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Review Article

A Solution for Knee Osteoarthritis with Adipose-Derived Autologous Stem Cells in Middle-Aged People

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Abstract

Background: Adipose tissue has achieved a great relevance as possible fount of mesenchymal stem cells for the healing of different articular pathologies including Knee Osteoarthritis (KOA). Stem cells derived from the Adipose Tissue (ADSCs) have a possibility to differentiate into chondrocyte, can reduce the immune response and can stimulate a local tissue repair, improving also the intra-articular

Methods and Findings: Intra-articular injections of ADSCs with other conservative or surgical treatments can lead to an improving of all clinical and functional postoperative outcomes evaluated in middle-aged patients with KOA or chondral lesions. Moreover, some scores based on Magnetic Resonance Imaging (MRI) demonstrated an incremented quality of repaired cartilage in comparison with the pre-treatment. We observed no serious advent events.

Conclusion: The use of ADSCs appeared to be out of danger, effective and it can be supposed an alternative procedure for the healing of chondral lesions and degenerative OA suitable for middle-aged athlete but no specific studies have been focus on this population and no long term follow-up data are available.

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Keywords

Adipose-derived Stem Cells; Knee Osteoarthritis; Middle-Aged Athletes; Clinical Outcomes; Radiological Outcomes

Abbreviations

AAA: Arthroscopic Abrasion Arthroplasty; ADSCs: Adipose-Derived Mesenchymal Stem Cells; BMAC: Bone Marrow Aspirate Concentrate; BMP: Bone Morphogenetic Protein; EQOL: Emory Quality of Life; ESWT: Extracorporeal Shockwave Therapy; HA: Hyaluronic Acid; HTO: High Tibial Osteotomy; ICRS: International Cartilage Repair Society; IKDC: International Knee Documentation Committee; KOA: Knee Osteoarthritis; KOOS: Knee Injury and Osteoarthritis Outcome Score; MFAT: Microfragmented Adipose Tissue; MOAKS: MRI Analysis using MRI Osteoarthritis Knee Score; MOCART: Magnetic Resonance Observation of Cartilage Repair Tissue; MRI: Magnetic Resonance Imaging; NRS: Numeric Pain Rating Scale; NRS-11: Numerical Pain Rating Scale-11; PRP: Platelet-Rich Plasma; SF-36: Short Form 36; SVR: Stromal Vascular Fraction; TGF: Transforming Growth Factor; VAS: Visual Analog Scale; WOMAC: Western Ontario and McMaster Universities Arthritis Index; WJMSCSc: Wharton's Jelly-Derived Mesenchymal Stem Cells; WOMS: Whole-Organ Magnetic Resonance Imaging

Introduction

Knee Osteoarthritis (KOA) is an increasingly widespread disorder that is often unreceptive to non-surgical treatments, among which non-pharmacological interventions, treatment with systemic drugs and intra-articular therapies, lowering level of activity [1].

Middle aged athletes are higher demanding compared to no active people with higher impact and stress on joints structures including the knee and this can lead to progression to cartilage wear and knee osteoarthritis [2]. For that reason, a suitable approach among the possible treatment is the use of stem cells for managing of initial stages of KOA [3]. ADSCs therapy can lead to tissue regeneration even in the late stages (III and IV) of knee osteoarthritis. This procedure is cost friendly, economical and addressed to all categories of people. However, the treatment yielded poorer results in patients with late-stage of KOA (KL grade IV) than in patients with the early and middle-stage of KOA (KL grade I-III) [4].

The use of ADMSCs is also evaluated in the treatment of Osteochondral Lesions (OCL) of the ankle in combination with arthroscopic procedure of OCL removal, with reported progressive improvements as measured by the validated Foot and Ankle Disability Index [5]. Preliminary

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results with injection of mesenchymal stem cells are also assessed by Dall'Oca, et al., in the treatment of hip osteoarthritis with an improvement of postoperative HHS and WOMAC scores compared with the baseline values. Moreover, a recent study of Freitag, et al., showed the use of ADMSCs in the treatment of acromioclavicular joint OA led to a structural improvement with reduction in subchondral oedema, synovitis and subchondral cysts and an improvement of pain and function assessed by the Disability of Arm, Shoulder and Hand Score and Numeric Pain Rating Scale [6,7].

