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Mesenchymal stem cells for enhancing biological healing after meniscal injuries

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Abstract

The meniscus is a semilunar fibrocartilage structure that plays important roles in maintaining normal knee biomechanics and function. The roles of the meniscus, including load distribution, force transmission, shock absorption, joint stability, lubrication, and proprioception, have been well established. Injury to the meniscus can disrupt overall joint stability and cause various symptoms including pain, swelling, giving-way, and locking. Unless treated properly, it can lead to early degeneration of the knee joint. Because meniscal injuries remain a significant challenge due to its low intrinsic healing potential, most notably in avascular and aneural inner two-thirds of the area, more efficient repair methods are needed. Mesenchymal stem cells (MSCs) have been investigated for their therapeutic potential *in vitro* and *in vivo*. Thus far, the application of MSCs, including bone marrow-derived, synovium-derived, and adipose-derived MSCs, has shown promising results in preclinical studies in different animal models. These preclinical studies could be categorized into intra-articular injection and tissue-engineered construct application according to delivery method. Despite promising results in preclinical studies, there is still a lack of clinical evidence. This review describes the basic knowledge, current treatment, and recent studies regarding the application of MSCs in treating meniscal injuries. Future directions

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for MSC-based approaches to enhance meniscal healing are suggested.

Key Words: Meniscus; Meniscus healing; Cell-based treatment; Mesenchymal stem cell; Tissue engineering

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Core Tip: The meniscus is important for maintaining normal knee joint function and should be preserved as much as possible to avoid rapid degeneration of the knee joint. Because the intrinsic meniscal healing potential is limited, an efficient repair method is necessary. Mesenchymal stem cells (MSCs) have shown promising results in recent preclinical and clinical studies. Further investigations for safe and efficient cell sources and scaffolds are necessary to validate safety and efficacy of MSC-based approaches for enhanced meniscal healing.

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INTRODUCTION

The meniscus is an essential intra-articular structure of the knee joint. Meniscal injury can negatively affect the overall function of the knee joint, especially in young and physically active populations[1]. The incidence rate of meniscal injury ranges from 0.31 to 0.70 per 1000 person-years[2-4]. Meniscal disorders include a discoid meniscus in the pediatric population, traumatic injuries in athletes, and degenerative tears in older adults[1]. In the past, meniscal injuries were treated with surgical removal because the meniscus was once considered a functionless remnant tissue[5]. However, these techniques have been avoided because of the deterioration of articular cartilage and progression to early osteoarthritis (OA)[6]. The current meniscal injury management paradigm has shifted toward preserving as much of the native meniscus as possible[7].

Indeed, successful meniscus repair results in better long-term clinical and radiographic outcomes[8]. However, after repair, the recovery of the meniscus is inherently affected by its poor vascularity and lack of cellularity[9]; therefore, biological augmentation strategies are implemented to overcome such healing limitations[10]. Among various methods, mesenchymal stem cells (MSCs) have been extensively explored at the clinical, *in vitro*, and *in vivo* levels because of their extensive proliferative ability[11], migration to the site of injury[12], and reparative capacities[13]. The purpose of this article is to summarize current treatments for meniscal injury and their limitations and review recent preclinical and clinical studies using MSCs to enhance biological healing after meniscal injuries.

ROLE OF THE MENISCUS: WHY SHOULD WE PRESERVE THE MENISCUS?

The meniscus is a small intra-articular structure; however, it plays an essential role in maintaining knee-joint function. The roles of the meniscus, including load distribution, force transmission, shock absorption, joint stability, lubrication, and proprioception, have been well established[5]. Loss of the meniscus predisposes the knee joint to degenerative changes. Biomechanical studies have demonstrated that at least 50% of the compressive load of the knee joint is transmitted through the meniscus during knee extension and that approximately 85% of the compressive load is transmitted at 90° of knee flexion[14]. In the meniscectomized status, the contact area is reduced by approximately 75%, and the peak contact stress on the articular cartilage increased by

235% [15]. Finally, meniscectomized knees cause damage and degeneration of the cartilage and OA. It has been shown that the degree of OA following meniscectomy is directly proportional to the amount of removed meniscus [16]. In an experimental study, after removing 15% to 34% of the meniscus, the contact pressure increased by more than 350% [17]. Even in partial meniscectomy, knee biomechanics are remarkably disrupted with increased contact pressure on other soft tissue structures [18]. Therefore, the meniscus should be preserved as much as possible.

BASIC ANATOMY OF THE MENISCUS

The menisci are semilunar fibrocartilaginous structures divided into medial and lateral components situated between the tibial plateau and femoral condyle and attached to the tibial plateau by their anterior and posterior roots (Figure 1) [9]. Their wedge shape provides better articulation between the flat tibial plateau and the rounded femoral condyle and allows for stability and low contact pressure [19]. The menisci are further stabilized by the meniscal ligament complex composed of the medial collateral ligament, transverse meniscal ligament, meniscofemoral ligaments, and coronary ligaments [20].

The biochemical composition of the meniscus is 72% water, 22% collagen, 0.8% glycosaminoglycans (GAGs), and the remaining dry weight is composed of proteins, glycoproteins, and interspersed cells [19,21]. The meniscus cells are referred to as fibrochondrocytes because they appear to be a mixture of chondrocytes and fibroblasts [19]. The interaction of collagens, GAGs, and proteins contributes to the compressive load resistance, lubrication, and semi-elastic deformation functions of the meniscus [19,22].

Type I collagen comprises approximately 90% of the collagen expressed throughout the meniscus, while type II collagen is mostly found in the inner portion [9,23]. These two types of structural fibers are organized into three distinct layers from the surface to the core: superficial, lamellar, and deep [24]. Fibers in the superficial layer show random orientation, and while fibers in the lamellar layer also show no specific orientation, there are radially oriented fibers in the anterior and posterior sections. Circumferential fibers can be found in the outer and inner deep portions and convert the vertical axial load to horizontal tensile forces, dispersing it through the meniscus [25,26].

THE LIMITED HEALING POTENTIAL OF A TORN MENISCUS

The meniscus has limited intrinsic healing capacity, most notably in its avascular and aneural central (inner) two-thirds of the area. The perimeniscal capillary network originating in the capsular and synovial tissues provides a direct blood supply to the outer third of the meniscus [27]. The peripheral (outer) rim of the meniscus is described as a red-red vascular zone, while the inner central zone is known as a white-white avascular zone [9]. The healing potential of meniscal injury depends on the injury location, in which the red-red zone presents a better prognosis because of a direct blood supply, while the white-white zone has a poor prognosis for repair due to a lack of blood supply [28]. The intermediate zone, described as a red-white zone, receives some degree of blood supply and has a fair prognosis if the injury occurs at the border of vascular zone [28,29].

HOW TO EVALUATE THE MENISCUS HEALING

As the importance of meniscal preservation is strongly emphasized, various meniscus repair techniques have evolved and improved. To evaluate healing effects of these new techniques, they are generally first assessed in animal models. In a recent systematic review regarding animal model studies of meniscus repair and regeneration, Bansal *et al* [30] analyzed a total of 128 full-length peer-reviewed manuscripts. Authors demonstrated that most studies conducted histologic (90%), macroscopic (85%), and healing/integration (83%) analyses in terms of meniscal healing outcome parameters. In addition to these outcome measures, biochemical analysis, magnetic resonance imaging (MRI), assessment of vascularization, gene expression, immunohistochemistry, and arthroscopy were also performed to assess the

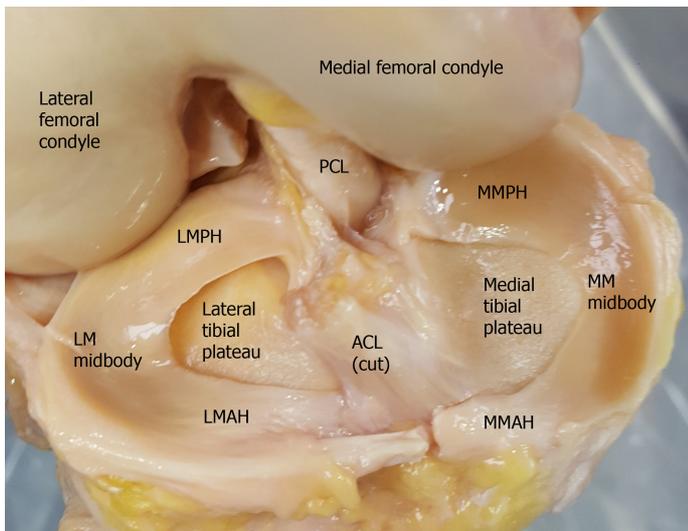


Figure 1 Anatomy of the meniscus in a cadaveric knee joint. ACL: Anterior cruciate ligament; MM: Medial meniscus; MMAH: Medial meniscus anterior horn; MMPH: Medial meniscus posterior horn; LM: Lateral meniscus; LMAH: Lateral meniscus anterior horn; LMPH: Lateral meniscus posterior horn; PCL: Posterior cruciate ligament.

meniscus healing. In clinical studies, there have been various subjective and objective evaluation methods for assessing the meniscus healing. In terms of subjective evaluation methods, some patients reported outcome measures (PROMs) are currently available to assess the function, symptoms and quality of life of patients with meniscal injuries[31,32]. These include the Hughston Clinic Questionnaire[33], International Knee Documentation Committee (IKDC) subjective knee form[34], Knee injury and Outcome Osteoarthritis Score (KOOS)[35], Lysholm Knee Scale[36], Western Ontario McMaster Osteoarthritis Index (WOMAC)[37], EuroQoL-5 dimension (EQ-5D)[38], Twenty-six-item Knee Quality of Life (KQoL-26)[39], Short Form-6 dimensions (SF-6D) [40], Western Ontario Meniscal Evaluation Tool (WOMET)[41], Tegner Activity Scale [42], Cincinnati Knee Score[43], Tapper and Hoover Meniscal Grading Score[44], Knee Outcome Survey-Activities of Daily Living Scale (KOS-ADLS)[45], Short Form-12 Item Health Survey (SF-12)[46]. Although there are many PROMs to assess meniscal injuries and healing, evidences for the validity of these PROMs are still insufficient[31]. In terms of objective evaluation methods, there are several methods to assess the meniscus healing. Although the most reliable examination tool is arthroscopy[47,48], it is an invasive method and still depends largely on the surgeons' skills[49]. As a non-invasive method, conventional MRI sequences have been widely used to assess meniscal injuries and healing. However, using conventional MRI, assessing meniscal tissue composition changes ahead of surface breakdown is challenging[50]. Recently, quantitative MRI techniques, such as T2 mapping, are used to assess the meniscus healing more effectively[50,51]. Some authors recommended magnetic resonance arthrography or computed tomography arthrography as an alternative objective evaluation method[52-55].

CURRENT TREATMENT FOR MENISCAL INJURIES

The role of nonoperative treatment for meniscal injuries has been well investigated in patients with degenerative tears. Herrlin *et al*[56,57] conducted a prospective randomized trial to compare partial meniscectomy with supervised exercise in middle-aged patients with non-traumatic medial meniscal tears. The two groups showed similar functional outcomes at six months, maintained throughout the 5-year follow-up period. Similar results were found in a large, multicenter, randomized controlled trial involving 351 patients over 45 years of age with a meniscal tear and evidence of OA. No significant differences were found between the partial meniscectomy and physical therapy groups in functional and pain improvement up to 1 year. It should be noted that 30% of the patients assigned to the physical therapy group underwent surgery within 6 mo, but their functional outcomes after 1 year were similar to those of patients who underwent surgery initially[58]. Another multicenter, randomized controlled trial involving 146 patients aged 35- to 65-years with a degenerative medial

meniscus tear and no OA found results consistent with those of previous studies. There were no significant differences in functional outcomes between the partial meniscectomy and sham surgery groups at 1 and 2 years[59,60]. These studies suggest that patients with degenerative tears can be treated conservatively, and if this conservative management fails, patients can undergo meniscectomy[29]. Unlike the role of non-operative treatment in degenerative tears, its role in acute tears in younger populations remains unclear[5,29].

Meniscectomy is a fast and effective method to relieve pain and joint swelling (Figure 2). In the past, the meniscus was once thought to be an unnecessary tissue that could be sacrificed without further consideration of any sign of injury[5]. However, cadaveric studies have decreased the intra-articular contact area and increased the peak contact pressure following total meniscectomy[14,61]. These findings were echoed by a clinical study that confirmed that increased pressure leads to radiographic evidence of OA[62]. The understanding of devastating biomechanical changes in the knee following total meniscectomy shifted the paradigm to retain as much meniscus as possible. In previous studies, partial meniscectomy, which focuses on removing the only torn piece of the meniscus while preserving as much normal meniscus, resulted in favorable outcomes[63,64] and more satisfactory outcomes than total meniscectomy [65]. Nonetheless, long-term studies have found that the amount of degenerative changes after partial meniscectomy is proportional to the amount of removed meniscus and that patients will eventually undergo accelerated degeneration[29,66]. Therefore, partial meniscectomy might be beneficial for short-term treatments but may cause long-term damage.

Due to the long-term adverse outcomes after meniscectomy, there has been an increasing tendency toward choosing meniscal repair[29]. Indeed, previous studies have shown that compared with partial meniscectomy, healed meniscal repair leads to better long-term outcomes[67,68]. Moreover, repair of vertical meniscal tears was protective against the progression of OA compared with partial meniscectomy[69]. However, the success of meniscal repair mainly depends on blood supply. Only injuries in the red-red or red-white zone are expected to be repaired, while healing of the inner white-white avascular zone is limited (Figure 3). Therefore, several methods such as fibrin clots and trephination have been used to improve meniscal repair outcomes in avascular zone tears. In a previous case-series study, exogenous fibrin clots were used to repair five cases of a tear involving the posterolateral aspect of the lateral meniscus[70]. All patients returned to the previous activity level with healing identified in the second-look arthroscopy. Trephination is the procedure of creating a channel from the vascularized zone to the tear and has shown favorable outcomes[71, 72].

When patients have irreparable meniscal tears or have already undergone total or partial meniscectomy, meniscal allograft transplantation (MAT) may be considered as an option to restore knee function[73,74]. Indications for MAT included patients younger than 50 years of age with a history of meniscectomy without articular cartilage damage, uncorrectable joint malalignment, or knee instability. Previous studies have reported survivorship as high as 89% at 10 years and functional improvements[74]. However, complications associated with MAT include graft failure, infection, extrusion, and the need for revision. Furthermore, it is challenging to resolve resources, shape matching, and ethical issues[75].

A CELL-BASED APPROACH FOR ENHANCED MENISCUS HEALING

The meniscus has a limited healing capacity, especially in the inner two-thirds avascular zone. To overcome the poor intrinsic healing capacity, cell-based and tissue engineering approaches have emerged as an alternative means for the regeneration of the injured meniscus[76,77]. Several preclinical studies have recently shown that cell-based regenerative treatment could be a good option[78-82].

