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Limited evidence for adipose-derived stem cell therapy on the treatment of osteoarthritis

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Abstract

Purpose The purpose of this systematic review is to evaluate the effects of adipose derived mesenchymal stem cells (ADSCs) in the treatment of osteoarthritis (OA) in the clinical setting.

Methods A literature search was performed in the MEDLINE, EMBASE, and The Cochrane Library Database up to January 2017 for inclusion and exclusion criteria. Criteria for inclusion were clinical studies demonstrating the effects of ADSCs on OA, and written in English. The following variables were analyzed: donor site, volume of adipose tissue, preparation of ADSCs, clinical outcomes, and complication rate.

Results Sixteen studies (knee: 14 studies, multiple joints: 1 study, ankle: 1 study) were included in this systematic review. All of the studies prepared ADSCs in the form of the stromal vascular fraction (SVF). Inconsistencies between studies were found with regards to reported clinical variability, donor sites of SVF, and reported clinical outcomes. Nine studies used either platelet-rich plasma (PRP) (7/16) or fibrin (4/16) or both PRP and Fibrin (1/16), as an adjunct at time of SVF injection. All of the studies reported an improvement in clinical outcomes with the use of SVF. Five studies reported a 90% satisfaction rate, and no study reported any complications with liposuction. Five studies reported on complications, with a 5% incidence of swelling and pain.

Conclusions This systematic review demonstrated that ADSCs are currently used in the form of SVF. While SVF may produce favorable clinical outcomes with minimal risk of side effects on osteoarthritis, the variability in the data and the use of biological adjuvants have confounded the effectiveness of ADSCs. This study will help surgeons understand the limitations in the literature on ADSCs.

Level of evidence Level IV, systematic review of level IV studies.

Keywords Adipose-derived stem cells · Cartilage · Osteoarthritis · Systematic review

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Introduction

Osteoarthritis (OA) is a highly prevalent, progressive, debilitating joint disease characterized by gradual loss of articular cartilage, damage to the subchondral bone and the surrounding soft tissue [1]. The avascular nature of articular cartilage limits its capacity for self-repair, resulting in progressive cartilage loss ultimately contributing to widespread degeneration of the affected joint [2]. Consequently, OA has become a primary focus for orthopaedic surgeons to provide a biologic milieu that will facilitate some form of endogenous cartilage healing [3].

Various biologic adjuncts have been described that may affect repair including growth factors and stem cells. Much of the recent literature has focused on bone marrow-derived

mesenchymal stem cells (MSC) for chondrogenesis [4]. However, the clinical use of bone marrow MSCs has presented problems, including donor site morbidity and pain and low cell number upon harvest [5]. This has led to the investigation of alternative sources for MSCs [6]. Several potential donor sites have been identified for harvesting MSCs, including periosteum, muscle, synovial membrane and adipose tissue [7]. All MSCs share similar characteristics in that they have the capacity to differentiate into chondrocytes, osteoblasts, myoblasts, adipocytes, and fibroblasts depending on their differentiation potential and the conditions in which they are stimulated.

Adipose tissue has become an attractive alternative source of MSCs because of its relatively easy accessibility and abundance [8]. Although adipose may not have the same degree of differentiation as bone marrow MSCs, the relative abundance of MSCs may be more advantageous, but there is evidence suggesting that adipose derived mesenchymal stem cells (ADSCs) have reduced chondogrenic potential relating to its bone morphogenic protein characteristics and the increased age of the patient [5, 8–10]. However, recent evidence suggests that ADSCs obtained from lipoaspirates can be induced to express gene and matrix markers associated with chondrocyte pathways under specific conditions [11]. Significant chondrogenic effects from the application of ADSCs have been shown in in-vitro studies, proposing that ADSCs possess the CD73, CD90, CD105 and CD106 markers, which are surface markers required for cell differentiation into cartilage [12]. In addition, recent animal model studies confirmed the chondrogenesis effect of ADSCs in vivo [13]. There is also a paracrine effect of ADSCs on OA chondrocytes as they promote inhibitory macrophages and T regulatory cells, which may decrease inflammatory markers and improve clinical outcomes alongside potential cartilage regeneration [14]. This has prompted several studies to investigate the role of ADSCs in human clinical trials.

