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Intra-articular administration of peripheral blood stem cells with platelet-rich plasma regenerated articular cartilage and improved clinical outcomes for knee chondral lesions

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ABSTRACT

Purpose: To determine whether intra-articular injections of peripheral blood stem cells improved the regeneration of articular cartilage in patients with osteochondral knee injuries.

Methods: This prospective study included 20 patients with grade 3b knee osteochondral lesions who underwent knee arthroscopies. All were white, and all had performed physical activity at least five times a week. International Knee Documentation Committee (IKDC) and visual analog scale scores were recorded before surgery, six months and one year after surgery, and then yearly until five years after surgery. Magnetic resonance imaging scans were obtained six months preoperatively and then yearly and were evaluated by musculoskeletal radiologists blinded to the patient data. Tissue repair was quantified using the International Cartilage Repair Society morphologic score system. Unpaired *t*-tests were used for comparisons between the time points.

Results: The mean preoperative IKDC score was 50.5 (42–61). At the six-month follow-up, the mean values were 60.79 ($P = 0.32$) and 90.97. At the six-month follow-up, the mean values were 70.8 ($P = 0.043$). At the end of the five-year follow-up, the IKDC was 82.2 ($P = 0.024$). At five-year follow-up, the visual analog scale score was 1.1 ($P = 0.0018$). The main morphologic score system score was 3.2 preoperatively and 9.7 $\pm$ 1.6 at five-year follow-up ($P = 0.0021$). No infection, tumors, or synovitis were reported at the end of the follow-up.

Conclusions: Intra-articular peripheral blood stem cells with platelet-rich plasma regenerated articular cartilage and improved clinical outcomes for knee chondral lesions at five years of follow-up.

1. Introduction

The treatment of chondral lesions is currently an important topic of study in traumatology because of the low spontaneous healing capacity of articular cartilage and the lack of a standard treatment that can consistently restore its structure and function. The hyaline cartilage of the knee has a low capacity for regeneration and is generally replaced by fibrocartilage. It also has a low capacity to withstand mechanical stress over time. Many authors have reported progressive deterioration of neoformed chondral tissue at 24–36 months [1–3], with poor stimulation of progenitor cells at the lesion site [4].

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Recently, researchers have focused on cell therapy as a therapeutic alternative; this can promote the regeneration of articular cartilage in a lasting way, with in vitro and in vivo studies in animals and humans showing encouraging results [5–8]. Several types of cells obtained from various sources have been used in the treatment of articular cartilage lesions, such as in vitro expanded autologous chondrocytes [9] and mesenchymal stem cells. Mesenchymal stem cells are usually autologous and obtained from tissues such as bone marrow, adipose tissue, skin, or peripheral blood, or from an umbilical cord donor. These cells can be used directly without manipulation or can initially be expanded in vitro to increase their number, or they can be applied in combination with a carrier material such as platelet-rich plasma (PRP) or collagen [10].

The intra-articular infiltration of peripheral blood stem cells (PBSCs) has shown promising results in clinical studies for osteochondral lesions [7], with an efficacy comparable with that of using bone marrow cells [8]. The aim of this study was to determine whether an intra-articular injection of PBSCs suspended in autologous PRP improves the regeneration of durable articular cartilage in patients with osteochondral knee injuries who undergo arthroscopic microfracture surgery. Our hypothesis is that the use of intra-articular administration of PBSCs with PRP regenerated articular cartilage improved outcomes for knee chondral lesions.

2. Methods

2.1. Patients

In this prospective study, we recruited 20 otherwise healthy Caucasian patients who underwent arthroscopic knee surgery at our center between March 2010 and January 2012 for knee osteochondral lesions classified as grade 3b according to the classification of the International Cartilage Repair Society (ICRS) [11] and who had not responded to nonsurgical treatment for at least four months. All performed physical activity at least five times a week. The clinical diagnosis of osteochondral lesion was confirmed by 2.0-T magnetic resonance imaging (MRI). The inclusion and exclusion criteria for this study were as follows.

