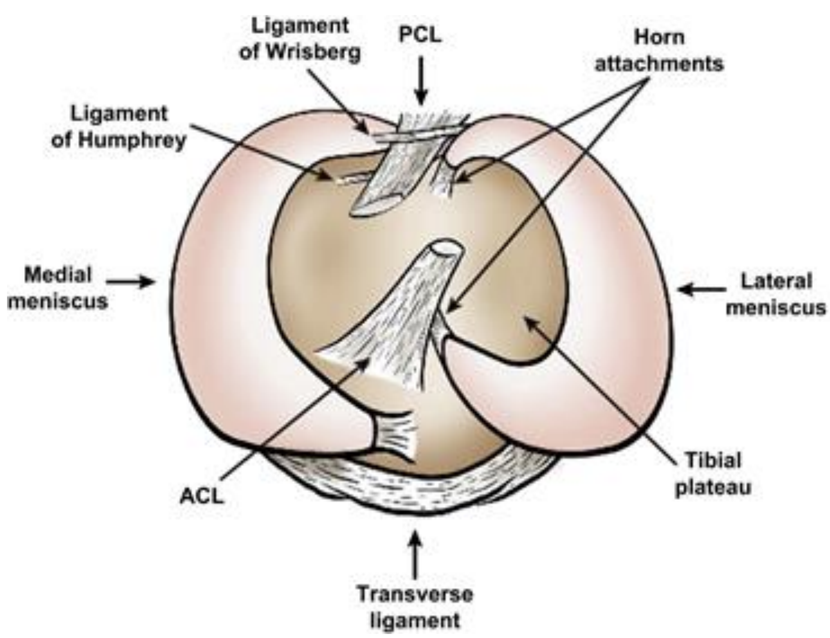

Figure 2: Outlines meniscus anatomy including a superior view of the tibial plateau [10].

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The lateral side of the meniscus appears circular shape and constant width from posterior to anterior. Occupying a greater portion of articular surface (~ 80%) than the medial meniscus (~ 60%) the meniscus's lateral side is more mobile. The horns of the lateral side of the meniscus are connected to the tibia. Insertion of anterior horn of lateral side of the meniscus is adjacent to the attachment site of the ACL and anterior to intercondylar eminence. The posterior horn of meniscus's lateral side will insert anteriorly to the insertion of the posterior horn of the medial meniscus and posteriorly to the lateral tibial spine [3].

A dense extracellular matrix composes the meniscus and is made up of 72% water, 22% collagen and additional interposed cells. The remaining dry weight is glycoproteins, proteoglycans, and non-collagenous proteins. A mixture of chondrocytes and fibroblasts make up the cells of the meniscus and are referred to as fibro chondrocytes [3].

The avascular inner area known as the red-white and white-white zones and the vascularized peripheral 30% known as the red-red zone describe the vascular supply of the meniscus [1,13]. The meniscus is thick, convex & attached to the joint capsule at the peripheral and vascular border. The thin free edge is tapered by the innermost border [3]. Between these two zones is a red-white area that has decreased vascularity. Tears involving inner zone have been reported to show the lowest possible healing due to the overall decrease in blood supply [2,14,15].

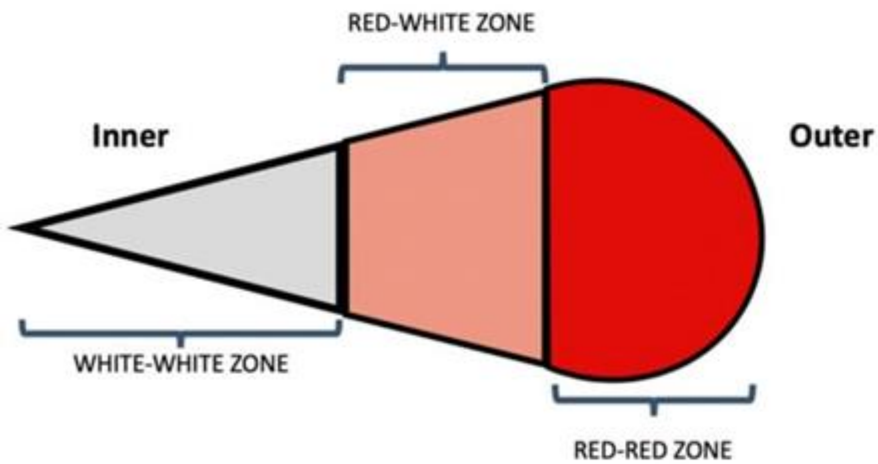

Figure 3: Outlines cross-sectional image of the body of the meniscus showing the vascular areas related to the meniscus [2].

The meniscus is essential to the knee joint and serves significant functions biochemically and adds to the stability, joint lubrication, nutrition, shock absorption, load transmission, and proprioception. During daily activities, the femur is applying a downward force on the menisci. Due to the wedge shape of the meniscus, the femur is exerting this force at an angle. This creates a vertical component countered by the force going upward from the tibia. The meniscus experiences an outward force from the femur. The attachments at horns anteriorly and posteriorly of the meniscus counter this

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horizontal force. A circumferential stress is created along the meniscus when compression occurs. Menisci convert circumferential tensile loads to compressive loads. The meniscus is deformed radially as forces are developed between the fibers of collagen located in the meniscus. 70% of load transmission across the joint describes the lateral meniscus [2,10,16,17]. Micro canals within the meniscal tissue will help transport the synovial fluid allowing for the nourishment of articular cartilage. The meniscus contains Pacinian corpuscles and Ruffini endings, proprioceptive mechanical receptors, located in the anterior and posterior horns of menisci. This helps contribute to the sensory feedback and certain join position [2].