However, due to the relative novelty of using ADSCs, there has been no systematic review that demonstrates its efficacy in osteoarthritic joints to date. The purpose of this systematic review is to evaluate the effects of ADSCs in the treatment of OA in the clinical setting. The hypothesis is that ADSCs would produce effective outcome on OA repair in clinical settings supported by clinical evidence.

Materials and methods

Search strategy

The following search terms were used in MEDLINE, EMBASE and the Cochrane Library Database, databases on January 7th 2017: "(cartilage OR cartilage injury OR cartilage damage OR cartilage repair OR cartilage defect OR osteochondral injury OR osteoarthritis) AND (adipose stem OR adipose stem cell OR adipose stem cells OR adipose derived OR adipose derived stem cell OR adipose derived stem cells OR adipose derived mesenchymal stem OR adipose derived mesenchymal stem cell OR adipose derived mesenchymal stem cells OR adipose derived msc OR svf OR stromal vascular fraction of adipose tissue)". No time limit was given to publication date.

Eligibility criteria

The inclusion criteria were: (1) clinical studies demonstrating the effects of ADSCs on OA, (2) published in a peer reviewed journal, (3) written in English, and (4) full-text of studies available. Exclusion criteria were the following: (1) review studies, (2) case report, (3) in vitro studies, and (4) animal studies.

Study selection

Two independent reviewers performed the literature search and reviewed the search results. The title and abstract were reviewed for all search results, and potentially eligible studies received full text review. In addition, the reference lists of all publications, including systematic reviews found in the search results, were manually screened for additional articles, which met the inclusion criteria that were potentially not identified through our electronic search. If a consensus could not be reached, a senior author was consulted who had the final decision.

Data extraction/analysis

The level of evidence (LOE) was evaluated based on previously published criteria [6]. The methodological index for non-randomized studies (MINORS) score [15] was used to evaluate the methodological quality of the clinical evidence (MQOE), with a score of 0–8 for case series and 0–12 for cohort studies.

The data of each clinical study was then extracted using a standardized data sheet with a list of 30 standardized variables (Table 1) [16]. The following variables were analyzed: donor site locations, volume of adipose tissue, donor site complications, adjunctive biologic therapies, concomitant treatment and clinical outcomes. In addition, the preparation and delivery methods of ADSCs was also recorded and analyzed.

Results

Search and literature selection

The literature search revealed 2475 total studies and 1728 studies after duplicates were removed. Sixteen clinical studies with 635 joints were included in this review (Fig. 1).

Table 1 Data reported

	Reported (%)	Not reported (%)
General (total)	94	6
Sex	100	0
Mean age + range	88	12
Patient history (total)	16	84
BMI	56	44
Mean duration of symptoms	6	94
Previous traumatic experience(s)	0	100
Activities of daily living/athletic participation	0	100
Study design (total)	88	12
Type of study	100	0
Number of patients	100	0
Percentage of patients in follow-up	100	0
Consecutive patients	100	0
Follow-up time + range/standard deviation	100	0
Method of lesion size measurement	50	50
Lesion classification system utilized	50	50
Surgical Approach to access lesion ($n=12$)	100	0
Clinical variables (total)	36	64
Diagnostic arthroscopy	25	25
Associated pathology	6	94
Associated procedures	100	0
Lesion size	38	65
Lesion location	0	100
Rehabiliation description	31	69
Second-look arthroscopy	50	50
Imaging data (total)	38	62
Diagnostic radiograph	44	56
Diagnostic magnetic resonance imaging	69	29
Diagnostic computed tomography scan	0	100
Follow-up radiograph	44	56
Follow-up magnetic resonance imaging	71	29
Follow-up computed tomography scan	0	100
Patient satisfaction (total)	77	23
Pain, function, and activity scale, pre operative	100	0
Pain, function, and activity scale, at follow-up	100	0
Patient satisfaction	31	29

Reported clinical variability in included studies

The clinical variability of the included 16 studies is shown in Table 1. A mean of 61% of the characteristic data was reported. General demographics including age and sex were reported in 94% of studies. While the study design and patient satisfaction were all well reported variables with 88 and 77%, respectively, patient history, clinical variables and imaging data were the least reported criteria with 16, 36, and 38% of the data being reported, respectively.

