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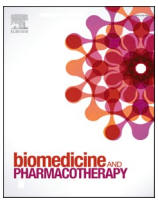

Lipoaspirate processing for the treatment of knee osteoarthritis: a review of clinical evidences

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ABSTRACT

The autologous lipoaspirate processing allows to obtain a tissue product to be transplanted for regenerative purposes in multiple pathological sites, such as the knee joint affected by osteoarthritic disease. Recently, multiple protocols and devices have been designed for lipoaspirate processing. These protocols and devices do not use enzymatic digestion and respect the principles of the so-called "minimal manipulation in a closed system". In this study, we performed a systematic review of the literature to identify studies in which osteoarthritis was treated by minimally manipulated intra-articular SVF injection and assessment of therapeutic response was reported. All bias scores were analyzed based on the Coleman methodology score modified by Kon et al. [27] and a subsequent linear classification system of articles was proposed. We identified 12 clinical trials in which clinical evaluations were performed inconsistently using different scales of analysis. All studies reported a significant decrease in the patient's symptomatic discomfort, with improvement in joint function and reduction in pain. Most studies do not reach a high-quality level on the linear scale based on the Coleman-Kon scores. Although the treatment of osteoarthritis of the knee with regenerative methods is undoubtedly of interest, being aimed at healing the disease, this study highlights that the trials are numerically limited, and qualitatively not optimal according to the Coleman-Kon score. Reasonably, greater standardization of devices protocols will be desirable in the future. The high clinical potential offered by these methods could be optimized for all patients.

1. Introduction

Rheumatic diseases comprise a heterogeneous group of chronic disorders affecting the locomotor system and are the main causes of disability in the adult population [1]. In particular, osteoarthritis (OA) is among the most common [2] and involves a progressive degeneration and aberrant remodelling of the joint components, culminating in a symptomatic picture of pain, loss of functionality and disability. Moreover, a high prevalence of physical and psychological comorbidities is commonly reported [3,4]. Although the causes of OA are not yet well defined, it is known that the uncontrolled inflammatory response and deregulations of the released cytokine network have been shown to be deeply involved in the etiology and symptomatic manifestation of this pathology [5,6].

In the last few years, a new therapeutic approach based on the use of autologous adipose tissue transplants for the treatment of rheumatic diseases (e.g., OA) has spread [7]. This therapeutic perspective has implied a strong impetus for studies aimed at defining the cellular components that constitute adipose tissue [8]. Initially considered only inert filler, today its role has been extended to dynamic tissue with regenerative properties in multiple contexts of tissue injury and inflammatory conditions, including rheumatic pathology and therefore OA [9]. The biological basis of this regenerative potential is due to the relatively high content of mesenchymal stromal stem cells (Adipose Derived Stem Cell, ADSC), located in the Stromal Vascular Fraction (SVF) [8,10]. These are progenitor cells endowed with multilinear plasticity towards adipocytic, chondrocytic, and osteocytic differentiation and with regenerative, immunomodulatory, and pro- angiogenic properties [7,11]. In the context of OA, the use of autologous ADSC transplantation is an extraordinary potential tool to allow not only the shutdown of chronic inflammatory processes, but also for a potential regenerative purpose of the synovium and the chondral surface [9].

In recent years, the literature on musculoskeletal diseases has been enriched with numerous studies aimed at evaluating the clinical response to ADSCs-based treatments [7,12]. The standard laboratory procedure for isolating ADSCs involves an enzymatic digestion of tissue

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with collagenase [13]. The major disadvantages of this procedure are the requirement of considerable processing time, and the impossibility to considering it as a so-called "minimal tissue manipulation procedure", a fundamental prerogative for the use of stem cells in clinical practice [14]. In fact, the Good Manufacturing Practice regulations [15] of the European Parliament and Council (EC regulation no. 1394/2007), EMA (European Medical Agency) and FDA (Food and Drug Administration) (FDA-2017-D-6146) ban the enzymatic manipulation of stem cells in the clinical setting.

