



# Effects of intra-articular administration of autologous bone marrow aspirate on healing of full-thickness meniscal tear: an experimental study on sheep\*

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**Objective:** The aim of this study was to evaluate the effects of bone marrow-derived mesenchymal stem cell and bone marrow elements on the healing of meniscal tears.

**Methods:** This study was performed on twelve, 2-year-old male Tahirova sheep. In each subject, one knee was used for experiment purposes and the other knee was used as a control. After creating a longitudinal full-thickness tear in the red-white zone of the medial meniscus, aspirated autologous bone marrow material was injected into the tear site in the experiment group. The control group received no intervention for secondary healing.

**Results:** In the macroscopic evaluation of meniscus, a bridging reparation tissue and adhesion were observed between the rims of the tear in the experiment group. There was no statistical difference in collagen fibril formation between the groups ( $p=0.16$ ). There was significantly more neovascularization in the experiment group than the control group ( $p=0.003$ ). The cell count was also a significantly higher in the experiment group ( $p=0.004$ ) and formation of cartilage plaques was more frequent in the experiment group ( $p=0.016$ ). There was no evidence suggesting intrinsic repair in the meniscus of control group by light and electron microscopy.

**Conclusion:** An injection of bone marrow into the meniscus tear site improves healing in a meniscal tear model as demonstrated by both light and electron microscopic findings.

**Key words:** Bone marrow; electron microscopy; meniscal tear; mesenchymal stem cell.

Meniscal injuries are among the most common problems in orthopedic surgery. The meniscus is a fibrocartilaginous tissue and has several functions that are

essential for a healthy knee joint.<sup>[1-3]</sup> In the past, the prevailing treatment modality for meniscus injuries was total meniscectomy. However, in recent years, it

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has been emphasized that such injuries should be repaired and allowed to heal. Some fundamental trials have shown an increased articular contact pressure even after partial meniscectomy.<sup>[4]</sup>

Various surgical reconstruction or repair techniques have been used to prevent the progression to secondary osteoarthritis. These new techniques include scaffold, biodegradable polyurethane scaffold, growth factors, pediculated synovial flaps, submucosa of the small intestine, fibrin glue and placement of nonfunctional meniscus with autogenic and allogenic tissues. However, the outcomes of such therapies are debatable.<sup>[5-10]</sup>

Healing is problematic in the red-white zone, which is avascular or has variable vascularity. While repairing tears in these zones, it is useful to apply techniques that will improve healing potential.<sup>[11,12]</sup> These techniques include rasping one side of the synovial membrane surrounding the meniscus and meniscal tear to form vascular channels, to place a fibrin clot and micro-fractures of intercondylar notch. Common aspects of these techniques are intra-articular administration of bone marrow and blood elements.<sup>[13-16]</sup> Many studies have demonstrated improvement in the healing rate of meniscal tears by the addition of blood, particularly bone marrow elements with pluripotent stem cells experimentally.<sup>[13,15]</sup> Bone marrow is the most extensively investigated source of stem cells because of the ease in the recruitment of stem cells, low neoplastic differentiation and the absence of ethic issues.<sup>[17]</sup>

Bone marrow aspirate is a rich source for growth factors such as the transforming growth factor  $\beta$  (TGF- $\beta$ ), platelet-derived growth factor (PDGF) and vascular endothelial growth factor (VEGF). These growth factors are released from platelets and mesenchymal stem cells (MSC), involving alpha granules.<sup>[18-22]</sup>

The aim of this study was to evaluate the effects of bone marrow-derived mesenchymal stem cell and bone marrow elements on the healing of meniscal tears.

## Materials and methods

The study protocol was reviewed and approved by Ethics Committee of Erciyes University (Study Number: TT0748). Twelve male Tahirova sheep (two years old, mean body weight: 35 kg) were used. All subjects underwent surgery involving both knees. In each subject, one knee was used for experiment purposes and the other knee was used as a control. Knees in the experimental group were injected with aspirated autologous bone marrow material into the tear site and the control group received no intervention for secondary healing.

