The Physician and Sportsmedicine

ISSN: 0091-3847 (Print) 2326-3660 (Online) Journal homepage: https://www.tandfonline.com/loi/ipsm20

Autologous adipose stem cell therapy for knee osteoarthritis: where are we now?

Alessio Biazzo, Riccardo D'Ambrosi, Francesco Masia, Vincenzo Izzo & Francesco Verde

To cite this article: Alessio Biazzo, Riccardo D'Ambrosi, Francesco Masia, Vincenzo Izzo & Francesco Verde (2020): Autologous adipose stem cell therapy for knee osteoarthritis: where are we now?, The Physician and Sportsmedicine, DOI: 10.1080/00913847.2020.1758001

To link to this article: https://doi.org/10.1080/00913847.2020.1758001

Accepted author version posted online: 20 Apr 2020.

Publisher: Taylor & Francis & Informa UK Limited, trading as Taylor & Francis Group

Journal: *The Physician and Sportsmedicine*

DOI: 10.1080/00913847.2020.1758001

Autologous adipose stem cell therapy for knee osteoarthritis: where are we now?

A systematic review of randomized controlled trials

Alessio Biazzo[1], Riccardo D'Ambrosi[2], Francesco Masia[1], Vincenzo Izzo[1], Francesco Verde[1].

[1]Hip and Knee Reconstructive Surgery Department, Humanitas Gavazzeni, via M. Gavazzeni 21, Bergamo, Italy
[2]IRCCS Istituto Ortopedico Galeazzi, Via Riccardo Galeazzi, 4, 20161 Milano, Italy

Author correspondence: ale.biazzo@yahoo.it

Abstract

Introduction

The purpose of this study was to evaluate the efficacy and safety of adipose-derived stem cell (ADSC) or stromal vascular fraction (SVF) injections for knee osteoarthritis (OA) treatment by analyzing all randomized controlled trials dealing with this topic.

Materials and Methods

The following search terms were used in PUBMED, EMBASE, Scopus and the Cochrane Library Database on 14th November 2019: "adipose derived stem cell" OR "stromal vascular fraction" OR "SVF" OR "multipotent mesenchymal stromal cells" OR "stem cell" OR "derived stem cell" OR "autologous" AND "knee" OR "osteoarthritis" OR "chondral defect" OR "randomized" OR "controlled trial". No time limit was given to publication date. We included randomized controlled

trials (RCTs) based on the following criteria: (1) English studies; (2) patient population diagnosed with knee OA and treated with ADSCs or SVF injections; (3) comparison group treated with placebo, surgery or adjuvant injections, such as platelet rich-plasma or hyaluronic acid.

Results

Intra-articular injections of adipose stem cell therapy in the form of ADSC or SVF is a safe procedure for the treatment of knee OA, with good clinical and radiological outcomes in the early follow-up period (12-24 months). In addition, treatment with fat-derived cells showed a very low complication rate (16.15%) of which all were considered to be minor.

Conclusions

ADSCs and SVF seem to produce promising good to excellent clinical results for the treatment of knee OA. However, the length and modalities of follow-up in the different conditions are extremely variable. Nevertheless, it appears that the use of adipose-derived stem cells is associated with clinical and radiological improvements and minimal complication rates. To avoid bias deriving from the use of biological adjuvants or surgical procedures, randomized controlled trials comparing ADSCs or SVF and other treatments (for example platelet rich-plasma or hyaluronic acid injections) should be performed.

Key words: knee; osteoarthritis; adipose stem cell; stromal vascular fraction; regenerative medicine; randomized controlled trials; systematic review.

Introduction

Osteoarthritis (OA) is a debilitating disease characterized by alteration of cell homeostasis, loss of articular cartilage, damage to the subchondral bone and the surrounding soft tissues. The avascular nature of the cartilage itself limits its capacity for self-repairing, resulting in progressive cartilage loss and joint degeneration [1].

Treatment options for low-grade OA and chondral defects range from conservative to surgical interventions such as microfractures (MFX), autologous chondrocyte implantation (ACI), matrix-induced autologous chondrocyte implantation (MACI), autologous matrix-induced chondrogenesis (AMIC) or osteochondral autograft transfer (OATS) [2]. These latter methods are characterized by high failure rate [3,4]. MFX is the most used technique because it is cheap and easy to perform, exposing bone marrow derived pluripotent cells to the articular surface and creating an environment amenable to healing; however, the resulting fibrocartilage is characterized by poor load bearing quality and consequently no good results in the long-term follow-up and lesions >1.5cm^2 are reported [5]. In the effort to regenerate articular cartilage, mesenchymal stem cells (MSC) have been used in various forms, with promising long-term results [6-8]. The most commonly used tissue sources for isolating MSCs apart from bone marrow are the adipose tissue, umbilical cord, placenta, and dental pulp. However, autologous or allogeneic bone marrow MSCs are currently the most widely used cell type in clinical trials for various disease indications. They are considered the "gold standard" MSC type because of their extensive characterization that took place for over 5 decades.