The need to reduce processing times (for an immediate clinical use) and regulatory restrictions on the degree of human lipoaspirate manipulation have led to the development of numerous devices for the non-enzymatic mechanical processing of harvested adipose tissue [16–18]. These protocols, with inherent variations, are characterized by three common phases: harvesting, processing, and reinjection [18]. The harvesting is performed in easily accessible anatomical regions such as the subcutaneous tissue, in order to provide a product to be re-injected in the areas affected by pathological alterations. In particular, by comparing the adipose samples extracted from thigh and abdomen, the former provides a higher number of ADSCs [19]. Processing includes one or more manipulation techniques that commonly vary depending on the choice of surgeon and site of re-injection [18].

Several reviews of clinical studies aimed at evaluating SVF therapy in knee OA are already present in the literature, but all also include enzymatic-based trials conducted in non-US or non-EU areas [20–25], and some define the comparison between ADSC and the bone marrow-derived mesenchymal stromal stem cells therapy [20–24]. None of these reviews focused on the types of devices used for the mechanical

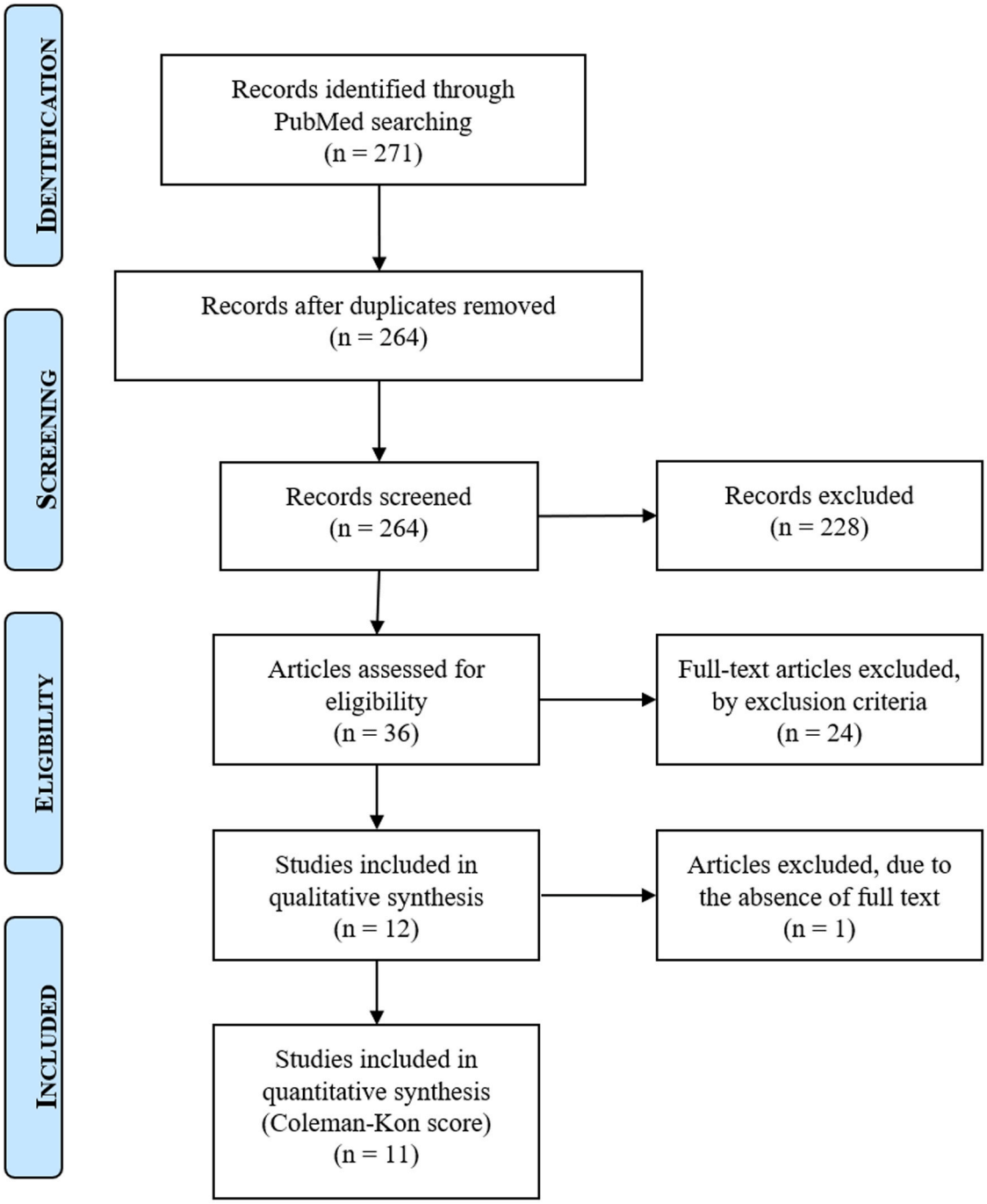

Fig. 1. PRISMA flowchart of the literature review.

lipoaspirate processing. Considering this lacuna, we believe that an updated and thoughtful review is necessary, to evaluate the state of the art of knee OA therapy based on the use of technological devices and clinically applicable protocols, already present in today's clinical practice.

2. Material and methods

We performed a systematic literature review of the articles published up to June 2021, consulting the PubMed, Embase, Medline Ovid and the Cochrane Central Register of Controlled Trials databases; search strings included the terms: "stromal vascular fraction - SVF" OR / AND "adipose (derived) stem / stromal cell - ASC/ADSC" AND "knee" AND "osteoarthritis", differently combined.