Preoperative epidural anesthesia was performed to reduce postoperative pain. A medial parapatellar incision extending from the distal femur to the distal site of the tibial tubercle was made. The knee joint was exposed by opening the capsule at the medial side in the same line with the skin incision. The patella was subluxated laterally. Standard incisions were performed on the medial meniscus in both groups. The meniscal tear was created by taking the meniscocapsular junction as a reference point, using a specially developed instrument with a 3 mm space between a Kirschner wire and a number 12 lancet. A 10 mm, full-thickness longitudinal tear was bilaterally created in all subjects. Care was taken to obtain a full-thickness tear at the meniscus, which were 3 mm far from the meniscocapsular junction at the anterior horn of the meniscus. The created tear was located in the red-white zone of the meniscus.

Surgical procedures were performed by the same surgeon on all subjects. Bone marrow was aspirated from the medullar cavity of the femur at the intercondylar notch with a 14 gauge aspiration needle. In the experiment group, 5 cc of autologous bone marrow was injected into the tear site. In the control group, the tear site was left to secondary healing without any intervention following the creation of the meniscal tear. In order to allow the subjects to perform knee joint motion, no external fixation or cast application was applied.

In the postoperative period, prophylactic antibiotic treatment was given to all subjects. A first dose of cefquinome sulfate (Cobactan<sup>®</sup> 2.5%; Intervet Vet. İlaç. Ltd. Şti., Istanbul, Turkey) was given intramuscularly 30 minutes prior to surgical procedure at a dose of 1 mg/kg live body weight. The same dosage was maintained for 3 days after the surgical procedure. Additionally, 1 ml/50 kg live body weight per day procaine penicillin G + crystallized penicillin G + streptomycin sulfate (Strepto-Veticilline<sup>®</sup>; Eczacıbaşı İlaç San. ve Tic. A.Ş., Istanbul, Turkey) was administered intramuscularly for 3 days postoperatively. Flunixin meglumin (Fluvil<sup>®</sup>; Vilsan Veteriner İlaçları Tic. San. A.Ş., Ankara, Turkey) was given intravenously for 3 days postoperatively at a dose of 1 ml/45 kg live body weight as non-steroidal anti-inflammatory and analgesic drug.

All subjects were killed by decapitation method under ketalar anesthesia at the 16th postoperative week. The knee joint was exposed by dissecting the capsule and ligaments. The medial meniscus was excised totally for histopathological evaluation. The meniscus excised en bloc were placed into Petri dishes containing phosphate buffered saline. The meniscus was divided into

two pieces involving the tear site. One of the pieces was processed with a light microscope and the remaining piece was cut into slices of 1 mm<sup>3</sup> and examined with electron microscope.

Tissue samples were fixed in 10% formalin and then dehydrated. They were embedded in paraffin blocks, with a proper angle to meniscal incision. Four  $\mu$  thick sections were cut from paraffin blocks and then stained by Masson's trichrome. Images were captured and increase in neovascularization, collagen fibrils, cell numbers and the presence of cartilage plaques on light microscope were evaluated by a histologist blind to groups.

In the macroscopic and histological scoring system for open wound healing proposed by Okamoto<sup>[23]</sup> and Tsuboi and Rifkin,<sup>[24]</sup> re-epithelization, formation of granulation tissue, inflammatory cell count, fibroblast count and neovascularization were assessed. The above-mentioned scoring system was modified in the present study. Accordingly, the formation of collagen fibril, neovascularization, level of cell count and formation of cartilage plaque were rated from 1 to 4 (Table 1).

Transmission Electron Microscope (TEM) evaluation was performed in the laboratory of Hacettepe University, Faculty of Medicine, Histology and Embryology Department. Tissue samples were fixed by immersion in 2.5% buffered glutaraldehyde. Fixed samples were rinsed in phosphate buffer and post-fixed in 2% osmium tetroxide. Again, samples were rinsed in phosphate buffer and dehydrated. Plastic blocks were prepared with an Araldite 6005 kit.