The Adipose Mesenchymal Stem Cells (ADSCs) can be harvested from the fatty tissue as it is simple to collect and available in large quantities [8]. ADSCs can offer similar clinical results to the ones harvested from iliac crest with minor morbidity [9]. The potential to transform into chondrocytes gives stem cells therapy regenerative because, once introduced near the lesion, they convert into novel cells that replace aged or damaged ones by remodeling the tissues [10,11].

ADMSCs secrete a variety of growth factors, cytokines and Extracellular Vesicles (EVs), which have been reported to promote cell proliferation and inhibit apoptosis of chondrocytes [12].

Therefore, *in-vitro* and *in-vivo* models suggest that the use of expanded ASCs improve bone healing through direct differentiation into mature osteoblast and paracrine effects that facilitate migration and differentiation of resident precursors.

The most common adverse effect of ADSCs treatment includes pain that can be avoided with local anesthetics. In the setting of allogeneic cell therapy studies, where the production of specific anti-bodies toward donor cells was examined, it was noted that 19%-35% of patients develop antibodies, but the consequence of this is unknown [13].

Methods

The inclusion criteria for this clinical study were people that have a minimum age of eighteen years and older with symptomatic knee pain and Grade II-IV knee osteoarthritis in line with the modified Kellgren-Lawrence (KL) classification, symptomatic cartilage lesions or failure of non-surgical therapies after three, six or more months [14-19].

The exclusion criteria for this clinical study were people with a recent traumatic knee injury and ligament lesions or meniscal tears knee instability chondromatosis of the knee or villonodular synovitis previous arthroscopic-assisted surgery for KOA joint infection inflammatory or metabolic arthritis axial knee deformity of five degrees and more pregnancy breast feeding, malignancy bleeding and coagulation disorders and people with more of seventy years old [15-19].

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The most commonly used tissue sources for isolating mesenchymal stem cells apart from bone marrow are the adipose tissue, umbilical cord, placenta and dental pulp [12]. Adipose tissue has become an attractive alternative because it is a source easy to access and in literature it is reported that ADSCs can usually be obtained by abdominal lipoharvest procedure by subpatellar fat-pad or by buttock subcutaneous fat [14-22].

The surgical time based on a lateral abdominal approach [14]. In the first place, a percutaneous infiltration with saline solution mixed with lidocaine, ropivacaine and adrenaline was performed [14,19]. After fifteen minutes, the abdominal subcutaneous fat lipoaspiration was performed using a metal cannula [14,16,19]. Koh and Choi harvested the adipose tissue from the infrapatellar fat pad using an enlargement of the cutaneous incision at the arthroscopic lateral portal side. Kim and Tsubosaka reported that one day before arthroscopic surgery the fat tissue was collected from the patient's buttocks via tumescent liposuction [18,22].

After that, the lipoaspirate was processed for isolation and expansion of autologous ADMSCs in the lab [14,16]. The adipocytes were divided from the Stromal Vascular Fraction (SVF) by centrifugation as reported by Zuk, et al., as a result of an enzymatic digestion with the use of collagenase [16,24]. After-wards, these Adipose Cells (ADSCs) were cultured and isolated using a hypoxic condition and appeared as a mean of 9.4% (range 8.2-10.9 %) of the stromal vascular fraction cells [14,16,18].

In alternative, the harvested fat was instead be processed and the final microfragmented tissue was transferred to a syringe and injected intra-articularly [25].

Results

ADSCs can be used via injection as unique procedure or associated to other conservative or surgical treatments to enhance their biological and clinical effect.

A lot of scientific studies reporting ADSCs injections for the management of KOA proved notable improvements in terms of knee function and pain in comparison with baseline data, up to 24 months of follow-up [14-19,21-23,25-37].

Basic science studies and clinical studies outlined the positive effect of injective mesenchymal stem cell-based treatments for knee osteoarthritis [26].

Tsubosaka, et al., evaluated 57 people who were subjected to an injection of adipose-derived SVF for knee OA [22]. This study showed that knee extension angle at six and twelve months postoperatively was significantly better than the preoperative angle. Moreover, the Visual Analog Scale (VAS), the total Western Ontario and McMaster Universities Arthritis Index (WOMAC) and the Knee Injury and Osteoarthritis Outcome Score (KOOS) scores at one,

three, six and twelve months postoperatively were considerably better than preoperative scores [22].

Lu, et al., compared a group of 26 patients treated with ADSCs injections with another one treated with HA injections [27]. They found significant improvements in WOMAC, VAS and SF-36 scores in both groups. In particular, compared with the HA group, significantly more patients achieved 50% improvement of WOMAC and more patients achieved a 70% improvement rate in ADSCs group. Meanwhile, there was notably more increase in articular cartilage volume of both knees in ADSCs group than in the HA group after 12 months as measured by MRI scores [27].