A PRISMA flowchart [26] of the selection method is reported in Fig. 1. Duplicated works were removed. Then, the inclusion criteria for the remaining articles were applied: only peer-reviewed studies, written in English; any study design; based on the intra-articular injection of minimally manipulated SVF and on the evaluation of the therapeutic response aimed at the regenerating the articular cartilage. Conference presentations, narrative reviews, editorials, and expert opinion were excluded, in order to integrate studies with clinical evidence.

The exclusion criteria subsequently applied were: studies that included an enzymatic manipulation of the collected tissue or that integrated an enzymatic approach with the mechanical one. Furthermore, if no statistical analyzes were reported in the studies, the articles were excluded from the analysis.

The selected articles were first analyzed on the basis of their conceptualization (study design, experimental model, clinical evaluation tools used). Clinical outcomes were highlighted and some considerations were made on the technical instruments and procedures applied. All bias assessments were evaluated according to the Coleman methodology score modified by Kon et al. [27] (Table 1). This score is a recognized standard used to assess the quality level of cartilage regeneration studies, not the outcome of the procedure itself. It consists of a general assessment part (A) and a specific assessment part (B) for joint cartilage studies. In part A, scores are assigned to 8 parameters (study size, follow-up duration, number of surgeries, type of study, description of surgery, description of postoperative rehabilitation, imaging investigations, histological investigations), with a maximum of 75 points. Part B considers 3 parameters (outcome criteria, clinical outcome assessment procedure, description of the subject selection process), with a maximum of 25 points. The total is obtained from the sum of items, which composed both parts (maximum 100 points). Given the absence of a defined classification of the numerical data provided by the score, we utilized a subjective evaluation based on the linearity of the scale: <25 points are considered scarce; 25–50 points not optimal; 50–75 points partially optimal; >75 points optimal.

Table 1
Coleman methodology score modified by Kon-Verdonk [27].