Different types of cell sources have been investigated to enhance the biological healing of the meniscus. The meniscus contains distinct cell populations, such as fibrochondrocytes, fibroblast-like cells, and superficial zone cells. These meniscal cells can be isolated from the meniscus tissue and reinserted into the lesions. Although these cells have been studied *in vitro*[83-85], there is a lack of *in vivo* studies[77]. In recent years, the use of MSCs has dramatically increased in the regenerative treatment of musculoskeletal disorders. MSCs are pluripotent cells found in numerous human tissues, including bone marrow and adipose tissue, and have self-renewal capacity and can differentiate into multiple lineages[86]. In addition, owing to their specific

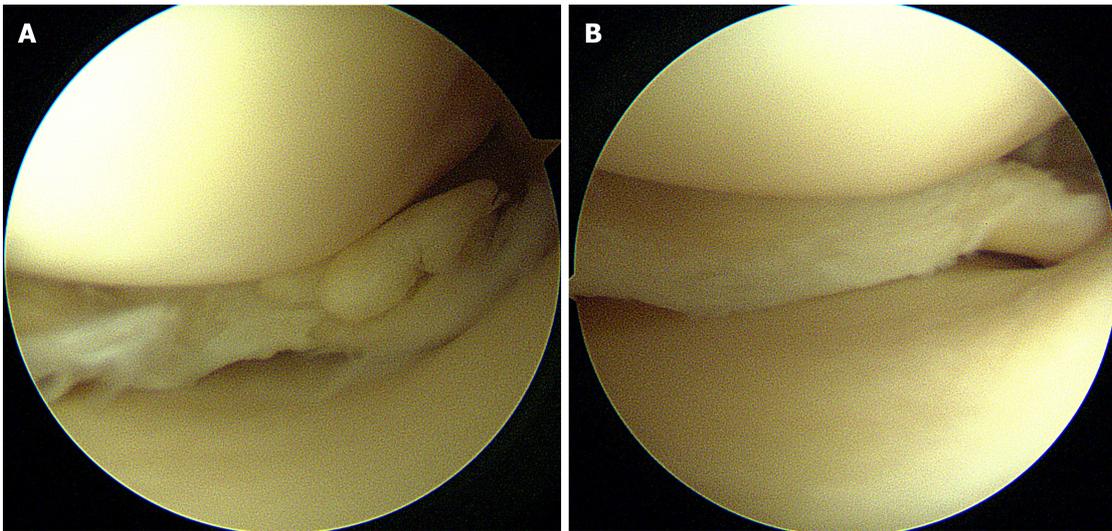


Figure 2 Arthroscopic images of partial meniscectomy. A: Degenerative complex tear of the medial meniscus posterior horn; B: Remnant meniscus after partial meniscectomy.

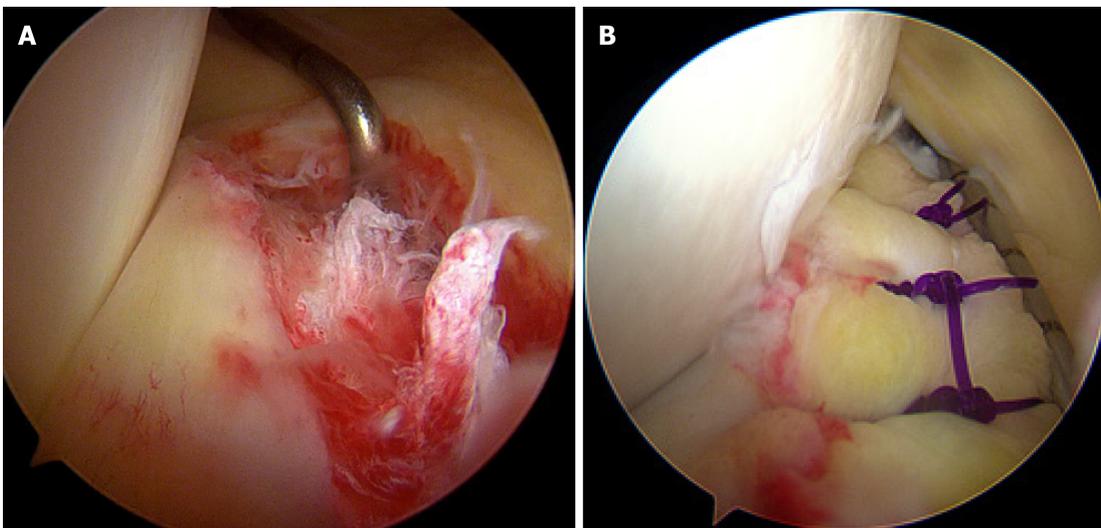


Figure 3 Arthroscopic images of meniscus repair. A: Longitudinal tear in red-red zone of the medial meniscus posterior horn; B: Meniscus repair using all-inside suture technique.

immunological properties, MSCs can be applied even in a non-autologous manner [87]. MSCs have received increasing interest as a potential biological approach for treating meniscal injuries. In a recent animal study comparing autologous MSCs and meniscus cells, Zellner *et al*[77] demonstrated that both MSCs and meniscal cells improved meniscal healing. However, donor-site morbidity, reduced availability, and reduced chondrogenic differentiation of meniscal cells favor MSCs for clinical use in cell-based meniscus regeneration[77].

APPLICATION OF MSCS IN BIOLOGICAL MENISCUS HEALING

The use of MSCs seems to be an attractive approach for meniscal healing, as these cells have high proliferative and chondrogenic potential. The precise roles and mechanisms of MSCs for enhanced meniscus healing are still unknown. Although there are some controversies, it is recently accepted that the therapeutic effects derived from MSCs in various musculoskeletal therapies are mainly due to their paracrine effects[88,89]. Various growth factors can be secreted by the paracrine functions of MSCs, which might lead to enhanced angiogenesis, cell differentiation and migration, and various additional regenerative effects[88,90,91]. Preclinical studies using MSCs have shown

promising results in regenerating meniscus tissue[77,81,82,92,93]. In addition to these direct MSC application studies, Driscoll *et al*[94] demonstrated that marrow stimulation by drilling on the femoral intercondylar notch apex led to modest improvements in the quality and quantity of reparative tissue bridging a meniscal defect in a rabbit model study. The authors reported an increased intra-articular population of pluripotent MSCs might stimulate meniscal healing and regeneration. However, clinical data regarding MSC application for meniscal lesions are still limited [95-99].

MSCs can be harvested and isolated from various sources. Among these MSC sources, bone marrow-derived MSCs (BM-MSCs)[77,96,100-102], synovium-derived MSCs (S-MSCs)[81,92,93,98,103], and adipose-derived MSCs (A-MSCs)[99,100,104-106] have been used to demonstrate promising results in meniscal healing. Currently, there is no consensus on which source is the best, because each has its own advantages and disadvantages.

BM-MSCs have been investigated and most commonly used for various mesenchymal tissue healing processes. BM-MSCs were first discovered by Friedenstein *et al*[107-109] in 1968 and have been widely used and investigated since then. Although it is clear that BM-MSCs are a very attractive cell source with high osteogenic, chondrogenic, and adipogenic potential, the procedure for harvesting BM-MSCs can be invasive and painful, yielding only a small amount as they only make up 0.0017% to 0.0201% of bone marrow cells. Furthermore, these cells have a propensity for hypertrophic differentiation, which may be detrimental to tissue regeneration[110-113].

S-MSCs are a relatively new source of MSCs compared with BM-MSCs. The number of S-MSCs is known to increase after meniscus injuries, and it has been suggested that this cell population might be crucial in meniscal repair[77,114,115]. S-MSCs are colony-forming cells isolated from the synovium of the knee during arthroscopy[116,117]. Some studies have indicated that S-MSCs might be better than BM-MSCs in terms of chondrogenic, osteogenic, and adipogenic capacities[118-121]. Nonetheless, the synovium contains only a few multipotent cells that form colonies[117,122]. In addition, in the long term, a high osteogenic capacity may induce joint diseases such as OA from stem cell-induced mineralization and calcification[6]. Therefore, long-term studies are needed to establish the efficacy of S-MSCs in meniscal healing.

A-MSCs are also a promising cell source for a biological meniscus healing strategy. A-MSCs are easier to produce *via* liposuction or adipose tissue biopsy and can be collected in larger quantities through less invasive methods than BM-MSCs[123-127]. A-MSCs have been shown to have low risk of rejection and to be more genetically stable[128-131]. The most accessible source for A-MSCs is subcutaneous fat tissue, but recently, several studies found supra- and infra-patellar fat pads to be suitable sources for A-MSC harvest[132-134]. Although these cells are derived from adipose tissue, they possess chondrogenic capacity. Nonetheless, A-MSCs have limited chondrogenic potentials compared with BM-MSCs[111,135] and inferior chondrogenic and osteogenic differentiation capacities compared with S-MSCs[118]. Furthermore, one study suggested that repetitive induction of A-MSCs might confer an elevated hypertrophic state with concurrent decreased chondrogenic potential which may be detrimental to meniscus repair[136].

In addition to BM-MSCs, S-MSCs, and A-MSCs, meniscal fibrochondrocytes (MFCs) and meniscus-derived MSCs (M-MSCs) have recently been used for biologic meniscus healing. MFCs were first described by Webber *et al*[137]. These cells have the unique properties of both fibroblasts and chondrocytes[138,139]. Previous studies suggested that the periphery of the meniscus, responsible for shock absorption, behaves more like fibroblasts, while the inner rim of the meniscus, acting as a direct contact point for the femoral condyle, resembles chondrocytes[139-141]. Therefore, MFCs and M-MSCs display different morphologies and biochemical properties depending on whether they are located at the periphery or inner zone[85,142,143]. MFCs and M-MSCs have been shown to exhibit multilineage differentiation and express common markers of MSCs[85]. However, there are several problems associated with applying autologous MFCs and M-MSCs for meniscal healing. First, these cell populations are scarce in the meniscus[85,144,145], and the procedure to harvest these cells is invasive and lengthy. Even worse, this procedure may inevitably injure a healthy meniscus[61,85,146].

INTRA-ARTICULAR INJECTION OF MSCS FOR MENISCUS HEALING

Intra-articular injection is a simple treatment for intra-articular pathologies that improves structure and function. Recently, there have been ongoing preclinical and

clinical trials regarding intra-articular or direct intralesional injection using different sources of MSCs (Table 1).

Animal studies

Rabbit model: Among various MSC sources, BM-MSCs have been the most frequently investigated for meniscal healing in various animal models. The first preclinical study using BM-MSCs was published in 1997[147]. Ishimura *et al*[147] evaluated the healing properties of a full-thickness defect in the avascular portion of the rabbit meniscus in the control group (C group), fibrin glue only group (F group), and fibrin glue-containing BM-MSCs group (M group). The authors demonstrated that the remaining defects in F and M groups were significantly less than those in the C group, and the histological study showed earlier mature healing of the meniscal defects in the M group than in the F group. Horie *et al*[148] used allogeneic S-MSCs in a rabbit model. The authors made a 1.5-mm diameter full-thickness cylindrical defect in the inner two-thirds of the anterior horn of the medial meniscus. Then, 2×10^6 S-MSCs in 50 mL of phosphate-buffered saline (PBS) solution were injected directly into the defect using a 27-gauge needle. The quantity of regenerated tissue in the treated group was greater at all time points, reaching statistical significance at 4 and 12 wk ($P < 0.05$). Tissue quality scores were also higher in the treated group at all endpoints, achieving statistical significance at 12 and 24 wk ($P = 0.008$ and 0.021 , respectively). Injected S-MSCs were identified in the regenerated tissue with differentiation into type I and II collagen-expressing cells for up to 24 wk. Hatsushika *et al*[149] reported relatively long-term results of intra-articular injection of S-MSCs in a rabbit massive meniscal defect model. After creating a large defect in the anterior half of the medial meniscus, 1×10^7 S-MSCs in 100 mL PBS solution were injected into the knee joint. The S-MSCs and control groups were compared macroscopically and histologically for up to 6 mo. The meniscus size in the treated group was larger than that in the control group at 1 and 3 mo. However, the difference in the size between the two groups was indistinct at 4 and 6 mo. The histological score was better in the treated group at 1, 3, 4, and 6 mo. Grossly, although the surface of the medial femoral condyle was fibrillated in the control group, it appeared nearly intact in the treated group at 6 mo. Histologically, articular cartilage and subchondral bone were better preserved in the treated group. Ruiz-Ibán *et al*[150] performed a preclinical study to determine whether A-MSCs affect the healing rate of meniscal lesions in the avascular zone in a rabbit model. In the treated group, the authors injected 1×10^5 allogeneic A-MSCs marked with bromodeoxyuridine in the lesion before suturing. After 12 wk, in group A (short lesion, acute repair), six of 12 A-MSC-treated menisci and none of 12 controls showed some healing ($P = 0.014$). In group B (short lesion, delayed repair), two of eight A-MSC-treated menisci and one of eight controls had some healing ($P = 0.5$). In group C (long lesion, acute repair), six of 12 A-MSC-treated menisci and none of 12 controls showed some healing ($p = 0.014$). In group D (long lesion, delayed repair), four of eight A-MSC-treated menisci and none of eight controls showed some healing ($P = 0.07$). Generally, the intralesional injection of A-MSCs enhanced the healing rate [odds ratio, 32 (range, 3.69 to 277); $P = 0.002$]. Histological analysis of the healed areas showed well-formed meniscal fibrocartilage with cells derived from A-MSCs. Qi *et al*[105] assessed the effect of targeted intra-articular injection of superparamagnetic iron oxide (SPIO)-labeled A-MSCs in a rabbit model of a massive meniscal defect. At 12 wk, clear hypointense artifacts caused by SPIO (+) cells in the meniscus were detected using MRI. Histological analysis revealed that the anterior portion of the medial meniscus was similar to that of the native tissue, with typical fibrochondrocytes surrounded by richer extracellular matrix in the SPIO (+) A-MSCs group. The collagen-rich matrix bridging the interface and the neo-meniscus integrated well with the host meniscus. Although degenerative changes occurred in all groups, intra-articular injection of A-MSCs alleviated these degenerative changes. Prussian blue staining showed that the injected A-MSCs were directly associated with tissue regeneration.

Rat model: Agung *et al*[151] investigated the mobilization of BM-MSCs into injured intra-articular tissues and their regeneration in a rat model study. BM-MSCs were obtained from green fluorescent protein (GFP) transgenic Sprague-Dawley (SD) rats and injected into normal SD rats with injured anterior cruciate ligament (ACL), medial meniscus, and femoral condyle cartilage. Four weeks after intra-articular injection, GFP (+) cells were identified only in the injured ACL in all eight knees in the 1×10^6 BM-MSC injection group. In the 1×10^7 BM-MSC injection group, GFP (+) cells were observed in the injured ACL of all eight knees and in the injured medial meniscus and articular cartilage in six of eight knees. In addition, extracellular matrix stained by toluidine blue was found around GFP (+) cells in the injured femoral condyle cartilage

Table 1 Summary of recent preclinical and clinical studies regarding intra-articular mesenchymal stem cell injection for meniscus healing