Donor site locations, volume of adipose tissue, and complications

All of the studies reported the location of the harvesting of adipose tissue. The most common sites included the buttock (nine studies [2, 17–23, 30]), abdomen (four studies [25–28]), and infrapatellar fat pad (two studies [24, 29]). One study did not report the harvesting site [31]. The weighted average volume of harvested adipose tissue in the buttock (reported in 6/9 studies [17–20, 22, 30]) was 140 ml, in the abdomen (reported in 4/4 studies [25–28]) was 103 ml, and in the infrapatellar fat pad (two studies [24, 29]) was 9.26 g. All of the studies using the buttock or abdomen harvested with liposuction and no study reported complications in the liposuction procedure. The two studies utilizing the infrapateller fat pad harvested via open excision [29, 30].

Preparation method of SVF

All of the studies prepared ADSCs in the form of the stromal vascular fraction (SVF). SVF is a component of the lipoaspirate obtained by liposuction, comprised of ADSCs as well as variety of other cells including pericytes, vascular adventitia cells, fibroblasts, preadipocytes, monocytes, macrophages, and red blood cells [31]. Eleven studies used the Zuk et al. method of ADSC preparation [32]. Eight studies [2, 19–23, 29, 30] reported liposuction the day before surgery, four studies [24–26, 28] reported liposuction the day of, and four studies [18, 21, 27, 31] did not report the date of liposuction. After the liposuction, the procedure of the adipose tissue was transported to the laboratory, where adipocytes and connective tissue were separated from the stromal vascular fraction (SVF) by centrifugation, according to the method by Zuk et al. [32]. The majority of the studies analyzed the SVF cells to confirm chondrogenic potential, including 12 studies via flow cytometry, three studies via cell count, 13 studies via culture in a medium. Only two studies did not report analysis of SVF cells [25, 28]. The mean concentration number of ADSCs in the SVF was 6.3×10^6 (range; $1.2\times10^6-4.2\times10^7$) in the ten studies that reported this [2, 17–20, 22, 23, 28–30]. The mean percentage of ADSCs in the SVF was 9.2% (range 8.5–9.7%) in the 5 studies [2, 18, 20, 23, 30] that reported this. One study [31] used three different doses with dose escalation: low dose (2×10^6 cells), medium dose (10×10^6), and high dose (50×10^6).