Semi-thin sections (1  $\mu$ ) were stained with blue-azure II and examined with a Leica DMR microscope (Leica Microsystems, Wetzlar, Germany). Images were captured with a Leica DC500 digital camera (Leica Camera AG, Solms, Germany). The area to be evaluated was trimmed and thin sections (70 nm) of this area were mounted on formvar-coated copper grids and stained with uranyl acetate and lead citrate with an automated staining machine (Leica Microsystems, Wetzlar, Germany). All samples were analyzed on a transmission electron microscope (Jeol JEM 1400) attached to a Gatan Orius SC-1000 digital camera for ultra structure of meniscus by a histologist blinded to groups.

Differences between groups were assessed using the Mann-Whitney U test. Increase in neovascularization, collagen fibril formation, increase in the number of cells and cartilage plaque formation in the meniscal tear healing area were compared between groups. P values of less than 0.05 were considered significant. Statistical analysis was performed using the Statistical Package for the

**Table 1.** Modification of scoring system of Okamoto,<sup>[23]</sup> Tsuboi and Rifkin,<sup>[24]</sup> for meniscal tear healing model.

Collagen fibril formation		Increase in cell count	
None	1	None	1
Fine	2	Low	2
Intermediate	3	Moderate	3
Thick	4	High	4
Neovascularization		Cartilage plaques	
None	1	None	1
Low	2	Low	2
Moderate	3	Moderate	3
High	4	High	4

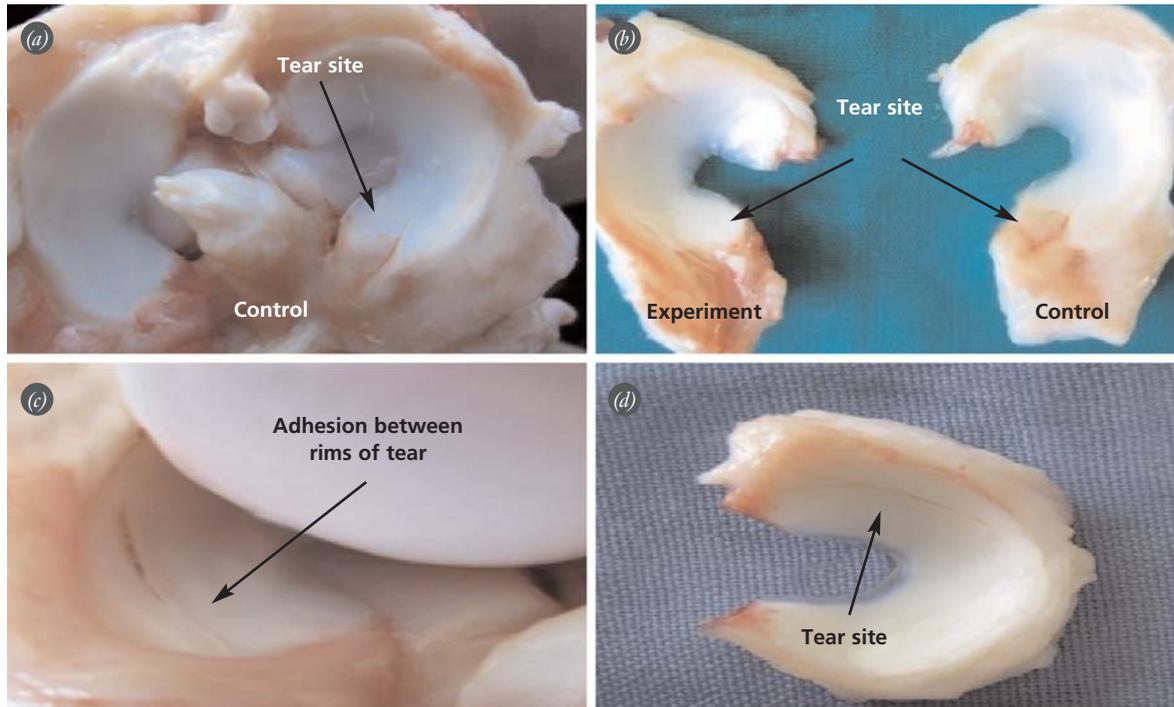
Social Sciences for Windows (SPSS/PC+ Inc., Release 17.0; SPSS Inc., Chicago, IL, USA).