Inclusion criteria:

- A diagnosis of symptomatic localized chondral lesion 3b ICRS without a response to non-surgical treatment for at least four months.
- Absence of osteoarthritis.
- Healthy, without systemic disease.
- Radiographic images in anteroposterior, axial, and lateral projections, computed tomography scan (alignment), and 2.0-T MRI.
- Size of the lesion: 8.5–25 mm in diameter alone without other images of osteoarthritis in the affected knee.
- Time between confirmed diagnosis and treatment less than six months.
- Surgical indication and general condition compatible with the intervention.
- The same surgical team performed all procedures using the same surgical technique and the same anesthetic protocol and pain management.

Exclusion criteria:

- Presence of radiological signs of osteoarthritis.
- Chondral lesion produced by osteochondritis and lesion greater than 25 mm diameter.
- Knee instability (cruciate ligament rupture).
- Use of intra-articular corticosteroids in the last six months.
- Chronic treatment with oral corticosteroids.
- Presence of concomitant injury such as meniscus tears, or previous surgery to the affected knee.
- Concomitant rheumatic disease.
- Diabetes mellitus.
- Current or previous hemato-oncologic disease.
- The inability to give informed consent All patients provided written informed consent, and this study was approved by our institution's ethics committee.

2.2. Mobilization and collection of PBSCs and autologous PRP

For the three consecutive days before surgery, the patients received a dose of 30 MU of filgrastim each day. On the day of surgery, prior to the procedure, a peripheral blood unit (about 450 ml) was obtained from the patient and centrifuged to remove the buffy coat and plasma. The plasma was again centrifuged at 3500 rpm for 10 min to obtain the PRP fraction. In parallel, the PBSC-enriched mononuclear fraction was extracted from the buffy coat by Ficoll density gradient centrifugation at 1800 rpm for 20 min and then resuspended in autologous PRP to a volume of approximately 50 ml (430,000 PBSC $\pm$270.000 per ml and 640,000,000 $\pm$ 110,000 PRP per ml). From this, the first dose (~10 ml) was applied fresh to the patient during the surgical procedure, with 10% dimethylsulfoxide added to the remainder, which was preserved for later use in a cryopreservation unit (Thermo Scientific) in liquid nitrogen at -195 °C, using five-ml cryotubes.

2.3. Surgical procedure and administration of PBSC suspended in PRP

The surgical procedure used knee arthroscopy with blood tourniquet under spinal anesthesia. After performing the usual diagnostic procedure, the chondral lesion was measured and then delimited by debriding until the healthy cartilage was reached, and the calcified plaque was resected with a curette. Microdrilling was performed at the level of the tibial condyles and cymbals at low speed with a 1.2-mm bit to a depth of seven millimeters, leaving a stable bone bridge between them. In the patella, low-speed drilling with a 1.2-mm bit was performed in an out–in fashion, locating the fenestrations approximately every four millimeters using a guide as commonly used in anterior cruciate ligament surgery. Following the procedure, the joint fluid was removed by infusing 20 ml of air to visualize the dry lesion, and then 10 ml of PBSC suspended in autologous PRP was injected into the lesion as a clot adherent. The same procedure was used for patellar lesions. After the procedure, a compression dressing was installed, and the emptying sleeve was released. The joint was immobilized for 24 h. After surgery, intra-articular injections of five milliliters of the previously cryopreserved PBSC + PRP were administered into the compromised joint once a week for three weeks; according to previously reported study of Saw et al. [7], this was performed by the same surgeon.

2.4. Care of the patient

The same pain-management protocol was used for all patients. Nonsteroidal anti-inflammatory drugs (300 mg of ketoprofen in 500 ml of Ringer's solution) was administered at 10 ml/h for 24 h. The patients were then prescribed one gram of acetaminophen every eight hours for 15 days. In addition, all patients received enoxaparin 5000 U/day for 21 days to prevent thromboembolism. No epidural blocks, femoral blocks, or possible opioid rescue was used.

All patients underwent the same rehabilitation protocol. The first-stage protocol was aimed at protection; no weight bearing and in knee immobilizer for four weeks even for the patellar lesions and included avoiding loading the limb during this period. The intermediate stage consisted of articular range-of-motion exercises and exercises to improve flexibility and knee stability. As impact protection, all patients were instructed to avoid running, jumping, and similar exercise for up to one year after surgery [12]. This stage included sports-specific training without running or jumping and continued for one year, after which the patient was allowed to return to full sports participation.