Ref.	Cell source	Preclinical/clinical	Model	Results
Ishimura <i>et al</i> [147], 1997	BM- MSCs	Preclinical	Rabbit	Meniscal defects in the fibrin glue group (F group) and fibrin glue with MSC group (M group) were significantly smaller than those in the controls. Histological study showed earlier healing in the M group than F group
Murphy <i>et al</i> [156], 2003	BM- MSCs	Preclinical	Goat	At 6 wk, marked regeneration was identified with implanted cells detected in the newly formed tissue in treated joints. Reduced cartilage degeneration, osteophytic remodeling, and subchondral sclerosis were found in the treated joints than the controls
Abdel-Hamid <i>et al</i> [157], 2005	BM- MSCs	Preclinical	Canine	After 12 wk, angiogenesis, chondrogenesis, immune cell infiltrate, and proliferation of the fibroblasts were significantly higher in the treated group
Agung <i>et al</i> [151], 2006	BM- MSCs	Preclinical	Rat	At 4 weeks, green fluorescent protein (GFP) (+) cells were identified in injured ACL in all 8 knees in the 1×10^6 MSC group. In the 1×10^7 MSC group, GFP (+) cells were observed in the injured ACL in all 8 knees and in the injured meniscus in 6 of 8 knees. Extracellular matrix stained by toluidine blue was visible around GFP (+) cells indicating tissue regeneration
Mizuno <i>et al</i> [152], 2008	S- MSCs	Preclinical	Rat	One day after injection, the meniscal defect was filled with the cells. The MSC group expressed type II collagen, exhibited characteristics of chondrocytes at 8 wk, and still observed at 12 wk. Histological score improved within 12 wk without statistical difference
Centeno <i>et al</i> [161], 2008	BM- MSCs	Clinical	Human	At 3 mo, MRI analysis demonstrated an increased meniscus volume. Modified VAS scores decreased from 3.33 to 0.13
Horie <i>et al</i> [153], 2009	S- MSCs	Preclinical	Rat	After 12 wk, regenerated menisci were LacZ (+), produced type II collagen, and showed meniscal features on electron microscopy. LacZ gene derived from MSCs was not detected in other distant organs
Dutton <i>et al</i> [154], 2010	BM- MSCs	Preclinical	Pig	At 8 wk, gross examination of group 1 (control) showed no healing. In group 2 (suture with fibrin glue), no healing was found in 12 knees and incomplete healing in 7 knees. Group 3 (suture with MSCs) had complete healing in 21 knees, incomplete healing in 5 knees, and no healing in 2 knees ($P < 0.001$). Biomechanical study showed a significant improvement in group 3 compared with group 1 and 2. Microscopic analysis showed fluorescence in group 3
Ruiz-Ibán <i>et al</i> [150], 2011	A- MSCs	Preclinical	Rabbit	At 12 wk, intralesional injection of A- MSCs increased the healing rate ($P = 0.002$). Histologic analysis showed well-formed meniscal fibrocartilage with cells derived from the MSCs
Al Faqeh <i>et al</i> [158], 2012	BM- MSCs	Preclinical	Sheep	At 6 wk, injection of BM- MSCs either chondrogenically induced or not, could retard the OA progression. The induced cells showed better meniscal regeneration
Horie <i>et al</i> [148], 2012	S- MSCs	Preclinical	Rabbit	Quantity of regenerated tissue in MSC group was greater at all time points, reaching significance at 4 and 12 weeks ($P < 0.05$). Tissue quality scores were superior in MSC group than controls at all end points, achieving significance at 12 and 24 wk. MSCs were observed in the regenerated tissue with differentiation up to 24 wk
Hatsushika <i>et al</i> [149], 2013	S- MSCs	Preclinical	Rabbit	Meniscus size in MSC group was larger than in control group at 1 and 3 mo. Histological score was better in MSC group up to 6 mo. The femoral condyle cartilage looked intact in MSC group at 6 mo. Histologically, cartilage and subchondral bone were better preserved in MSC group
Caminal <i>et al</i> [159], 2014	BM- MSCs	Preclinical	Sheep	At 12 mo, evidence of meniscus regeneration was case-dependent. However, statistically significant improvement was observed in specific macroscopic and histological parameters
Hatsushika <i>et al</i> [155], 2014	S- MSCs	Preclinical	Porcine	Meniscus regeneration was significantly better in MSC group on histological and MRI analyses up to 16 wk. Grossly, the meniscal defect was filled with synovial tissue at 2 wk. Articular cartilage and subchondral bone were also significantly better preserved in MSC group
Ferris <i>et al</i> [160], 2014	BM- MSCs	Preclinical	Horse	At 24 mo follow-up, 43% of horses returned to previous work level, 33% returned to work, and 24% failed to return. In horses with meniscal damage ($n = 24$) a higher percentage (75%) returned to some level of work compared with those in previous reports (63%) treated with arthroscopy alone ($P = 0.038$)
Pak <i>et al</i> [104], 2014	A- MSCs	Clinical	Human	At 3 mo, patient's symptoms improved and repeated MRI showed almost complete disappearance of the meniscal lesion. Until 18 mo, symptom improvement persisted without any serious side effects
Okuno <i>et al</i> [103], 2014	S- MSCs	Preclinical	Rat	At 4 wk, syngeneic and minor mismatched transplantation of MSCs promoted meniscus regeneration better than major mismatched transplantation
Vangsnæs <i>et al</i>	BM-	Clinical	Human	No important safety issues were identified. Significantly increased meniscal volume was

<i>al</i> [95], 2014	MSCs			determined by quantitative MRI in MSC group at 12 mo ($P = 0.022$). In patients with OA, MSC group experienced a significant reduction in pain than control group on the basis of VAS assessments
Nakagawa <i>et al</i> [92], 2015	S-MSCs	Preclinical	Microminipig	At 12 wk, meniscal healing was significantly better in MSC group macroscopically, histologically and by T1rho mapping analysis. Transmission electron microscopy showed the meniscus lesion occupied by dense collagen fibrils in MSC group. Biomechanical test revealed higher tensile strength in MSC group than in control group. Synovial tissue covered better the meniscus lesion in MSC group at 2 and 4 wk. Labeled MSCs were detected in the meniscus lesion by MRI at 2 wk
Qi <i>et al</i> [105], 2016	A-MSCs	Preclinical	Rabbit	At 12 wk, hypointense artifacts caused by SPIO (+) cells in the meniscus were detected by MRI. Histological analysis revealed that the healed meniscus was similar to native tissue in treated group. Collagen-rich matrix integrated well with its host meniscus. Although degenerative changes occurred in all groups, injection of MSCs alleviated these degenerative changes
Sekiya <i>et al</i> [98], 2019	S-MSCs	Clinical	Human	Lysholm knee scores were significantly higher at 1 yr than before the treatment, and maintained at 2 yr. KOOS for daily living pain, and sports and recreational activities increased significantly at 2 yr. NRS scores continually increased and showed significant improvement at 2 yr, 3D MRI showed indistinguishable healing at the meniscal lesion
Onoi <i>et al</i> [99], 2019	A-MSCs	Clinical	Human	No serious adverse events were reported during 6-mo follow-up. Pain and function were significantly improved in treated knees up to 6 mo. At 6 mo, second-look arthroscopy showed repaired meniscus
Ozeki <i>et al</i> [81], 2021	S-MSCs	Preclinical	Microminipig	Proteoglycan content stained with safranin-o disappeared 1 wk after treatment in both MSC and control groups, but increased at 8 wk only in MSC group. At 8 wk, histological scores were significantly higher and T2 values were significantly closer to those of normal meniscus in MSC group

BM-MSCs: Bone marrow-derived mesenchymal stem cells; MSC: Mesenchymal stem cell; GFP: Green fluorescent protein; ACL: Anterior cruciate ligament; S-MSCs: Synovium-derived mesenchymal stem cells; MRI: Magnetic resonance imaging; VAS: Visual analog scale; A-MSCs: Adipose-derived mesenchymal stem cells; OA: Osteoarthritis; SPIO: Superparamagnetic iron oxide; KOOS: Knee injury and outcome osteoarthritis score; NRS: Numerical rating scale.

and medial meniscus, indicating tissue regeneration. The authors concluded that injected BM-MSCs could mobilize into injured intra-articular tissues, and might contribute to tissue regeneration. In 2008, Mizuno *et al*[152] first reported intra-articular injection of S-MSCs in an animal model. Authors injected 10^5 , 10^6 , or 10^7 GFP (+) S-MSCs into the knee joint after creating a defect in the anterior horn of the medial meniscus in a rat model. One day after injection, green fluorescence was not detected in the 10^5 MSC group. In the 10^6 MSC-injected group, only very faint fluorescence was visible. However, GFP fluorescence was visible in the 10^7 MSC-injected group. Therefore, the authors analyzed the data obtained from 10^7 MSC-injected rats. At 8 wk, the meniscal defect was filled with cartilage matrix in both the treated and control groups. Injected GFP (+) cells still existed in the meniscal defect, producing type II collagen, although its expression was lower than that in the native meniscus. Electron microscopy showed several short processes with lacunae, characteristic of chondrocytes. At 12 wk, the chondrocytes matured morphologically in both groups. The authors concluded that the injected S-MSCs adhered to the meniscal defect and survived to differentiate into cartilage cells. Horie *et al*[153] investigated whether intra-articular injection of S-MSCs enhanced meniscal regeneration in a massive meniscal defect in a rat model. After creating a meniscal defect, 5×10^6 Luc/LacZ (+) S-MSCs were injected into the knee joint. Two to eight weeks after Luc/LacZ (+) S-MSC injection, macroscopic meniscal regeneration was much better in the treated group than in the control group. After 12 wk, the regenerated menisci were LacZ (+), producing type II collagen, and the characteristic meniscal features were identified by transmission electron microscopy. The LacZ gene derived from S-MSCs could not be detected in other distant organs by real-time PCR. Okuno *et al*[103] compared the effect of syngeneic and allogeneic transplantation of S-MSCs for meniscal regeneration in a rat model to identify the influence of allogeneic transplantation of S-MSCs. After removal of the anterior half of the medial meniscus in the knees of F344 rats, 5×10^6 S-MSCs derived from F344 (syngeneic transplantation), Lewis (minor mismatched transplantation), and ACI (major mismatched transplantation) were injected into the knee joints of F344 rats. Four weeks after intra-articular injection of S-MSCs, the regeneration area was significantly larger in the F344 group than in the ACI group. At 8 wk, histological assessment using the modified Pauli's score showed significantly better scores in the F344 and Lewis groups than in the ACI group. DiI-labeled cells were observed in the F344 group; however, they were hardly identified in the ACI

group after 1 wk. The immunological analysis showed that the number of ED1 (+) macrophages and CD8 T cells in the synovium around the meniscal defect was significantly lower in the F344 group than in the ACI group at 1 wk. Therefore, the authors concluded that syngeneic and minor mismatched transplantation of S-MSCs induced better regeneration of the meniscus defect than major mismatched transplantation.

Porcine model: Dutton *et al*[154] applied BM-MSCs together with a conventional suturing technique to assess improved healing in meniscal tear site in a porcine model. In their study using 28 adult pigs (56 knees), group 1 (nine knees) had a radial meniscal tear left untreated. In group 2 (19 knees), the tear was repaired with sutures and fibrin glue, and in group 3 (experimental group, 28 knees), the tear was treated by suturing with an injection of fibrin glue containing at least 2×10^6 autologous BM-MSCs. At 8 wk, macroscopic examination showed no healing in any of the specimens in group 1. In group 2, no healing was found in 12 knees, and incomplete healing was observed in seven knees. Group 3 showed complete healing in 21 knees, incomplete healing in five knees, and no healing in two knees ($P < 0.001$). A biomechanical study using the mean modulus of elasticity showed that there was a significant improvement in Group 3 compared with Group 1 ($P < 0.001$) and Group 2 ($P < 0.002$). In the microscopic analysis, although fluorescence was absent from group 2, fluorescence was observed in group 3. The authors concluded that avascular meniscal tears treated with autologous BM-MSCs could achieve good macroscopic healing with the formation of fibrocartilage-like tissue and improved biomechanical properties. Following a rabbit model study[149], Hatsushika *et al*[155] attempted repetitive allogeneic S-MSC injection in a porcine model. After creating a large defect in the anterior half of the medial meniscus, 5×10^7 allogeneic S-MSCs were injected into the knee joint at 0, 2, and 4 wk. Then, the authors evaluated the regenerated meniscus, adjacent articular cartilage, and subchondral bone using sequential MRI at 2, 4, 8, 12, and 16 wk. They were also assessed histologically and macroscopically at 16 wk. Based on histological and MRI analyses, meniscus regeneration was significantly better in the treated group than in the control group. The modified Pauli's histological score was significantly better in the treated group. Sequential MRI analysis showed that the resected area appeared less disorganized in the MSC group than in the control group at 8, 12, and 16 wk. In addition, quantification analyses demonstrated that the T2 value in the regenerative meniscus was significantly lower in the treated group for up to 16 wk. Grossly, the meniscal defect appeared to be filled with synovial tissue at 2 wk. Articular cartilage and subchondral bone at the medial femoral condyle were also significantly better preserved in the treated group based on macroscopic, histological, and MRI analyses. The intra-articular S-MSC injection effects were also investigated in a microminipig model by Nakagawa *et al*[92] and Ozeki *et al*[81]. Nakagawa *et al*[92] examined whether transplantation of S-MSCs promoted healing after meniscal repair in a pig model. After making a full-thickness longitudinal tear in the junction between the internal third and middle third of the meniscus in the avascular area, 2×10^7 S-MSCs were injected after meniscal repair in the treated group. At 12 wk, the meniscal healing was significantly better in the treated group than in the control group macroscopically, histologically, and by T1rho mapping analysis. Transmission electron microscopic analysis showed that dense collagen fibrils occupied the meniscus lesion only in the treated group. The tensile strength to failure was higher in the treated group than in the control group. At 2 and 4 wk, the synovial tissue covered the superficial layer from the outer zone into the meniscal lesion in the treated group. S-MSCs labeled with ferucarbotran were detected in the meniscus lesion and surrounding synovium by MRI at 2 wk. Recently, Ozeki *et al*[81] injected allogeneic S-MSCs at the injured site of the medial meniscus posterior horn after puncturing 200 times with a 23G needle. Proteoglycan content stained with safranin-O disappeared 1 wk after treatment in both the treated and control groups, but increased at 8 wk in the treated group. At 8 wk, histological scores were significantly higher in the treated group, and the T2 values were significantly closer to those of the healthy meniscus.

Goat model: Murphy *et al*[156] explored the role of BM-MSCs in tissue repair or regeneration of the OA-induced knee in a goat model. The authors injected 10×10^6 autologous BM-MSCs suspended in a dilute solution of sodium hyaluronan directly into the injured knee. At 6 wk following intra-articular MSC injection, marked regeneration of the meniscus was identified with implanted cells detected in the newly formed tissue of the treated group. Reduced cartilage degeneration, osteophytic remodeling, and subchondral sclerosis were found in the treated group (sodium hyaluronan only group). The authors concluded that intra-articular injection of BM-

MSCs stimulated regeneration of the meniscal tissue and retarded the progressive destruction of the OA joint.

Canine model: Abdel-Hamid *et al*[157] attempted autologous BM-MSCs in a canine model study. The authors evaluated the healing process both clinically and histologically. At 12 wk, the MSC-treated menisci showed significantly enhanced angiogenesis, chondrogenesis, immune cell infiltration, and proliferation of fibroblasts with marked deposition of collagen fibers compared with the non-treated group.

Sheep model: Al Faqeh *et al*[158] performed a sheep model study to determine whether intra-articular injection of autologous chondrogenic-induced BM-MSCs could retard the progressive destruction of surgically induced OA knees. At 6 wk after intra-articular injection, although undifferentiated BM-MSCs and control groups showed damage and absence of a meniscus, the chondrogenic-induced BM-MSC group showed the appearance of meniscal-like tissue formation at the injured meniscus. In a study by Caminal *et al*[159], a meniscal tear was created arthroscopically in the anterior horn of the medial meniscus. The animals were monitored by MRI and ultrasound, and macroscopic and histological analyses were conducted at 6 and 12 mo. Twelve months after injection, four out of the eight medial menisci treated with BM-MSCs presented healthy tissue features. However, the rest of the menisci showed some areas of erosion on the inner edge of the femoral side.

Horse model: Ferris *et al*[160] reported clinical outcomes after intra-articular injection of BM-MSCs in a horse model. At a mean 24 mo follow-up after intra-articular administration of autologous BM-MSCs, 43% of the enrolled horses returned to the previous level of work, 33% returned to work, and 24% failed to return to work. In horses with meniscal injury, a higher percentage (75%) returned to some level of work than those in previous reports (60%-63%) that were treated with arthroscopy alone ($P = 0.038$).

Human studies

BM-MSCs: As mentioned above, there have been promising preclinical results in intra-articular injection using various sources of MSCs over the past 20 years. Based on these successful preclinical results, though a limited number of studies, there have been clinical trials regarding the effects of intra-articular injection of MSCs for meniscal healing[95,98,99,104,161]. In 2008, Centeno *et al*[161] first reported intra-articular injection of BM-MSCs in a 36-year-old man. After 3 mo, MRI showed increased meniscus volume. The modified visual analog scale (VAS) scores decreased from 3.33 to 0.13. In 2014, Vangsness *et al*[95] reported a randomized, double-blind, controlled study. The authors examined the effect of a single intra-articular injection of BM-MSCs following partial meniscectomy. After partial meniscectomy, a single intra-articular injection of allogeneic BM-MSCs was administered. Patients were randomized into one of the three groups. In group A, patients received an injection of 50×10^6 allogeneic BM-MSCs. In group B, 15×10^7 allogeneic BM-MSCs were administered. Group C was the control group with only sodium hyaluronate (hyaluronic acid, hyaluronan). After treatment, no ectopic tissue formation was observed in the blinded MRI evaluation. After 1 year, a significant meniscal volume increase (defined as a 15% increase in meniscal volume) was determined by quantitative MRI in 24% of patients in group A and 6% in group B ($P = 0.022$), and the overall group comparison was significant at 2 years ($P = 0.029$). Based on VAS assessment, among patients with OA at the time of surgery, a significant improvement was observed in the BM-MSC groups compared with the control group up to 2 years.