## Results

An increase in the amount of intra-articular fluid was found in the knees of both the experiment and control groups. No fibrosis or infection was observed in the intra-articular structures. Synovial tissue was hypertrophic. There was no difference in articular cartilage. A synovial membrane with vascularization extended towards tear site in both groups. A bridging healing tissue and adhesion connecting the rims of the meniscus tear site was observed in the experiment group. However, there was a space between the two rims of the tear site in the control group (Fig. 1).

Increases in neovascularization, collagen fibril formation, increases in cell count and the presence of cartilage plaques were assessed in sections from meniscal samples. In the light microscope evaluations of the experiment group, healing was present at the access site of the tear and deep sites were partially filled by the newly formed cells which migrated from the capsule and proliferated at the meniscal tear healing site. Cells that displayed similar characteristics to capsules supported these macroscopic findings.

Healing site in the deeper areas of tear was covered by loose connective tissue including mononuclear cells and abundant fibroblasts and showed increased neovascularization. In addition, there was new granulation tissue in this healing area. Granulation tissue started to organize and had continuity with meniscal tissue; however, recently structuring collagen fibrils in the healing site were still thin and scarce. The formation of cartilage plaques was observed in the deepest part of incision in 5 subjects in the experiment group (Fig. 2).



**Fig. 1.** (a) Appearance of meniscus in the control group after dissection of knee ligaments. (b) Increase in synovial tissue and vascularization at the femoral and tibial surface of the meniscus in the experiment and control groups. (c) Appearance of the meniscus and adhesion formation in the experiment group at the postoperative 16th week macroscopically. (d) Healing meniscal tissue and adhesion and bridging between the rims of tear site in the experiment group. [Color figure can be viewed in the online issue, which is available at [www.aott.org.tr](http://www.aott.org.tr)]

The tear site failed to close in the control group which was left to secondary healing. There was a normal vascularization as well as no increase in the production of collagen fibrils. Additionally, this meniscal tear site was not filled with granulation tissue.

There was no statistical difference between groups in collagen fibril formation ( $p=0.16$ ). There was a significant difference between the experiment group and control group in neovascularization ( $p=0.003$ ). There was also a significant difference in the experiment group regarding cell count of the sections ( $p=0.004$ ). When sections were examined for formation of cartilage plaques, there was a significant difference in experiment group ( $p=0.016$ ) (Table 2).

In both the experiment and control groups, the collagen fibrils were arranged in a parallel manner at distant areas from the tear site. Chondrocytes were embedded between these collagen fibrils. The foot process of the cellular membrane and the scarcity of organelles in this area should also be mentioned.