Bone marrow mesenchymal stem cells present several limiting features. Harvesting involves the surgical removal of the matrix portion; this is subsequently disintegrated by mechanical stress. This process allows to isolate from 0.01% to 0.001% of mononuclear cells from the harvested cells. Adipose tissue has become an attractive alternative source because of its relatively easy accessibility and abundance [9].ADSCs can be obtained through enzymatic digestion (with collagenase) or mechanical fraction: both procedures aim to separate mature adipocytes from the stromal vascular fraction (SVF), which contains pre-adipocytes, endothelial cells, smooth muscle cells, pericytes, macrophages, fibroblasts and ADSCs (around 9.5%). However, unlike ADSCs, the stromal vascular fraction (SVF) requires no cell culture and is suitable immediately. Furthermore, SVF is prepared from a heterogeneous group of cells that includes various nonadherent hematopoietic lineage cells. SVF is primarily known to exhibit angiogenic and immunosuppressive effects [8-9]. ADSCs and SVF are promising candidates in regenerative medicine, including not

only treatment of cartilage disease, but also Crohn's disease [9], autoimmune [10] and allergic pathologies. ADSCs play with two different mechanism of action: direct differentiation in chondrogenic lineage and a "paracrine effect" with release of anti-apoptotic cytokine, anti-inflammatory molecules and different growth-factors [11].

The purpose of this study was to evaluate the efficacy and safety of ADSCs and SVF injections for knee OA treatment by analyzing all randomized controlled trials (RCTs) dealing with this topic.

Materials and methods

The following search terms were used in PUBMED, EMBASE, Scopus and the Cochrane Library Database on 14th November 2019: "adipose derived stem cell" OR "stromal vascular fraction" OR "SVF" OR "multipotent mesenchymal stromal cells" OR "stem cell" OR "derived stem cell" OR "autologous" AND "knee" OR "osteoarthritis" OR "chondral defect" OR "randomized" OR "controlled trial". No time limit was given to publication date.

We included RCTs based on the following criteria: (1) English studies; (2) patient population diagnosed with knee OA and treated with ADSC injections; (3) comparison group treated with placebo, surgery or adjuvant injections, such as platelet rich-plasma (PRP) or hyaluronic acid (HA). The assessment of level of evidence of the selected articles was performed according to 'The Oxford 2011 Levels of Evidence' [12]. Moreover no follow-up limit was required as inclusion or exclusion criteria. We excluded from the study congress abstract, reviews, meta-analyses, expert opinions, case reports, case series, animal studies, in vitro studies and editorials. Two independent reviewers analyzed and evaluated all the information available from the articles. In cases of disagreement between the two reviewers, a third senior reviewer was asked to evaluate and analyze the articles.

Data extraction

The following data was collected: first author, year of publication, number of patients, age, grade of knee OA, intervention, stem cell preparation, follow-up, functional outcomes and adverse events.

Assessment of quality of the article

This study was conformed to all PRISMA guidelines and reported the required information accordingly [13]. The methodological quality of the studies was independently evaluated by two of us according to the modified Jadad quality scale [14]. The modified Jadad quality scale consists of 6 items designed to evaluate randomization, blinding method, withdrawals and dropouts, inclusion and exclusion criteria, adverse effects, and statistical analysis. Scores of 8 to 4 represent excellent to good quality, whereas scores of 3 to 0 denote low to poor quality. If there is any disagreement, it should be resolved by discussion and consultation with senior authors.

Results

In the initial search, we identified 194 records. After examination of titles and abstracts, there were 6 full-text RCTs Level I or II of Evidence that satisfied all inclusion criteria and were included in this systematic review [15-20]. Flow-chart is reported in Figure 1.

Study characteristics

The study characteristics are presented in Table 1. The studies were published between 2014 and 2020. The sample size ranged from 16 to 80, with a total of 226 patients. Mean age of patients was 49.4 years.

Two study (33.3%) [19, 20] used autologous ADSCs, while two studies used SVF (66.7%) [15-18]. The studies treated grade I to IV knee OA according Kellgren-Lawrence classification: grade of OA ranged from I to IV [15,17-20], while one study (20%) used the International Cartilage Repair Society (ICRS) [16] score and included only patients with grade 3-4 ICRS symptomatic cartilage defects of the femoral condyle [21-22].

Clinical evaluation was assessed with Numeric Pain Rating Scale (NPRS) Knee Society Score, Visual Analogue Scale (VAS), Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC), Knee Injury and Osteoarthritis Outcome Score (KOOS) and Lysholm score [23-25].