Part A		**Score**
1	Study size: number of lesions	
	>60 | 41–60 | 20–40 | <20, not stated	10 | 7 | 4 | 0
2	Mean follow-up, months	
	>60 | 24–60 | 12–24 | <12, not stated	10 | 5 | 2 | 0
3	Number of surgical procedures included in each outcome	
	One procedure	10
	More than 1 surgical: <10% patients | >10% patients	7 | 4
	Not stated, unclear	0
4	Type of study	
	Randomized control trial	15
	Prospective cohort study	10
	Retrospective cohort study	0
5	Description of surgical procedure given	
	Adequate | Fair | Inadequate	5 | 3 | 0
6	Description of postoperative rehabilitation	
	Well described | Not adequately described | Protocol not reported	5 | 2 | 0
7	Inclusion MRI outcome/assessment	
	Reported for >80% of patients | <80% of patients	10 | 5
	Not reported	0
8	Inclusion histological outcome/assessment	
	Reported for >50% of patients | <50% of patients	10 | 5
	Not reported	0
Part B		**Score**
1	Outcome criteria	
	Clearly defined	2
	Outcome criteria (good reliability and sensitivity)	3
2	Procedure for assessing clinical outcomes	
	Patients recruited	3
	Investigator independent of surgeon	4
	Completion of assessment by patients themselves	2
3	Description of subject selection process	
	Selection criteria reported and unbiased	3
	Recruitment rate reported: >80% | <80%	5 | 3
	TOT	100 points

3. Results

After the duplicates were removed, 264 studies were reviewed. 36 human trials (14%) were selected utilizing the inclusion criteria. 12 studies (5%) remained after application of the exclusion criteria (28–39). Table 2 summarizes the experimental model, study design, processing device, follow-up period, and the most relevant results obtained.

Clinical evaluations were performed in a non-homogeneous way and different analysis scales were used: Knee Injury and Osteoarthritis Outcome Score (KOOS) [31,33–35,39]; Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) [28,30,37]; Visual Analog Scale (VAS) [29–35,37,38]; Tegner Lysholm Knee (TLK) [34,35]; International Knee Documentation Committee (IKDC) [34,35]; Emory Quality of Life (EQOL) [33]; Japanese Knee Osteoarthritis Measure (JKOM) [30]; International Knee Society (IKS) knee and function scores [38]. Nuclear magnetic resonance (MRI) imaging were also performed in four studies [28,29,32,37]. Only in Roato et al. [37] evaluations of immunohistochemistry (IHC) and scanning electron microscopy (SEM) were included.

For Peretti et al. [36] it was not possible to obtain the full text; with this assumption, the quantitative assessment using the Coleman-Kon score was not conducted (Fig. 1), while clinical data were obtained from the abstract.

3.1. Clinical findings

Our survey reports that 7 studies are prospective non-randomized trials [29–32,34,35,37], while 2 are prospective randomized [28,36] and 3 retrospective [33,38,39] trials.

Mautner et al. [33] included the largest number of knees in their study (106 knees, 76 patients). Onoi et al. [31] presented a case report of two patients, which cannot properly be consider as a clinical trial (3 knees). 9 studies (75%) were conducted with at least 12 months of follow-up [28,29,32–35,37–39], and 3 studies (25%) covered 6 months of follow-up [30,31,36].

In all studies, the clinical outcomes highlight a significant decrease in the patient's symptomatic distress, with improvement in joint function and reduction of pain.

Specifically, 8 out of 12 studies used the VAS pain scale to evaluate clinical outcomes. Boric et al. [29], and Hudetz et al. [32] reported an improvement in activity VAS from 7.73 ± 1.55–3.4 ± 1.65, and from 7.33 ± 1.72–3.17 ± 1.98, respectively. Resting VAS decreased from 4.45 ± 2.42–0.55 ± 1.04 for Boric et al. [29], and from 3.94 ± 2.56–0.56 ± 1.2 for Hudetz et al. [32]. Roato et al. [37] reported an improvement in overall VAS from 7.05 ± 0.4–3.34 ± 0.6. Mautner et al. [33], Russo et al. [34], Schiavone Panni et al. [38], and Yokota et al. [30] showed an improvement in VAS of 37%, 55%, 40% and 40%, respectively Onoi et al. [31] reported an improvement of at least 75%.