S-MSCs: Sekiya *et al*[98] examined the effects of intra-articular S-MSC injection after repairing the degenerative tears of the medial meniscus in five patients. No major adverse events leading to the study termination were identified. Lysholm scores were significantly higher at 1 year than before MSC treatment and were maintained at 2 years. KOOS scores for "daily living," "pain", and "sports and recreational activities" improved significantly at 2 years. The numerical rating scale (NRS) scores continually increased and showed significant improvement at 2 years. Three-dimensional MRI showed indistinguishable healing at the meniscal lesion at 2 years.

A-MSCs: In 2014, Pak *et al*[104] reported a case report of intra-articular injection of autologous A-MSCs in a 32-year-old woman. Three months after injection, the patient's symptoms improved, and repeated MRI showed almost complete disappearance of the meniscus lesion. After 18 mo, her symptom improvement

persisted without any serious side effects. Onoi *et al*[99] reported second-look arthroscopic findings in two cases of knee OA treated using an intra-articular injection of A-MSCs. The authors performed a second-look arthroscopy 6 mo after a single intra-articular injection of A-MSCs. During the 6-month follow-up, no serious adverse events were reported. Pain and function assessed by VAS and KOOS were significantly improved from baseline in the treated knees at 1, 3, and 6 mo. The second-look arthroscopy showed that almost all the cartilage defect areas were covered with regenerated cartilage, and the degenerative meniscal tear areas were repaired.

TISSUE ENGINEERING USING MSCS FOR MENISCUS HEALING

Tissue engineering is a promising approach for the treatment of various tissue defects. MSCs can be used as a source of repair cells or essential growth factors for tissue engineering. In the past 20 years, there have been several preclinical and clinical trials using various MSCs for meniscal healing (Table 2). Although one study did not show any significant differences between the control and MSC-treated groups[162], other studies have generally shown promising results.

Animal studies

Rabbit model: BM-MSCs are the most frequently used in preclinical studies. In 1999, Walsh *et al*[163] reported a preclinical study on applying a type I collagen scaffold containing BM-MSCs for meniscal defects in a rabbit model. After partial meniscectomy, the meniscal defect was left untreated (group 1) or treated with one of the following: a periosteal autograft (group 2), a type I collagen sponge (group 3), or the same sponge loaded with autologous BM-MSCs (group 4). In group 4, the regenerated tissue was more abundant at each time point than the other groups. Grossly, the transition zone was smooth and healed well. The regenerated meniscus established normal-appearing tissue connecting to the peripheral capsular attachments. At 24 wk, a predominant meniscus-like tissue with fibrochondrocytes was identified with mature collagen bundles and proteoglycan staining with safranin O-fast green. However, OA changes were observed in Group 4. Angele *et al*[18] tested a BM-MSC-loaded composite scaffold composed of 70% completely derivatized hyaluronan-ester and 30% gelatin for meniscal defects in a rabbit model. At 12 wk, the untreated defects showed a muted fibrous healing. Defects treated with cell-free scaffolds also showed predominantly fibrous tissue. The cross-sectional width of the repair tissue after treatment with cell-free scaffolds was significantly greater than that of the controls ($P < 0.05$). BM-MSC-loaded scaffolds integrated well with the host tissue, and eight of 11 contained meniscus-like fibrocartilage, compared with two of 11 in controls ($P < 0.03$). The mean cross-sectional width of the BM-MSC-loaded scaffolds group was greater than that of the control group ($P < 0.004$). Zellner *et al*[164] applied BM-MSCs in sponge scaffolds manufactured from 70% derivatized hyaluronan-ester and 30% gelatin for circular meniscus punch defects (2 mm) in a rabbit model. After 12 wk, untreated defects and defects treated with cell-free scaffolds exhibited muted fibrous healing responses. The implantation of precultured chondrogenic MSC constructs showed fibrocartilage-like repair tissue, which was only partially integrated with the native meniscus. Non-precultured MSCs in hyaluronan-collagen composite scaffolds showed the development of completely integrated meniscus-like repair tissue with significant differences compared with cell-free scaffolds ($P = 0.005$). Hong *et al* [162] investigated the biological healing responses after application of human BM-MSCs in a matrix gel scaffold for complete radial tear of the anterior horn of the medial meniscus in a rabbit model. However, after 8 wk, enhanced healing was not observed in the treatment group. There was no significant difference in the pathological criteria between the treated and control groups. Zellner *et al*[78] applied BM-MSCs in sponge scaffolds manufactured from 70% derivatized hyaluronan-ester and 30% gelatin for 4-mm longitudinal meniscal tears in the avascular zone of the lateral menisci in a rabbit model. At 12 wk, untreated defects, defects treated with suturing alone, with cell-free, or with platelet-rich plasma seeded scaffolds showed a muted fibrous healing. The MSC groups showed fibrocartilage-like repair tissue, and better integration and biomechanical properties were identified, especially in the precultured MSC-treated group. Zellner *et al*[77] compared the regeneration capacity of BM-MSCs seeded in a hyaluronan collagen composite matrix with autologous meniscal cells in a rabbit model. At 3 mo, the MSC group showed meniscal defects

Table 2 Summary of recent preclinical and clinical studies regarding tissue engineering using mesenchymal stem cells for meniscus healing

Ref.	Cell source	Preclinical/clinical	Model	Results
Walsh <i>et al</i> [163], 1999	BM-MSCs (type I collagen scaffold)	Preclinical	Rabbit	Meniscal defect was left untreated (group 1) or treated with periosteal autograft (group 2), a type I collagen sponge (group 3), or the sponge loaded with MSCs (group 4). In group 4, regenerated tissue was the most abundant. Grossly, transition zone was well healed. Regenerated meniscus established normal appearing tissue. At 24 wk, meniscus-like tissue was predominantly identified with proteoglycan staining on safranin O-fast green
Angele <i>et al</i> [18], 2008	BM-MSCs (composite scaffold composed of 70% completely derivatized hyaluronan-ester and 30% gelatin)	Preclinical	Rabbit	After 12 wk, pre-cultured implants integrated with the host tissue. 8 of 11 had meniscus-like fibrocartilage, compared with 2 of 11 in controls ($P < 0.03$). Cross-sectional width of the pre-cultured implant repair tissue was greater than controls ($P < 0.004$)
Zhang <i>et al</i> [166], 2009	BM-MSCs (transfection of human <i>hIGF-1</i> gene combined with injectable calcium alginate gel)	Preclinical	Goat	At 16 wk, in treated group, meniscal defects were filled with regenerated tissue similar to normal meniscal fibrocartilage. Repair tissue was composed of cells embedded within fiber matrix. The proteoglycan content in treated group was higher than those in control groups
Zellner <i>et al</i> [164], 2010	BM-MSCs (sponge scaffold manufactured from 70% derivatized hyaluronan-ester and 30% gelatin)	Preclinical	Rabbit	At 12 wk, implantation of precultured chondrogenic MSC constructs showed fibrocartilage-like repair tissue with only partial integration with native meniscus. Non-precultured MSC group showed development of completely integrated meniscus-like tissue
Hong <i>et al</i> [164], 2011	BM-MSCs (matrix gel scaffold)	Preclinical	Rabbit	At 8 wk, no groups showed the healing response. There was no significant difference in the pathological criteria between treated and control groups
Moriguchi <i>et al</i> [167], 2013	S-MSCs [scaffold-free tissue engineered construct (TEC)]	Preclinical	Miniature pig	At 6 mo, MSC group showed tissue repair with fibro-cartilaginous tissue and good integration. The ratio of Safranin O positive area was significantly higher in treated group than in control group ($P = 0.03$). The treated group showed significantly reduced chondral lesions ($P = 0.016$) and better ICRS scores ($P = 0.008$)
Zellner <i>et al</i> [78], 2013	BM-MSCs (sponge scaffold manufactured from 70% completely derivatized hyaluronan-ester and 30% gelatin)	Preclinical	Rabbit	At 12 wk, the MSC groups showed fibrocartilage-like repair tissue, and better integration and biomechanical properties were identified especially in the precultured-MSC applied group
Katagiri <i>et al</i> [169], 2013	S-MSCs (aggregate of S-MSCs)	Preclinical	Rat	At 4 wk, the regenerated meniscus was larger and histological findings were closer to the normal meniscus in MSC-aggregate groups than in MSC-suspension group. The effects of MSC-aggregate were still observed at 12 wk. Luminescence intensity remained higher after 3 wk in the MSC-aggregate group
Desando <i>et al</i> [82], 2016	BM-MSCs and bone marrow concentrate (BMC) (hyaluronan-based biodegradable polymer)	Preclinical	Sheep	At 12 wk, BMC group showed a better repair ability in inhibiting OA progression than BM-MSC group. In addition, the BMC group showed the best results in meniscus regeneration
Qi <i>et al</i> [168], 2016	BM-MSCs (transplantation of MSCs sheet)	Preclinical	Rat	At 8 wk, histological analysis revealed that healed meniscus was similar to native tissue in the treated group. Furthermore, predominant collagen-rich matrix bridging the interface was identified and the regenerated meniscus integrated well with surrounding host meniscus
González-Fernández <i>et al</i> [100], 2016	BM-MSCs or A-MSCs (collagen repair patch)	Preclinical	Horse	At 1 yr, the control group had full-thickness defects. Defects remained in only 1 of the 6 menisci in MSC groups without any differences between A-MSC and BM-MSC groups. Histologically, quantity of regenerated meniscal tissue was better in MSC groups than in controls ($P < 0.001$)
Moradi <i>et al</i> [165], 2017	A-MSCs and articular chondrocyte (AC) (Polyvinyl alcohol/Chitosan (PVA/Ch) scaffold)	Preclinical	Rabbit	At 7 mo, macroscopic and histologic studies revealed better results in AC/scaffold group followed by AC-A-MSC (co-culture)/scaffold and A-MSC/scaffold groups. Articular cartilages were best preserved in AC/scaffold group. Highest histologic scores were identified in the AC/scaffold group
Kondo <i>et al</i> [93], 2017	S-MSCs (aggregate of S-MSCs)	Preclinical	Monkey	The meniscus was larger and the modified Pauli's histological score was better in treated group at 8 and 16 wk. At 16 wk, Mankin's score for medial femoral condyle cartilage was better in treated group. T1rho values for regenerated meniscus was closer to the normal meniscus in treated group
Zellner <i>et al</i> [77], 2017	BM-MSCs (hyaluronan collagen composite matrix)	Preclinical	Rabbit	At 3 mo, MSC group showed meniscal defects completely filled with dense repair tissue. Histologically, regenerated tissue was meniscus-

				like with typical pericellular meniscal cavities and extensive extracellular matrix. Immunostaining for type II collagen was moderately positive. The repaired tissue showed typically radially orientated collagen fibers. MSC group had significantly increased type II collagen gene expression and production ($P < 0.05$)
Whitehouse <i>et al</i> [96], 2017	BM-MSCs (collagen scaffolds)	Clinical	Human	Five patients were treated and there was significant clinical improvement in 3 patients. The 3 patients were asymptomatic at 24 mo without re-tear in MRI. Two required subsequent meniscectomies at 15 mo
Toratani <i>et al</i> [106], 2017	A-MSCs (high-density MSC scaffold-free allograft constructs (HDMACs))	Preclinical	Rabbit	Grossly, tissue healing was significantly greater in treated group at 2, 4, and 8 wk ($P = 0.01$). Safranin-O staining was positive at 2 wk and increased gradually over time in treated group. Histological scores were significantly higher in treated group at all weeks ($P < 0.05$)
Koch <i>et al</i> [102], 2018	BM-MSCs (polyurethane scaffolds)	Preclinical	Rabbit	At 12 wk, in both cell-free and MSC groups showed well-integrated and stable meniscus-like repair tissue. But, accelerated healing was notice in MSC group
Olivos-Meza <i>et al</i> [97], 2019	Peripheral blood MSCs (polyurethane scaffolds)	Clinical	Human	In tibial T2 mapping, values in MSC group increased slightly at 9 mo but returned to initial values at 12 mo. In control group, decrease from 3 mo to 12 mo was observed. This difference tended to be lower in control group compared with MSC group at 1 yr ($P = 0.18$). In the femur, a slight increase in MSC group compared with control group was observed ($P > 0.05$)

BM-MSCs: Bone marrow-derived mesenchymal stem cells; MSC: Mesenchymal stem cell; S-MSCs: Synovium-derived mesenchymal stem cells; ICRS: International Cartilage Repair Society; A-MSCs: Adipose-derived mesenchymal stem cells; OA: Osteoarthritis; MRI: Magnetic resonance imaging.

completely filled with dense repair tissue with stable integration to the native meniscus. Histologically, the regenerated tissue was meniscus-like with a low cell density but typical pericellular meniscal cavities and an extensive extracellular matrix. Immunostaining for type II collagen was moderately positive. The architecture of the repaired meniscus typically showed radially oriented collagen fibers. The meniscal scoring system showed no statistically significant difference between the meniscal cell and MSC groups at 6 wk or 3 mo. However, the MSC group had significantly increased type II collagen gene expression and production compared with the meniscal cells group ($P < 0.05$). Furthermore, macroscopic joint assessment demonstrated donor-site morbidity during meniscal cell treatment. Koch *et al* [102] applied a polyurethane scaffold loaded with BM-MSCs to repair critical meniscus defects (7-mm broad lesions) in the avascular zone in a rabbit model. At 12 wk, both the cell-free and MSC-loaded groups showed well-integrated and stable meniscus-like repair tissue. However, accelerated healing was observed in the MSC group. Both groups showed dense vascularization throughout the repaired tissue. Moradi *et al* [165] evaluated the effects of polyvinyl alcohol/chitosan (PVA/Ch) scaffolds seeded with A-MSCs and articular chondrocytes (AC) on meniscus regeneration. At 7 mo, macroscopic, histologic, and immunofluorescent studies revealed better results in the AC/scaffold group followed by the AC-A-MSC (co-culture)/scaffold and A-MSCs/scaffold groups. In the control (cell-free scaffold) group, no apparent meniscal regeneration was observed. Articular cartilage was also best preserved in the AC/scaffold group. Modifying Pauli's scoring system showed the highest score (15 points) in the AC/scaffold group. Toratani *et al* [106] implanted scaffold-free 3-dimensional allogeneic A-MSC constructs for meniscal defects in a rabbit model. Macroscopically, the height of the healing tissue was significantly greater in the treated group than in the control group at 2 wk ($P = 0.01$), 4 wk ($P = 0.01$), and 8 wk ($P = 0.02$). Histologically, safranin-O staining was positive at 2 wk and increased gradually over time in the treated group. Histological tissue quality scores were significantly higher in the treated group than in the control group at all weeks ($P < 0.05$).

Goat model: Zhang *et al* [166] investigated whether BM-MSCs transfected with the human insulin-like growth factor 1 (*hIGF-1*) gene combined with injectable calcium alginate gel improved the repair of full-thickness meniscal defects in a goat model. At 16 wk, the meniscal defects in the treated group were filled with regenerated tissue, similar to that in normal meniscal fibrocartilage. The repaired tissue was composed of cells embedded within the fiber matrix. The proteoglycan content in the treated group was higher than that in the control group, and less than that in the normal meniscus.

Sheep model: Desando *et al* [82] investigated the regenerative potential of bone

marrow concentrate (BMC) and BM-MSCs engineered with a hyaluronan-based biodegradable polymer (Hyaff-11) for OA knees in a sheep model. At 12 wk, the BMC group showed a better repair ability in inhibiting OA progression than the BM-MSCs group, with a reduction in inflammation in the cartilage, meniscus, and synovium. In addition, the BMC group showed the best results for meniscal regeneration.