Radiological evaluation was assessed with MOCART (Magnetic Resonance Observation of Cartilage Repair Tissue) score, the whole-organ magnetic resonance imaging score (WORMS), the MRI OA Knee Score (MOAKS) system, Hip Knee Angle and the femorotibial angle (FTA) [26-28].

Four studies (80%) [15-18] used SVF as adjuvant with a surgery procedure (microfracture, high tibial osteotomy, arthroscopy), while two studies used ADSCs as an isolated injection [19,20].

The overall scores of methodological quality of all studies were relatively high, with a mean score of 5.7 (range 4-8). The detailed items of the modified Jadad quality scale and study characteristics for the included studies are listed in Table 2..

Preparation method of ADSCs

Liposuction was performed the same day of surgery in two studies [15, 17], the day before in the other two studies [16, 18] and was not specified in the study by Freitag et al. [19] while in an article by Lee et al the procedure was performed 3 weeks before injection [20]. Adipose tissue harvesting was from the buttocks in 3 studies [15, 16, and 18] and from the abdomen in the other 3 [17, 19, and 20]. The weighted average volume of harvested adipose tissue was between 20 and 150 ml (one study did not report the volume [17]). All studies collected a sample of the final SVF to perform cell counting and ADSC characterization [15-20]. SVF were prepared in two cases with enzymatic

digestion [15,17], in two cases with centrifugation and enzymatic digestion [16,18], while ADSCs were prepared both with culture expanded [19,20].

Treatment

Four studies [15-18] used SVF in association with a surgical procedure: arthroscopic debridement of unstable cartilage lesions, microfractures and high tibial osteotomy (interventional groups). In one study SVF was used in combination with PRP [18] and in one study with fibrin glue as scaffold [16]. The control group was represented by placebo [20], arthroscopic debridement [15], arthroscopic debridement + HA [13], HTO + PRP [18], microfractures [16] and conservative management [19]

Clinical outcomes

Clinical results are summarized in Table 3. Functional evaluation was assessed with VAS, NPRS, KSS, WOMAC, Lysholm and KOOS score at different follow-up times, ranging from 6 to 27 months. Hong et al. [17] treated 16 patients with bilateral knee grade 2-3 OA: in the study patients were randomized in two groups: each patient received 4 ml of SVF (group test) in one side and a single dose of 4 ml HA (group control) in the other side. Their results showed a significant statistical difference within the SVF group at all follow-up intervals (1-3-6-12 months) regarding VAS and WOMAC scores; a significant statistical difference (*p*-value non reported) was also reported within the control group for WOMAC stiffness subscale at all follow-up intervals, for WOMAC pain subscale at 6-12 month follow-up and for VAS score at 1-3 months. No intergroup analysis was performed [17].

Koh et al. presented a study of 80 patients, randomized in two groups: one received MFXs plus SVF with fibrin glue (test group) and the other received MFXs alone (control group). They reported a statistically significant difference in favor of the SVF group in KOOS pain (p=0.034) and symptom (p=0.005) sub scores and in VAS score (p=0.032); Lysholm score was improved in both groups but the intergroup difference was not statistically significant (p=0.431) [16].

Always Koh et al. in another study reported the clinical outcomes of a group of 44 patients randomized in two groups: the first received HTO + PRP + SVF injection (test group); the second received HTO + PRP injection. They reported a statistically significant difference between SVF and control group for KOOS pain (p< 0.001), symptom (p= 0.006) subscale scores and for VAS pain score (p< 0.001); the mean Lysholm score was also significantly improved in both groups (p< 0.001) but no difference were seen between the groups (p= 0.357) [18].

Peretti et al. presented the early outcomes of the first 16 patients treated with arthroscopy debridement versus arthroscopy + SVF for grade 3-4 knee OA and who completed the 6 month follow-up period. They reported higher functional outcomes for the SVF group especially regarding VAS, KOOS and WOMAC scores but without statistically significant difference (*p*-value not reported) [15].

Freitag et al. evaluate the efficacy of ADSCs therapy on pain, function and disease modification in knee osteoarthritis in 30 participants with symptomatic knee OA. Patients were randomized into three groups: two treatment groups received intra-articular ADSCs therapy consisting of either a single injection (100×10^6) or two injections (100×10^6 at baseline and 6 months). The third group served as control and continued conservative management. At the final follow-up no serious adverse events were observed. Both treatment groups receiving ADSCs showed clinically significant pain and functional improvement [19].

Lee et al. assessed the efficacy and safety of a single intra-articular injection of ADSCs for patients with knee osteoarthritis in a prospective double-blinded, randomized controlled, phase IIb clinical trial. ADSCs were administered to 12 patients (ADSCs group), and the group was compared with

12 knees with injection of normal saline (control group) up to 6 months. A single injection of ADSCs led to a significant improvement of the WOMAC score at 6 months. In the control group no significant change was noted. No serious adverse events were observed in either groups during the follow-up period [20].