Table 2
Clinical studies regarding the minimal manipulated SVF use in the treatment of knee OA.

	Therapeutic protocol	Evaluation	Study design	Device	FU	Conclusion
Garza et al. [28]	39 patients, 2 groups: high /low MFAT dose.	WOMAC score; MRI	Prosp, rand contr trial	GID SVF-2® (GID Group)	12 months	Dose-dependent decrease of symptoms and pain. MRI outcome: no changes.
Boric et al. [29]	17 patients, 18 knees: MFAT inject.	dGEMRIC; orthopedic physical examination; VAS.	Prosp, non-rand trial	Lipogems® (Lipogems International SpA)	24 months (continuation [32])	Significant increase of GAG content; significant clinical improvement.
Mautner et al. [33]	76 patients (BMAC 41, MFAT 35 inject) and 106 knees (BMAC 58, MFAT 48 inject).	KOOS; EQOL; VAS.	Retrosp	Lipogems® (Lipogems International SpA)	1 year	For both groups: improvement in EQOL, VAS, and all KOOS parameters. Post procedure scores: not significant different.
Onoi et al. [31]	2 patients: MFAT inject.	VAS; KOOS; arthroscopy.	Prosp, non-rand, trial (case report)	Celution® Centrifuge (Cytori Therapeutics)	6 months	VAS and KOOS improved. At 6th months FU: coverage of almost all cartilage defect areas.
Russo et al. [34]	30 patients: MFAT inject - 24 with associated surgery, 6 arthroscopy only.	TLK; VAS; IKDC-subjective; KOOS.	Prosp, non-rand trial	Lipogems® (Lipogems International SpA)	3 years (continuation [35])	Clinical outcomes improvement: 41% TLK; 55% VAS; 55% IKDC; 64% KOOS.
Peretti et al. [36]	2 groups: AD + intra-articular MFAT inject; only AD.	MRI; functional outcome.	Prosp, rand, contr trial	Fragmented Adipose Tissue (?)	6 months	Outcomes: no significant differences.
Roato et al. [37]	20 patients: MFAT inject.	VAS; WOMAC; biopsies; IHC; SEM.	Prosp, non-rand trial	Centrifugation	18 months	Pain reduction and increased functionality. Biopsy: layer of newly formed tissue.
Schiavone Panni et al. [38]	52 patients: AD + MFAT inject.	IKS knee; function scores; VAS.	Retrosp	Lipogems® (Lipogems International SpA)	24 months	Clinical and functional scores increasing at a mid-term follow-up.
Cattaneo et al. [39]	38 patients: AD + MFAT inject.	KOOS; physical examination.	Retrosp	Lipogems® (Lipogems International SpA)	12 months	Clinical improvement in 92% patients, 100% satisfied.
Hudetz et al. [32]	17 patients, 32 knees: MFAT inject.	dGEMRIC; VAS.	Prosp, non-rand trial	Lipogems® (Lipogems International SpA)	12 months	Increase in knee GAG content and in VAS score.
Yokota et al. [30]	13 patients: MFAT inject in both knees.	VAS; JKOM; WOMAC.	Prosp, non-rand trial	Celution® Centrifuge (Cytori Therapeutics)	6 months	At 1 month FU: overall improvement. At 6th months FU: 35% JKOM; 32% WOMAC; 40% VAS improvement.
Russo et al. [35]	30 patients: MFAT inject - 24 with associated surgery, 6 arthroscopy only.	TLK; VAS; IKDC-subjective; KOOS.	Prosp, non-rand trial	Lipogems® (Lipogems International SpA)	12 months	Total median improvement of 20 points in IKDC-subjective and total KOOS, and of 24 and 31 points in VAS and TLK respectively.