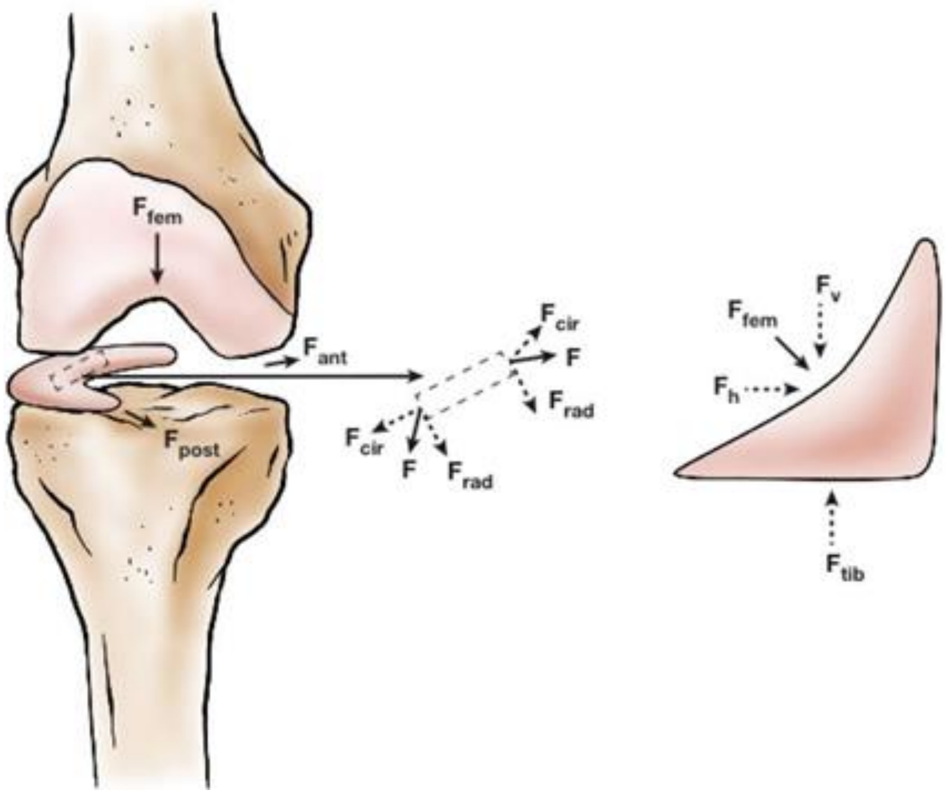

Figure 4: Outlines how force throughout the knee is transduced upon [10].

Meniscal tear classification

The International Society of Arthroscopy, Knee Surgery and Orthopedic Sports Medicine (ISAKOS) Meniscal Documentation Committee collaborated to develop a reliable, meniscal international evaluation and system of documentation to facilitate outcomes assessment. Provided by the ISAKOS classification of meniscal tears is a standardized measurement tool to evaluate meniscal tears outcomes of treatment utilizing the following parameters: tear location, depth, radial location, central to the popliteal hiatus, tear quality of the tissue, the pattern of tear, length of tear, and meniscus's excised percent and amount [18].

Diagnostic procedures

MRI are the most common radiographic test which can be used to observe meniscus tears,

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which has a specificity of 88% and a sensitivity of 93% for detecting a torn meniscus. Visualized on an MRI the high signal strength and shape abnormality can be observed [6]. One of the clinical tests that can be used to diagnose meniscal tears can be the McMurry test. The rotation of the knee is one part of the McMurry test. If there is a clicking/popping and pain in the knee then this is an indication that the McMurray test is positive. Apley's grinding is another test utilized. The knee is flexed to 90 degrees while the person lies in the prone position during Apley's grinding test. The physician rotates the knee in a medial and lateral pattern followed by distraction. Compression, instead of a distraction, follows a repetition of the evaluation process. A decreased rotation along with a painful knee helps diagnose a meniscus tear when the knee is compressed and rotated [6,19].

