

# Potential use of mesenchymal stem cells in human meniscal repair: current insights

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**Abstract:** The menisci of the human knee play an important role in maintaining normal functions to provide stability and nutrition to the articular cartilage, and to absorb shock. Once injured, these important structures have very limited natural healing potential. Unfortunately, the traditional arthroscopic meniscectomy performed on these damaged menisci may predispose the joint toward early development of osteoarthritis. Although a very limited number of studies are available, mesenchymal stem cells (MSCs) have been investigated as an alternative therapeutic modality to repair human knee meniscal tears. This review summarizes the results of published applications of MSCs in human patients, which showed that the patients who received MSCs (autologous adipose tissue-derived stem cells or culture-expanded bone marrow-derived stem cells) presented symptomatic improvements, along with magnetic resonance imaging evidences of the meniscal repair.

**Keywords:** adipose tissue-derived stem cells, bone marrow-derived stem cells, human knee, meniscal tear, articular cartilage, therapeutic modality

## Introduction

The menisci of a human knee are a pair of fibrocartilaginous structures that function to provide stability and nutrition to the articular cartilage, and to absorb shock.<sup>1-3</sup> Removing these structures, by either full or partial meniscectomy, disrupts the homeostasis of the knee and predisposes the joint to an early development of osteoarthritis (OA).<sup>4-7</sup>

The human meniscus has very limited vascularity. The inner one-third of the meniscus (also known as the white zone due to its lack of vascularity) has lesser natural healing potential than the middle (the red-white zone, with moderate vascularity), which in turn has lesser natural healing potential than the peripheral one-third (called the red zone due to relatively abundant vascularity).<sup>8,9</sup> Due to its lack of vascularity, symptomatic injury in the inner one-third of the meniscus may require a partial meniscectomy, even though a partial meniscectomy may result in an early development of OA of the treated knee.<sup>10,11</sup>

As an alternative treatment to the surgical repair of meniscal tears, mesenchymal stem cells (MSCs) have been investigated. MSCs are of special interest because of their multilineage plasticity, with potential induction toward both fibrocartilage and articular cartilage.<sup>12,13</sup> Numerous human studies have been published in the field of regenerative medicine regarding the regenerative potential of MSCs in articular cartilage.<sup>14-18</sup> Some of these studies have demonstrated the increased volume of meniscal fibrocartilage resulting in its regeneration.<sup>15-17</sup>

For example, Centeno et al first published a case study, in which culture-expanded, autologous bone marrow-derived MSCs were administered via a percutaneous and

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intra-articular injection into a 46-year-old male patient with a degenerative damage of a knee joint. As a result, significant meniscal cartilage regeneration was shown using magnetic resonance imaging (MRI).<sup>15</sup>

In 2011, Pak reported that two OA patients who received a percutaneous, intra-articular injection of non-expanded adipose tissue-derived stem cells (ASCs), in the form of stromal vascular fraction (SVF) with platelet-rich plasma (PRP), showed subsequent increased meniscal fibrocartilage volume, which was confirmed by MRI.<sup>17</sup>

These are two published examples of MSCs from different sources regenerating the meniscal cartilage. However, neither of these studies showed repair of meniscal tears. Because regenerating meniscal cartilage does not necessarily repair a meniscal lesion, it becomes important to look for actual cases of MSCs regenerating the torn meniscal lesions and thus improving its symptoms.

Currently, only a few human studies are available that have actually examined the effects of MSCs in potentially repairing meniscal tears in human patients.<sup>16,19,20</sup>

## Sources of MSCs

MSCs can be isolated from several tissues, including bone marrow,<sup>21</sup> synovial membrane,<sup>22</sup> and adipose tissue.<sup>23</sup>

Bone marrow has been one of the most common sources of adult MSCs. Numerous *in vitro* and *in vivo* studies are available using bone marrow-derived stem cells. However, the number of stem cells present in fresh human bone marrow is very low (~0.01% of the total mononucleated cells) and, therefore, the use of bone marrow requires *in vitro* cell expansion to obtain a sufficient quantity to be used for regenerative purposes.<sup>24</sup> Another possible drawback of bone marrow-derived MSCs for a meniscal cartilage regeneration is that they may retain osteogenic propensities.<sup>25</sup>

Adipose tissues are another source of MSCs. Lipoaspirates can be easily obtained by liposuction. Such a tissue contains far more MSCs than the bone marrow in an identical volume.<sup>26</sup> Due to the high number of such stem cells in adipose tissue, no cell expansion is necessary to yield regenerative effects.<sup>14,17,23</sup> Adipose tissue-derived MSCs have been used in regenerating articular cartilage in patients with OA.<sup>14</sup>

Lastly, the synovial membrane of a knee is a potential source of MSCs. Furthermore, it has been shown that the number of MSCs in synovial fluid increases after a meniscal injury.<sup>27,28</sup> Such autologous synovial MSCs were applied to cartilage injury.<sup>29</sup> Currently, only one clinical study repairing chondral defect using scaffold-free three-dimensional tissue engineered construct, derived from human synovial MSCs, was completed in March 2015; but, the outcomes of the study

were not reported.<sup>30,31</sup> This may be considered to be evident that these naturally occurring MSCs may play an important role in meniscal healing and regeneration.