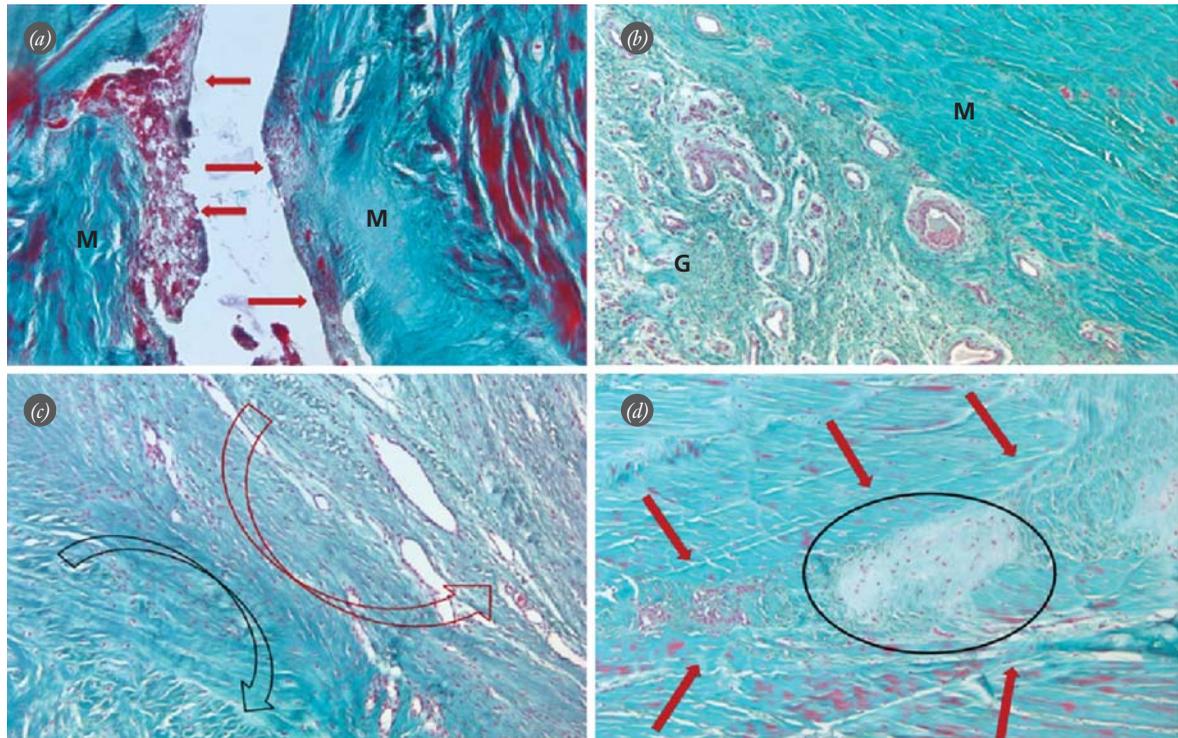
In the experiment group, well-developed organelles and chondroblasts were present in the vicinity of the meniscal healing area. In addition, there was an inten-

sive extracellular matrix synthesis and reduction in transverse striations of the newly formed collagen fibrils, which had an irregular, scattered and distant localization by electron microscope. This observation suggests the contribution of these cells to reparation tissue. Particularly, the rough endoplasmic reticulum was enlarged and prominent. Newly synthesized collagen fibrils with irregular localization were present in this area (Fig. 3).

No evidence suggesting intrinsic repair was observed by electron microscopy in the control group. Degenerated chondrocytes were present in the vicinity of the meniscal healing area.

**Table 2.** Statistical comparison in findings of light microscopy between the two groups.

Variables	Experiment (n=12) Median (25-75)	Control (n=12) Median (25-75)	P
Collagen fibrils	3 (2.5-4)	3 (2.5-3)	0.16
Neovascularization	4 (3-4)	3 (2-3)	0.003
Cell count	3 (3-3.5)	3 (2-2.5)	0.004
Cartilage plaque	1 (1-2)	1 (1-1)	0.016



**Fig. 2.** (a) A light microscopy sample of experiment group. Granulation tissue, formed by migrating and proliferating cells, are marked with red arrows. M: meniscus. D4 x200 Masson's trichrome. (b) G: Granulation tissue, in which increase of cellular infiltration, vascularization and collagen formation can be seen at the deeper sites of wedge-like tear. M: meniscus. D4 x100 Masson's trichrome. (c) A micrograph of experiment group. Black arrow: meniscus. Red arrow: granulation tissue. Increase of cellular infiltration and vascularization as well as thinner collagen fibrils (newly formed) in the granulation tissue can be seen. D2a x100 Masson's trichrome. (d) In the wedge-like tear site (red arrows), newly formed cartilage islets within the granulation tissue is marked with a black circle. D2 x100 Masson's trichrome. [Color figure can be viewed in the online issue, which is available at [www.aott.org.tr](http://www.aott.org.tr)]

## Discussion

Healing is problematic in the red-white zone which has variable or no vascularity. In the repair of tears in these zones, it is useful to add techniques which will improve healing potential.<sup>[11-15]</sup> In the present study, care was given to create the meniscal tear within the red-white zone in order to assess the effect of bone marrow elements on the healing of meniscal tissue in this zone.