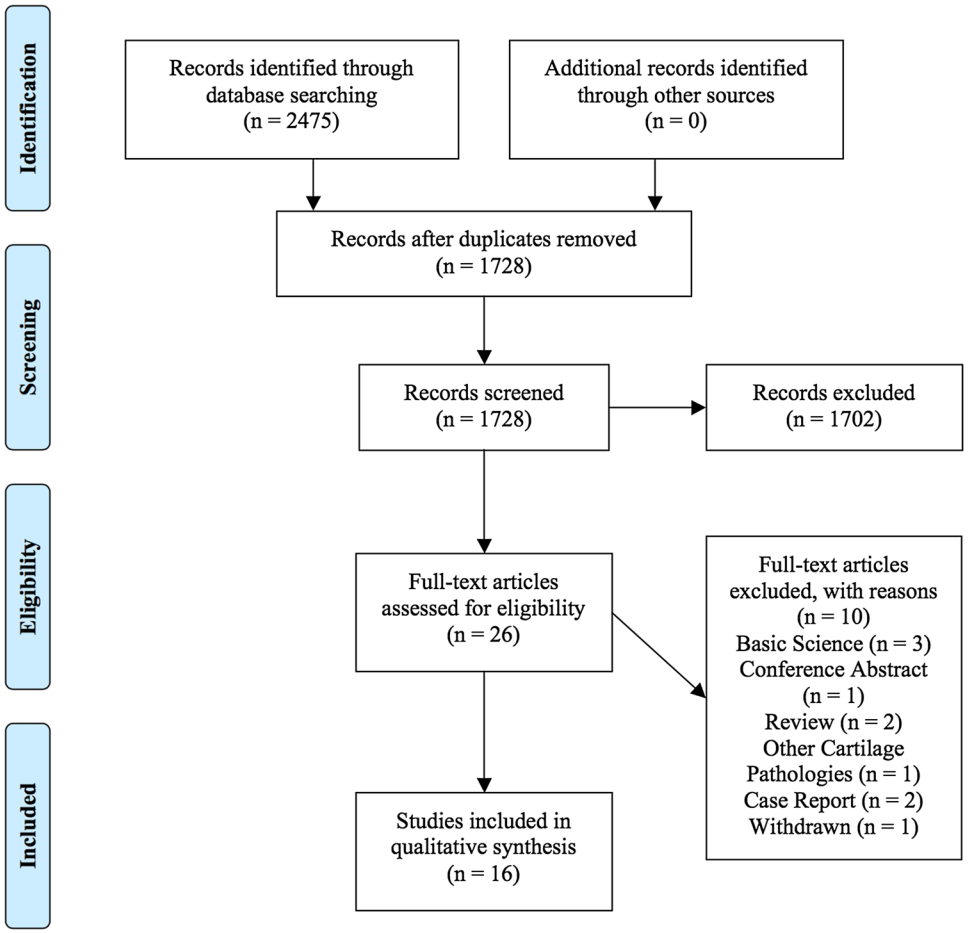

Fig. 1 PRISMA study selection flow diagram

Treatment

Of the 16 studies that treated patients using the SVF, 5 were case series (Table 2) involving OA knees using arthroscopic debridement, with 4 case series using injections in multiple OA joints [17, 18, 22, 24, 25, 26, 28, 29, 31]. All ten studies involved patients with OA joints and reported significant improvement in clinical outcome measures. In six studies, the SVF was used with biologics (PRP or fibrin) [17, 18, 24, 25, 28, 29]. The mean lesion size was reported by three of the ten studies, and ranged between 5.4 and 6.2 cm [2, 17, 22].

Of the 16 studies that treated patients using the SVF, 7 were comparative studies [2, 19, 20, 21, 23, 27, 30] (Table 3), All 7 comparative studies reported significant improvement of functional outcomes including three studies that compared SVF to no SVF. Six studies involved OA knees [2, 20, 21, 23, 27, 30], and one study involved OA ankles [19]. All studies in OA knees used SVF with a biologic (PRP or fibrin), while the study in the ankle compared SVF alone to no biologics. The mean lesion size was reported by three of the seven studies, and ranged between 4.6 and 6.4 cm [2, 20, 30]. The clinical outcomes of the comparative studies are reported in Table 4.

Radiological outcomes

Eight of the included studies reported the radiological outcomes using MRI or X-ray [18, 24, 25, 26, 27, 28, 30, 31]. The reported outcome measures were mixed, but the evidence was promising. MRI findings showed improved cartilage thickness in the majority of the included studies, with only one study finding no difference between the pre and post-treatment scores. Additionally, no study found any evidence of tumor formation. The radiological outcomes reported are shown in Table 5.

Patient satisfaction and complication rate

Five of the included studies reported the satisfaction rate, all of which were above 90% [2, 17, 23, 24, 26]. Seven of the included studies reported the complication rate. Two studies [28, 31] reported a 10 and 37% complication rate of swelling and four studies reported no complications [21,

Table 2 Study characteristics—case series

Study characteristics	Koh et al. [24]	Koh et al. [29]	Pak et al. [28]	Bui et al. [25]	Koh et al. [22]	Fodor et al. [26]	Kim et al. [18]	Kim et al. [17]	Pers et al. [31]
LOE	IV	IV	IV	IV	IV	IV	IV	IV	IV
MQOE	6	6	5	6	6	6	7	6	7
No. patients	18	30	91	21	35	6	20	49	18
No. procedures	18	30	100	21	37	8	24	55	18
Lesion site	Knee	Knee	Knee, hip, spine	Knee	Knee	Knee	Knee	Knee	Knee
OA grade (KL)	I/II	I/II	N/A	II/III	I/II	I-III	I/II	I/II	III/IV
Lesion size (cm)	N/A	N/A	N/A	N/A	5.4 ± 2.9	N/A	11 < 6.2 13 > 6.2	5.7 ± 2.4	N/A
Adipose donor site	Infra-patellar	Buttock	Abdomen	Abdomen	Buttock	Abdomen	Buttock	Buttock	N/A
Procedure	AD	AD	Injection	Injection	AD	Injection	AD	AD	Injection
Study design	Retro	Retro	N/A	Pro	Retro	Pro	Pro	Retro	Pro
Treatment	SVF + PRP	SVF + PRP	SVF + PRP	SVF + PRP	SVF	SVF	SVF + Fibrin	SVF + Fibrin	SVF
Mean F/U m	24.3	16.3	26.6	6	26.7	12	27.9	26.7	6
Mean age y.o	54.6	70.3	N/A	N/A	56.6	59	57.9	58.1	64.6