Radiological outcomes

Five studies (83.3%) reported radiological outcomes [15-19] but only four performed post-treatment MRI to evaluate cartilage changes [15, 16, 19, 20]. One study performed standing AP radiographs to measure FTA before and after treatment [18]. The MOCART scoring system was used in two studies [16, 17]; the WORMS was used in one study [16]; another study used the MOAKS system. [19], while Lee analyzed cartilage defect [20].

In the study presented by Hong et al. [17], WORMS and MOCART measurements revealed a significant improvement of articular cartilage repair in the SVF group compared to the control group: in particular, WORMS showed an important improvement in the test group at 6 ($p= 0.088$) and 12 months ($p< 0.05$); by contrast in the control group WORMS deteriorated from baseline to 6 and 12 months. In the test group, the mean MOCART score showed a significant improvement at 6 and 12 months ($p< 0.01$); however, in the control group the mean MOCART score was poor and showed no improvement ($p=0.924$) [17].

Koh et al. reported a statistically significant difference in MOCART score at 24 months between the SVF group and the control group ($p= 0.033$); in the test group, 65% of patients had complete cartilage coverage of the lesion at follow-up compared with 45% in the control group [16].

In the study by Freitag et al. a total of 67% of participants within the control group had progression of cartilage loss with a further 56% having extension of osteophyte formation. By comparison, in the one-injection group only 30% of participants had further cartilage loss although 50% had progression of osteophyte formation at 12 months. In the two-injection group, 89% of participants

had improvement in cartilage or no progression in cartilage loss with stabilization of OA also indicated by 89% having no progression in osteophyte formation [19].

Lee et al. demonstrated a K-L grade, joint space width of medial and lateral compartment, while HKA angle did not change significantly over 6 months in both groups. The size of the cartilage defect in MRI at 6 months was not significantly changed in the ADSCs group ($p = .5803$), whereas the size of the cartilage defect in the control group was significantly increased ($p = .0049$). Moreover, there was a significant difference between the two groups in the amount of change in cartilage defect after the injection ($p = .0051$) [20].

Koh et al. [18] did not perform MRI evaluation: they performed only standing AP radiographs before and after treatment (HTO) to evaluate FTA or weight-bearing lines but did not report any difference between the groups. Peretti et al. [15] did not present radiological outcomes.

Adverse events

The total number of complications identified in the present review is 32/226 (14.15%), most of which were minor, such as joint pain, abdominal pain or swelling. No major complications were reported.

Discussion

The most important finding from this systematic review was that ADSCs and SVF therapy, in the form of articular injection, is a safe procedure for the treatment of knee OA, with good clinical and radiological outcomes in the early follow-up period (12-24 months).

However, the results of the present review should be taken with caution, because these RCTs have several limitations and confounding factors. First of all, SVF is a mixture of pericytes, fibroblasts,

preadipocytes, monocytes, macrophages, red blood cells and ADSCs, with a percentage of 9-9.5%. Therefore, we cannot evaluate the effectiveness of the only stem cell component of the fraction. We should perform studies with only ADSCs, but this procedure is not cheap and requires two surgical steps, one for the liposuction and one for separation and cell culture. The advantages of SVF over ADSCs consist of the following: firstly, SVF is readily accessible from lipoaspirate without separation and cell culture; secondly, SVF is cheaper and faster than ADSCs because of the absence of culturing procedures; thirdly, the injection can be performed on the same day of the surgical procedure; fourthly, the characteristics and heterogeneous cellular components of SVF may explain the better therapeutic results reported in animal studies [29, 30].

This systematic review also highlighted that most of all RCTs used biological adjuvants and performed surgical procedures in association with stem cell therapy, which may have positively influenced the clinical outcomes and potentially confound the effects of SVF treatment.

Two studies performed arthroscopic debridement in association with SVF, one performed HTO [18] and one MFXs [16]. One study used PRP in association with SVF and HTO [18]: there is evidence that PRP contains growth factors that increase chondrocytes differentiation, as well as the synthetic capacity of MSC, which may prove beneficial in cartilage repair [31, 32]. One study used fibrin glue as scaffold to facilitate the effect of SVF [17]. Both PRP and fibrin glue are confounding factors, because there is evidence that both may enhance SVF adherence to cartilage lesions and promote their proliferation [33].

Three studies did not report adverse events [15, 16, 18]. Hong et al. described 4 cases of abdomen pain after liposuction and six patients with pain and swelling in bilateral knee joints for a few days after knee surgery [17]. Freitag et al. reported minor discomfort and bruising was commonly noted in both treatment groups after their lipoharvest procedure. This resolved without further intervention; two participants reported pain and swelling for 4 weeks following ADSC therapy and due to observed impact on their usual daily activity this was categorised as a severe adverse event [19]. Lee et al. noted that adverse events occurred in 10 (83%) patients in the ADSCs group and 7

(58%) patients in the control group. All adverse events of grade 3 by the NCI-CTCAE scale were arthralgia, but those completely disappeared within 3 days [20].