2.5. Clinical and radiological evaluation

For the clinical evaluation, we obtained each patient's International Knee Documentation Committee (IKDC) score and a visual analog scale (VAS) score at the following time points: before surgery, six months after surgery, one year after surgery, and then yearly until the last follow-up five years after surgery. We obtained MRI scans six months preoperatively, one year after surgery, and then yearly until the five-year-follow-up. The MRI was performed with a 2.0-T scanner. The MRI scans were evaluated by our two musculoskeletal radiologists, blinded to the patient data and they did not know the purpose of the study, with the evaluation including the repaired cartilage signal, the morphological characteristics of the repaired tissue, the integration of this tissue into the borders, and the presence of subchondral edema. To quantify the newly formed tissue repair, we used the ICRS morphologic score system (MSS) [3–11].

Statistical analyses were performed using SPSS 20.0 software. For the all-outcome measurements, the Shapiro–Wilk test was applied to check the normality of the data, and unpaired *t*-tests were used for comparisons, with the level of significance set at $\alpha = 0.05$. Data are presented as the mean ± standard deviation.

3. Results

Initially, 32 patients were eligible for the study, but eight were excluded according to the exclusion criteria, two did not return to complete the follow-up, and two did not wish to repeat the MRI yearly. The study population therefore included 20 patients, seven women and 13 men, with a mean age of 32.7 years (range 21–47 years) at the time of surgery. The mean time between diagnosis and surgery was 4.3 months, and the minimum follow-up period was 4.5 years (X: 5.1 years) (range 4.5–5.8 years). The locations of the lesions and their size and ICRS classification are summarized in Table 1, and the patients' demographic characteristics are presented in Table 2.

The mean preoperative IKDC score was 50.5 (42–61). At the six-month follow-up, the mean values were 60.79 and 90.97 ($P = 0.32$). At the six-month follow-up, the mean values were 70.8 ($P = 0.043$). At the end of the total follow-up period (five years), the mean IKDC score was 82.2; this was significantly higher than the preoperative score ($P = 0.024$) (Figure 1).

Table 1
Characteristics of the osteochondral knee injuries (n = 20).

Location	n	ICRS grade	Larger diameter (mm)
Trochlea	9	3.5 ± 0	21.7 ± 7.4
Femoral condyle	5	3.5 ± 0	16.5 ± 2.1
Patella	6	3.3 ± 0.8	12.6 ± 5.1

Data are expressed as mean ± standard deviation. ICRS, International Cartilage Repair Society.

Table 2
Demographic characteristics of the patients (n = 20).

Sex	13 (65%) men 7 (35%) women
Age (years)	32.7 ± 7.5 (21–47)
Height (m)	1.72 ± 0.07 (1.61–1.83)
Weight (kg)	76.9 ± 10 (58–98)
BMI (kg/m^2)	26.0 ± 2.7 (20.1–31.1)
IKDC pretreatment	50.5 ± 6.3 (42–61)
IKDC post-treatment	72.2 ± 13.3 (44–95)
MRI score	9.7 ± 1.6 (5–12)

Data are presented as mean ± standard deviation (range). BMI, body mass index; IKDC, International Knee Documentation Committee score; MRI, magnetic resonance imaging.

There was a significant difference in VAS scores between the mean preoperative score (5.3). At the end of the five-year follow-up period, the mean VAS score was 1.1, which was significantly less than the preoperative score ($P = 0.0018$).

In the evaluation of cartilage repair on MRI, the main MSS was 3.2 preoperatively and 9.7 ± 1.6 (range five to 12) at five-year follow-up; this difference was statistically significant ($P = 0.0021$). The specific and detailed data are summarized in Figure 2. Figures 3(a) and (b) and 4(a) and (b) present MRI images for patients showing the change between their preoperative lesions and their knees at the end of the five-year follow-up.

Only two patients reported a few side effects: myalgia and fever during the filgrastim administration. No infection, tumors, or synovitis was reported at the end of the follow-up.