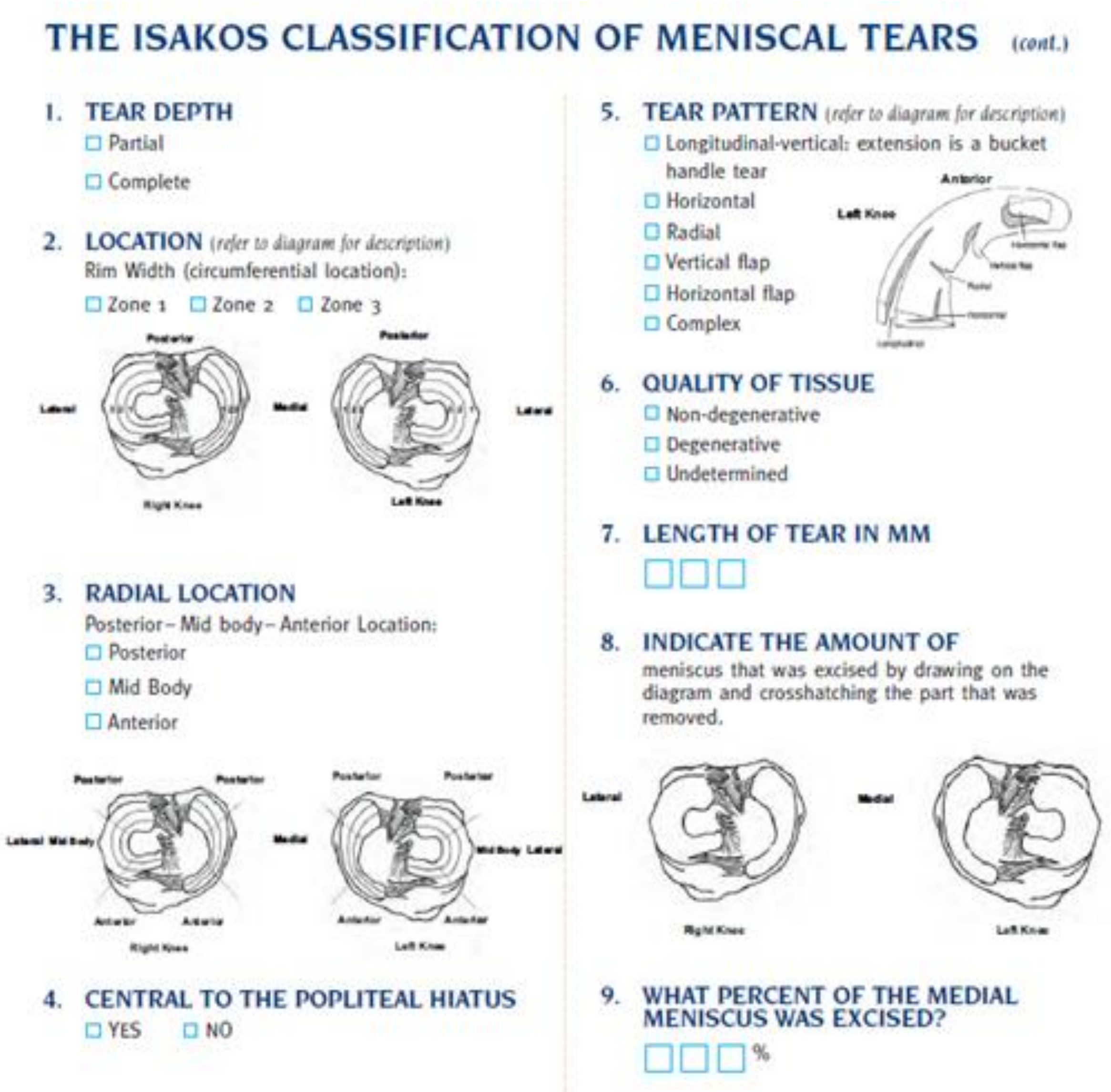

Figure 5: Outlines ISAKOS Classification of Meniscal Tears [18].

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Medical and surgical interventions for meniscus injuries

The intervention for traumatic acute knee with meniscal tears focuses on non-operative management. PRICE protocol (elevation, ice compression, and protection) is applied [12]. Non-operative management intervention including: analgesic and anti-inflammatory medications, bracing, strengthening exercise, modifications in activity and articular injections should be attempted for a minimum of three to six months. These interventions have been shown to temporarily reduce the symptoms in degenerative change associated with acute inflammation after inflammation and trauma [20,21]. If the patient's symptoms persist after this three to six-month trial period, surgical alternatives should be considered [12].

Types of surgery

Here are examples of when surgery is typically recommended if the patient demonstrates: red zone tear, young healthy candidate under 40 years of age, presence of a simultaneous ACL injury in acute tears that occurred greater than 6 weeks or complex meniscal rips less than 1cm [2,6,10-12,22,23].

Arthroscopic partial meniscectomy (APM) was the preferred treatment for meniscal injuries for the most recent years. However, patients with previous APM have three times higher risk for undergoing total knee replacement. An effective option for meniscal lesions is meniscal repair without the complicated effects of meniscectomy. At two-year follow up, meniscal repair outcomes show a failure rate of less than ten percent while failure rate which are long term have been reported between 23% and 30%. Lower satisfaction rates and more symptomatic relapse in people with knee osteoarthritis were observed when compared to people with traumatic meniscal lesions after undergoing arthroscopic treatment [2,6,10-12,22,23].

Meniscectomy can be complete or partial and performed through an approach that is either open or arthroscopic. Currently, total meniscectomy is rarely performed due side effects including osteoarthritis that is seen early. APM is more common due to it being less invasive, requiring decreased recovery time, and has a decrease in overall morbidity rates. Radial white-white zone meniscus tears and deteriorating meniscus injuries are signs of APM that have not responded to conservative management. Research demonstrates no major long benefits of APM over non-operative management of meniscus tears that are either atraumatic or traumatic. Female gender, obesity, and advanced osteoarthritis are all considered to be factors with poor outcome for APM. Current guidelines outlined by the ISAKOS suggest APM and should be utilized only in certain patients with who have meniscal tears that cannot be repaired and patients with mechanical symptoms that end up lasting longer than 3 months [2,6,10-12,22,23].

The arthroscopic approach and open surgical are two ways in which the meniscus can be repaired. Repair utilizing arthroscopy is typically preferred due to a decreased risk of damage done neurologically. Repairs of the meniscus have higher rate of reoperation compared to a meniscectomy. This repair shows better long-lasting functional outcomes, decreased rate of failure, and an increased level in activity. Repairs of the meniscus for acute traumatic meniscal tears within the red-red zone of the meniscus proved to be most successful. Tears which can be either longitudinal or horizontal show better results in meniscal repair compared to tears that are radial. A radial tear paired with the meniscus can be attempted in partially perfused red-white zones but may show lower rates of success. All inside surgical techniques, inside out, and outside in are all ways in which the meniscus can be repaired arthroscopically [2,6,10-12,22,23].

The inside-out surgical approach has demonstrated the greatest success rate. Through the extra-articular incision, sutures are passed from within the knee to an extra-capsular area. A knot is then fastened over the capsule which is joint. Meniscal damage in the posterior horn area typically uses the technique that utilizes the inside-out approach. However, the anterior horn tears will typically utilize the outside-in technique. In an outside manner the spinal need is passed through the rip in the meniscus. After the tip of the needle is visible the suture is passed through the arthroscopic portal. After this the suture will be brought back after an interference knot at the end is tied. Until the tear is stabilized, this procedure will continue. Cases of extreme meniscal rips posteriorly are when the all inside technique will prove to be most beneficial. Repair instruments are typically made of bioabsorbable compounds. These include different screws in staples that are used during this procedure. Arthroscopic techniques strive to decrease the overall risk of neurovascular problems; however, damage still has the potential to occur in all the above surgical procedures [2,6,10-12,22,23].