The complication rate of the liposuction procedure is very low, about 0.1% according to a national survey of 112.756 reported patient procedures [34]. Regarding the complication rate and incidence of adverse events after treatment with stem cells (including SVF, bone marrow and cultured ADSCs), a multicenter analysis performed among 2372 patients undergoing autologous stem cell therapy for different orthopedic conditions revealed that these procedures are safe [35]: the incidence of AEs was of 12.1% (the majority were pain and knee swelling), the incidence of serious AEs was 1.5% (neoplasm, neurologic and vascular events), the incidence of neoplasm was 0.3% (in contrast, the annual incidence of cancer in United States population in 2011 was 0.44% [36].

This systematic review shows some limitations. First of all, two of the RCTS were performed in the same center: the Center for Stem Cell & Arthritis Research, Department of Orthopaedic Surgery, Yonsei Sarang Hospital, Seoul, Korea [16, 18]. This may suggest that the results (these are the only 2 RCTs with statistically significant intergroup difference) could be partially attributed to surgeons' skills. Secondly, these RCTs treated different grades of knee OA or chondral defect ranging from grade 1 to 4, potentially leading to underestimate the clinical outcomes in patients with grade 4 OA and indication for total knee replacement; thirdly, the use of biological adjuvants (PRP, fibrin glue and HA) and surgical procedures may positively influence clinical results leading to overestimate the effects of adipose stem cells therapy; fourthly, the use of SVF instead of ADSCs alone (is an important confounding factor, because we are not able to evaluate the effectiveness of the only stem cell component of the fraction.

Conclusions

ADSCs and SVF seem to produce promising good to excellent clinical results for the treatment of knee OA. However, the length and modalities of follow-up in the different conditions are extremely variable. Nevertheless, it appears that the use of adipose derived stem cells is associated with

clinical and radiological improvements and minimal complication rates. To avoid bias deriving from the use of biological adjuvants or surgical procedures, randomized controlled trials comparing ADSCs or SVF and other treatments (for example platelet rich-plasma or hyaluronic acid injections) should be performed.

Conflict of interest: This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

References

1. Buckwalter JA, Mankin HJ. Articular cartilage. Part II: degeneration and osteoarthritis, repair, regeneration and transplantation. J Bone Joint Surg 1997;79: 612–32.
2. Freitag J, Ford J, Bates D et al. Adipose derived mesenchymal stem cell therapy in the treatment of isolated knee chondral lesions: design of a randomized controlled pilot study comparing arthroscopic microfracture versus arthroscopic microfracture combined with postoperative mesenchymal stem cell injections. BMJ Open. 2015;5(12):e009332.
3. Tuan R. A second-generation autologous chondrocyte implantation approach to the treatment of focal articular cartilage defects. Arthritis Res Ther 2007; 9:109–113.
4. D'Ambrosi R, Giacco F, Ragone V, et al. Arthroscopic treatment of osteochondral knee defects with resorbable biphasic synthetic scaffold: clinical and radiological results and long-term survival analysis. Int Orthop. 2019;43(9):2183-2189.
5. D'Ambrosi R, Ragone V, Ursino N. What future in the treatment of osteochondral knee defects? Ann Transl Med. 2018;6(Suppl 2):S100.