4. Discussion

The results of this prospective study with at least four years of follow-up showed that the intra-articular injection of PBSC suspended in autologous PRP favored clinical and radiological improvement of osteochondral knee lesions in patients who underwent arthroscopic microdrilling surgery in an enduring manner. This is the first report of a clinical series using this therapy with a follow-up of more than four years. We observed generally good results in around 85% of the patients, and all returned to participating in sports. Our results are consistent with those reported in previous studies that used PBSC for knee joint injuries [6,7]. Saw et al. [7], who assessed the effect of infiltration with PBSC in combination with hyaluronic acid after microfracture surgery, reported a significant clinical improvement, expressed as a mean IKDC score of 74.8 in the treatment group; in our series the mean IKDC score was 72.2. The authors demonstrated the formation of hyaline-like cartilage by biopsies at two years of follow-up. Our study, although it does not include biopsies, confirmed that there was no deterioration of neoformed cartilage or recurrence of the lesion at final follow-up (mean 4.5 years); this can only be explained by the neoformed tissue being of higher quality than that reported with microfractures alone [3–14]. Stem cells can easily be acquired, expanded, and used in cartilage injuries. They have been extensively studied in both in vitro and in vivo studies with promising studies [15–18]. In our study we found that differences between the expected results of microdrilling alone and the results of microdrilling plus PBSCs; this can only be explained by the neoformed tissue being of a higher quality than that reported with microfractures alone [3–14]. The deterioration of neoformed tissue with microfractures alone was widely reported [3–14]. Stem cells have many advantages that make them effective in the treatment of chondral lesions; for example, they have a high capacity for self-renewal, multipotentiality, and plasticity [19,20]. However, they also present disadvantages, such as eventual hypertrophy or tumorigenesis [20]. In our study, we

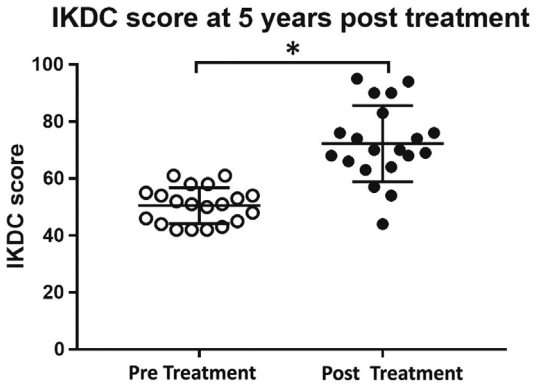

Figure 1. Change in International Cartilage Repair Society (ICRS) score between pretreatment and 5 years post-treatment. The increase in the statistically significant International Knee Documentation Committee (IKDC) score is shown. *$P = 0.024$ post-treatment vs. pretreatment (paired t-test). The horizontal lines indicate the mean and standard deviations.

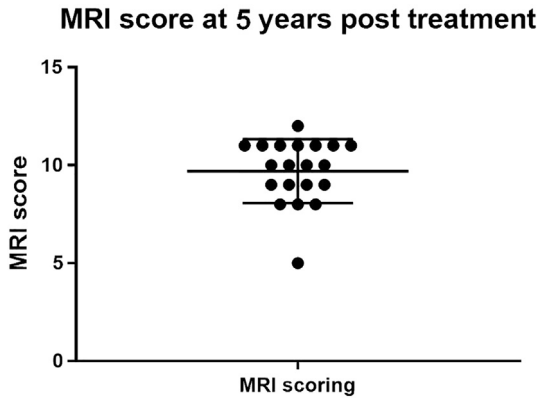

Figure 2. The patients' magnetic resonance imaging (MRI) scores at 5 years post-treatment. The International Cartilage Repair Society (ICRS) score is shown with a mean of 9.7. $P = 0.0021$. The horizontal lines indicate the mean and standard deviations.

observed a case of femoral trochlea lesion with cartilage hypertrophy seen on radiological images, but with no clinical consequences. We did not observe any cases with a benign or malignant tumor, either local or systemic, by the end of the follow-up period.