For tissue repair, transplantation of bone marrow-derived MSCs is a promising alternative. It is well-known that these cells can transform into several different tissue types such as osteogenic, chondrogenic and adipogenic tissues.<sup>[17]</sup>

Centeno et al.<sup>[25]</sup> were the first investigators to administer MSC in humans. They showed a significant improvement in volume of injured meniscus and cartilage by magnetic resonance imaging (MRI).

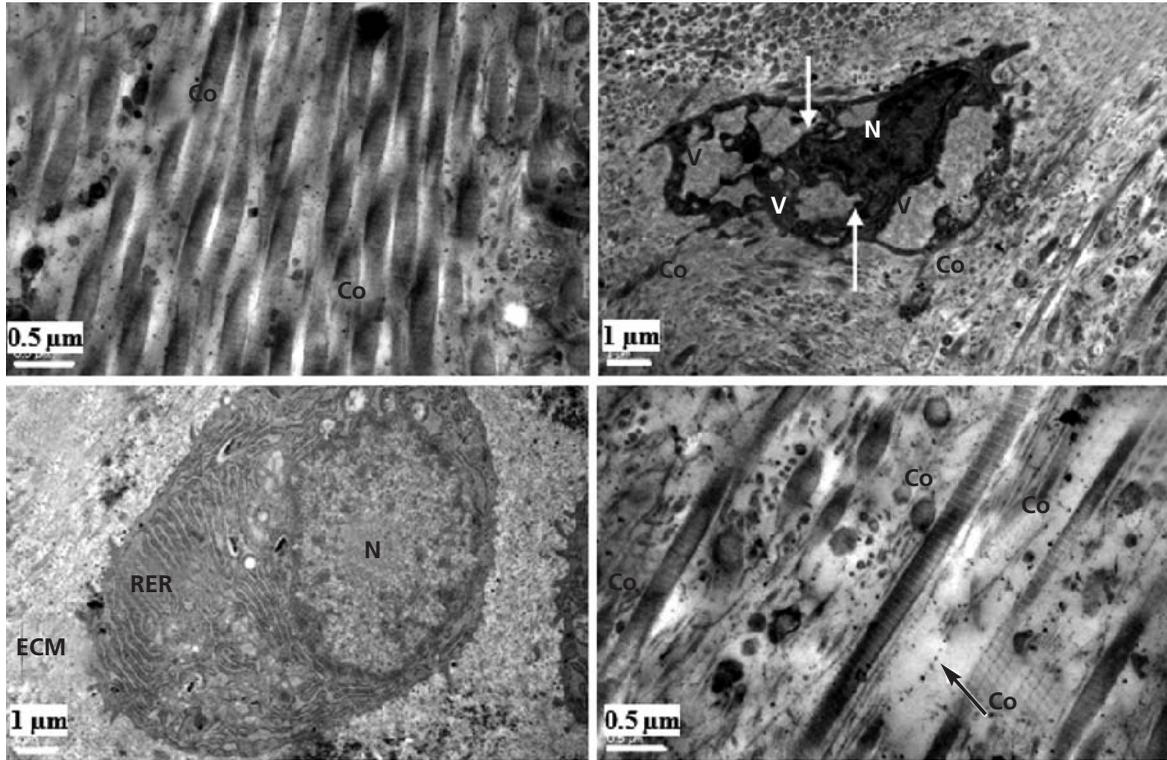
Fortier et al.<sup>[26]</sup> compared the outcomes of treatment in an equine model full-thickness cartilage injury. They applied bone marrow concentrate to the full-thickness

cartilage defect and showed the effects of bone marrow concentrate on healing of the defect which was superior to microfracture alone.