Freitag, et al., examined clinical results of some patients underwent only one or double injection and compared these results with another group underwent conservative treatment with no injections [14].

They observed a statistical and importantly improvement in pain and function in both treatment groups, as measured by validated outcome score including Numeric Pain Rating Scale (NRS), WOMAC and KOOS score [12]. In addition, MRI analysis using MRI Osteoarthritis Knee Score (MOAKS) indicated a variation of illness progression over 12 months of follow-up with largest stabilization reached by patients who received two injections of ADSCs [14].

Lee, et al., evaluated with a RCT trial 12 patients with KOA treated with ADSCs and compared to another group underwent an injection of saline solution [16]. At short term follow-up a significant improvement of pain and function was recorded with no adverse effect. Moreover, in MRI there was no significant change of cartilage lesion after ADSCs injection, whereas the lesion in the second group was increased at six months of follow-up [16].

Mautner, et al., evaluated clinical results of patients underwent Microfragmented Adipose Tissue (MFAT) therapy with another group underwent Bone Marrow Aspirate Concentrate (BMAC) injection [28]. They observed a significant prolonged improvement (>1 year) in pain and function with both MFAT and BMAC injections in people with symptomatic KOA, evaluated with the KOOS questionnaire, the Emory Quality of Life (EQOL) questionnaire and the Visual Analog Scale (VAS), without an important difference when comparing the two autologous tissue sources [28].

Pers, et al., evaluated an intra-articular injection of autologous ASCs in three consecutive cohorts of patients with symptomatic and severe knee OA with dose escalation: low dose (2 x 10⁶ cells), medium dose (10 x 10⁶ cells) and high dose (50 x 10⁶ cells) [17]. In particular, they observed an improvement of all clinical outcome parameters (pain, function and mobility according to the WOMAC score) regardless of the injected dose. However, significant improvements in pain levels and function were detected only for patients treated with the low dose of ASCs [17].

Jo, et al., assessed the efficacy of intra-articular injection of ADSCs in three dose escalation cohorts of patients (low dose with 1.0×10^7 cells, medium dose with 5.0×10^7 cells, high dose with 1.0×10^8 cells) [29]. Contrarily to the previous study, the WOMAC score improved at 6 months after injection in the high-dose group. Moreover, the dimension of cartilage lesion reduced, while the volume of cartilage grew in the medial tibial and femoral condyles of the high-dose group [29].

Similarly, Song, et al., considered three dose groups of patients with KOA treated with ADSCs injections (1×10^7 , 2×10^7 and 5×10^7 cells, respectively) [30]. This study showed intra-articular injection of ADSCs was correlated with a significant reduction of the WOMAC score and improvement in the Numerical Pain Rating Scale-11 (NRS-11) and Short Form 36 (SF-36) score in all the three dose groups of patients. In addition, it was associated with a significantly increased thickness of the articular cartilage, which was superior in the high dose group [30].

Ha, et al., in a systematic review found a positive effect of mesenchymal stem cell injections with improvement of pain and function at short term follow up and limited evidence for cartilage repair [31].

Lopa, et al., in their review outlined the lack of long-term study results with intra-articular injection of ADSCs for the management of KOA [26]. Moreover, they outlined that no source of stem cell has been proven to superior to another and the best stem cell dose has not been defined [26].

Controversially, Zhao, et al., in a recent systematic review compared ADSCs with platelet-rich plasma, hyaluronic acid and saline and they found ADSCs to be the best treatment in term of offering pain relief with VAS reduction [32].

Recently, Han, et al., in a network metanalysis found that cortisone and hyaluronic acid injection got better scored than ADSCs. They found that ADSCs to be not effective in obtaining a relevant reduction of pain and improvement of function [33].

Arthroscopic treatment with debridement has been shown a questionable effect for knee OA with moderate effects deteriorating at short term follow-up as it has been outlined by Thorlund, et al. [34].

Stem cells addition has been proposed as a potential adjuvant to enhance the biologic response after arthroscopic treatment of cartilage lesions or degenerative knee OA [35].

Panni, et al., reported intra-articular injection of ADSCs in association with arthroscopic debridement for the treatment of moderate KOA [19]. This study showed a significantly increasing of all clinical and functional scores evaluated (VAS score, IKS knee and function scores) at a mid-term follow-up [19].