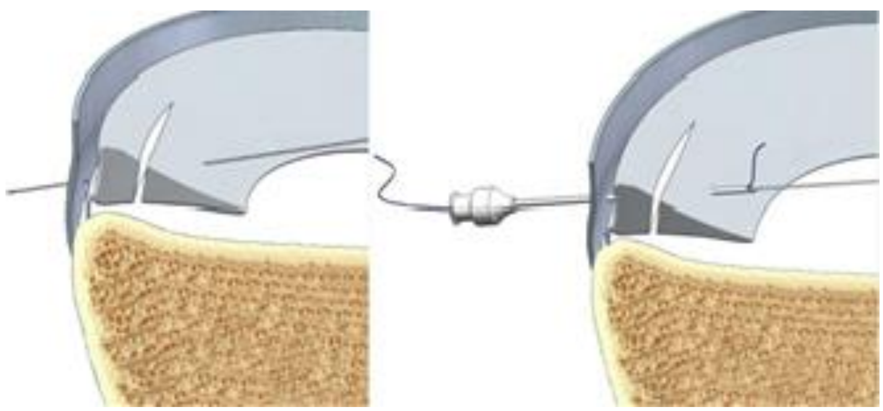

Figure 6: The inside-out technique for repairing of a medial meniscus tear including the posterior horn can be seen in the image above [24].

Meniscal Reconstruction is the least common performed surgery. Functional components of the meniscus are often times used to replace missing or resected ones during a meniscal reconstruction. Preventing deterioration that would result from poor biomechanics and reestablishing the overall functionality of the knee joins are the two main goals of this surgery. Reconstruction can be performed with meniscal allograft transplantation (MAT) or meniscal scaffolds. Conserving the meniscus allograft is one of the main ways in which MAT will utilize transplantation. Scaffold surgery of the meniscus fills meniscal defects through the utilization of synthetic biodegradable porous

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structures. This process will allow growth in vascular tissues within the structures to provide additional reinforcement [2,6,10-12,22,23].

Advancements in biological augmentation such as bone marrow stimulation, platelet rich plasma, fibrin clot, scaffolds and stem cell therapy have expanded options for meniscus surgery. Improved repair techniques and biological augmentation have provided additional options for meniscus repair surgeries [6,12,22,23].

Injuries are commonly seen in the meniscus with the existence of simultaneous acute anterior cruciate ligament (ACL) rupture. Up to 80% ACL ruptures have related meniscal tears. The method of care for this dual diagnosis is to repair both injuries simultaneously. 1332 patients with isolated meniscal tears undergoing meniscal repair were compared with patients with concomitant ACL injuries who underwent meniscal repair and ACL in a research study done by Wasserstein and colleagues. 42% risk reduction of reoperation was found for those patients undergoing concurrent ACL reconstruction and restoring of the meniscus as compared to patients only undergoing meniscal repair. 5.6 months for isolated meniscal repair versus 11.8 months in athletes when looking at the mean Return to Play (RTP) was found requiring concurrent ACL repair [1,25,26].

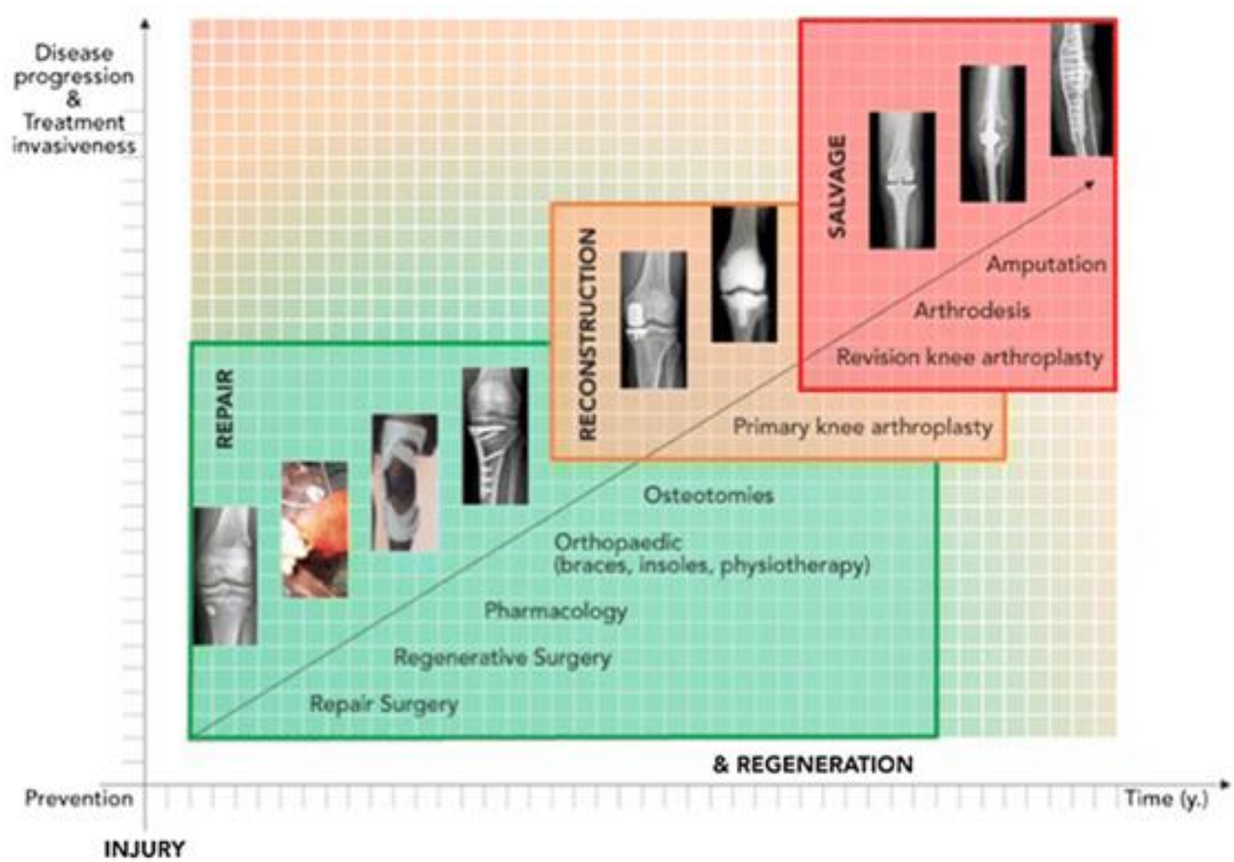

Figure 7: Outlines the growth of a disease and invasive treatment in the long term after an injury and deterioration of the knee [11].