## Intra-articular delivery of MSCs

Many modes of injecting stem cells into a human knee are available. Of those, the most attractive strategy may be percutaneous intra-articular injections of MSCs. Some of the advantages of these injections are: 1) ability to carry out the procedure in an outpatient setting, 2) minimal downtime after the procedure, and 3) ease of repeatability.

## Meniscal lesions

Injuries to the meniscus occur in different patterns and shapes. Meniscal tear patterns can be classified as longitudinal-vertical, horizontal, radial, vertical flap, horizontal flap, and complex tears.<sup>32</sup> Until the widespread recognition of the side effect of early development of OA in the treated knee, all these types of meniscal tears are used to be routinely resected by a total meniscectomy. However, even with partial meniscectomy, performed only when necessary to improve symptoms in injured knees, early development of OA is still a major side effect.<sup>33</sup>

With regard to the alternative repair of the meniscal tears with MSCs, it is not yet known if these different categories of meniscal tears may respond differently. It is very likely that different types of meniscal tears may require different strategies, such as different dosages of stem cells, differing periods of immobilization after stem cell injection, or possible concomitant arthroscopic resection of the tears.

## Applications of MSCs in repairing meniscal tears in humans

Currently, only a few studies are available to assess the role of MSCs in repairing meniscal tears in human patients. The main features of these studies are summarized in Table 1.

In 2013, Pak et al reported a safety cohort study involving 91 patients with various joint disorders.<sup>20</sup> A subset of 32 of these patients with degenerative and nondegenerative meniscal tears were treated with a mixture of autologous ASCs in the form of SVF, PRP, hyaluronic acid, and CaCl<sub>2</sub>. The ASCs-containing SVF was obtained by processing autologous lipoaspirates with collagenase. Then, the mixture was administered through a percutaneous intra-articular injection into the patients with meniscal tears. The patients received additional doses of PRP with CaCl<sub>2</sub>. The study concluded that there was symptomatic improvement as measured on a visual analog scale (VAS) and a functional ratings index, along with MRI evidence of the meniscal cartilage regeneration.<sup>20</sup>

In 2014, a randomized, double-blind, placebo-controlled study involving 55 patients, who underwent a partial meniscectomy (resection of at least 50%), was conducted. Patients were randomly assigned to receive allogeneic, culture-expanded, bone marrow-derived stem cells.<sup>16</sup> Patients were randomized into one of three treatment groups: Group A, in which patients received an intra-articular injection of  $50 \times 10^6$  allogeneic MSCs; Group B, who received  $150 \times 10^6$  allogeneic MSCs; and the control group, who received sodium hyaluronate as a placebo. The patients who received MSCs showed clinical improvement, assessed with the VAS and self-Lysholm knee scale, and also showed significant meniscal volume regeneration, seen on MRI at 1 year postimplantation.<sup>16</sup>

In 2014, Pak et al reported a case study in which a percutaneous intra-articular injection of autologous ASCs, in the form of SVF, along with PRP, hyaluronic acid, and  $\text{CaCl}_2$ , repaired a meniscal tear in a 32-year-old female by regenerating a meniscal cartilage.<sup>19</sup> Again, the ASCs-containing SVF was obtained by processing autologous lipoaspirates with collagenase. The mixture (ASCs-containing SVF with PRP, hyaluronic acid, and  $\text{CaCl}_2$ ) was then injected into the medial tibiofemoral joint of the patient on the same day the SVF was obtained. The patients received four additional doses of PRP with  $\text{CaCl}_2$  and hyaluronic acid on days 3, 7, 14, and 28. Afterward, a near-complete repair of the torn meniscus was seen on a repeat MRI performed at 3 months postimplantation.<sup>19</sup>

In 2016, a single-center, prospective, open-label study involving five patients with an avascular meniscal tear was conducted.<sup>34</sup> Autologous MSCs were isolated from an iliac crest bone marrow biopsy, expanded, and seeded into the collagen scaffold. The resulting human MSC/collagen-scaffold implant was placed into the meniscal tear of five patients. The patients were followed for 24 months. All five patients treated showed significant clinical improvement on repeated measures analysis (Tegner–Lysholm score, range of motion, and the International Knee Documentation Committee [IKDC] score). Three of the five patients were asymptomatic at 24 months with clinical improvement in knee function scores and without any evidence of recurrent meniscal tear on MRI studies. Two patients required subsequent meniscectomy due to re-tear or nonhealing of the meniscal tear at ~15 months after implantation. No other adverse events occurred.<sup>34</sup>

## Discussion

Currently, only a few successful applications of MSCs in repairing human meniscal tears have been documented. Thus, before general application of this potentially promising,

minimally invasive, nonsurgical alternative, many issues (challenges and limitations) need to be resolved. First, more human studies are required, using a variety of different sources of MSCs and applying them to different categories of meniscal tears.