Russo, et al., assessed injections of ADSCs in a cohort of 30 patients in association with other arthro-scopic and surgical knee procedures (ACL/LCL reconstruction, high tibial osteotomy, meniscectomy) [36]. They observed that more than 50% of the patients improved at least 20 points in all the considered scores (KOOS, IKDC-subjective, Tegner Lysholm Knee) and 55% of the patients improved at least 30 points in the VAS pain scale [36].

Freitag, et al., reported a study of 26 patients presenting grade IV knee OA treated with ADSCs injections plus Arthroscopic Abrasion Arthroplasty (AAA) [36]. This study showed all patients had significant reduction in knee pain and improvement in knee function with no serious complication after ADSCs+AAA and hyaline-like cartilage regeneration was seen in all participants [37].

Zhou, et al., studied the effect of infrapatellar fat pad extracted cells in a RCT showing that the treatment group of 29 patients, who underwent knee debridement with knee infrapatellar fat pad cell concentrates, obtained better scores for VAS, WOMAC and MOCART scales [23].

Koh and Choi studied the effects of a single injection of ADSC lipoaspirate from infrapatellar fat pad after arthroscopic debridement in 25 patients with a control group detecting a 94% of satisfaction rate for the patients but an abnormal cartilage repair tissue rate at second look arthroscopy of 74% [25].

Koh, et al., in a RCT studied the effect of ADSCs added to microfracture treatment for symptomatic focal defects of the knee larger than 3 cm [38]. Similar results for functional scores, return to sports and quality of life were obtained with improvement in the ADSCs group for the subscores of pain and radiological results (Fig. 1-3) [38].

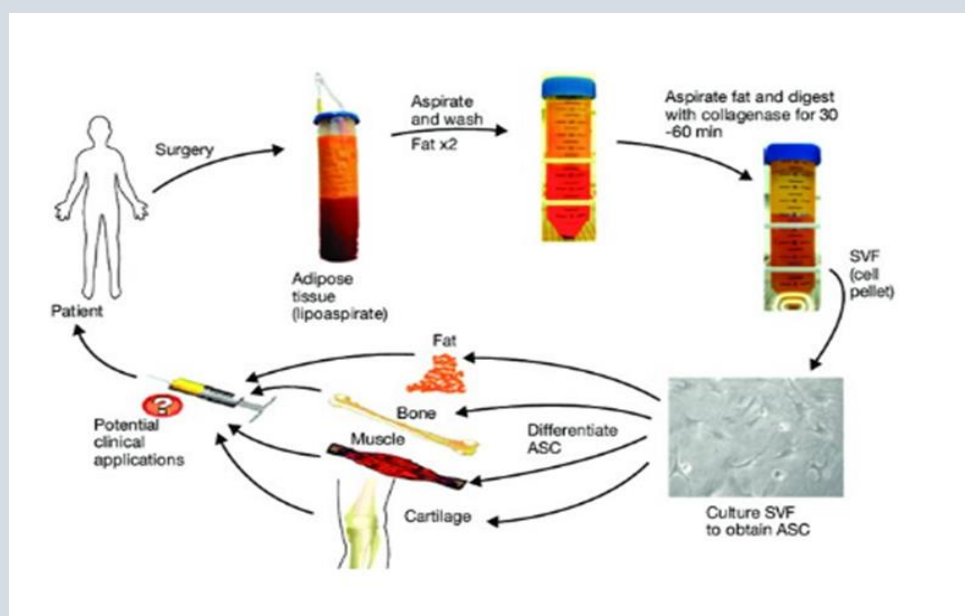


Figure 1: Human adipose-derived stem cells isolation and differentiation for clinical usage.

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Figure 2: Adipose derived mesenchymal stem cells harvesting technique.



Figure 3: The result of lipo-aspiration procedure.

Discussion

Several articles in literature reported the associated treatment with Hyaluronic Acid (HA), Platelet Rich Plasma (PRP) and shockwaves can potentiate the positive effects of ADSCs injections in the treatment of KOA [15,27,38,40,41].

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HA may restore the damaged HA layer on the articular cartilage surface and bring about an alleviation of the arthritic condition and an arrest of the progress of the disease [27,38,42].

PRP can act as a biological scaffold, widely used as a mesenchymal stem cells carrier for clinical chondrogenesis, based on the concept that platelets contain growth factors that when released have chemotactic and mitogenic effects on mesenchymal stem cells and osteoblasts when applied to bony tissues [15,40].