LOE level of evidence, *MQOE* methodological quality of evidence, *No* number, *OA* osteoarthritis, *KL* Kellgren Stromal Vascular Fraction, *PRP* platelet rich plasma, *F/U* follow-up, *m* months, *y.o.* years old, *N/A* not available, *AD* arthroscopic retrospective, *Pro* prospective

Table 3 Study characteristics—comparative studies

Study characteristics	Koh and Choi [21]	Koh et al. [23]	Kim et al. [2]	Kim et al. [20]	Koh et al. [30]	Nguyen et al. [27]	Kim and Koh [19]
LOE	III	II	III	III	II	II	III
MQOE	9	11	10	9	11	10	10
No. of patients	25	44	54	40	8	30	49
No. of procedures	25	44	56	40	80	30	49
Lesion site	Knee	Knee	Knee	Knee	Knee	Knee	Ankle
OA grade	I/II	I/II	I/II	I/II	I/II	II/III	IV
Lesion size (cm)	N/A	N/A	5.4 ± 1.6/6.4 ± 1.6	5.44 ± 1.4/5.8 ± 1.8	4.8 ± 1.9/4.6 ± 1.7	N/A	N/A
Adipose donor site	Infrapatellar	Buttock	Buttock	Buttock	Buttock	Abdomen	Buttock
Procedure	AD	AD w/HTO	AD	AD	AD/Mfx	AD/Mfx	AD/Mfx + LSCO
Study design	Retro	Pro	Retro	Retro	Pro	Pro	Retro
Treatment	SVF + PRP	SVF + PRP	SVF	SVF + PRP	SVF + Fibrin	SVF + PRP	SVF
Control	PRP	PRP	SVF + Fibrin	SVF + Fibrin	None	None	None
Mean F/U m	16.4	24.6/24.2	27.1	28.5/28.8	24.3	18	27.5/27.7
Mean Age y.o	54.2	52.3/54.2	57.5	59.4/59.1	38.4/39.1	58.658.2	54.3/53.6

LOE level of evidence, *MQOE* methodological quality of evidence, *No* Number, *OA* osteoarthritis, *KL* Kellgren and Lawrence, *SVF* Stromal Vascular Fraction, *PRP* platelet rich plasma, *HA* Hyaluronic Acid, *F/U* follow-up, *m* months, *y.o.* years old, *LSCO* lateral sliding calcaneal osteotomy, *N/A* not available, *AD* arthroscopic debridement, *Retro* retrospective, *Pro* prospective, *KL* Kellgren and Lawrence

Table 4 Study results—comparative studies

Koh and Choi [21]	Despite lower preoperative mean Lysholm, Tegner activity scale, and VAS scores in the SVF group than the control group, the clinical outcomes at final follow-up visit were similar and not significantly
Koh et al. [23]	SVF resulted in improved cartilage healing, VAS scores, and KOOS subscores compared to PRP alone, but they both resulted in similar functional outcomes
Kim et al. [2]	The mean IKDC and Tegner scores improved significantly from baseline in both groups, although there was no difference in functional outcomes. The patients treated with SVF and a fibrin scaffold had better ICRS scores
Kim et al. [20]	SVF implantation in OA knees resulted in better clinical outcomes and second-look arthroscopic ICRS scores than an SVF injection
Koh et al. [30]	MFX and SVF with fibrin glue provided radiologic and KOOS pain and symptom subscore improvements compared to MFX alone
Nguyen et al. [27]	Patients treated with SVF had significantly reduced pain and WOMAC scores, and increased Lysholm and VAS scores compared with the placebo group
Kim and Koh [19]	Significant improvements in VAS and AOFAS scores, and better ICRS grades, were achieved at short-term follow-up after MFX with and SVF injection compared to the control

VAS visual analogue scale, *MSC* mesenchymal stem cells, *SVF* stromal vascular fraction, *KOOS* knee injury and osteoarthritis outcome score, *PRP* platelet-rich plasma, *IKDC* international knee documentation committee, *OA* osteoarthritis, *MFX* microfracture, *WOMAC* Western Ontario and McMaster Universities Osteoarthritis Index, *AOFAS* American Orthopaedic Foot and Ankle Score