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Physical therapy

Focusing on the advancement of activities allowed by a patient is the main focus of physical therapy rehabilitation. It takes close to 6 weeks in order for a patient to return to activities such as jumping, running, and other sport specific training options. The knee pain has typically lessened and hamstring/quadriceps has usually returned to relatively normal at this point in time. Protective, restorative, and return to activity/sports preparation are three categories in which physical therapy can be broken up into following a repair of the meniscus. Early patellar mobilization maintenance of knee extension and neuromuscular training are points of focus during the first 6 weeks following surgery. This stage is known as the protective phase.

Box 1 **Rehabilitation protocol following meniscus repair**	
Phase I: 0 to 2 weeks	• Full wight bearing (WB) in extension • ± Brace • Range of motion (ROM) 0 to 90 while non-WB (NWB) • Isometric quadriceps strengthening
Phase II: 2 to 6 weeks	• Full WB in extension • Continue ROM 0 to 90 while NWB • Add closed chain exercises, terminal knee extensions
Phase III: 6 to 12 weeks	• Full WB • Discontinue brace, if using • Progress to full ROM • Begin hamstring and proprioception exercises • Leg presses 0 to 90 • Add stationary bike
Phase IV: 12 to 20 weeks	• Progress with exercises and activities • Swim at 12 weeks • At 16 weeks begin sport specifics and run/jump protocol

Table 2: Outlines rehabilitation protocol following meniscus repair [13].

Meniscus tears in athletes

One of the most difficult tasks that is seen in orthopedic surgeons is being able to manage an athlete with a meniscus tear. Coaches and other teammates may add to the overall pressure to a player as they are attempting to get them to return to play as soon as possible. Dragging out the return time to sports can have cost burdens and consequences on the career of the athlete. Cutting and pivoting movements causes common acute traumatic

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tears in young athletes. The minimization of risk for reinjury and increased speed in return to play are two reasons that early functional rehabilitation programs were created [9,13,16,27,28].

Meniscus tears occur at a rate of 2.98 injuries per 10,000 athletic exposures (AEs) in athletes in high school and make up for approximately 10% to 20% of all knee injuries. Player-on-player contact sports are the sports in which meniscus injuries are most frequent. Sports such as wrestling, basketball, soccer had the highest rates of meniscus injuries. However, swimming, cheerleading, track and field had the lowest occurrence of injuries. In college sports, soccer, wrestling, football, etc. had more frequent meniscal injuries compared to ice hockey, lacrosse, baseball etc. [9,13,16,27,28].

Sports associated with meniscus injury	
Level of risk	Sports (Highest to lowest risk)
High	Football>soccer>basketball>wrestling
Moderate	Gymnastics>lacrosse>ice hockey>field hockey>baseball/softball
Low	Track and field>swimming>cheerleading

Table 3: Outlines sports associated with meniscus injury [9].

The rate of meniscus injury is 1.58 per 10,000 athletic encounters in the NBA for professional sports. 58% to 60% of all meniscus tears were lateral and result in a loss of 40-50 days of playing time. 51% of all NFL players had sustained a prior knee injury in some way or form and 12% stated that these injuries involved their meniscus. The lateral meniscus was the area the was made up the majority of these meniscal tears in the NFL. In the MLB there were 4263 missed days of playing per season as a result of meniscal injuries. The majority of the injuries were a result of them sliding as 9% of all sliding injuries resulted in an injury involving the meniscus [9]. Off road motorcycling (20% of all injuries) and skiing (10%-20% of all injuries) are two other sports in which a sport has been identified as a potentially high risk for a meniscus injury [9].

Some incentives have been put in place to address meniscus injuries without the need for surgery for an athlete that is currently in a season; however, surgical interventions may occur if an athlete's performance is not at a high level or the pain is persistent [1,29]. A surgeon must regard the athlete and team training staff when it comes to the meniscal surgery outcomes and recovery. 7 to 9 weeks for meniscectomy and 5.6 months for a full repair of the meniscus are the typical number of times that an athlete has to sit out before they can return to play [1,27,30].

In a study done Ostin and colleagues observed 41 athletes with partial lateral meniscectomy. They observed that it took an average of 55 days in order for them to return to play in 98% of the athletes. Isolated simple longitudinal tear patients returned the earliest (average 41 days) [31]. Kim and colleagues evaluated return to play and found a large difference in return to play time based on age (<30, 54 days; >30, 89 days) and their level of competition (elite, 54 days; competition, 53 days; recreational, 88 days) [32].

Nawabi and colleagues researched a group of 90 professional soccer players that underwent medial vs lateral meniscectomy. 42 of the 90 researched soccer players had a lateral meniscectomy and 48 had a medial meniscectomy. The median time to return to play was longer in the lateral group 7 weeks compared to the medial group at 5 weeks. Events related to swelling and pain was more (69% vs 8%) in lateral meniscectomy patients and required a second arthroscopy [33].

Box 1 **Return-to-play criteria**
• Full, painless knee ROM that is symmetric to the uninjured limb • No reactive effusions with sport-specific activities • Return of normalized running mechanics • Appropriate neuromuscular coordination demonstrated by the ability to perform regular and single leg jumps, agility ladder drills, lateral hops, and change in direction/cutting drills • Greater than 90% of strength regained for knee extension, flexion, and single-leg press • Psychologically ready for return demonstrated by lack of apprehension with sport-specific activities

Table 4: Outlines return to play criteria [1].

77 NFL players were evaluated by Aune. Lateral meniscal injury among NFL players could possibly lead to career threatening outcomes. Sixty-one percent (n=47) of athletes that underwent partial lateral meniscectomies returned to play at previous levels of competition. 8.5 months was their average return to play time. During the follow up it was found that nineteen (40%) of those who returned to play were still active in the NFL. The first 4 round players who were drafter were 3.7 times more likely to return to play compared those after these first four rounds. 2.8 times as many athletes who started more than 46.2% of their games were likely to return to play. Speed position players, running backs, receivers, defensive backs, linebackers etc. are less likely to return than non-speed position players by almost 4 times [16].