Porcine model: Although limited, S-MSCs have also been used preclinically in tissue engineering for meniscus healing. Moriguchi *et al*[167] performed a preclinical study to test the feasibility of a scaffold-free tissue-engineered construct (TEC) derived from S-MSCs for meniscal defects (4-mm cylindrical defect) in a miniature pig model. At 6 mo, the treated group showed tissue repair with fibrocartilaginous tissue and good integration to the host meniscal tissue. However, the control group showed either partial or unrepaired defects. The ratio of Safranin O-positive area was significantly higher in the treated group than in the control group ($P = 0.03$). Moreover, the treated group showed significantly reduced size and severity of post-traumatic chondral lesions on the tibial plateau ($P = 0.0163$) and better International Cartilage Repair Society (ICRS) scores ($P = 0.008$).

Rat model: Qi *et al*[168] investigated whether the use of BM-MSCs sheets could effectively regenerate the meniscus in a rat model. At 8 wk, histological analysis revealed that the healed anterior portion of the meniscus was similar to that of the native tissue with typical fibrochondrocytes surrounded by richer extracellular matrix in the treated group. The histological scores in the treated group were 5.5 ± 0.8 and 3.8 ± 0.6 at 4 and 8 wk, respectively. These scores were significantly lower than those in the control group, 9.8 ± 1.5 and 16.3 ± 2.4 at 4 and 8 wk ($P < 0.05$). Furthermore, a predominant collagen-rich matrix bridging the interface was identified, and the regenerated meniscus integrated well with the surrounding host meniscus. Katagiri *et al*[169] investigated whether S-MSCs aggregates regenerated a meniscus more effectively than S-MSCs suspension when the same number (25000) of the cells was used in a rat model. At 4 wk, the regenerated meniscus area was more extensive and the histological findings were closer to that of the normal meniscus in the S-MSCs aggregate groups than in the S-MSCs suspension group. The effects of S-MSCs aggregate transplantation remained at 12 wk. Luminescence intensity remained higher at 3 wk and thereafter in the aggregate S-MSCs group than in the suspension S-MSCs group.

Monkey model: Based on the results of Katagiri *et al*[169], Kondo *et al*[93] tried aggregates of S-MSCs for meniscus regeneration in a monkey model. After the anterior halves of the medial menisci were removed, the authors transplanted an average of 14 aggregates consisting of 250000 S-MSCs for the meniscus defect. The meniscus was larger and the modified Pauli's histological score was better in the treated group than in the control group at 8 and 16 wk. At 16 wk, Mankin's score for the medial femoral condyle cartilage was better in the treated group than in the control group in all primates. T1rho values for both the regenerated meniscus and medial femoral condyle cartilage were closer to the normal meniscus in the treated group than in the control group at 16 wk.

Horse model: González-Fernández *et al*[100] examined the ability of meniscus regeneration using a collagen repair patch (scaffold) seeded with BM-MSCs or A-MSCs in a horse model. At 1 year, macroscopically, the control group had full-thickness defects in all samples. Defects remained in only one of the six menisci in the MSC groups. There were no macroscopic differences between the A-MSCs and BM-MSCs groups. Histologically, the quantity of regenerated meniscal tissue (determined by staining with Safranin O fast green) was better in meniscal defects treated with MSCs than in control defects ($P < 0.001$).

Human studies

BM-MSCs: Tissue engineering techniques using engineered scaffolds and MSCs have achieved promising results in preclinical studies. Some authors have attempted tissue engineering using MSCs in clinical studies based on these preclinical studies. However, these clinical studies are limited in number. In 2017, Whitehouse *et al*[96] reported the clinical outcomes of BM-MSCs seeded collagen scaffold application in five patients. The BM-MSCs/collagen-scaffold implant was applied to the meniscal tear prior to repairing vertical mattress sutures. The follow-up period was two years. Of the five treated patients, the implant survived without further treatment in three cases. However, the remaining two patients subsequently underwent meniscectomy due to recurrent symptoms after approximately 15 mo. The three successfully treated patients

showed improvements in all clinical scores over the first year, and these changes were maintained for up to 2 years. After 1 year, MRIs of the three patients showed no evidence of displacement or re-tearing.

Peripheral blood MSCs: Olivos-Meza *et al*[97] attempted the first clinical application of polyurethane scaffolds with peripheral blood MSCs in 11 patients with meniscal defects. Patients enrolled in the treated group received a daily subcutaneous injection of 300 µg of G-CSF (Filgrastim) for 3 consecutive days to increase the pool of MSCs in the peripheral blood stream. The author assessed the articular cartilage changes with T2 mapping in the femur and tibia. The tibia values in the treated group increased slightly after 9 mo but returned to their initial values after 12 mo ($P > 0.05$). In the control group, a marked decrease from 3 mo to 12 mo was observed ($P > 0.05$). This difference was significantly lower in the control group than in the treated group ($P = 0.18$). In the femur, a slight increase in the treated group (47.8 ± 3.4) compared with the control group (45.3 ± 4.9) was observed ($P > 0.05$). The authors concluded that the addition of MSCs did not show any advantage in protecting articular cartilage over acellular scaffolds.

CONCLUSION

Meniscus injuries are common and can lead to rapid degeneration of the knee joint. Due to limited intrinsic healing capacity, current reparative treatments fail to produce long-term improvements, and thus, alternative regenerative strategies, including MSCs and tissue engineering are being tried. Recent preclinical and clinical studies have suggested that MSCs appear to be safe and effective for enhanced meniscal healing. However, the number of studies was limited. Therefore, despite the positive and promising results, there is still no consensus on the ideal cell sources and scaffold manufacturing techniques for meniscus regeneration. Most of the current studies have tried BM-MSCs, S-MSCs, and A-MSCs. To identify proper cell sources and optimize their clinical application, further investigations of multiple cell source types, including meniscal cells and MSCs derived from other tissues, are necessary. In terms of tissue engineering, the application of various scaffolds should be validated based on their long-term efficacy and safety. Considering the complexity of the structure and function of the meniscus, further anatomical and biomechanical investigations are necessary to manufacture successful scaffolds. Although many preclinical studies have shown positive and promising results, only a few clinical studies have been conducted with a limited number of patients and a short follow-up period. Further advancements in future clinical studies with many patients, long-term follow-up, various cell sources, and proper control groups could validate the safety and efficacy of MSC application in clinical settings to enhance meniscal healing and slow or delay the progression of knee OA.

REFERENCES

- 1 **Gee SM**, Tennent DJ, Cameron KL, Posner MA. The Burden of Meniscus Injury in Young and Physically Active Populations. *Clin Sports Med* 2020; **39**: 13-27 [PMID: [31767103](#) DOI: [10.1016/j.csm.2019.08.008](#)]
- 2 **Logerstedt DS**, Scalzitti DA, Bennell KL, Hinman RS, Silvers-Granelli H, Ebert J, Hambly K, Carey JL, Snyder-Mackler L, Axe MJ, McDonough CM. Knee Pain and Mobility Impairments: Meniscal and Articular Cartilage Lesions Revision 2018. *J Orthop Sports Phys Ther* 2018; **48**: A1-A50 [PMID: [29385940](#) DOI: [10.2519/jospt.2018.0301](#)]
- 3 **Hede A**, Jensen DB, Blyme P, Sonne-Holm S. Epidemiology of meniscal lesions in the knee. 1,215 open operations in Copenhagen 1982-84. *Acta Orthop Scand* 1990; **61**: 435-437 [PMID: [2239168](#) DOI: [10.3109/17453679008993557](#)]
- 4 **Jones JC**, Burks R, Owens BD, Sturdivant RX, Svoboda SJ, Cameron KL. Incidence and risk factors associated with meniscal injuries among active-duty US military service members. *J Athl Train* 2012; **47**: 67-73 [PMID: [22488232](#) DOI: [10.4085/1062-6050-47.1.67](#)]
- 5 **Woodmass JM**, LaPrade RF, Sgaglione NA, Nakamura N, Krych AJ. Meniscal Repair: Reconsidering Indications, Techniques, and Biologic Augmentation. *J Bone Joint Surg Am* 2017; **99**: 1222-1231 [PMID: [28719562](#) DOI: [10.2106/JBJS.17.00297](#)]
- 6 **Twomey-Kozak J**, Jayasuriya CT. Meniscus Repair and Regeneration: A Systematic Review from a Basic and Translational Science Perspective. *Clin Sports Med* 2020; **39**: 125-163 [PMID: [31767102](#) DOI: [10.1016/j.csm.2019.08.003](#)]
- 7 **Seil R**, Becker R. Time for a paradigm change in meniscal repair: save the meniscus! *Knee Surg*

- Sports Traumatol Arthrosc* 2016; **24**: 1421-1423 [PMID: 27107860 DOI: 10.1007/s00167-016-4127-9]
- 8 **Xu C**, Zhao J. A meta-analysis comparing meniscal repair with meniscectomy in the treatment of meniscal tears: the more meniscus, the better outcome? *Knee Surg Sports Traumatol Arthrosc* 2015; **23**: 164-170 [PMID: 23670128 DOI: 10.1007/s00167-013-2528-6]
 - 9 **Makris EA**, Hadidi P, Athanasiou KA. The knee meniscus: structure-function, pathophysiology, current repair techniques, and prospects for regeneration. *Biomaterials* 2011; **32**: 7411-7431 [PMID: 21764438 DOI: 10.1016/j.biomaterials.2011.06.037]
 - 10 **Moran CJ**, Busilacchi A, Lee CA, Athanasiou KA, Verdonk PC. Biological augmentation and tissue engineering approaches in meniscus surgery. *Arthroscopy* 2015; **31**: 944-955 [PMID: 25687715 DOI: 10.1016/j.arthro.2014.11.044]
 - 11 **da Silva Meirelles L**, Caplan AI, Nardi NB. In search of the *in vivo* identity of mesenchymal stem cells. *Stem Cells* 2008; **26**: 2287-2299 [PMID: 18566331 DOI: 10.1634/stemcells.2007-1122]
 - 12 **Fong EL**, Chan CK, Goodman SB. Stem cell homing in musculoskeletal injury. *Biomaterials* 2011; **32**: 395-409 [PMID: 20933277 DOI: 10.1016/j.biomaterials.2010.08.101]
 - 13 **Caplan AI**, Dennis JE. Mesenchymal stem cells as trophic mediators. *J Cell Biochem* 2006; **98**: 1076-1084 [PMID: 16619257 DOI: 10.1002/jcb.20886]
 - 14 **Ahmed AM**, Burke DL. In-vitro measurement of static pressure distribution in synovial joints--Part I: Tibial surface of the knee. *J Biomech Eng* 1983; **105**: 216-225 [PMID: 6688842 DOI: 10.1115/1.3138409]
 - 15 **Shoemaker SC**, Markolf KL. The role of the meniscus in the anterior-posterior stability of the loaded anterior cruciate-deficient knee. Effects of partial vs total excision. *J Bone Joint Surg Am* 1986; **68**: 71-79 [PMID: 3753605]
 - 16 **Cox JS**, Nye CE, Schaefer WW, Woodstein IJ. The degenerative effects of partial and total resection of the medial meniscus in dogs' knees. *Clin Orthop Relat Res* 1975; 178-183 [PMID: 1173359 DOI: 10.1097/00003086-197506000-00026]
 - 17 **Radin EL**, de Lamotte F, Maquet P. Role of the menisci in the distribution of stress in the knee. *Clin Orthop Relat Res* 1984; 290-294 [PMID: 6546709]
 - 18 **Angele P**, Johnstone B, Kujat R, Zellner J, Nerlich M, Goldberg V, Yoo J. Stem cell based tissue engineering for meniscus repair. *J Biomed Mater Res A* 2008; **85**: 445-455 [PMID: 17729255 DOI: 10.1002/jbm.a.31480]
 - 19 **Fox AJ**, Bedi A, Rodeo SA. The basic science of human knee menisci: structure, composition, and function. *Sports Health* 2012; **4**: 340-351 [PMID: 23016106 DOI: 10.1177/1941738111429419]
 - 20 **Kusayama T**, Harner CD, Carlin GJ, Xerogeanes JW, Smith BA. Anatomical and biomechanical characteristics of human meniscofemoral ligaments. *Knee Surg Sports Traumatol Arthrosc* 1994; **2**: 234-237 [PMID: 8536047 DOI: 10.1007/BF01845594]
 - 21 **Herwig J**, Egner E, Buddecke E. Chemical changes of human knee joint menisci in various stages of degeneration. *Ann Rheum Dis* 1984; **43**: 635-640 [PMID: 6548109 DOI: 10.1136/ard.43.4.635]
 - 22 **Fithian DC**, Kelly MA, Mow VC. Material properties and structure-function relationships in the menisci. *Clin Orthop Relat Res* 1990; 19-31 [PMID: 2406069]
 - 23 **Sweigart MA**, Athanasiou KA. Toward tissue engineering of the knee meniscus. *Tissue Eng* 2001; **7**: 111-129 [PMID: 11304448 DOI: 10.1089/107632701300062697]
 - 24 **Petersen W**, Tillmann B. Collagenous fibril texture of the human knee joint menisci. *Anat Embryol (Berl)* 1998; **197**: 317-324 [PMID: 9565324 DOI: 10.1007/s004290050141]
 - 25 **Aspden RM**, Yarker YE, Hukins DW. Collagen orientations in the meniscus of the knee joint. *J Anat* 1985; **140** (Pt 3): 371-380 [PMID: 4066476]
 - 26 **Voloshin AS**, Wosk J. Shock absorption of meniscectomized and painful knees: a comparative *in vivo* study. *J Biomed Eng* 1983; **5**: 157-161 [PMID: 6687914 DOI: 10.1016/0141-5425(83)90036-5]
 - 27 **Arnoczky SP**, Warren RF. Microvasculature of the human meniscus. *Am J Sports Med* 1982; **10**: 90-95 [PMID: 7081532 DOI: 10.1177/036354658201000205]
 - 28 **Forriol F**. Growth factors in cartilage and meniscus repair. *Injury* 2009; **40** Suppl 3: S12-S16 [PMID: 20082784 DOI: 10.1016/S0020-1383(09)70005-1]
 - 29 **Mordecai SC**, Al-Hadithy N, Ware HE, Gupte CM. Treatment of meniscal tears: An evidence based approach. *World J Orthop* 2014; **5**: 233-241 [PMID: 25035825 DOI: 10.5312/wjo.v5.i3.233]
 - 30 **Bansal S**, Keah NM, Neuwirth AL, O'Reilly O, Qu F, Seiber BN, Mandalapu S, Mauck RL, Zgonis MH. Large Animal Models of Meniscus Repair and Regeneration: A Systematic Review of the State of the Field. *Tissue Eng Part C Methods* 2017; **23**: 661-672 [PMID: 28622089 DOI: 10.1089/ten.TEC.2017.0080]
 - 31 **Abram SGF**, Middleton R, Beard DJ, Price AJ, Hopewell S. Patient-reported outcome measures for patients with meniscal tears: a systematic review of measurement properties and evaluation with the COSMIN checklist. *BMJ Open* 2017; **7**: e017247 [PMID: 29030413 DOI: 10.1136/bmjopen-2017-017247]
 - 32 **Al-Dadah O**, Shepstone L, Donell ST. Patient reported outcome measures in meniscal tears and arthroscopic meniscectomy: The value of outcome score prediction. *Orthop Traumatol Surg Res* 2021; **107**: 102803 [PMID: 33434690 DOI: 10.1016/j.otsr.2021.102803]
 - 33 **Flandry F**, Hunt JP, Terry GC, Hughston JC. Analysis of subjective knee complaints using visual analog scales. *Am J Sports Med* 1991; **19**: 112-118 [PMID: 2039061 DOI: 10.1177/036354659101900204]
 - 34 **Irrgang JJ**, Anderson AF, Boland AL, Harner CD, Kurosaka M, Neyret P, Richmond JC, Shelborne