Table 5 Study results—radiographic evidence

Koh et al. [24]	MRI at the final follow-up visit showed a the WORMS improved significantly over the study period
Pak et al. [28]	MRIs did not find any evidence of tumor formation at the SVF implantation site
Bui et al. [25]	MRI analysis showed that the cartilage was partly regenerated at the injured sites. MRI also showed that the cartilage layer was also thicker after 6 months of treatment
Fodor et al. [26]	No significant differences were detectable between 0 and 3 months in the MRI after SVF therapy
Kim et al. [18]	The MOAKS grades at follow-up were significantly better than the preoperative values after treatment with SVF
Koh et al. [30]	The MOCART score at 24 months was significantly higher in the group treated with SVF then in the group without SVF
Nguyen et al. [27]	The differences in the OS scores were nonsignificant ($p > .05$), but the trend was clearly different between the two groups: OS scores increased in the placebo group over time but decreased in the treatment group
Pers et al. [31]	There positive MRI changes suggesting a possible cartilage improvement in three of the six patients

MRI magnetic resonance imaging, *WORMS* Whole-Organ Magnetic Resonance Imaging Score, *MOAKS* MRI osteoarthritis knee score, *MOCART* magnetic resonance observation of cartilage repair tissue, *SVF* stromal vascular fraction, *OS* Outerbridge classification system

24, 25, 27]. The other included studies did not mention any complications.

Discussion

The most important finding of this systematic review was that ADSCs in the form of SVF produce favorable clinical outcomes with minimal complications in the treatment of OA. Additionally, several studies showed that patients receiving SVF had better radiographic outcomes compared to the baseline [18, 24, 25, 27, 29]. However, caution should be taken to interpret the outcomes of the present study. This systematic review demonstrates the variability in both the data collected and the use of biological adjuvants between studies, thereby limiting proper cross-study comparisons and potentially confounding the effects of ADSCs. Therefore, while SVF may produce favorable clinical outcomes for patients with OA, the confounding factors limit our understanding of the effectiveness of ADSCs.

There have been many studies evaluating the effects of ADSCs in cartilage repair; however, the terminology describing the use of ADSCs has been inconsistent and confusing with terms including adipose-derived adult stem (ADAS) cells, adipose-derived mesenchymal stem cells (AD-MSCs), adipose MSCs (AMSCs), and adipose stromal/stem cells (ASCs). The results from this systematic review demonstrated inconsistencies on what components of ADSC were used in the various studies reviewed when evaluating the effects of ADSCs. The results demonstrate that analysis has focused on the SVF rather than ADSCs. The SVF contains different proportions of ADSCs, pericytes, vascular adventitia cells, fibroblasts, preadipocytes, monocytes, macrophages, and red blood cells [33]. Therefore, analysis of the SVF limits the ability to evaluate the effectiveness of only the stem cell component of the fraction. There has been limited data evaluating other components of SVF such

as pericytes and the vascular fraction and therefore these human trials cannot determine the role each factor has in cartilage regeneration.

The results of this systematic review also demonstrate the use of an adjunctive procedure in the majority of the studies evaluated (12/16 studies). These studies utilized either PRP (7/16) or fibrin (4/16), with one study comparing both biologic adjuncts. These studies demonstrated favorable outcomes when SVF and a biologic were used. Few studies have compared SVF to the adjunctive biologic itself, confounding meaningful analysis. There is evidence that PRP contains growth factors that increases chondrocyte viability and differentiation, as well as the synthetic capacity of MSCs, which may prove beneficial in cartilage repair [34, 35]. There have been several level I and II clinical studies demonstrating significant effects and positive clinical outcomes of PRP applications in the treatment of OA and osteochondral defects [36, 37]. There is also evidence of fibrin as a stem cell carrier [34], however, its effect on cartilage repair is largely unknown. Both PRP and fibrin can act as a scaffold and may enhance ADSC adherence to cartilage lesions and promote their proliferation [38]. The application of either PRP or fibrin confounds the effects of ADSCs in OA; therefore, the advantages of ADSCs beyond the use of these adjuncts cannot be determined from this study.