An informed cohesive decision needs to be made between the athletes, doctor, physical therapist, athletic trainer before allowing an athlete to RTP. There should be a symmetric, full, and pain-free ROM without any strength discrepancies. The psychological and mental status of the athlete also needs to be considered before they can RTP. The athlete must demonstrate usual running

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biomechanics and constant control of their neuromuscular system when participating in dynamic sport-specific activities before they can come back to play [1,9,13,16,27,28,32,34].

Pre-clinical studies

Stem cell injection

Zellner, et al., in 2017 evaluated the source of cells, through a rabbit model the source of cells for autologous meniscal repair that can be seen in early osteoarthritis. Medial menisci and bone marrow were gathered four weeks prior to surgery. Mesenchymal and meniscal stem cells were grown, seeded, and isolated onto collagen-hyaluronan scaffolds before they were implanted. Gross joint morphology and OARSI grade were assessed at 6 and 12 weeks. After resections of the medial meniscus, every knee demonstrated early osteoarthritic changes. Meniscal cells or MSCs were used to repair punch abnormalities of the meniscus successfully. Human MSCs were found to have significantly increased collagen type II gene expression and production when compared to meniscal cells. Regenerative potential of the meniscus by an autologous cell-based tissue engineering approach was shown in a setting of early osteoarthritis. The healing of an animal model demonstrated improvement when using autologous meniscal cells and mesenchymal stem cells [35].

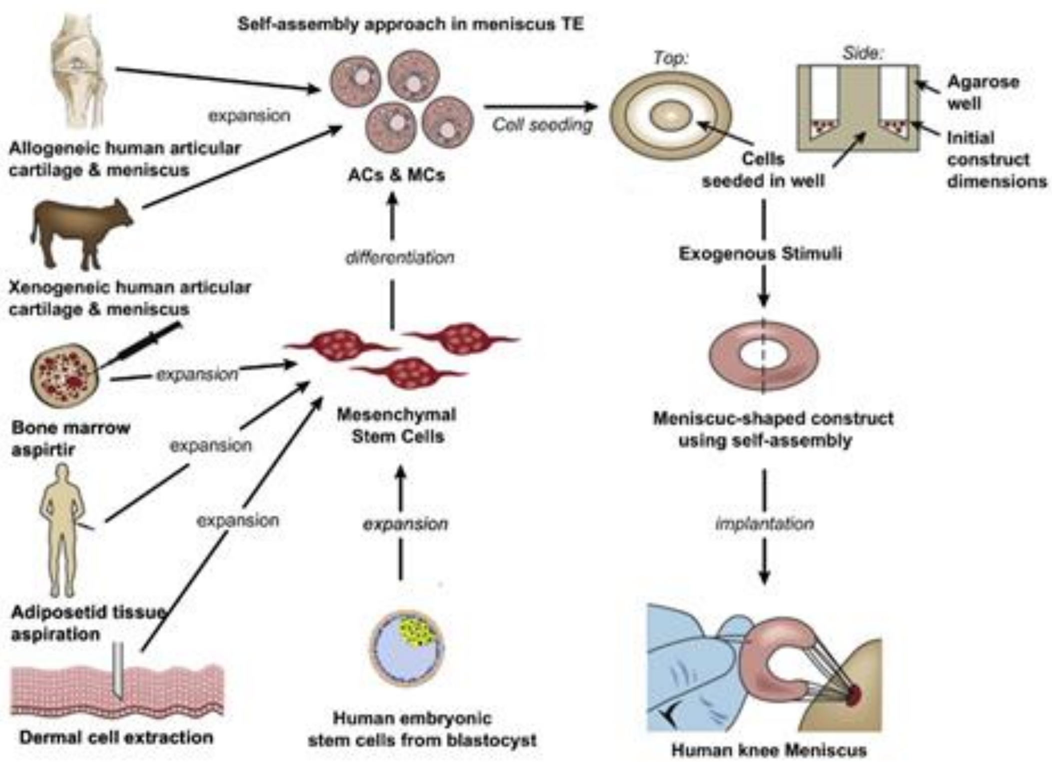

Figure 8: Outlines the strategy of meniscus tissue engineering utilizing self-assembly [10].

When looking at a meniscal defect, Nakagawa, et al., in 2015 utilized a porcine model to combine a suture repair to allogenic synovial MSCs. After 12 weeks had passed, the MSC group demonstrated higher collagen deposition, strength, and histology scores of

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the site being repaired. During this study no reactions were immunologic. This study suggests synovial MSCs utilized at suture sites show improved outcomes in an animal model [36].

Hatsusuika, et al., in 2014 investigated the use of allogeneic synovial MSCs utilizing multiple doses of intraarticular synovial MSC injections in a porcine model. The subjects were given MSCs and the front half of the meniscus was removed. At 2 weeks, when filled with synovial tissue, the MSC group showed a fault. At 16 weeks, the MSC group had higher quality tissue with enhanced collagen I II & safranin-o straining when they were compared to a control group. This study supported the use of synovial MSCs to promote meniscal regeneration and repeated intraarticular injection demonstrated better results in an animal model [37].

Ferris, et al., in 2014 administered intraarticular injection of mesenchymal cells from the bone marrow (BMMSCs) into horse stifle joints with meniscal tears diagnosed by arthroscopy. Subjects gained only intraarticular BMMSC injection and debridement. No surgical suture repair was practiced in addition to BMMSC injection treatment of the twenty-four horses, eighteen returned to work when documented with meniscal lesions (75%), and 9 horses resumed to prior levels of activity. Positive outcomes in BMMSC injections from this study was significant for the treatment of horses with meniscal lesions [38].

Abdel-Hamid, et al., in 2005 evaluated canine meniscus tears for the use of autologous BMMSCs. The team discovered improved responses to treatment in BMMSC subjects when looking at both the subjects and the controls. BMMSC subjects demonstrated a better histology with marked collagen deposition, proliferation, chondrogenesis, and angiogenesis. This research supported regenerating meniscus tissue while using BMMSCs. BMMSC could be used as mediator release signaling or BMMSC differentiation, a healing mechanism in an animal model [39].