AD: arthroscopic debridement, BMAC: bone marrow aspirate concentrate, contr: controlled, dGEMRIC: delayed gadolinium (Gd)-enhanced magnetic resonance imaging of cartilage, EQOL: Emory Quality of Life, FU: Follow-up, IHC: Immunohistochemistry, IKDC: International Knee Documentation Committee, inject: injection, JKOM: Japanese Knee Osteoarthritis Measure, KOOS: Knee Injury and Osteoarthritis Outcome Score, MFAT: micro-fragmented adipose tissue, MRI: Magnetic Resonance Imaging, prosp: prospective, rand: randomized, retrosp: retrospective, SEM: scanning electron microscopy, TLK: Tegner Lysholm Knee, VAS: Visual Analog Scale, WOMAC: Western Ontario and McMaster Universities Osteoarthritis Index.

Four out of 12 studies utilized WOMAC index. Cattaneo et al. [39], Garza et al. [28], and Yokota et al. [30] found an improvement in this index of at least 79%, 68.2%, and 32%. Roato et al. [37] reported the change in score from 45.9 ± 2.8–13.0 ± 2.3.

Another 4 studies reported an improvement in the KOOS index of at least 73% [39], and 18% [31], about 30% [33], and 64% [34].

When performed, MRI did not consistently provide cartilage morphological improvement data. Peretti et al. [36] emphasized that imaging investigations were still ongoing and therefore not available. Garza et al. [28] found no changes, while Boric et al. [29], and Hudetz et al. [32] reported an increase in the content of cartilaginous glycosaminoglycans in the treated joints with a variation of the order of 15%.

Only two studies partially characterized the processed fat, from the biological point of view. With histological and immunohistochemical investigations on biopsy samples taken in the context of post-treatment prosthetics, Roato et al. [37] reported the presence of a layer of cartilage neoformation in the joint region characterized by osteochondral lesion. In the context of a second-look arthroscopy (6 months after treatment), Onoi et al. [31] reported the presence of an almost total coverage of cartilage defects, with repair of the compromised meniscal areas (dimensions of the filled areas: 2.5–3 ×1.5 cm in the first patient, 1.5–2 ×1.5 cm in the second patient).

As already highlighted, Onoi et al. [31] presented a case report of two patients: despite this and considering the limitation of the studies found, the report was still integrated into our investigation. The clinical evaluations of this study, although reported, are not considered statistically significant for the non-representative cohort.

3.2. Technical findings

In 7 studies (58%) (Fig. 2) the device adopted was Lipogems® [29,32–35,38,39]. By performing a manual shaking, this mechanical device allows the fragmentation of the lipoaspirate by means of steel balls. The product obtained is filtered and injected directly in the joint, without

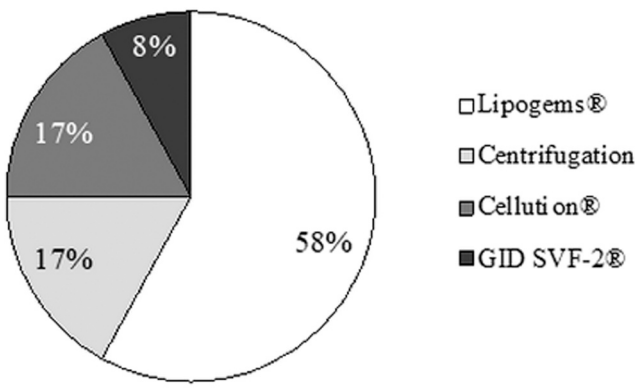

Fig. 2. Percentage of devices used in the different studies investigated.

performing centrifugation [16].

Garza et al. [28] used GID SVF-2®, which is a recent modular tissue processing platform based on a manual pureeing of the lipoaspirate [40]; in the literature, we found only two other trials using the same device [41,42]. Centrifugation is performed at 600 g for 6 min; then, after a further pureeing, for another 4 min.