Stem cells can be obtained from several types of tissue. The most important three sources are aspirated bone marrow with cell expansion [5–21], adipose tissue [22,23], and peripheral blood [7]. In practice, these cells are easy to obtain and have a high potential for differentiation to chondrogenesis. Other sources include the periosteum, muscle cells, synovial tissue, embryonic tissue, placental umbilical cord, and amniotic (allogeneic) fluid. In our protocol, we decided to use PBSCs obtained from peripheral blood because their use, after mobilization from peripheral blood and extraction by apheresis, is technically easy to implement, cost limited, and mostly automated, reducing the risk of contamination. Their use requires the administration of filgrastim, a drug with very low toxicity that has extensively been used in bone marrow transplants. Filgrastim is a man-made form of a protein that stimulates the growth of white blood cells. Common side effects include aching or pain in the bones and muscles, diarrhea, constipation, hair loss, headache, feeling tired, skin rash, nosebleeds, or injection site reactions (redness, swelling, itching, lumps or bruising), or fever. In our series only two patients reported a few side effects: myalgia and fever during the filgrastim administration. Filgrastim is contraindicated in patients who have hypersensitivity to proteins derived from *Escherichia coli*, or any component of the product. Filgrastim has interactions with lithium (excessive or unexpected increase in white blood cells); Vincristine (severe peripheral neuropathy) and with Topotecan (prolonged duration of neutropenia).

The indications approved by the United States Food and Drug Administration (FDA) for the use of filgrastim are febrile neutropenia in non-myeloid malignancies that occur after chemotherapy myelosuppression or after transplantation of progenitor cells and in patients with acute myeloid leukemia receiving chemotherapy, prophylaxis. Neutropenic, chronic (severe), symptomatic, adult and pediatric disorders, except for neonates and autoimmune neutropenia of childhood. In our study, the use of filgrastim was approved by informed consent and by the ethical committee.

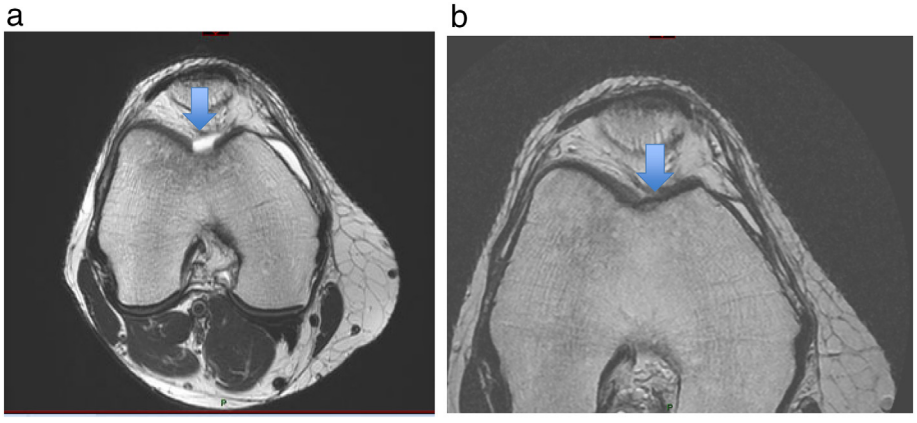

Figure 3. (a) A 24-year-old male with International Cartilage Repair Society (ICRS) b troclear osteochondral lesion. (b) The same patient at 5 years after treatment with complete and stable cartilage coverage (arrows).

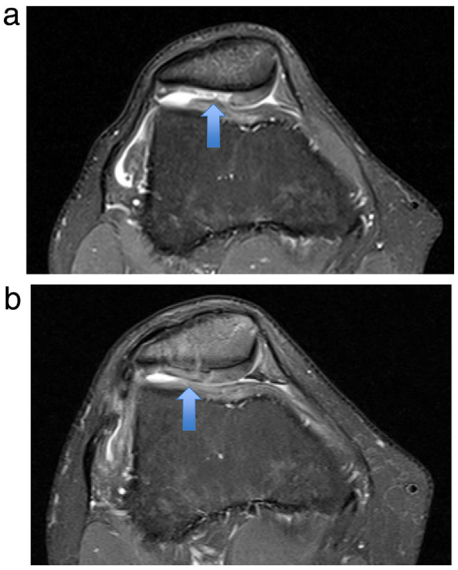

Figure 4. (a) A 34-year-old, female with International Cartilage Repair Society (ICRS) 3b patellar oteochondral lesion. (b) The same patient at 5 years after treatment with complete and stable cartilage coverage (arrows).