Many adult tissues contain stem cells that have the capacity for renewal after trauma, disease or aging. The adult bone marrow also contains MSCs, which contribute to the regeneration of mesenchymal tissues, such as bone, cartilage, muscle, ligament, tendon, adipose, and stroma.<sup>[27]</sup> Pittenger et al. reported the isolation, expansion, and characterization of the multipotent human MSCs.<sup>[17]</sup>

MSCs have been successful in terms of cartilage regeneration in animal models and bone regeneration in human models.<sup>[28-30]</sup> Caplan and Dennis<sup>[31]</sup> inferred that mesenchymal stem cells trophically enhanced the regeneration of the meniscus by a mechanism similar to those outlined above for heart and stroke models.

In the sheep meniscal tear model in this study, a follow-up of four months was sufficient to see the maturation or degeneration of reparation tissue that formed at



**Fig. 3.** (a) Parallel localization of collagen fibrils (Co) in the experiment group (Co). Uranyl acetate-lead citrate x40,000. (b) Micrograph of degenerated chondrocyte in a sample from control group. N: nucleus of chondrocyte, V: vacuole, Co: collagen fibrils, Arrow: perinuclear halo. Uranyl acetate-lead citrate x15,000. (c) Well-developed rough endoplasmic reticulum can be seen in a micrograph of experiment group. N: nucleus of chondroblast, ECM: extracellular matrix, RER: rough endoplasmic reticulum. Uranyl acetate-lead citrate x15,000. (d) Irregular, scattered and distant localization of newly formed collagen fibrils (Co) in a section of experiment group. Arrow: transverse striation in collagen fibrils. Uranyl acetate-lead citrate x40,000.

the meniscal tear healing site. To observe the contribution of the bone marrow-derived MSCs to the repair process, no primary repair to the tear site of meniscus was performed.

Integration of the reparation tissue with the normal tissue at the meniscal healing site was better in the experiment group. In the control group, there was a gap at the meniscal tear site and tear site was filled by cells which migrated from the capsule but not integrated to the healing tissue.

In the experiment group there were statistically significant findings of neovascularization ( $p=0.003$ ), increase in cell count ( $p=0.004$ ), and cartilage plaque formation ( $p=0.016$ ). In the present study, the TEM findings supported the macroscopic and light microscopic findings. Formation of cartilage islets, which were seen under light microscope, was supported by well-developed organelles and the presence of active chondroblasts with euchromatic nuclei on TEM. The rough endoplasmic reticulum of these cells was enlarged and prominent. This pattern of chondroblast

cells indicates active protein synthesis and contribution to the repair process. Observation of intensive extracellular matrix synthesis and newly synthesized collagen fibrils around these cells also favors this contribution.

In the experiment group, there was obvious signs of healing and formation of cartilage tissue, especially in five subjects at the end of four months. There was no healing observed macroscopically and histopathologically in the control group. These results showed that intra-articular injection of bone marrow-derived MSCs and marrow elements may be an option to cure meniscal tears.

As supported by light and electron microscopy findings, autologous bone marrow aspirate and marrow elements, administered into the joint together, stimulated meniscal tear healing and contributed to tissue regeneration.

A weakness of the study was that cell isolation and preculture of the bone marrow-derived MSCs could not be performed to achieve the maximum MSC con-

centration. However, further experimental and clinical investigations are needed to demonstrate the efficiency of this technique. As a result, non-invasive therapies may emerge without the need for arthroscopy or arthroscopy in clinical practice usage.

As demonstrated in this study by both light and electron microscopic findings, the healing potential of the meniscal tear was better in the experiment group. In conclusion, the administration of bone marrow aspirate improved healing of the meniscal tear site.

**Conflicts of Interest:** No conflicts declared.

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