- KD. Development and validation of the international knee documentation committee subjective knee form. *Am J Sports Med* 2001; **29**: 600-613 [PMID: 11573919 DOI: 10.1177/03635465010290051301]
- 35 **Roos EM**, Roos HP, Lohmander LS, Ekdahl C, Beynnon BD. Knee Injury and Osteoarthritis Outcome Score (KOOS)--development of a self-administered outcome measure. *J Orthop Sports Phys Ther* 1998; **28**: 88-96 [PMID: 9699158 DOI: 10.2519/jospt.1998.28.2.88]
- 36 **Lysholm J**, Gillquist J. Evaluation of knee ligament surgery results with special emphasis on use of a scoring scale. *Am J Sports Med* 1982; **10**: 150-154 [PMID: 6896798 DOI: 10.1177/036354658201000306]
- 37 **Bellamy N**. The WOMAC Knee and Hip Osteoarthritis Indices: development, validation, globalization and influence on the development of the AUSCAN Hand Osteoarthritis Indices. *Clin Exp Rheumatol* 2005; **23**: S148-S153 [PMID: 16273799]
- 38 **EuroQol Group**. EuroQol--a new facility for the measurement of health-related quality of life. *Health Policy* 1990; **16**: 199-208 [PMID: 10109801 DOI: 10.1016/0168-8510(90)90421-9]
- 39 **Garratt AM**, Brealey S, Robling M, Atwell C, Russell I, Gillespie W, King D; DAMASK Trial Team. Development of the knee quality of life (KQoL-26) 26-item questionnaire: data quality, reliability, validity and responsiveness. *Health Qual Life Outcomes* 2008; **6**: 48 [PMID: 18616820 DOI: 10.1186/1477-7525-6-48]
- 40 **Brazier J**, Roberts J, Deverill M. The estimation of a preference-based measure of health from the SF-36. *J Health Econ* 2002; **21**: 271-292 [PMID: 11939242 DOI: 10.1016/s0167-6296(01)00130-8]
- 41 **Kirkley A**, Griffin S, Whelan D. The development and validation of a quality of life-measurement tool for patients with meniscal pathology: the Western Ontario Meniscal Evaluation Tool (WOMET). *Clin J Sport Med* 2007; **17**: 349-356 [PMID: 17873546 DOI: 10.1097/JSM.0b013e31814c3e15]
- 42 **Tegner Y**, Lysholm J. Rating systems in the evaluation of knee ligament injuries. *Clin Orthop Relat Res* 1985; 43-49 [PMID: 4028566]
- 43 **Noyes FR**, Barber SD, Mooar LA. A rationale for assessing sports activity levels and limitations in knee disorders. *Clin Orthop Relat Res* 1989; 238-249 [PMID: 2670388]
- 44 **Tapper EM**, Hoover NW. Late results after meniscectomy. *J Bone Joint Surg Am* 1969; **51**: 517-26 passim [PMID: 5778287]
- 45 **Irrgang JJ**, Snyder-Mackler L, Wainner RS, Fu FH, Harner CD. Development of a patient-reported measure of function of the knee. *J Bone Joint Surg Am* 1998; **80**: 1132-1145 [PMID: 9730122 DOI: 10.2106/00004623-199808000-00006]
- 46 **Ware J Jr**, Kosinski M, Keller SD. A 12-Item Short-Form Health Survey: construction of scales and preliminary tests of reliability and validity. *Med Care* 1996; **34**: 220-233 [PMID: 8628042 DOI: 10.1097/00005650-199603000-00003]
- 47 **Ahn JH**, Lee YS, Yoo JC, Chang MJ, Koh KH, Kim MH. Clinical and second-look arthroscopic evaluation of repaired medial meniscus in anterior cruciate ligament-reconstructed knees. *Am J Sports Med* 2010; **38**: 472-477 [PMID: 20097926 DOI: 10.1177/0363546509348102]
- 48 **Miao Y**, Yu JK, Ao YF, Zheng ZZ, Gong X, Leung KK. Diagnostic values of 3 methods for evaluating meniscal healing status after meniscal repair: comparison among second-look arthroscopy, clinical assessment, and magnetic resonance imaging. *Am J Sports Med* 2011; **39**: 735-742 [PMID: 21220542 DOI: 10.1177/0363546510388930]
- 49 **Kopf S**, Beaufils P, Hirschmann MT, Rotigliano N, Ollivier M, Pereira H, Verdonk R, Darabos N, Ntangiopoulos P, Dejour D, Seil R, Becker R. Management of traumatic meniscus tears: the 2019 ESSKA meniscus consensus. *Knee Surg Sports Traumatol Arthrosc* 2020; **28**: 1177-1194 [PMID: 32052121 DOI: 10.1007/s00167-020-05847-3]
- 50 **Berton A**, Longo UG, Candela V, Greco F, Martina FM, Quattrocchi CC, Denaro V. Quantitative Evaluation of Meniscal Healing Process of Degenerative Meniscus Lesions Treated with Hyaluronic Acid: A Clinical and MRI Study. *J Clin Med* 2020; **9** [PMID: 32709084 DOI: 10.3390/jcm9072280]
- 51 **Yamasaki S**, Hashimoto Y, Nishida Y, Teraoka T, Terai S, Takigami J, Nakamura H. Assessment of Meniscal Healing Status by Magnetic Resonance Imaging T2 Mapping After Meniscal Repair. *Am J Sports Med* 2020; **48**: 853-860 [PMID: 32167835 DOI: 10.1177/0363546520904680]
- 52 **Ciliz D**, Ciliz A, Elverici E, Sakman B, Yüksel E, Akbulut O. Evaluation of postoperative menisci with MR arthrography and routine conventional MRI. *Clin Imaging* 2008; **32**: 212-219 [PMID: 18502349 DOI: 10.1016/j.clinimag.2007.09.008]
- 53 **Magee T**. Accuracy of 3-Tesla MR and MR arthrography in diagnosis of meniscal re-tear in the post-operative knee. *Skeletal Radiol* 2014; **43**: 1057-1064 [PMID: 24752876 DOI: 10.1007/s00256-014-1895-5]
- 54 **Vives MJ**, Homesley D, Ciccotti MG, Schweitzer ME. Evaluation of recurring meniscal tears with gadolinium-enhanced magnetic resonance imaging: a randomized, prospective study. *Am J Sports Med* 2003; **31**: 868-873 [PMID: 14623651 DOI: 10.1177/03635465030310062301]
- 55 **Pujol N**, Panarella L, Selmi TA, Neyret P, Fithian D, Beaufils P. Meniscal healing after meniscal repair: a CT arthrography assessment. *Am J Sports Med* 2008; **36**: 1489-1495 [PMID: 18483200 DOI: 10.1177/0363546508316771]
- 56 **Herrlin S**, Hållander M, Wange P, Weidenhielm L, Werner S. Arthroscopic or conservative treatment of degenerative medial meniscal tears: a prospective randomised trial. *Knee Surg Sports Traumatol Arthrosc* 2007; **15**: 393-401 [PMID: 17216272 DOI: 10.1007/s00167-006-0243-2]
- 57 **Herrlin SV**, Wange PO, Lapidus G, Hållander M, Werner S, Weidenhielm L. Is arthroscopic

- surgery beneficial in treating non-traumatic, degenerative medial meniscal tears? *Knee Surg Sports Traumatol Arthrosc* 2013; **21**: 358-364 [PMID: 22437659 DOI: 10.1007/s00167-012-1960-3]
- 58 **Katz JN**, Brophy RH, Chaisson CE, de Chaves L, Cole BJ, Dahm DL, Donnell-Fink LA, Guermazi A, Haas AK, Jones MH, Levy BA, Mandl LA, Martin SD, Marx RG, Miniaci A, Matava MJ, Palmisano J, Reinke EK, Richardson BE, Rome BN, Safran-Norton CE, Skonieczki DJ, Solomon DH, Smith MV, Spindler KP, Stuart MJ, Wright J, Wright RW, Losina E. Surgery vs physical therapy for a meniscal tear and osteoarthritis. *N Engl J Med* 2013; **368**: 1675-1684 [PMID: 23506518 DOI: 10.1056/NEJMoa1301408]
- 59 **Sihvonen R**, Paavola M, Malmivaara A, Itälä A, Joukainen A, Nurmi H, Kalske J, Järvinen TL; Finnish Degenerative Meniscal Lesion Study (FIDELITY) Group. Arthroscopic partial meniscectomy vs sham surgery for a degenerative meniscal tear. *N Engl J Med* 2013; **369**: 2515-2524 [PMID: 24369076 DOI: 10.1056/NEJMoa1305189]
- 60 **Sihvonen R**, Paavola M, Malmivaara A, Itälä A, Joukainen A, Nurmi H, Kalske J, Ikonen A, Järvelä T, Järvinen TAH, Kanto K, Karhunen J, Knifund J, Kröger H, Kääriäinen T, Lehtinen J, Nyrhinen J, Paloneva J, Päiväniemi O, Raivio M, Sahlman J, Sarvilinna R, Tukiainen S, Välimäki VV, Äärimaa V, Toivonen P, Järvinen TLN; FIDELITY (Finnish Degenerative Meniscal Lesion Study) Investigators. Arthroscopic partial meniscectomy vs placebo surgery for a degenerative meniscus tear: a 2-year follow-up of the randomised controlled trial. *Ann Rheum Dis* 2018; **77**: 188-195 [PMID: 28522452 DOI: 10.1136/annrheumdis-2017-211172]
- 61 **Baratz ME**, Fu FH, Mengato R. Meniscal tears: the effect of meniscectomy and of repair on intraarticular contact areas and stress in the human knee. A preliminary report. *Am J Sports Med* 1986; **14**: 270-275 [PMID: 3755296 DOI: 10.1177/036354658601400405]
- 62 **Roos H**, Laurén M, Adalberth T, Roos EM, Jonsson K, Lohmander LS. Knee osteoarthritis after meniscectomy: prevalence of radiographic changes after twenty-one years, compared with matched controls. *Arthritis Rheum* 1998; **41**: 687-693 [PMID: 9550478 DOI: 10.1002/1529-0131(199804)41:4<687::AID-ART16>3.0.CO;2-2]
- 63 **Burks RT**, Metcalf MH, Metcalf RW. Fifteen-year follow-up of arthroscopic partial meniscectomy. *Arthroscopy* 1997; **13**: 673-679 [PMID: 9442319 DOI: 10.1016/s0749-8063(97)90000-1]
- 64 **Jaureguito JW**, Elliot JS, Lietner T, Dixon LB, Reider B. The effects of arthroscopic partial lateral meniscectomy in an otherwise normal knee: a retrospective review of functional, clinical, and radiographic results. *Arthroscopy* 1995; **11**: 29-36 [PMID: 7727009 DOI: 10.1016/0749-8063(95)90085-3]
- 65 **Northmore-Ball MD**, Dandy DJ, Jackson RW. Arthroscopic, open partial, and total meniscectomy. A comparative study. *J Bone Joint Surg Br* 1983; **65**: 400-404 [PMID: 6874710 DOI: 10.1302/0301-620X.65B4.6874710]
- 66 **Hasan J**, Fisher J, Ingham E. Current strategies in meniscal regeneration. *J Biomed Mater Res B Appl Biomater* 2014; **102**: 619-634 [PMID: 24030973 DOI: 10.1002/jbm.b.33030]
- 67 **Paxton ES**, Stock MV, Brophy RH. Meniscal repair vs partial meniscectomy: a systematic review comparing reoperation rates and clinical outcomes. *Arthroscopy* 2011; **27**: 1275-1288 [PMID: 21820843 DOI: 10.1016/j.arthro.2011.03.088]
- 68 **Nepple JJ**, Dunn WR, Wright RW. Meniscal repair outcomes at greater than five years: a systematic literature review and meta-analysis. *J Bone Joint Surg Am* 2012; **94**: 2222-2227 [PMID: 23318612 DOI: 10.2106/JBJS.K.01584]
- 69 **Lutz C**, Dalmay F, Ehkirch FP, Cucurulo T, Laporte C, Le Henaff G, Potel JF, Pujol N, Rochcongar G, Salledechou E, Seil R, Gunepin FX, Sonnery-Cottet B; French Arthroscopy Society. Meniscectomy vs meniscal repair: 10 years radiological and clinical results in vertical lesions in stable knee. *Orthop Traumatol Surg Res* 2015; **101**: S327-S331 [PMID: 26439421 DOI: 10.1016/j.otsr.2015.09.008]
- 70 **van Trommel MF**, Simonian PT, Potter HG, Wickiewicz TL. Arthroscopic meniscal repair with fibrin clot of complete radial tears of the lateral meniscus in the avascular zone. *Arthroscopy* 1998; **14**: 360-365 [PMID: 9620646 DOI: 10.1016/s0749-8063(98)70002-7]
- 71 **Fox JM**, Rintz KG, Ferkel RD. Trephination of incomplete meniscal tears. *Arthroscopy* 1993; **9**: 451-455 [PMID: 8216578 DOI: 10.1016/s0749-8063(05)80321-4]
- 72 **Zhang Z**, Arnold JA. Trephination and suturing of avascular meniscal tears: a clinical study of the trephination procedure. *Arthroscopy* 1996; **12**: 726-731 [PMID: 9115563 DOI: 10.1016/s0749-8063(96)90178-4]
- 73 **Lee SR**, Kim JG, Nam SW. The tips and pitfalls of meniscus allograft transplantation. *Knee Surg Relat Res* 2012; **24**: 137-145 [PMID: 22977790 DOI: 10.5792/ksrr.2012.24.3.137]
- 74 **A Cavendish P**, DiBartola AC, Everhart JS, Kuzma S, Kim WJ, Flanigan DC. Meniscal allograft transplantation: a review of indications, techniques, and outcomes. *Knee Surg Sports Traumatol Arthrosc* 2020; **28**: 3539-3550 [PMID: 32415360 DOI: 10.1007/s00167-020-06058-6]
- 75 **Rosso F**, Bisicchia S, Bonasia DE, Amendola A. Meniscal allograft transplantation: a systematic review. *Am J Sports Med* 2015; **43**: 998-1007 [PMID: 24928760 DOI: 10.1177/0363546514536021]
- 76 **Jacob G**, Shimomura K, Krych AJ, Nakamura N. The Meniscus Tear: A Review of Stem Cell Therapies. *Cells* 2019; **9** [PMID: 31905968 DOI: 10.3390/cells9010092]
- 77 **Zellner J**, Pattappa G, Koch M, Lang S, Weber J, Pfeifer CG, Mueller MB, Kujat R, Nerlich M, Angele P. Autologous mesenchymal stem cells or meniscal cells: what is the best cell source for regenerative meniscus treatment in an early osteoarthritis situation? *Stem Cell Res Ther* 2017; **8**: 225 [PMID: 29017608 DOI: 10.1186/s13287-017-0678-z]