The intra-articular infiltration of PBSCs has shown promising results in clinical studies for osteochondral lesions, with an efficacy comparable with that of using bone marrow cells [7–24]. In addition, this procedure has already been used in other medical specialties [25], demonstrating its safety and low cost. There are also several matrices of suspension of these stem cells; in hyaluronic acid, in PRP clots, and in physiological serum are among the most used. In our study, we included them within a PRP clot because of the biological stability that this confers inside the lesion, and also because previous reports have shown the effectiveness of this method when used with microdrilling, as these factors directly influence the differentiation of the stem cells.

Although the modulation of cartilage repair has been verified in clinical practice, the exact underlying mechanism is not known. Similar to other authors [26,27], we believe that the increased expression of growth factors, such as platelet-derived growth factor and transforming growth factor, are essential to the healing process. Traumatic injury results in the formation of a platelet-rich hematoma, and this releases growth factors and initiates the recruitment of inflammatory cells. These inflammatory cells release additional growth factors and cytokines that continue the healing process. In this regard, PRP may facilitate tissue healing by increasing the differentiation of avascular hyaline such as cartilage at the injury site [26]. In vitro studies have shown that PRP significantly increases cell proliferation in a similar way. Cartilage-derived morphogenetic protein 2, in conjunction with other growth factors, such as insulin-like growth factor (IGF-1), transforming growth factor beta-1 (TGF-b1), and platelet-derived growth factor, shows the capability for restorative healing, inflammation modulation, and cartilage repair [28–30]. All surgical procedures generate a degree of inflammation that arises from the operative trauma. It is known that, under such circumstances, there is a natural release of growth factors because of the inflammatory response to injury, and that this may induce similar phenomena inherent to the reparative process [26,27]. We believe that adding these growth factors in great concentrations could stimulate early repair and would probably result in fewer undesired inflammatory symptoms, such as pain and swelling.

A wide variety of clinical and radiological evaluations can be used for clinical follow-up. Commonly reported methods include VAS scoring systems and the Knee Injury and Osteoarthritis Outcome Score [31–36]. In our study, we decided to use a VAS method and the IKDC scale because these are the most commonly used methods in the current literature on this subject and because they are by far the most efficient to administer to patients with traumatic (rather than osteoarthritic) osteochondral lesions. Several scales and techniques for the analysis of radiological imaging of the cartilage [37] or of whole-organ MRI [38] have also been described. For our series, we decided to use the MSS developed by Mithoefer et al. and developed by the ICRS [3–12], because this allows effective and reproducible quantification, especially of the amount and quality of the neoformed chondral tissue [7]. For the MRI, we used a 2.0-T scanner with the results evaluated descriptively according to the MSS by two independent radiologists blinded to the patient data. We observed the progression to chondral maturation in 87% of patients, with a mean MSS score of 10.2 at the end of follow-up (a statistically significant improvement); this was very similar to the mean score (9.9) obtained by Saw et al. [7]. For our series, we used a microdrilling technique, which has been extensively used in clinical trials [39]. The great advantage of this technique for classical microfractures lies in the reduced damage to the subchondral plaque [3]. However, in microfractures, which in many cases do not penetrate to the bone marrow, when bleeding is observed, it does communicate to the bone marrow; it blocks ingression channels of Fortier and small drills to ± 10 mm allow more cell incursion than that achieved with certainty with microdrilling. All previous reports of this technique have been observed clinically, and with

imaging show that, after recovery, a substantial proportion of the cases show deterioration in the quality of the neoformed tissue at 24 months [3]. In our series, our patients achieved clinical stabilization with no involution of the neoformed tissue reported with microfractures; indeed, the lesions were repaired with stable tissue without any imaging evidence of involution or tissue deterioration at five years## of follow-up.

4.1. Limitations

This study had several limitations. First, it was not controlled, and it was potentially underpowered and thus statistical analysis highlights trends rather than confirming significance. Second, only two observers evaluated the postoperative MRI scans. Third, the timing of the MRI scans may not have been ideal. Changes in the cartilage may not have been resolved by 4.5 years, even though our results suggest that they were. We chose to use only the IKDC and MSS scoring in this study because, at the time of the study, these were the most used tools for the topic at hand; we recognize this as a limitation, and it may have been better to include other scales such as the whole-organ MRI outcome score. Finally, 10 years of follow-up and MRI re-evaluation may have been preferable, but this was not possible.

5. Conclusion

The intra-articular administration of PBSCs with PRP regenerated articular cartilage and improved clinical outcomes for knee chondral lesions, with clinically stable recovery and no imaging evidence of tissue deterioration at 5-year follow-up.