Second, the mechanism of how MSCs may repair meniscal tears is unclear. Some of the possible mechanisms are: 1) secretory and trophic effects of the stem cells injected<sup>35,36</sup>; 2) direct engraftment and differentiation of the stem cells introduced into the joints<sup>37,38</sup>; or 3) the combination of mechanisms (1) and (2). MSCs secrete a variety of cytokines, chemokines, growth factors, and exosomes.<sup>39,40</sup> These factors have positive effects on the growth of the surrounding progenitor cells. Furthermore, some evidence exists that the injected stem cells may actually become engrafted into the tissue and differentiate into tissue-specific cells.<sup>41</sup>

Third, the fate of MSCs injected into a joint needs to be further elucidated. According to a preclinical study,<sup>42</sup> knee-injected MSCs stays only in the knee joint after the injection. However, the ultimate fate of MSCs injected into a joint is not yet clear in clinical studies. MSCs may stay in the joint, attached to the lesion, and may become integrated into the target tissue, prolonging their own survival. However, some of the MSCs that are not integrated into the tissue may be removed slowly while secreting various trophic factors.

Lastly, properly designed clinical studies with valid control treatments (eg, saline) may be necessary to make an accurate conclusion regarding the effect of MSCs in regenerating meniscal cartilage. Currently, there are studies comparing PRP to MSCs to confirm the regenerative effects of MSCs.<sup>43,44</sup> However, it is also necessary to include saline or other inert placebo therapy in a control group to establish the real regenerative effects of MSCs.

## Conclusion

A comprehensive review of the literature suggests that MSCs possess an intrinsic therapeutic potential that can directly and indirectly contribute to cartilage regeneration, thus potentially healing meniscal tears and offering great potential as an alternative treatment modality. The meniscal tissue is a crucial structure that functions to provide knee stability, shock absorption, and nutrition to articular cartilages. However, once the knee is injured, the current treatment modality of meniscectomy may lead to an early development of OA in the treated knee. Thus, new treatment strategies are necessary to regenerate the damaged tissue without causing such detrimental side effects. Regenerative medicine using MSCs may offer an alternative strategy that does not result in an early development of OA in the treated knee.

**Table 1** Current and clinical use of MSCs for human knee meniscus tears

Study (year)	Intervention treatment	Study type	Number of subjects	Subject characteristic (age [year]; gender)	Previous therapy	Concurrent treatment	Follow-up (months)	Outcome measures	Results	Authors' conclusion
Pak et al <sup>20</sup>	Adipose SVF (ASC)+PRP+HA via percutaneous injections	Cohort study	32	Mean 47.8 (range: 18–78); 20 M Mean 51.6 (range: 29–77); 12 F	Various conservative treatments without success	None	24	VAS; functions (FRI, ROM); MRI	VAS/function improvements and MRI evidence of meniscus cartilage regeneration	ASC+PRP+HA: effective in repairing meniscal tears
Vangness et al <sup>16</sup>	Culture expanded, allogeneic bone marrow-derived stem cells via intra-articular injections	Randomized, double-blind, placebo-controlled study; MSCs vs HA vehicle control	55	Mean 46.0 (range: 18–60); 38 M and 17 F	None 3 months prior	Partial arthroscopic meniscectomy	24	VAS; functions (Lysholm); MRI	VAS and Lysholm improvements and MRI evidence of meniscus cartilage regeneration in non-control groups	Allogeneic culture-expanded bone marrow-derived MSCs (non-control group) are effective in regenerating meniscus and improving symptoms
Pak et al <sup>19</sup>	Adipose SVF (ASC) +PRP+HA via percutaneous injections	Case report	1	32; 1 F with chronic knee pain due to meniscus tear	Various conservative treatments without any success	None	3	VAS; functions (FRI, ROM); MRI	VAS/function improvements and MRI evidence of cartilage regeneration	ASC+PRP+HA: effective in repairing meniscal tears
Whitehouse et al <sup>34</sup>	Culture-expanded, autologous bone marrow-derived stem cells + collagen-scaffold via arthroscopic implantation	Prospective open-label study	5	Median 37 (range: 30–38); 4 M ND; 1 M	None	None	24	Functions (IKDC score, ROM, Tegner–Lysholm score); MRI	Three of five patients showed function improvements and MRI evidence of meniscal repair	Culture-expanded, autologous bone marrow-derived stem cells + collagen-scaffold: effective in repairing meniscal tears

**Note:** Tegner, Tegner activity scale.

**Abbreviations:** ASC, adipose tissue-derived stem cells; F, female; FRI, functional rate index; HA, hyaluronic acid; IKDC, International Knee Document Committee; Lysholm, Lysholm scores; M, male; MRI, magnetic resonance imaging; MSC, mesenchymal stem cell; ND, not described; PRP, platelet-rich plasma; ROM, range of motion; SVF, stromal vascular fraction; VAS, visual analogue scale; yr, years.

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## Disclosure

The authors report no conflicts of interest in this work.

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