Extracorporeal Shockwave Therapy (ESWT) has been reported to have chondroprotective effects in KOA [38]. In particular, some studies have shown that ESWT promotes neovascularization, bone-healing, anti-inflammatory effects and wound-healing [41,43].

Hong, et al., assessed a cohort of 16 patients with symptomatic grade 1-3 Lawrence stage knee OA treated with ADSCs plus HA injections compared with another cohort of 16 patients (control group) treated only with HA injections [39]. This study showed significantly improvement in the mean VAS, WOMAC scores and ROM at 12-months follow-up visit. In contrast, the mean VAS, WOMAC scores and ROM of the control group became even worse but not significant from base-line to the last follow-up visit [39]. Moreover, the Whole-Organ Magnetic Resonance imaging (WORMS) score and the Magnetic resonance Observation of Cartilage Repair Tissue (MOCART) score based on MRI revealed a significant improvement of articular cartilage repair in the first group compared with the control group [39].

	Associated Treatments	Clinical Parameters and Index Changes
Hong, et al. [39]	ADSCs + HA	VAS, WOMAC, ROM, WORMS, MOCART
Koh, et al. [15]	ADSCs + PRP	VAS, Lysholm score, Tegner activity scale
Kim, et al. [18]	ADSCs + HTO	IKDC, Lysholm score, ICRS grades
Tan, et al. [47]	ADSCs + HTO	Lysholm score, KOOS, IKDC
Cheng, et al. [45]	ADSCs + ESWT	TSG-6, PRG-4, BMP-2, BMP-6, type II collagen
Hsu, et al. [41]	ADSCs + ESWT	TGF- β , BMP-4, type II collagen

Table 1: Associated treatments and clinical parameters evaluated in several clinical studies.

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Only the study of Bakowski, et al., compared outcomes of PRP and ADSCs therapy for KOA [40]. They reported both procedures are safety treatment options of KOA. The most common complications after the intra-articular injection are pain and swelling of treated knee, but this improves after cold compression and NSAIDs [40]. Moreover, there were no cancer incidents reported after ADSCs or PRP implantation [40]. In term of regenerative proprieties, in literature it was not reported one pro-cedure is better than the other one. However, Van Pham, et al., showed PRP-pretreated ADSCs improved healing of injured articular cartilage in a mouse model compared with untreated ADSCs [44].

Koh, et al., compared a study group of patients treated with ADSCs plus PRP injections compared with a control group treated only with arthroscopic debridement and PRP injections without stem cells [15]. They reported the mean Lysholm, Tegner activity scale and VAS scores of patients in the study group improved significantly by the last follow-up visit. However, these outcomes at the final follow-up visit were similar to the outcomes obtained by Hsu, et al., that com-pared a group of patients treated with ADSCs injections plus Extracorporeal Shockwave Therapy (ESWT) with another group treated with ESWT plus human umbilical cord Wharton's Jelly-Derived Mesenchymal Stem Cells (WJMSCs) [41]. This study demonstrated that ESWT+ADMSCs group had a synergistic effect greater than that of ESWT+WJMSCs group for the treatment of early knee OA in term of increased expressions of Transforming Growth Factor (TGF)- β , Bone Morphogenetic Protein (BMP)-4 and type II collagen. In particular, it showed the first group exhibited increased trabecular thickness and bone volume as compared with the ESWT+WMSCs group using micro Computed Tomography (CT) and Immunohistochemistry (IHC) staining [41].

Cheng, et al., demonstrated that ADSCs combined with shockwave treatment had a better effect to improve osteoarthritic pathological factors in knee OA joints decreasing Tumor Necrosis factor-inducible Gene (TSG)-6 and Proteoglycan (PRG)-4, while increasing tissue inhibitor matrix, one Morphogenetic Protein (BMP)-2, BMP-6 metalloproteinase, Tissue Inhibitor of Metalloproteinase (TIMP)-1 and type II collagen [45].

High Tibial Osteotomy (HTO) can be considered a viable option for treatment of unicompartmental knee arthritis or focal damage to medial compartment and varus alignment with possible return to sport [41]. The potential of adding injections of ADSCs to improve the results of HTO has been inves-tigated in several studies [18,46].