References

[1] Hunziker E. Articular cartilage repair: basic science and clinical progress. A review of current status and prospects. Osteoarthr Cartil 2002;10:432–63.
[2] Korhonen RK, Wong M, Arokoski J, et al. Importance of the superficial tissue layer for the indentation stiffness of articular cartilage. Med Eng Phys 2002;24:99–108.
[3] Mithoefer K, Williams RJ, Warren RF, et al. The microfracture technique for the treatment of articular cartilage lesions in the knee. A prospective cohort study *J Bone Joint Surg Am* 2005;87:1911–20.
[4] Vinatier C, Bouffi C, Merceron C, et al. Cartilage tissue engineering: Towards a biomaterial-assisted mesenchymal stem cell therapy. Curr Stem Cell Res Ther 2009;4:318–29 [Review].
[5] Reissis D, Tang QO, Cooper NC, et al. Current clinical evidence for the use of mesenchymal stem cells in articular cartilage repair. Expert Opin Biol Ther 2016;16:535–57.
[6] Saw KY, Hussin P, Loke SC, et al. Articular cartilage regeneration with autologous marrow aspirate and hyaluronic acid: An experimental study in a goat model. Arthroscopy 2009;25:1391–400.
[7] Saw KY, Anz A, Siew-Yoke Jee C, et al. Articular cartilage regeneration with autologous peripheral blood stem cells versus hyaluronic acid: A randomized controlled trial. Arthroscopy 2013;29:684–94.
[8] Skowroński J, Rutka M. Osteochondral lesions of the knee reconstructed with mesenchymal stem cells — Results. Ortop Traumatol Rehabil 2013;15:195–204.
[9] Giannini S, Buda R, Cavallo M, et al. Cartilage repair evolution in post-traumatic osteochondral lesions of the talus: From open field autologous chondrocyte to bone-marrow-derived cells transplantation. Injury 2010;41:1196–203.
[10] Reissis D, Tang QO, Cooper NC, et al. Current clinical evidence for the use of mesenchymal stem cells in articular cartilage repair. Expert Opin Biol Ther 2016;16:535–57.
[11] Mainil-Varlet P, Aigner T, Brittberg M, et al. Assessment of cartilage repair: A report by the histology endpoint Committee of the International Cartilage Repair Society (ICRS). J Bone Joint Surg Am 2003;85:45–57.
[12] Whyte GP, Gobbi A, Sadlik B. Dry arthroscopic single-stage cartilage repair of the knee using a hyaluronic acid-based scaffold with activated bone marrow-derived mesenchymal stem cells. Arthrosc Tech 2016;5:e913–8.
[13] Ellermann JM, Donald B, Rohr S, et al. Magnetic resonance imaging of osteochondritis dissecans: Validation study for the ICRS classification system. J Acad Radiol 2016;23:724–49.
[14] Brittberg M, Winalski C. Evaluation of cartilage injuries and repair. J Bone Surg Am 2003;85:58–69.
[15] Tang QO, Carasco CF, Gamie Z, Korres N, Mantalaris A, Tsiridis E. Preclinical and clinical data for the use of mesenchymal stem cells in articular cartilage tissue engineering. Expert Opin Biol Ther 2012;12:1361–82.
[16] Pastides P, Chimutengwende-Gordon M, Maffulli N, Khan W. Stem cell therapy for human cartilage defects: A systematic review. Osteoarthr Cartil 2013;21:646–54.
[17] Sampson S, Botto-van Bemden A, Aufiero D. Autologous bone marrow concentrate. Phys Sportsmed 2013;41.
[18] Filardo G, Madry H, Jelic M, Roffi A, Cucchiarini M, Kon E. Mesenchymal stem cells for the treatment of cartilage lesions: from preclinical findings to clinical application in orthopaedics. Knee Surg Sports Traumatol Arthrosc 2013;21:1717–29.
[19] Chen FH, Tuan RS. Mesenchymal stem cells in arthritic diseases. Arthritis Res Ther 2008;10:223.
[20] Koh YG, Choi YJ, Kwon OR, Kim YS. Second-look arthroscopic evaluation of cartilage lesions after mesenchymal stem cell implantation in osteoarthritic knees. Am J Sports Med 2014;42:1628–37.
[21] Haleem AM, El Singergy AA, Sabry D, et al. The clinical use of human culture–expanded autologous bone marrow mesenchymal stem cells transplanted on platelet-rich fibrin glue in the treatment of articular cartilage defects: A pilot study and preliminary results. Cartilage 2010;1:253–61.
[22] Raynaud CM, Rafii A. The necessity of a systematic approach for the use of MSCs in the clinical setting. Stem Cells Int 2013;2013:892340.
[23] Pers YM, Rackwitz L, Ferreira R, et al. Adipose mesenchymal stromal cell-based therapy for severe osteoarthritis of the knee: A phase I dose-escalation trial. Stem Cells Transl Med 2016;5:847–56.
[24] Turajane T, Chaweewannakorn U, Larbpaiboonpong V, et al. Combination of intra-articular autologous activated peripheral blood stem cells with growth factor addition/preservation and hyaluronic acid in conjunction with arthroscopic microdrilling mesenchymal cell stimulation improves quality of life and regenerates articular cartilage in early osteoarthritic knee disease. J Med Assoc Thai 2013;96:580–8.
[25] Xiang H, Zhang X, Yang C, et al. Autologous bone marrow stem cell transplantation for the treatment of ulcerative colitis complicated with herpes zoster: A case report. Front Med 2016;10:522–6.
[26] Lyras DN, Kazakos K, Verettas D, et al. The influence of platelet-rich plasma on angiogenesis during the early phase of tendon healing. Foot Ankle Int 2009;30:1101–6.
[27] Visser LC, Arnoczky SP, Caballero O, Egerbacher M. Platelet-rich fibrin constructs elute higher concentrations of transforming growth factor-b1 and increase tendon cell proliferation over time when compared to blood clots: A comparative in vitro analysis. Vet Surg 2010;39:811–7.
[28] Virchenko O, Fahlgren A, Skoglund B, Aspenberg P. CDMP-2 injection improves early tendon healing in a rabbit model for surgical repair. Scand J Med Sci Sports 2005;15:260–4.