These studies support the use MSCs in meniscal regeneration. Subjects displayed improved healing and histology, whether it was combined with the repair or not, when they were given a stem cell injection [2].

Tissue engineering

Techniques used in tissue engineering focused MSCs used in meniscus regeneration in combination with growth factors and engineered scaffolds in order to achieve better regenerative and repair quality tissue [2].

Zhang, et al., in 2009 investigated insulin resembling growth factor (hIGF-1) transfecting capacity of healing of BMMSCs. The team looked at the full thickness meniscal defect in a calcium alginate gel when delivered into 48 goats. Three control groups were included in this study: the alginate gel alone, the cells with no hIGF-1 transfection, and the cells without any form of treatment whatsoever. The group with the reparative tissue with margins that was difficult to describe from nearby neighboring tissue was the grouped repaired with hIGF-1. This group also showed higher glycosaminoglycan content, higher cell count, and increased cartilaginous tissue than control groups. This study supports the combination of MSCs with the *in vivo* application of growth factor (hIGF-

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1) to promote and enhance regeneration of the meniscus in an animal model [40].

Moriguchi, et al., in 2013 investigated the use of a naturally engineered tissue construct (TEC) comprised of high-density single layer culture of allogenic synovial mesenchymal stem cells in the presence of ascorbic acid in porcine models. In a porcine meniscus model cylindrical defects were created and repaired using TEC or they were left untreated for control. The implanted issues with TEC filled with repair tissue that was well integrated and controls remained partially filled or empty. Histological assessment of repair using revealed cartilage resembling cells that were expressive of the fibro-cartilaginous tissue. Chondral injury defect occurrence was significantly smaller in group with TEC compared to the control group 6 months after injury. TEC in this study was validated as an effective repair method for meniscal lesions with preventative effects from meniscal body deterioration and post traumatic arthritis development in an animal model utilizing an implant that was stem cell based [41].

Kondo, et al., in 2017 studied the repair of meniscal defects in a certain primate model through the use of autologous synovial mesenchymal stem cell aggregates. The team reported the closer to center meniscus in MSC repair group to have greater regeneration after eight and sixteen weeks. The meniscus that was regenerated was evaluated through MRI and was similar to meniscal tissue. The mesenchymal stem cells and control group both showed changes in OA and the MSC group that was treated showed greater scores. The regeneration potential of synovial mesenchymal stem cells was seen in an animal model was seen in this study [42].

Desando, et al., in 2016 used BMMSCs seeded with hyaluronic acid scaffold in meniscal defects in sheep. The BMMSC hyaluronic scaffold group showed positive proteoglycan content and increased repair with smooth restored surface. The hyaluronic group seeded with bone marrow was more chondroprotective compared to control group. Studies have shown meniscal repairs with BMMSCs could be effective and lessen the biochemical changes with the progression of OA in an animal model [43].

Stem cell injection

Human clinical studies evaluating effects of MSC injections in knee joints are emerging. Vangsness et al., in 2014 researched the effects of MSC injections post medial meniscectomy in a double-blind controlled study that was random. A percutaneous injection of allogeneic MSCs was administered to fifty-five human subjects that were divided into 3 groups. Group one received 50×10^6 cells, group 2 received 150×10^6 cells, and group 3 (control group) received only hyaluronic acid. There was a significant increase in the MRI scan results in meniscal volume in 24% of patients receiving 50×10^6 cells and 6% receiving 150×10^6 cells at 12 month follow up. For the control group, none of the patients demonstrated increased meniscal volume. After the treatment with allogenic human MSCs, an improvement in meniscal reconstruction and knee pain was reported. The use of human MSCs for knee tissue reconstruction and protective effects in human models proved to be successful following this study [44].

Pak, et al., in 2014 reported results of single patient with an isolated meniscus tear that received a guided ultrasound autologous stem

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cell with adipose (ASC) injection intraarticularly into the knee joint. The final injection mixture contained ASCs, calcium chloride, hyaluronic acid, and enriched plasma with platelets. The patient received later injections of dexamethasone, plasma enriched with platelets, and hyaluronic acid. The patient showed continued improvement in knee pain scores and function for 18 months after the follow up. The meniscal tear seemed to be back to normal after a 3-month MRI scan. This limited study supports the need for continued investigation into the use of ASCs for the treatment of meniscus tear injuries in human subjects [45].

Centeno, et al., in 2008 reported a single patient case that received intraarticular injection of BMMSCs expanded by the use of platelet lysate that was taken from patient's own blood. After MRI diagnosis of degenerative changes in medial femoral condyle and meniscus, the patient's knee was injected with BMMSCs after growth factors were increasing in present platelet lysate. The patient received 2 additional injections of 1mg/mL dexamethasone and platelet lysate. At the patient's 3-month post procedure follow up, the patient reported improved pain scores and MRI scans revealed evidence of increased meniscus volume. This limited study supports the need for continued investigation into the use of BMMSCs with platelet lysate for the treatment of meniscus tear injuries in human subjects [46].

Onoi, et al., in 2019 reported second look knee arthroscopy results for 2 patients that received regenerative cell injections derived from adipose. Arthroscopy was completed for only one of the treated patients. The patient had a partial meniscectomy in the posterior horn of the meniscus. At 6 months after the injection of adipose derived regenerative cells, a second look arthroscopy showed improved cartilage status and repair of the resected part of meniscus. Six months after the patient received adipose derived regenerative cell injections, the second look arthroscopy revealed almost all the cartilage defect areas were covered by regenerative cartilage and meniscus tear areas were repaired. This limited study supports the need for continued investigation into the use of regenerative cells from adipose for the resolution of meniscus tear injuries in human subjects [47].