Kim, et al., assessed clinical outcomes of some patients underwent ADSCs therapy plus HTO for the management of knee varus osteoarthritis and compared these results with a control HTO group [18]. They found the mean IKDC score and Lysholm score significantly increased in the first group than in the second group as evidence of improved joint function and sport activities. Similarly, the ICRS grades improved more in people with ADSCs therapy than in the second group as a sign of improved quality of repaired cartilage [18].

Koh, et al., evaluated the effects of HTO plus PRP and HTO plus PRP+ADSCs and they did not find better outcomes in the second group in term of VAS reduction, improved clinical scores and cartilage healing [15].

Tan, et al., in a systematic review and meta-analysis on 4 studies with 224 patients undergoing HTO and MSCs and they found a significant but modest difference for functional scores such as Lysholm, KOOS and IKDC [47].

Hohmann, et al., in a recent commentary network meta-analysis assessed the effectiveness of PRP injections as in comparison with HA and ADSCs injections. These studies suggest that platelet-rich plasma provides the best functional improvement and safety for the management of knee OA, despite ADSCs provide excellent pain relief [48].

Conclusion

ADSCs injections isolated or combined with surgical treatments are used in middle aged and active people with positive results for both clinical and functional scores with radiological short term limited evidence in limiting the progression of knee OA and improving the cartilage condition.

No data relating to athletes and the preoperative level of activity have not been outlined in any study. The potential benefit of ADSCs may be useful in athletes who frequently have symptomatic cartilage lesions or early to medium osteoarthritis and their use can improve the benefit obtained from surgical treatments with no specific side effect reported.

There are ongoing controversies in the available literature and it is therefore necessary that new adequate powered studies using appropriated evaluation scales, advanced imaging and long enough follow-up have to be produced.

Conflict of Interest

All the authors declare no conflict of interest regarding any aspect of the manuscript.

References

1. Jang S, Lee K, Ju JH. Recent updates of diagnosis, pathophysiology, and treatment on osteo-arthritis of the knee. *J Int J Mol Sci.* 2021;22(5):2619.
2. Richmond JC. The treatment of osteoarthritis in the middle-aged athlete. *Sports Med Arthrosc Rev.* 2013;21(1):1.
3. Caplan AI. Adult mesenchymal stem cells: When, where, and how. *Stem Cells Int.* 2015;2015:628767.

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DOI: <https://doi.org/10.46889/JOSR.2022.3305>