[29] Murray DH, Kubiak EN, Jazrawi LM, et al. The effect of cartilage-derived morphogenetic protein 2 on initial healing of a rotator cuff defect in a rat model. J Shoulder Elbow Surg 2007;16:251–4.
[30] Kon E, Buda R, Filardo G, et al. Platelet-rich plasma: Intra-articular knee injections produced favorable results on degenerative cartilage lesions. Knee Surg Sports Traumatol Arthrosc 2010;18:472–9.
[31] Bijur PE, Silver W, Gallagher EJ. Reliability of the visual analog scale for measurement of acute pain. Acad Emerg Med 2001;8:1153–7.
[32] Hefti E, Müller W, Jakob R, Stäubli H. Evaluation of knee ligament injuries with the IKDC form. Knee Surg Sports Traumatol Arthrosc 1993;1:226–34.
[33] 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.
[34] SooHoo NF, Shuler M, Fleming LL. American Orthopaedic Foot and Ankle Society. Evaluation of the validity of the AOFAS clinical rating systems by correlation to the SF-36. Foot Ankle Int 2003;24:50–5.
[35] Lysholm J, Gillquist J. Evaluation of knee ligament surgery results with special emphasis on use of a scoring scale. Am J Sports Med 1982;10:150–4.
[36] Tegner YLJ. Rating systems in the evaluation of knee ligament injuries. Clin Orthop Relat Res 1985:43–9.
[37] Anderson DE, Williams RJ, DeBerardino TM, et al. Magnetic resonance imaging characterization and clinical outcomes after neocart surgical therapy as a primary reparative treatment for knee cartilage injuries. Am J Sports Med 2017;45:875–83.
[38] Peterfy CG, Guermazi A, Zaim S, et al. Whole-Organ Magnetic Resonance Imaging Score (WORMS) of the knee in osteoarthritis. Osteoarthr Cartil 2004;12:177–90.
[39] Broyes JE, Stagg MP. Microdrilling surgery augmented with intrarticular bone marrow aspirate concentrate platelet rich plasma and hialuronic aci: A technique for cartilage repair in the knee. Arthrosc Tech 2017;13(6):201–6.