The results from the current study demonstrate large variability in the data reported thereby limiting the ability to analyze the results through meta-analytical methods. Two different sites including the knee and ankle were evaluated in the literature, which result in variable responses in cartilage repair. In addition, many studies failed to report lesion size, which is an important prognostic factor in the repair process of cartilage [39]. Another reported variable was in the donor sites location, which varied between the buttock and infrapatellar fat pad. Although liposuction has been shown to produce a higher percentage of viable cells in lipoaspirates when compared to surgical resection of adipose tissue [35, 37], the number of nucleated cells can range from 500,000 to 2,000,000 cells per gram of adipose tissue [40]. Recent evidence has shown that different individuals have variable density in different locations of adipose tissue [41] and that there may be differences in the multi-potency of ADSCs depending on the harvest location [42, 43]. In addition to the extraction methods and the differences in adipose tissue, the process and preparation of SVF are an important assessment area in this systematic review.

There was significant variability in the preparation methods reported in the included studies, and in the reported methods of assessing chondrogenic potential. The reported percentage of ADSCs in the SVF was only 9.2% in the studies assessing this, showing that the majority of the injected material was in fact the pericytes, vascular adventitia cells, fibroblasts, preadipocytes, monocytes, macrophages, and red blood cells. Additionally, those studies found a wide-ranging difference in the percentage of included ADSCS in SVF, although no analysis of factors relating to differences where performed. Previously, studies have found that older patients have decreased growth factors and chondrogenic potential in autologous blood products compared to younger patients [44]. While the Zuk method of SVF preparation [32] originally reported using collagenase to separate the ADSC from the surrounding area, the authors in the included studies did not report using any collagenase indicating that the method may have been altered. It is worth noting that collagenase digestion cannot be used in the United States. The concentration and incubation time of collagenase can affect the yield of ADSCs as higher dosages or exposures have been shown to be toxic to ADSCs [38]. Excess amounts of collagenase can decrease the ADSC viability while insufficient amounts may result in inefficient and inadequate amounts of ADSC yield [12, 38]. Although all of the included studies reported improved clinical outcomes, the lack of standardization in the clinical outcome measures, the operative treatment, and concomitant biologic use limits adequate comparison thus confounding any meaningful clinical analysis.

Five of the studies (42%) reported on patient's reported outcomes with all above 90% satisfaction. However, of the five studies reporting on patient satisfaction only 2 reported radiological findings, with mixed results. Koh et al. found high patient satisfaction alongside improved radiological outcome measures, while Fodor et al. showed high patient satisfaction with no change in radiological measures at 3 months [23, 26]. These findings suggest that the patient satisfaction may be at least partially due to the paracrine effect of the SVF rather than true cartilage repair alone. Six (50%) of the included studies reported an improvement in VAS scores. The complication rate of the liposuction procedure was not reported in any of the included studies. Previous evidence has shown this to be a safe procedure, with complication rates of only 0.1% in a national survey of 112,756 reported patient procedures [45]. The outcomes from this study, therefore, suggest that injection of ADSCs in the form of SVF may be a safe procedure with a low complication rate.

This systematic review has several inherent limitations and potential biases. The search criterion was limited to MEDLINE, EMBASE and The Cochrane Library Database articles published exclusively in English. Eleven of the surgical studies came from one center: The Center for Stem Cell & Arthritis Research, Department of Orthopaedic Surgery, Yonsei Sarang Hospital, Seoul, Korea. This may suggest that the results could be partially attributed to the surgeons' skill sets, as there is a lack of variance in the operating surgeons for the procedures compared to normal systematic reviews. There were few studies that included a true control, as the majority compared the results to patients treated with PRP

alone, which limits the comparison. There is also evidence that ADSCs have a paracrine effect on OA chondrocytes by producing cytokines, anti-inflammatory mediators, immunoregulatory molecules, and there is a potential placebo effect from the injections, both which may explain at least partially explain the improvement in clinical symptoms [14]. The overall quality of evidence of published studies was variable in this review. The LOE in the included studies was low with 14 (82%) of the studies being LOE III or IV, with no reported randomized clinical trials.

Conclusions

This systematic review demonstrates that the majority of studies in the current literature utilize ADSCs in the form of SVF when evaluating the outcomes in the treatment of OA. While SVF may produce favorable clinical outcomes with minimal risk of side effects on osteoarthritis, the variability in the data and the use of biological adjuvants have confounded the effectiveness of ADSCs.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval This manuscript is a systematic review and does not contain any studies with human participants or animals performed by any of the authors.

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