4. Kim JD, Lee GW, Jung GH. Clinical outcome of autologous Bone Marrow Aspirates Concentrate (BMAC) injection in degenerative arthritis of the knee. *Eur J Orthop Surg Traumatol*. 2014;24:1505-11.
5. Freitag J, Wickham J, Shah K. Effect of autologous adipose-derived mesenchymal stem cell therapy in the treatment of an osteochondral lesion of the ankle. *BMJ Case Rep*. 2020;13(7):e234595.
6. Dall'Oca C, Breda S, Elena N. Mesenchymal stem cells injection in hip osteoarthritis: pre-liminary results. *Acta Biomed*. 2019;90(1):75-80.
7. Freitag J, Wickham J, Shah K. Effect of autologous adipose-derived mesenchymal stem cell therapy in the treatment of acromioclavicular joint osteoarthritis. *BMJ Case Rep*. 2019;12(2):e227865.
8. Nakagami H, Morishita R. Adipose tissue-derived stromal cells as a novel option for regenerative cell therapy. *J Atheroscler Thromb*. 2006;13(2):77-81.
9. Narbona-Carceles J, Vaquero J, Suárez-Sancho S. Bone marrow mesenchymal stem cell as-pirates from alternative sources: is the knee as good as the iliac crest? *Injury*. 2014;45(Suppl 4):S42-7.
10. Kern S, Eichler H, Stoeve J. Comparative analysis of mesenchymal stem cells from bone marrow, umbilical cord blood, or adipose tissue. *Stem Cells*. 2006;24(5):1294-301.
11. Lalu ML, McIntyre L. Safety of cell therapy with mesenchymal stromal cells (safe cell): a systematic review and meta-analysis of clinical trials. *PLoS ONE*. 2012;7(10):e47559.
12. Liu Y, Lin L, Zou R. MSC-derived exosomes promote proliferation and inhibit apoptosis of chondrocytes via IncRNA-KLF3-AS1/miR-206/GIT1 axis in osteoarthritis. *Cell Cycle*. 2018;17(21-22):2411-22.
13. Toyserkani NM, Jørgensen MG, Tabatabaeifar S. Concise review: a safety assessment of adipose-derived cell therapy in clinical trials: a systematic review of reported adverse events. *Stem Cells Transl Med*. 2017;6(9):1786-94.
14. Freitag J, Bates D, Wickham J. Adipose-derived mesenchymal stem cell therapy in the treatment of knee osteoarthritis: a randomized controlled trial. *Regen Med*. 2019;14(3):213-30.
15. Koh YG, Choi YJ. Infrapatellar fat pad-derived mesenchymal stem cell therapy for knee osteoarthritis. *Knee*. 2012;19(6):902-7.
16. Lee WS, Kim HJ, Kim KI. Intra-articular injection of autologous adipose tissue-derived mesenchymal stem cells for the treatment of knee osteoarthritis: a phase IIb, randomized, place-bo-controlled clinical trial. *Stem Cells Transl Med*. 2019;8(6):504-11.
17. Pers YM, Rackwitz L, Ferreira R. Adipose mesenchymal stromal cell-based therapy for severe osteoarthritis of the knee: a phase I dose escalation trial. *Stem Cells Transl Med*. 2016;5(7):847-56.
18. Kim YS, Koh YG. Comparative matched-pair analysis of open-wedge high tibial osteotomy with versus without an injection of adipose-derived mesenchymal stem cells for varus knee osteoarthritis: clinical and second-look arthroscopic results. *Am J Sports Med*. 2018;46(11):2669-77.
19. Panni AS, Vasso M, Braile A. Preliminary results of autologous adipose-derived stem cells in early knee osteoarthritis: identification of a subpopulation with greater response. *Int Orthop*. 2019;43(1):7-13.
20. García-Olmo D, García-Arranz M, García LG. Autologous stem cell transplantation for treatment of rectovaginal fistula in perianal Crohn's disease: a new cell based therapy. *Int J Colorectal Dis*. 2003;18(5):451-4.
21. Kyriakidis T, Iosifidis M, Michalopoulos E. Good mid-term outcomes after adipose-derived culture-expanded mesenchymal stem cells implantation in knee focal cartilage defects. *Knee Surg Sports Traumatol Arthrosc*. 2020;28(2):502-8.
22. Tsubosaka M, Matsumoto T, Sobajima S, Matsushita T, et al. The influence of adipose-derived stromal vascular fraction cells on the treatment of knee osteoarthritis. *BMC Musculoskelet Disord*. 2020;21(1):207.
23. Zhou Y, Li H, Xiang D. The clinical efficacy of arthroscopic therapy with knee infrapatellar fat pad cell concentrates in treating knee cartilage lesion: a prospective, randomized, and con-trolled study. *J Orthop Surg Res*. 2021;16(1):87.
24. Zuk PA, Zhu M, Mizuno H. Multilineage cells from human adipose tissue: implications for cell-based therapies. *Tissue Eng*. 2001;7(2):211-28.
25. Bianchi F, Maioli M, Leonardi E. A new nonenzymatic method and device to obtain a fat tissue derivative highly enriched in pericyte-like elements by mild mechanical forces from human lipoaspirates. *Cell Transplant*. 2013;22:2063-77.