6. Diekman B, Rowland C, Lennon D et al. Chondrogenesis of adult stem cells from adipose tissue and bone marrow: induction by growth factors and cartilage matrix. Tissue Eng Part A 2010; 16: 523–533.
7. Chen YC, Chen CH, Chen PL et al. Donor site morbidity after harvesting of proximal tibia bone. Head Neck. 2006 Jun; 28(6):496-500.
8. Usuelli FG, D'Ambrosi R, Maccario C, et al. Adipose-derived stem cells in orthopaedic pathologies. Br Med Bull. 2017;124(1):31-54.
9. García-Olmo D, García-Arranz M, García LG et al. Autologous stem cell transplantation for treatment of rectovaginal fistula in perianal Crohn's disease: a new cell-based therapy. Int J Colorectal Dis. 2003 Sep; 18(5):451-454.
10. Riordan NH, Ichim TE, Min WP et al. Non-expanded adipose stromal vascular fraction cell therapy for multiple sclerosis. J Transl Med. 2009 Apr 24;7:29.
11. Kern S, Eichler H, Stoeve J et al. Comparative analysis of mesenchymal stem cells from bone marrow, umbilical cord blood, or adipose tissue. Stem Cells. 2006 May; 24(5):1294-1301.
12. Marx RG, Wilson SM, Swiontkowski MF. Updating the assignment of levels of evidence. J Bone Joint Surg Am. 2015; 97(1):1-2.
13. Moher D, Liberati A, Tetzlaff J et al.; PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. PLoS Med. 2009; 6(7):e1000097.
14. Jadad AR[1], Moore RA, Carroll D, Jenkinson C, Reynolds DJ, Gavaghan DJ, McQuay HJ. Assessing the quality of reports of randomized clinical trials: is blinding necessary? Control Clin Trials. 1996;17(1):1-12.
15. Peretti GM, Ulivi M, De Girolamo L et al. Evaluation of the use of autologous micro-fragmented adipose tissue in the treatment of knee osteoarthritis: preliminary results of a randomized controlled trial. J Biol Regul Homeost Agents. 2018;32(6 Suppl. 1):193-199.
16. Koh YG, Kwon OR, Kim YS et al. Adipose-Derived Mesenchymal Stem Cells With Microfracture Versus Microfracture Alone: 2-Year Follow-up of a Prospective Randomized Trial. Arthroscopy. 2016;32(1):97-109.
17. Hong Z, Chen J, Zhang S et al. 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):1123-1134
18. Koh YG, Kwon OR, Kim YS et al. Comparative outcomes of open wedge high tibial osteotomy with platelet-rich plasma alone or

in combination with mesenchymal stem cell treatment: a prospective study. Arthroscopy. 2014;30(11):1453-1460.

19. Freitag J, Bates D, Wickham J, et al. Adipose-derived mesenchymal stem cell therapy in the treatment of knee osteoarthritis: a randomized controlled trial. Regen Med. 2019;14(3):213-230.
20. Lee WS, Kim HJ, Kim KI, et al. Intra-Articular Injection of Autologous Adipose Tissue-Derived Mesenchymal Stem Cells for the Treatment of Knee Osteoarthritis: A Phase IIb, Randomized, Placebo-Controlled Clinical Trial. Stem Cells Transl Med. 2019 Jun;8(6):504-511.
21. KELLGREN JH, LAWRENCE JS. Radiological assessment of osteo-arthrosis. Ann Rheum Dis. 1957;16(4):494-502.
22. ICRS Cartilage Injury Evaluation Package. International Cartilage Society repair. Available at: http://www.cartilage.org/_files/contentmanagement/ICRS_evaluation.pdf. Published January 2000. Updated April 28, 2000.
23. Bellamy N, Buchanan WW, Goldsmith CH et al. Validation study of WOMAC: A health status instrument for measuring clinically important patient relevant outcomes to antirheumatic drug therapy in patients with osteoarthritis of the hip or knee. J Rheumatology, 1988;15(12):1833-1840.
24. Roos EM, Roos HP, Lohmander LS et al. Knee Injury and Osteoarthritis Outcome Score (KOOS)--development of a self-administered outcome measure. J Orthop Sports Phys Ther. 1998;28(2):88-96.
25. Lysholm J, Gillquist J. Evaluation of knee ligament surgery results with special emphasis on use of a scoring scale. Am J Sports Med. 198210(3):150-154.
26. Marlovits S, Singer P, Zeller P et al. Magnetic resonance observation of cartilage repair tissue (MOCART) for the evaluation of autologous chondrocyte transplantation: determination of interobserver variability and correlation to clinical outcome after 2 years. Eur J Radiol. 2006;57(1):16-23.
27. Peterfy CG, Guermazi A, Zaim S et al. Whole-Organ Magnetic Resonance Imaging Score (WORMS) of the knee in osteoarthritis. Osteoarthritis Cartilage. 2004; 12(3):177-190.
28. Hunter DJ, Guermazi A, Lo GH et al. Evolution of semi-quantitative whole joint assessment of knee OA: MOAKS (MRI Osteoarthritis Knee Score). Osteoarthritis Cartilage. 2011; 19(8):990-1002.

29. Bora P, Majumdar AS. Adipose tissue-derived stromal vascular fraction in regenerative medicine: a brief review on biology and translation. Stem Cell Res Ther 2017 8(1):145
30. You D, Jang MJ, Kim BH et al. Comparative study of autologous stromal vascular fraction and adipose-derived stem cells for erectile function recovery in a rat model of cavernous nerve injury. Stem Cells Transl Med 2015;4(4):351–358.
31. Krüger JP, Freymannx U, Vetterlein S et al. Bioactive factors in platelet-rich plasma obtained by apheresis. Transfus Med Hemother 2013;40:432–440
32. Schreml S, Babilas P, Fruth S et al. Harvesting human adipose tissue-derived adult stem cells: resection versus liposuction. Cytotherapy 2009;11:947–957
33. Pak J, Lee JH, Kartolo WA, Lee SH. Cartilage regeneration in human with adipose tissue-derived stem cells: current status in clinical implications. BioMed Res Int 2016;4702674
34. Teimourian B, Rogers WB. A national survey of complications associated with suction lipectomy: a comparative study. Plast Reconstr Surg 1989;84(4):628–631.
35. Centeno CJ, Al-Sayegh H, Freeman MD et al. A multi center analysis of adverse events among two thousand, three hundred and seventy twoadult patients undergoing adult autologous stem cell therapy for orthopedic conditions. Int Orthop. 2016 Aug; 40(8):1755-1765.
36. SEER (2014) Fast stats: compare statistics by data type. http://seer.cancer.gov/faststats/

Figure 1. Flow-chart of the reviewed studies according to PRISMA guidelines.