Sekiya, et al., in 2019 investigated 5 patients how the effects of the increase of synovial MSCs on deteriorating medial meniscus lesions would look. Each patient underwent arthroscopy to confirm lesions, repair with stitches, and a biopsy on the synovia was performed. Synovial tissue cultures were increased for 14 days. Arthroscopy was performed again and synovial the cell suspension was transported to the repair site. By 2 years, patients reported improvement in their clinical score and results in their 3D MRI revealed no evidence of a tear at the site that was repaired. This limited study supports the need for continued investigation into the treatment of meniscus tear injuries in human subjects using mesenchymal stem cells [48].

Tissue engineering

Combining tissue engineering and mesenchymal stem cells is a growing field in clinicals. Additional studies are needed to focus on locating an answer for defects in the cartilage.

Whitehouse, et al., in 2017 reports cases for five patients with BMMSCs injected onto a collagen scaffold and sutured in a meniscal tear which is avascular. Beyond 12 months, 3/5 patients (60%) showed positive outcomes with substantially increased scores in clinicals. Scans with an MRI revealed original site repair along with a decrease in the scaffold's abnormal signal. There was a failure of treatment with two patients who had repeat tears at 15 months. Results of this study reported that collagen-scaffolds covered with mesenchymal stem cells can be safely added into patients with a torn avascular meniscus. This approach shows potential for improving some patient's reconstruction of damaged meniscus. This limited study supports the need for continued investigation into the use of BMMSCs combined with scaffolds of collagen for the treatment of meniscus tear injuries in human subjects [49].

Olivios-Meza, et al. in 2019 joined mesenchymal cells and polyurethane meniscal scaffold for meniscal repair. Seventeen people with past meniscectomies were divided amongst 2 groups: one with an acellular scaffold repair with MSCs. MSC production vitalized patients in the MSC group receiving filgrastim. CD90+ cells were gathered and cultured in the scaffold made of polyurethane. Arthroscopically, the scaffolds were then added into patients who received meniscectomy in the past. Significant radiological and clinical improvement was reported for both groups. There was no observed advantage in the protection of articular cartilage over acellular scaffolds when MSC were added. This limited study supports the need for continued investigation into the use of MSCs and polyurethane scaffolds for the treatment of meniscus tear injuries in human subjects [50].

Discussion

A promising and hopeful area of research within the medical field of musculoskeletal surgery is stem cell research. The most frequent cell types used in meniscal stem cell procedures include cells that are articular, meniscal cells, and mesenchymal stem cells (MSC). MSCs cells can multiply and change into cartilaginous cells with some of the extracellular matrix (ECM) found in the native meniscus. Cell source election can lead to positive outcomes in stem cell therapy. The most common sources for MSCs include bone marrow, adipose, synovium, and blood [2,51-55].

MSCs have demonstrated the largest number of similarities to the human meniscus with increased ECM depositions including collagen and glycosaminoglycans. Additionally, MSCs exhibit self-renewal capacity and multilineage change which can lead to regeneration. MSCs can re-establish homeostasis for joints and increase tissue repair through the process of secretion of anti-inflammatory factors and paracrine. MSCs from bone marrow are the most preferred main cell source of MSCs because they have an increased audiogenic, chondrogenic, and osteogenic potential and they can be made with ease and limited morbidity [2,6,52-54,56-58].

MSCs were found in synovial fluid after meniscus injury from knees. Synovial fluid with meniscus injury shows an increased number of MSCs compared to normal knees. The presence of Spontaneous meniscus healing is contributed to by the potential

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increase in MSC in synovial fluid following a meniscus injury [59].

Osawa and colleagues studied healing patterns for vascular regions of the meniscus. Surgical meniscus tear repairs in the vascular region typically heal better than surgical repairs performed in the avascular region. Osawa and colleagues hypothesized the vascular derived stem cells were richer in the vascular region compared to the avascular region. The peripheral region contained an increased number of CD146 and CD34 cells compared to the avascular region. They concluded that the avascular region had a decreased number of stem cells compared to the vascular region of the meniscus. Regeneration of the meniscus was contributed the these meniscal-derived stem cells [60].

A potential treatment of meniscal tears is a new approach known as tissue engineering . Stimulating the differentiation of cells into tissue that has phenotypical features similar to the original meniscus is a method for meniscal regeneration. This technology can be utilized for the reconstruction and repair of meniscal tears of a partial or complete meniscus following a subtotal, partial, or total meniscectomy [6,56].

Tissue self-assembly for the engineering of meniscus tissue was outlined by Makris and colleagues. Biologic tissue constructs were formed utilizing a hydrogel mold. In order to gain the large numbers needed for robust tissue engineering there is an expansion in an articular chondrocytes and meniscus cells. Cells are seeded in high density in a biomaterial mold, secreting ECM that coalesces into a continuous tissue. In order to increase neo tissues activity both synthetically and functionally exogenous stimuli are added during culture. This is eventually implanted *in vivo* [10].

Managing MSCs and growth factors for the purpose of meniscal TE are observed in two ways: intra-articular (IA) injections and seeding onto a scaffold or a meniscal construct made of biomaterial. IA injection's main purpose includes: morbidity has limited performance, ability to be repeated, and ability to prevent the systemic spreading of injected cells. For scaffolds, the most promising characteristics include: cell-instructive, architectural mimic of the native meniscus, multiplication and differentiation of the seeded cells, persistence to mechanical forces acting on the joint, allowing deposition of ECM, and the prevention of an immunogenic reaction using biocompatibility [6,56].

Conclusion

Current treatment options for orthopedic procedures including meniscus tear repair offer surgery as well as the use of MSC transplantation in both human and animal subjects. Meniscus tear surgeries may lead to extensive medical issues, unforeseen side effects, and extended rehabilitation time. Researchers have found MSC transplantation demonstrated increased functional and clinical outcomes in models of animals including: regeneration of meniscus, improved healing response, improved tensile strength, and improved level of function and activity level.

Human trials have shown increased meniscal volume, partial or completely healed meniscus tears, improved ROM, and improved function and activity levels. In order to understand the functional effects and outcomes of stem cell transplantation in human patients, additional research trials will need to be conducted.

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