26. Lopa S, Colombini A, Moretti M. Injective mesenchymal stem cell-based treatments for knee osteoarthritis: from mechanisms of action to current clinical evidences. *Knee Surg Sports Traumatol Arthrosc.* 2019;27(6):2003-20.
27. Lu L, Dai C, Zhang Z. Treatment of knee osteoarthritis with intra-articular injection of autologous adipose-derived mesenchymal progenitor cells: a prospective, randomized, double-blind, active-controlled, phase IIb clinical trial. *Stem Cell Res Ther.* 2019;10(1):143.
28. Mautner K, Bowers R, Easley K. Functional outcomes following microfragmented adipose tissue versus bone marrow aspirate concentrate injections for symptomatic knee osteoarthritis. *Stem Cells Transl Med.* 2019;8(11):1149-56.
29. Jo CH, Lee YG, Shin WH. Intra-articular injection of mesenchymal stem cells for the treatment of the knee: a proof-of-concept clinical trial. *Stem Cells.* 2014;32:1254-66.
30. Song Y, Du H, Dai C. Human adipose-derived mesenchymal stem cells for osteoarthritis: a pilot study with long-term follow-up and repeated injections. *Regen Med.* 2018;13(3):295-307.
31. Ha CW, Park YB, Kim SH. Intra-articular mesenchymal stem cells in osteoarthritis of the knee: a systematic review of clinical outcomes and evidence of cartilage repair. *Arthroscopy.* 2019;35(1):277-88.
32. Zhao D, Pan JK, Yang WY. Intra-articular injections of platelet-rich plasma, adipose mesenchymal stem cells, and bone marrow mesenchymal stem cells associated with better outcomes than hyaluronic acid and saline in knee osteoarthritis: a systematic review and network meta-analysis. *Arthrosc.* 2021;37(7):2298-314.
33. Han SB, Seo IW, Shin YS. Intra-articular injections of hyaluronic acid or steroids associated with better outcomes than platelet-rich plasma, adipose mesenchymal stromal cells, or placebo in knee osteoarthritis: a network meta-analysis. *Arthrosc.* 2021;37(1):292-306.
34. Thorlund JB, Juhl CB, Roos EM. Arthroscopic surgery for degenerative knee: systematic review and meta-analysis of benefits and harms. *BMJ.* 2015;350:h2747.
35. Dyrna F, Herbst E, Hoberman A. Stem cell procedures in arthroscopic surgery. *Eur J Med Res.* 2016;21(1):29.
36. Russo A, Screpis D, Di Donato SL. Autologous micro-fragmented adipose tissue for the treatment of diffuse degenerative knee osteoarthritis: an update at 3 years follow-up. *J Exp Orthop.* 2018;5:52.
37. Freitag J, Wickham J, Shah K. Mesenchymal stem cell therapy combined with arthroscopic abrasion arthroplasty regenerates cartilage in patients with severe knee osteoarthritis: a case series. *Regen Med.* 2020;15(8):1957-77.
38. Koh YG, Kwon OR, Kim YS. Adipose-derived mesenchymal stem cells with microracture versus microfracture alone: 2-year follow-up of a prospective randomized trial. *Arthroscopy.* 2016;32(1):97-109.
39. Hong Z, Chen J, Zhang S. Intra-articular injection of autologous adipose-derived stromal vascular fractions for knee osteoarthritis: a double-blind randomized self-controlled trial. *Int Orthop.* 2019;43(5):1123-34.
40. Bąkowski P, Kaszyński J, Walecka J. Autologous adipose tissue injection versus Platelet-Rich Plasma (PRP) injection in the treatment of knee osteoarthritis: a randomized, controlled study - study protocol. *BMC Musculoskelet Disord.* 2020;21(1):314.
41. Hsu CC, Cheng JH, Wang CJ. Shockwave therapy combined with autologous adipose-derived mesenchymal stem cells is better than with human umbilical cord Wharton's jelly-derived mesenchymal stem cells on knee osteoarthritis. *Int J Mol Sci.* 2020;21(4):1217.
42. Lamo-Espinosa JM, Mora G, Blanco JF. Intra-articular injection of two different doses of autologous bone marrow mesenchymal stem cells versus hyaluronic acid in the treatment of knee osteoarthritis: Multicenter randomized controlled clinical trial (phase I/II). *J Transl Med.* 2016;14:246.
43. Wang CJ, Yang YJ, Huang CC. The effects of shockwave on systemic concentrations of nitric oxide level, angiogenesis and osteogenesis factors in hip necrosis. *Rheumatol Int.* 2011;31(7):871-7.
44. Van Pham P, Bui KH, Ngo DQ. Activated platelet-rich plasma improves adipose-derived stem cell transplantation efficiency in injured articular cartilage. *Stem Cell Res Ther.* 2013;4(4):91.
45. Cheng JH, Yen KT, Chou WY. Autologous adipose-derived mesenchymal stem cells combined with shockwave therapy synergistically ameliorates the osteoarthritic pathological factors in knee joint. *Pharmaceuticals (Basel).* 2021;14(4):318.

46. Belsey J, Yassen SK, Jobson S. Return to physical activity after high tibial osteotomy or unicompartmental knee arthroplasty: a systematic review and pooling data analysis. *Am J Sports Med.* 2021;49(5):1372-80.
47. Tan SHS, Kwan YT, Neo WJ. Outcomes of high tibial osteotomy with versus without mesenchymal stem cell augmentation: a systematic review and meta-analysis. *Orthop J Sports Med.* 2021;9(6):23259671211014840.
48. Hohmann E. Editorial commentary: injection of platelet-rich plasma appears superior to hyaluronic acid and adipose- or bone-derived marrow stem cells for knee osteoarthritis. *Arthroscopy.* 2021;37(7):2315-7.