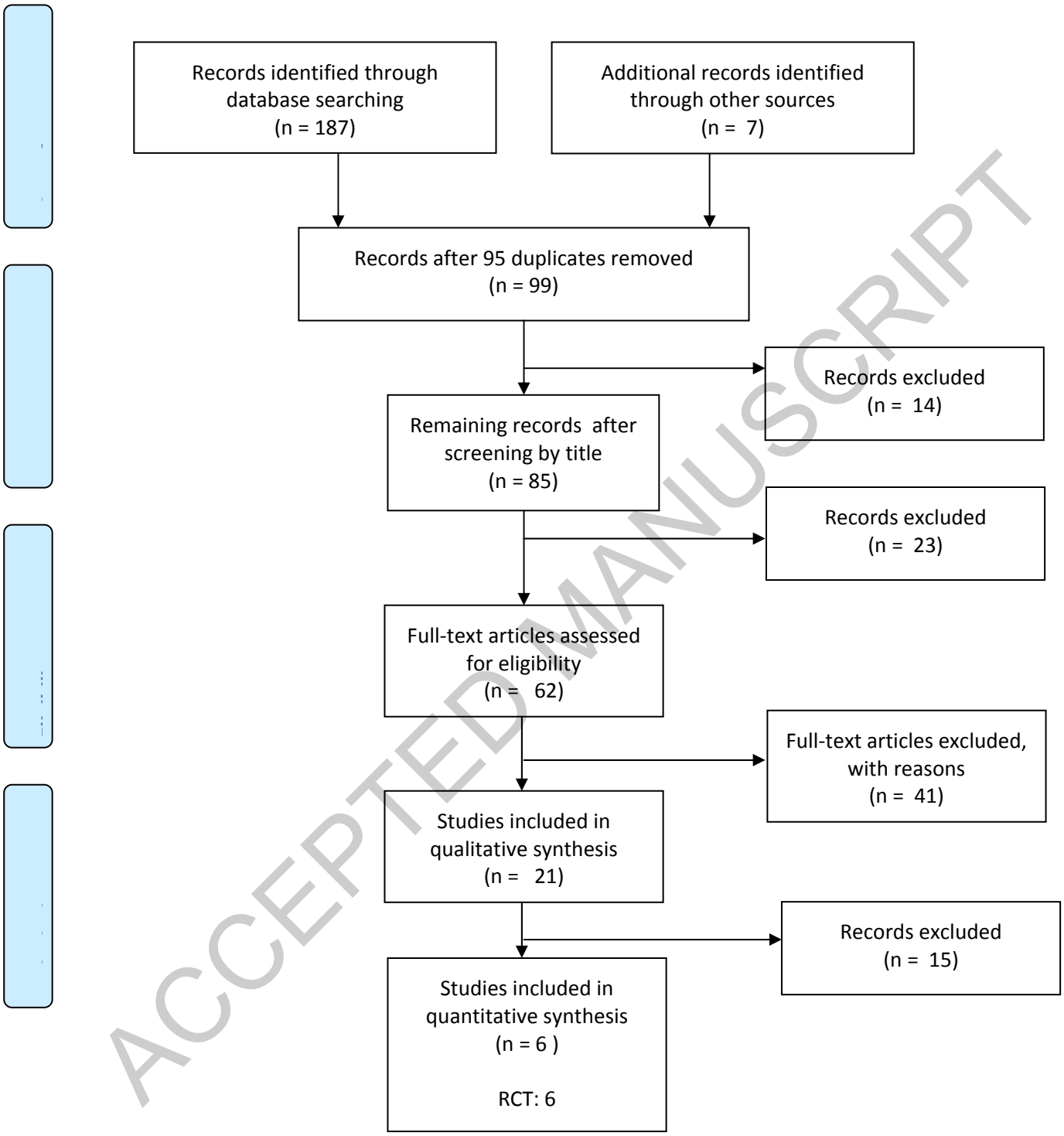

Table 1. General data and studies characteristics

Author	Journal	Number of Patients	Mean Age (Years)	OA Grade	Follow-Up	Stem Cell Type	Preparation	Main Number of Cells
Peretti et al. 2018 [15]	J Biol Regul Homeost Agents	8 cases 8 controls	58.3	III-IV Kellgren Lawrence	6 months	SVF and Micro-fragmented adipose tissue	Enzymatic Digestion	n.a.
Koh et al. 2016 [16]	Arthroscopy	40 cases 40 controls	38.8	3-4 ICRS	27 months	SVF	Centrifugation and enzymatic digestion	7.45 x 10 (6)/ml
Hong et al. 2018 [17]	Int Orthop	16 cases 16 controls	52	II-III Kellgren Lawrence	12 months	SVF	Enzymatic digestion	4.11 x 10 (6)/ml
Koh et al. 2014 [18]	Arthroscopy	21 cases 23 controls	53.2	I-II-III Kellgren Lawrence	24 months	SVF	Centrifugation and enzymatic digestion	4.97 x 10^6/ml
Freitag et al. 2019 [19]	Regen Med	10 cases (single Injection 10 cases (two injections) 10 controls	53.6	Unilateral II-III Kellgren Lawrence	12 months	ADSCs	Culture expanded	One Injection: 103.9 million Two Injections: 95.1 million 102.6 million
Lee et al. 2019 [20]	Stem Cells Transl Med	12 cases 12 controls	63,5	II-III-IV Kellgren Lawrence	6 months	ADSCs	Culture expanded	1 x 10^8

OA=osteoarthritis; ICRS=International Cartilage Repair Society; SVF=Stromal vascular fraction; ADSCs=adipose derived stem cells

Table 2. Quality Assessment of the modified Jadad scale of Included Studies

Article	**Was the research described as randomized?**	**Was the approach of randomization appropriate?***	**Was the research described as blinding?**	**Was the approach of blinding appropriate**	**Was there a presentation of withdrawals and dropouts?**	**Was there a presentation of the inclusion/exclusion criteria?**	**Was the approach used to assess adverse effects described?**	**Was the approach of statistical analysis described?**	**Total**
Peretti et al. 2018 [15]	1	1	0	0	1	1	0	0	4
Koh et al. 2018 [16]	1	1	0	0	1	1	0	1	5
Hong et al. 2018 [17]	1	1	1	1	0	1	0	1	6
Koh et al. 2014 [18]	1	1	0	0	1	1	0	1	5
Freitag et al. 2019 [19]	1	1	0	0	1	1	1	1	6
Lee et al. 2019 [20]	1	1	1	1	1	1	1	1	8