- 78 **Zellner J**, Hierl K, Mueller M, Pfeifer C, Berner A, Dienstknecht T, Krutsch W, Geis S, Gehmert S, Kujat R, Dendorfer S, Prantl L, Nerlich M, Angele P. Stem cell-based tissue-engineering for treatment of meniscal tears in the avascular zone. *J Biomed Mater Res B Appl Biomater* 2013; **101**: 1133-1142 [PMID: 23564690 DOI: 10.1002/jbm.b.32922]
- 79 **Fox DB**, Warnock JJ. Cell-based meniscal tissue engineering: a case for synoviocytes. *Clin Orthop Relat Res* 2011; **469**: 2806-2816 [PMID: 21360210 DOI: 10.1007/s11999-011-1824-z]
- 80 **Pabbruwe MB**, Kafienah W, Tarlton JF, Mistry S, Fox DJ, Hollander AP. Repair of meniscal cartilage white zone tears using a stem cell/collagen-scaffold implant. *Biomaterials* 2010; **31**: 2583-2591 [PMID: 20053438 DOI: 10.1016/j.biomaterials.2009.12.023]
- 81 **Ozeki N**, Kohno Y, Kushida Y, Watanabe N, Mizuno M, Katano H, Masumoto J, Koga H, Sekiya I. Synovial mesenchymal stem cells promote the meniscus repair in a novel pig meniscus injury model. *J Orthop Res* 2021; **39**: 177-183 [PMID: 32886427 DOI: 10.1002/jor.24846]
- 82 **Desando G**, Giavaresi G, Cavallo C, Bartolotti I, Sartoni F, Nicoli Aldini N, Martini L, Parrilli A, Mariani E, Fini M, Grigolo B. Autologous Bone Marrow Concentrate in a Sheep Model of Osteoarthritis: New Perspectives for Cartilage and Meniscus Repair. *Tissue Eng Part C Methods* 2016; **22**: 608-619 [PMID: 27151837 DOI: 10.1089/ten.TEC.2016.0033]
- 83 **Hennerbichler A**, Moutos FT, Hennerbichler D, Weinberg JB, Guilak F. Repair response of the inner and outer regions of the porcine meniscus in vitro. *Am J Sports Med* 2007; **35**: 754-762 [PMID: 17261570 DOI: 10.1177/0363546506296416]
- 84 **Zellner J**, Mueller M, Xin Y, Krutsch W, Brandl A, Kujat R, Nerlich M, Angele P. Dynamic hydrostatic pressure enhances differentially the chondrogenesis of meniscal cells from the inner and outer zone. *J Biomech* 2015; **48**: 1479-1484 [PMID: 25698240 DOI: 10.1016/j.jbiomech.2015.02.003]
- 85 **Mauck RL**, Martinez-Diaz GJ, Yuan X, Tuan RS. Regional multilineage differentiation potential of meniscal fibrochondrocytes: implications for meniscus repair. *Anat Rec (Hoboken)* 2007; **290**: 48-58 [PMID: 17441197 DOI: 10.1002/ar.20419]
- 86 **Berebichez-Fridman R**, Gómez-García R, Granados-Montiel J, Berebichez-Fastlicht E, Olivos-Meza A, Granados J, Velasquillo C, Ibarra C. The Holy Grail of Orthopedic Surgery: Mesenchymal Stem Cells-Their Current Uses and Potential Applications. *Stem Cells Int* 2017; **2017**: 2638305 [PMID: 28698718 DOI: 10.1155/2017/2638305]
- 87 **Jang KM**, Lim HC, Jung WY, Moon SW, Wang JH. Efficacy and Safety of Human Umbilical Cord Blood-Derived Mesenchymal Stem Cells in Anterior Cruciate Ligament Reconstruction of a Rabbit Model: New Strategy to Enhance Tendon Graft Healing. *Arthroscopy* 2015; **31**: 1530-1539 [PMID: 25882182 DOI: 10.1016/j.arthro.2015.02.023]
- 88 **Hofer HR**, Tuan RS. Secreted trophic factors of mesenchymal stem cells support neurovascular and musculoskeletal therapies. *Stem Cell Res Ther* 2016; **7**: 131 [PMID: 27612948 DOI: 10.1186/s13287-016-0394-0]
- 89 **Tarafder S**, Gulko J, Sim KH, Yang J, Cook JL, Lee CH. Engineered Healing of Avascular Meniscus Tears by Stem Cell Recruitment. *Sci Rep* 2018; **8**: 8150 [PMID: 29802356 DOI: 10.1038/s41598-018-26545-8]
- 90 **Maxson S**, Lopez EA, Yoo D, Danilkovitch-Miagkova A, Leroux MA. Concise review: role of mesenchymal stem cells in wound repair. *Stem Cells Transl Med* 2012; **1**: 142-149 [PMID: 23197761 DOI: 10.5966/sctm.2011-0018]
- 91 **Maacha S**, Sidahmed H, Jacob S, Gentilcore G, Calzone R, Grivel JC, Cugno C. Paracrine Mechanisms of Mesenchymal Stromal Cells in Angiogenesis. *Stem Cells Int* 2020; **2020**: 4356359 [PMID: 32215017 DOI: 10.1155/2020/4356359]
- 92 **Nakagawa Y**, Muneta T, Kondo S, Mizuno M, Takakuda K, Ichinose S, Tabuchi T, Koga H, Tsuji K, Sekiya I. Synovial mesenchymal stem cells promote healing after meniscal repair in microminipigs. *Osteoarthritis Cartilage* 2015; **23**: 1007-1017 [PMID: 25683149 DOI: 10.1016/j.joca.2015.02.008]
- 93 **Kondo S**, Muneta T, Nakagawa Y, Koga H, Watanabe T, Tsuji K, Sotome S, Okawa A, Kiuchi S, Ono H, Mizuno M, Sekiya I. Transplantation of autologous synovial mesenchymal stem cells promotes meniscus regeneration in aged primates. *J Orthop Res* 2017; **35**: 1274-1282 [PMID: 26916126 DOI: 10.1002/jor.23211]
- 94 **Driscoll MD**, Robin BN, Horie M, Hubert ZT, Sampson HW, Jupiter DC, Tharakan B, Reeve RE. Marrow stimulation improves meniscal healing at early endpoints in a rabbit meniscal injury model. *Arthroscopy* 2013; **29**: 113-121 [PMID: 23200846 DOI: 10.1016/j.arthro.2012.06.023]
- 95 **Vangsness CT Jr**, Farr J 2nd, Boyd J, Dellaero DT, Mills CR, LeRoux-Williams M. Adult human mesenchymal stem cells delivered via intra-articular injection to the knee following partial medial meniscectomy: a randomized, double-blind, controlled study. *J Bone Joint Surg Am* 2014; **96**: 90-98 [PMID: 24430407 DOI: 10.2106/JBJS.M.00058]
- 96 **Whitehouse MR**, Howells NR, Parry MC, Austin E, Kafienah W, Brady K, Goodship AE, Eldridge JD, Blom AW, Hollander AP. Repair of Torn Avascular Meniscal Cartilage Using Undifferentiated Autologous Mesenchymal Stem Cells: From In Vitro Optimization to a First-in-Human Study. *Stem Cells Transl Med* 2017; **6**: 1237-1248 [PMID: 28186682 DOI: 10.1002/sctm.16-0199]
- 97 **Olivos-Meza A**, Pérez Jiménez FJ, Granados-Montiel J, Landa-Solis C, Cortés González S, Jiménez Aroche CA, Valdez Chávez M, Renán León S, Gomez-Garcia R, Martínez-López V, Ortega-Sánchez C, Parra-Cid C, Velasquillo Martinez C, Ibarra C. First Clinical Application of Polyurethane Meniscal Scaffolds with Mesenchymal Stem Cells and Assessment of Cartilage

- Quality with T2 Mapping at 12 Months. *Cartilage* 2019; 1947603519852415 [PMID: 31387368 DOI: 10.1177/1947603519852415]
- 98 **Sekiya I**, Koga H, Otabe K, Nakagawa Y, Katano H, Ozeki N, Mizuno M, Horie M, Kohno Y, Katagiri K, Watanabe N, Muneta T. Additional Use of Synovial Mesenchymal Stem Cell Transplantation Following Surgical Repair of a Complex Degenerative Tear of the Medial Meniscus of the Knee: A Case Report. *Cell Transplant* 2019; **28**: 1445-1454 [PMID: 31313604 DOI: 10.1177/0963689719863793]
- 99 **Onoi Y**, Hiranaka T, Nishida R, Takase K, Fujita M, Hida Y, Fujishiro T, Okamoto K. Second-look arthroscopic findings of cartilage and meniscus repair after injection of adipose-derived regenerative cells in knee osteoarthritis: Report of two cases. *Regen Ther* 2019; **11**: 212-216 [PMID: 31489345 DOI: 10.1016/j.reth.2019.07.010]
- 100 **González-Fernández ML**, Pérez-Castrillo S, Sánchez-Lázaro JA, Prieto-Fernández JG, López-González ME, Lobato-Pérez S, Colaço BJ, Olivera ER, Villar-Suárez V. Assessment of regeneration in meniscal lesions by use of mesenchymal stem cells derived from equine bone marrow and adipose tissue. *Am J Vet Res* 2016; **77**: 779-788 [PMID: 27347833 DOI: 10.2460/ajvr.77.7.779]
- 101 **Yuan X**, Wei Y, Villasante A, Ng JJD, Arkonac DE, Chao PG, Vunjak-Novakovic G. Stem cell delivery in tissue-specific hydrogel enabled meniscal repair in an orthotopic rat model. *Biomaterials* 2017; **132**: 59-71 [PMID: 28407495 DOI: 10.1016/j.biomaterials.2017.04.004]
- 102 **Koch M**, Achatz FP, Lang S, Pfeifer CG, Pattappa G, Kujat R, Nerlich M, Angele P, Zellner J. Tissue Engineering of Large Full-Size Meniscus Defects by a Polyurethane Scaffold: Accelerated Regeneration by Mesenchymal Stromal Cells. *Stem Cells Int* 2018; **2018**: 8207071 [PMID: 29853919 DOI: 10.1155/2018/8207071]
- 103 **Okuno M**, Muneta T, Koga H, Ozeki N, Nakagawa Y, Tsuji K, Yoshiya S, Sekiya I. Meniscus regeneration by syngeneic, minor mismatched, and major mismatched transplantation of synovial mesenchymal stem cells in a rat model. *J Orthop Res* 2014; **32**: 928-936 [PMID: 24644154 DOI: 10.1002/jor.22614]
- 104 **Pak J**, Lee JH, Lee SH. Regenerative repair of damaged meniscus with autologous adipose tissue-derived stem cells. *Biomed Res Int* 2014; **2014**: 436029 [PMID: 24592390 DOI: 10.1155/2014/436029]
- 105 **Qi Y**, Yang Z, Ding Q, Zhao T, Huang Z, Feng G. Targeted transplantation of iron oxide-labeled, adipose-derived mesenchymal stem cells in promoting meniscus regeneration following a rabbit massive meniscal defect. *Exp Ther Med* 2016; **11**: 458-466 [PMID: 26893631 DOI: 10.3892/etm.2015.2944]
- 106 **Toratani T**, Nakase J, Numata H, Oshima T, Takata Y, Nakayama K, Tsuchiya H. Scaffold-Free Tissue-Engineered Allogenic Adipose-Derived Stem Cells Promote Meniscus Healing. *Arthroscopy* 2017; **33**: 346-354 [PMID: 27670757 DOI: 10.1016/j.arthro.2016.07.015]
- 107 **Friedenstein AJ**, Piatetzky-Shapiro II, Petrakova KV. Osteogenesis in transplants of bone marrow cells. *J Embryol Exp Morphol* 1966; **16**: 381-390 [PMID: 5336210]
- 108 **Friedenstein AJ**, Ivanov-Smolenski AA, Chajlakjan RK, Gorskaya UF, Kurolesova AI, Latzinik NW, Gerasimow UW. Origin of bone marrow stromal mechanocytes in radiochimeras and heterotopic transplants. *Exp Hematol* 1978; **6**: 440-444 [PMID: 350596]
- 109 **Friedenstein AJ**, Petrakova KV, Kurolesova AI, Frolova GP. Heterotopic of bone marrow. Analysis of precursor cells for osteogenic and hematopoietic tissues. *Transplantation* 1968; **6**: 230-247 [PMID: 5654088]
- 110 **Alvarez-Viejo M**, Menendez-Menendez Y, Blanco-Gelaz MA, Ferrero-Gutierrez A, Fernandez-Rodriguez MA, Gala J, Otero-Hernandez J. Quantifying mesenchymal stem cells in the mononuclear cell fraction of bone marrow samples obtained for cell therapy. *Transplant Proc* 2013; **45**: 434-439 [PMID: 23375334 DOI: 10.1016/j.transproceed.2012.05.091]
- 111 **Diekman BO**, Rowland CR, Lennon DP, Caplan AI, Guilak F. Chondrogenesis of adult stem cells from adipose tissue and bone marrow: induction by growth factors and cartilage-derived matrix. *Tissue Eng Part A* 2010; **16**: 523-533 [PMID: 19715387 DOI: 10.1089/ten.TEA.2009.0398]
- 112 **Mueller MB**, Tuan RS. Functional characterization of hypertrophy in chondrogenesis of human mesenchymal stem cells. *Arthritis Rheum* 2008; **58**: 1377-1388 [PMID: 18438858 DOI: 10.1002/art.23370]
- 113 **Pelttari K**, Winter A, Steck E, Goetzke K, Hennig T, Ochs BG, Aigner T, Richter W. Premature induction of hypertrophy during *in vitro* chondrogenesis of human mesenchymal stem cells correlates with calcification and vascular invasion after ectopic transplantation in SCID mice. *Arthritis Rheum* 2006; **54**: 3254-3266 [PMID: 17009260 DOI: 10.1002/art.22136]
- 114 **Matsukura Y**, Muneta T, Tsuji K, Koga H, Sekiya I. Mesenchymal stem cells in synovial fluid increase after meniscus injury. *Clin Orthop Relat Res* 2014; **472**: 1357-1364 [PMID: 24338094 DOI: 10.1007/s11999-013-3418-4]
- 115 **King D**. The healing of semilunar cartilages. 1936. *Clin Orthop Relat Res* 1990; 4-7 [PMID: 2406072]
- 116 **Morito T**, Muneta T, Hara K, Ju YJ, Mochizuki T, Makino H, Umezawa A, Sekiya I. Synovial fluid-derived mesenchymal stem cells increase after intra-articular ligament injury in humans. *Rheumatology (Oxford)* 2008; **47**: 1137-1143 [PMID: 18390894 DOI: 10.1093/rheumatology/ken114]
- 117 **Korpershoek JV**, de Windt TS, Hagmeijer MH, Vonk LA, Saris DB. Cell-Based Meniscus Repair and Regeneration: At the Brink of Clinical Translation? *Orthop J Sports Med* 2017; **5**:

- 2325967117690131 [PMID: 28321424 DOI: 10.1177/2325967117690131]
- 118 **Sakaguchi Y**, Sekiya I, Yagishita K, Muneta T. Comparison of human stem cells derived from various mesenchymal tissues: superiority of synovium as a cell source. *Arthritis Rheum* 2005; **52**: 2521-2529 [PMID: 16052568 DOI: 10.1002/art.21212]
- 119 **Yamazaki K**, Tachibana Y. Vascularized synovial flap promoting regeneration of the cryopreserved meniscal allograft: experimental study in rabbits. *J Orthop Sci* 2003; **8**: 62-68 [PMID: 12560888 DOI: 10.1007/s007760300010]
- 120 **Liu H**, Wei X, Ding X, Li X, Zhou G, Li P, Fan Y. Comparison of cellular responses of mesenchymal stem cells derived from bone marrow and synovium on combined silk scaffolds. *J Biomed Mater Res A* 2015; **103**: 115-125 [PMID: 24616406 DOI: 10.1002/jbm.a.35154]
- 121 **Hatakeyama A**, Uchida S, Utsunomiya H, Tsukamoto M, Nakashima H, Nakamura E, Pascual-Garrido C, Sekiya I, Sakai A. Isolation and Characterization of Synovial Mesenchymal Stem Cell Derived from Hip Joints: A Comparative Analysis with a Matched Control Knee Group. *Stem Cells Int* 2017; **2017**: 9312329 [PMID: 28115945 DOI: 10.1155/2017/9312329]
- 122 **De Bari C**, Dell'Accio F, Tylzanowski P, Luyten FP. Multipotent mesenchymal stem cells from adult human synovial membrane. *Arthritis Rheum* 2001; **44**: 1928-1942 [PMID: 11508446 DOI: 10.1002/1529-0131(200108)44:8<1928::AID-ART331>3.0.CO;2-P]
- 123 **Morcos MW**, Al-Jallad H, Hamdy R. Comprehensive Review of Adipose Stem Cells and Their Implication in Distraction Osteogenesis and Bone Regeneration. *Biomed Res Int* 2015; **2015**: 842975 [PMID: 26448947 DOI: 10.1155/2015/842975]
- 124 **Aust L**, Devlin B, Foster SJ, Halvorsen YD, Hicok K, du Laney T, Sen A, Willingmyre GD, Gimble JM. Yield of human adipose-derived adult stem cells from liposuction aspirates. *Cytotherapy* 2004; **6**: 7-14 [PMID: 14985162 DOI: 10.1080/14653240310004539]
- 125 **Rodriguez AM**, Elabd C, Amri EZ, Ailhaud G, Dani C. The human adipose tissue is a source of multipotent stem cells. *Biochimie* 2005; **87**: 125-128 [PMID: 15733747 DOI: 10.1016/j.biochi.2004.11.007]
- 126 **Zhu Y**, Liu T, Song K, Fan X, Ma X, Cui Z. Adipose-derived stem cell: a better stem cell than BMSC. *Cell Biochem Funct* 2008; **26**: 664-675 [PMID: 18636461 DOI: 10.1002/cbf.1488]
- 127 **Zuk PA**, Zhu M, Mizuno H, Huang J, Futrell JW, Katz AJ, Benhaim P, Lorenz HP, Hedrick MH. Multilineage cells from human adipose tissue: implications for cell-based therapies. *Tissue Eng* 2001; **7**: 211-228 [PMID: 11304456 DOI: 10.1089/107632701300062859]
- 128 **Bertozzi N**, Simonacci F, Grieco MP, Grignaffini E, Rapisio E. The biological and clinical basis for the use of adipose-derived stem cells in the field of wound healing. *Ann Med Surg (Lond)* 2017; **20**: 41-48 [PMID: 28702186 DOI: 10.1016/j.amsu.2017.06.058]
- 129 **Dahl JA**, Duggal S, Coulston N, Millar D, Melki J, Shahdadfar A, Brinchmann JE, Collas P. Genetic and epigenetic instability of human bone marrow mesenchymal stem cells expanded in autologous serum or fetal bovine serum. *Int J Dev Biol* 2008; **52**: 1033-1042 [PMID: 18956336 DOI: 10.1387/ijdb.082663jd]
- 130 **Daher SR**, Johnstone BH, Phinney DG, March KL. Adipose stromal/stem cells: basic and translational advances: the IFATS collection. *Stem Cells* 2008; **26**: 2664-2665 [PMID: 18818434 DOI: 10.1634/stemcells.2008-0927]
- 131 **Gonzalez-Rey E**, Gonzalez MA, Varela N, O'Valle F, Hernandez-Cortes P, Rico L, Büscher D, Delgado M. Human adipose-derived mesenchymal stem cells reduce inflammatory and T cell responses and induce regulatory T cells *in vitro* in rheumatoid arthritis. *Ann Rheum Dis* 2010; **69**: 241-248 [PMID: 19124525 DOI: 10.1136/ard.2008.101881]
- 132 **Tangchitphisut P**, Srikaew N, Numhom S, Tangprasittipap A, Woratanarat P, Wongsak S, Kijkunathian C, Hongeng S, Murray IR, Tawonsawatruk T. Infrapatellar Fat Pad: An Alternative Source of Adipose-Derived Mesenchymal Stem Cells. *Arthritis* 2016; **2016**: 4019873 [PMID: 27239342 DOI: 10.1155/2016/4019873]
- 133 **Spasovski D**, Spasovski V, Bašćarević Z, Stojiljković M, Vreća M, Anđelković M, Pavlović S. Intra-articular injection of autologous adipose-derived mesenchymal stem cells in the treatment of knee osteoarthritis. *J Gene Med* 2018; **20** [PMID: 29243283 DOI: 10.1002/jgm.3002]
- 134 **Muñoz-Criado I**, Meseguer-Ripolles J, Mellado-López M, Alastrue-Agudo A, Griffeth RJ, Forteza-Vila J, Cugat R, García M, Moreno-Manzano V. Human Suprapatellar Fat Pad-Derived Mesenchymal Stem Cells Induce Chondrogenesis and Cartilage Repair in a Model of Severe Osteoarthritis. *Stem Cells Int* 2017; **2017**: 4758930 [PMID: 28769981 DOI: 10.1155/2017/4758930]
- 135 **Diekmann BO**, Christoforou N, Willard VP, Sun H, Sanchez-Adams J, Leong KW, Guilak F. Cartilage tissue engineering using differentiated and purified pluripotent stem cells. *Proc Natl Acad Sci U S A* 2012; **109**: 19172-19177 [PMID: 23115336 DOI: 10.1073/pnas.1210422109]
- 136 **Hamid AA**, Idrus RB, Saim AB, Sathappan S, Chua KH. Characterization of human adipose-derived stem cells and expression of chondrogenic genes during induction of cartilage differentiation. *Clinics (Sao Paulo)* 2012; **67**: 99-106 [PMID: 22358233 DOI: 10.6061/clinics/2012(02)03]
- 137 **Webber RJ**, Harris MG, Hough AJ Jr. Cell culture of rabbit meniscal fibrochondrocytes: proliferative and synthetic response to growth factors and ascorbate. *J Orthop Res* 1985; **3**: 36-42 [PMID: 3981294 DOI: 10.1002/jor.1100030104]
- 138 **Brindle T**, Nyland J, Johnson DL. The meniscus: review of basic principles with application to surgery and rehabilitation. *J Athl Train* 2001; **36**: 160-169 [PMID: 16558666]
- 139 **Sweigart MA**, Aufderheide AC, Athansiou KA. Fibrochondrocytes and their use in tissue

- engineering of the meniscus. In: Ashammakhi N, Ferretti P. Topics in Tissue Engineering. Linnanmaa, Finland: University of Oulu, 2003: 1-19
- 140 **Upton ML**, Chen J, Guilak F, Setton LA. Differential effects of static and dynamic compression on meniscal cell gene expression. *J Orthop Res* 2003; **21**: 963-969 [PMID: [14554206](#) DOI: [10.1016/S0736-0266\(03\)00063-9](#)]
- 141 **Moon MS**, Kim JM, Ok IY. The normal and regenerated meniscus in rabbits. Morphologic and histologic studies. *Clin Orthop Relat Res* 1984; 264-269 [PMID: [6546362](#)]
- 142 **Hellio Le Graverand MP**, Ou Y, Schield-Yee T, Barclay L, Hart D, Natsume T, Rattner JB. The cells of the rabbit meniscus: their arrangement, interrelationship, morphological variations and cytoarchitecture. *J Anat* 2001; **198**: 525-535 [PMID: [11430692](#) DOI: [10.1046/j.1469-7580.2000.19850525.x](#)]
- 143 **Hellio Le Graverand MP**, Sciore P, Eggerer J, Rattner JP, Vignon E, Barclay L, Hart DA, Rattner JB. Formation and phenotype of cell clusters in osteoarthritic meniscus. *Arthritis Rheum* 2001; **44**: 1808-1818 [PMID: [11508433](#) DOI: [10.1002/1529-0131\(200108\)44:8<1808::AID-ART318>3.0.CO;2-B](#)]
- 144 **McDevitt CA**, Webber RJ. The ultrastructure and biochemistry of meniscal cartilage. *Clin Orthop Relat Res* 1990; 8-18 [PMID: [2406077](#)]
- 145 **Setton LA**, Guilak F, Hsu EW, Vail TP. Biomechanical factors in tissue engineered meniscal repair. *Clin Orthop Relat Res* 1999; S254-S272 [PMID: [10546651](#) DOI: [10.1097/00003086-199910001-00025](#)]
- 146 **Rath E**, Richmond JC. The menisci: basic science and advances in treatment. *Br J Sports Med* 2000; **34**: 252-257 [PMID: [10953895](#) DOI: [10.1136/bjism.34.4.252](#)]
- 147 **Ishimura M**, Ohgushi H, Habata T, Tamai S, Fujisawa Y. Arthroscopic meniscal repair using fibrin glue. Part I: Experimental study. *Arthroscopy* 1997; **13**: 551-557 [PMID: [9343641](#) DOI: [10.1016/S0749-8063\(97\)90179-1](#)]
- 148 **Horie M**, Driscoll MD, Sampson HW, Sekiya I, Caroom CT, Prockop DJ, Thomas DB. Implantation of allogenic synovial stem cells promotes meniscal regeneration in a rabbit meniscal defect model. *J Bone Joint Surg Am* 2012; **94**: 701-712 [PMID: [22517386](#) DOI: [10.2106/JBJS.K.00176](#)]
- 149 **Hatsushika D**, Muneta T, Horie M, Koga H, Tsuji K, Sekiya I. Intraarticular injection of synovial stem cells promotes meniscal regeneration in a rabbit massive meniscal defect model. *J Orthop Res* 2013; **31**: 1354-1359 [PMID: [23595964](#) DOI: [10.1002/jor.22370](#)]
- 150 **Ruiz-Ibán MÁ**, Díaz-Heredia J, García-Gómez I, Gonzalez-Lizán F, Elías-Martín E, Abraira V. The effect of the addition of adipose-derived mesenchymal stem cells to a meniscal repair in the avascular zone: an experimental study in rabbits. *Arthroscopy* 2011; **27**: 1688-1696 [PMID: [22001734](#) DOI: [10.1016/j.arthro.2011.06.041](#)]
- 151 **Agung M**, Ochi M, Yanada S, Adachi N, Izuta Y, Yamasaki T, Toda K. Mobilization of bone marrow-derived mesenchymal stem cells into the injured tissues after intraarticular injection and their contribution to tissue regeneration. *Knee Surg Sports Traumatol Arthrosc* 2006; **14**: 1307-1314 [PMID: [16788809](#) DOI: [10.1007/s00167-006-0124-8](#)]
- 152 **Mizuno K**, Muneta T, Morito T, Ichinose S, Koga H, Nimura A, Mochizuki T, Sekiya I. Exogenous synovial stem cells adhere to defect of meniscus and differentiate into cartilage cells. *J Med Dent Sci* 2008; **55**: 101-111 [PMID: [19845155](#)]
- 153 **Horie M**, Sekiya I, Muneta T, Ichinose S, Matsumoto K, Saito H, Murakami T, Kobayashi E. Intra-articular Injected synovial stem cells differentiate into meniscal cells directly and promote meniscal regeneration without mobilization to distant organs in rat massive meniscal defect. *Stem Cells* 2009; **27**: 878-887 [PMID: [19350690](#) DOI: [10.1634/stemcells.2008-0616](#)]
- 154 **Dutton AQ**, Choong PF, Goh JC, Lee EH, Hui JH. Enhancement of meniscal repair in the avascular zone using mesenchymal stem cells in a porcine model. *J Bone Joint Surg Br* 2010; **92**: 169-175 [PMID: [20044699](#) DOI: [10.1302/0301-620X.92B1.22629](#)]
- 155 **Hatsushika D**, Muneta T, Nakamura T, Horie M, Koga H, Nakagawa Y, Tsuji K, Hishikawa S, Kobayashi E, Sekiya I. Repetitive allogeneic intraarticular injections of synovial mesenchymal stem cells promote meniscus regeneration in a porcine massive meniscus defect model. *Osteoarthritis Cartilage* 2014; **22**: 941-950 [PMID: [24795274](#) DOI: [10.1016/j.joca.2014.04.028](#)]
- 156 **Murphy JM**, Fink DJ, Hunziker EB, Barry FP. Stem cell therapy in a caprine model of osteoarthritis. *Arthritis Rheum* 2003; **48**: 3464-3474 [PMID: [14673997](#) DOI: [10.1002/art.11365](#)]
- 157 **Abdel-Hamid M**, Hussein MR, Ahmad AF, Elgezawi EM. Enhancement of the repair of meniscal wounds in the red-white zone (middle third) by the injection of bone marrow cells in canine animal model. *Int J Exp Pathol* 2005; **86**: 117-123 [PMID: [15810983](#) DOI: [10.1111/j.0959-9673.2005.00420.x](#)]
- 158 **Al Faqeh H**, Nor Hamdan BM, Chen HC, Aminuddin BS, Ruszymah BH. The potential of intra-articular injection of chondrogenic-induced bone marrow stem cells to retard the progression of osteoarthritis in a sheep model. *Exp Gerontol* 2012; **47**: 458-464 [PMID: [22759409](#) DOI: [10.1016/j.exger.2012.03.018](#)]
- 159 **Caminal M**, Fonseca C, Peris D, Moll X, Rabanal RM, Barrachina J, Codina D, García F, Cairó JJ, Gòdia F, Pla A, Vives J. Use of a chronic model of articular cartilage and meniscal injury for the assessment of long-term effects after autologous mesenchymal stromal cell treatment in sheep. *N Biotechnol* 2014; **31**: 492-498 [PMID: [25063342](#) DOI: [10.1016/j.nbt.2014.07.004](#)]
- 160 **Ferris DJ**, Frisbie DD, Kisiday JD, McIlwraith CW, Hague BA, Major MD, Schneider RK, Zubrod CJ, Kawcak CE, Goodrich LR. Clinical outcome after intra-articular administration of bone marrow

- derived mesenchymal stem cells in 33 horses with stifle injury. *Vet Surg* 2014; **43**: 255-265 [PMID: 24433318 DOI: 10.1111/j.1532-950X.2014.12100.x]
- 161 **Centeno CJ**, Busse D, Kisiday J, Keohan C, Freeman M, Karli D. Regeneration of meniscus cartilage in a knee treated with percutaneously implanted autologous mesenchymal stem cells. *Med Hypotheses* 2008; **71**: 900-908 [PMID: 18786777 DOI: 10.1016/j.mehy.2008.06.042]
- 162 **Hong JH**, Park JI, Kim KH, Kim YM, Joo YB, Jeon YS. Repair of the Complete Radial Tear of the Anterior Horn of the Medial Meniscus in Rabbits: A Comparison between Simple Pullout Repair and Pullout Repair with Human Bone Marrow Stem Cell Implantation. *Knee Surg Relat Res* 2011; **23**: 164-170 [PMID: 22570829 DOI: 10.5792/ksrr.2011.23.3.164]
- 163 **Walsh CJ**, Goodman D, Caplan AI, Goldberg VM. Meniscus regeneration in a rabbit partial meniscectomy model. *Tissue Eng* 1999; **5**: 327-337 [PMID: 10477855 DOI: 10.1089/ten.1999.5.327]
- 164 **Zellner J**, Mueller M, Berner A, Dienstknecht T, Kujat R, Nerlich M, Hennemann B, Koller M, Prantl L, Angele M, Angele P. Role of mesenchymal stem cells in tissue engineering of meniscus. *J Biomed Mater Res A* 2010; **94**: 1150-1161 [PMID: 20694982 DOI: 10.1002/jbm.a.32796]
- 165 **Moradi L**, Vasei M, Dehghan MM, Majidi M, Farzad Mohajeri S, Bonakdar S. Regeneration of meniscus tissue using adipose mesenchymal stem cells-chondrocytes co-culture on a hybrid scaffold: In vivo study. *Biomaterials* 2017; **126**: 18-30 [PMID: 28242519 DOI: 10.1016/j.biomaterials.2017.02.022]
- 166 **Zhang H**, Leng P, Zhang J. Enhanced meniscal repair by overexpression of hIGF-1 in a full-thickness model. *Clin Orthop Relat Res* 2009; **467**: 3165-3174 [PMID: 19526274 DOI: 10.1007/s11999-009-0921-8]
- 167 **Moriguchi Y**, Tateishi K, Ando W, Shimomura K, Yonetani Y, Tanaka Y, Kita K, Hart DA, Gobbi A, Shino K, Yoshikawa H, Nakamura N. Repair of meniscal lesions using a scaffold-free tissue-engineered construct derived from allogenic synovial MSCs in a miniature swine model. *Biomaterials* 2013; **34**: 2185-2193 [PMID: 23261221 DOI: 10.1016/j.biomaterials.2012.11.039]
- 168 **Qi Y**, Chen G, Feng G. Osteoarthritis prevention and meniscus regeneration induced by transplantation of mesenchymal stem cell sheet in a rat meniscal defect model. *Exp Ther Med* 2016; **12**: 95-100 [PMID: 27347022 DOI: 10.3892/etm.2016.3325]
- 169 **Katagiri H**, Muneta T, Tsuji K, Horie M, Koga H, Ozeki N, Kobayashi E, Sekiya I. Transplantation of aggregates of synovial mesenchymal stem cells regenerates meniscus more effectively in a rat massive meniscal defect. *Biochem Biophys Res Commun* 2013; **435**: 603-609 [PMID: 23685144 DOI: 10.1016/j.bbrc.2013.05.026]



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