Table 3. Clinical results of the studies included in the review

Author	Treatment Group	Number of Injection	Timing of Stem Cell Harvesting	Control Group	Scores	Clinical Outcome
Peretti et al. 2018 [15]	Arthroscopic debridement + SVF	1	Same day of Surgery	Arthroscopic Debridement	VAS, KSS, KOOS, WOMAC and SF-12	Clinical improvement in both difference
Koh et al. 2016 [16]	MFX + SVF + fibrin glue	1	The day before surgery	MFX	VAS, Lysholm and KOOS	The improvements in the m symptom subscores were si treatment group. Lysholm significantly improved in intergroup differences. VAS significantly in both groups
Hong et al. 2018 [17]	Arthroscopy + SVF (right knee) + HA (left knee)	1	Same day of Surgery	Arthroscopy + ADSC (left knee) + HA (right knee)	VAS and WOMAC	The SVF-treated knees showe improvement in the mean VAS and ROM at 12-months follow with the baseline.
Koh et al. 2014 [18]	HTO + PRP + SVF	1	The day before surgery	HTO + PRP	VAS, Lysholm and KOOS	The patients in the SVF- significantly greater improve subscales for pain and syn PRP-only group. No differenc score while , the MSC-PI significantly greater improver score.
Freitag et al. 2019 [19]	-One-injection group: a single intra-articular injection of ADSCs -Two-injection group: two intra-articular injections of ADSCs (baseline and 6 months).	1 or 2	N.A.	Conventional conservative management only	NPRS, KOOS and WOMAC	Both treatment groups receivi showed clinically significant p improvement at completion of months.
Lee et al. 2019 [20]	1x 10^8 cells of ADSCs in 3 mL of saline was administered intra-articularly	1	3 weeks before injection	3 mL of saline (NaCl 9 mg/mL) was administered intra-articularly	WOMAC, KOOS and VAS	Single injection of ADSCs led improvement of the WOMAC the control group, there was no the WOMAC score at 6 months.

ADSC: adipose derived stem cell; HTO: high tibial osteotomy; PRP: platelet rich-plasma; HA: hyaluronic acid; NPRS: Numeric Pain RatingScale; KOOS:the Knee Injury andOsteoarthritisOutcome Score; WOMAC: Western Ontario and McMaster Universities Osteoarthritis Index; VAS: visual analogue scale for pain