Yokota et al. [30], and Onoi et al. [31] reported the use of the Cellution® centrifuge [43]. This is a CE-marked technology developed by Cytori to allow real-time access to a concentrated single cell suspension of autologous SVF. The system integrates mechanical manipulation with enzymatic processing, replacing collagenase with two process reagents and centrifugation performed at 400 g for 10 min. Having CE certification, this procedure is interpreted as applicable in our clinical context. It should be noted that ADSCs are the result of culturing the plastic-adherent fraction of the SVF from fat, since the precursors of the ADSCs already reside in the SVF and cannot be separated from it.

Roato et al. [37] used a simple centrifugation at 3000 rpm for 3 min to separate the oily supernatant from the SVF.

In the trial of Peretti et al. [36] the exact protocol for SVF processing could not be recognized; it had to be a simple centrifugation without the use of particular devices.

3.3. Coleman-Kon methodology score

Although clinical results were positive, the Coleman-Kon methodology score (Table 3, Fig. 3) was extremely poor, with a mean of 46.4 ± 12.5 points, 67 maximum points for Roato et al. [37], and 33 minimum point for Cattaneo et al. [39]. For three of the studies considered [30,32,37], the score was already available in the literature [24]. After comparing the congruity of the data obtained by Di Matteo et al. [24] with our ratings, we decided to report their scores in this study.

Considering all the obtained Coleman-Kon scores, we deduced that the risk of bias is high as most of the selected studies are not at a high-quality level. With reference to our subjective classification, no study has a qualitatively optimal score (>70 points).

4. Discussion

Among the sources of mesenchymal stromal stem cells, adipose tissue is one of the main [7], easier to access with minimal discomfort for the patient. The use of adipose tissue for regenerative purposes has been practiced for a long time, but recently there has been an increase in studies aimed at investigating the biological potential [7,10,44]. The possibility of having a regenerative chondrocytes source could therefore guarantee a restoration of compromised joint function [45]. In this perspective, the use of autologous ADSC transplantation seems to be an extraordinary potential tool to allow not only the shutdown of chronic inflammatory processes, but also for a potential regenerative purpose of the synovium and the chondral surface. The clinical application of the processed lipoaspirate underlies the use of devices suitable for minimal manipulation, i.e. capable of leaving the isolated stem niche unaltered to be transplanted into the pathological joint. It should be noted that the fact that cultured ADSCs have chondrogenic capacity and suppression of inflammation does not guarantee that their precursors in fat / SVF will do the same. Vice versa, the fact that fat / SVF administration tempers inflammation and reduces pain does not mean that this is governed by ADSCs. Further studies are needed to verify both the anti-inflammatory potential and the regenerative potential of the graft.

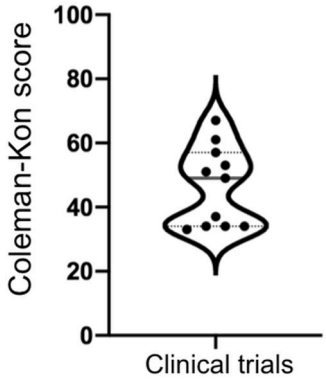

Fig. 3. Violin plot of Coleman-Kon's scores. A poor quality of the investigated studies and a high risk of bias induction are highlighted.

The present systematic review clearly demonstrates that the available literature is particularly scarce regarding the use of devices for minimally invasive therapy based on processed lipoaspirate. This could be due to ongoing investigations not yet published, with reference to the topicality and innovation of this field of study.

In the studies considered, the most evaluated protocol is Lipogems®, which was used in perspective, retrospective, randomized and non-randomized trials [29,32–35,38,39]. This evidence is particularly relevant: Lipogems® is one of the best documented devices in the literature, perhaps for the protocol known for more than ten years.

From a clinical point of view, the treatments significantly increased clinical outcomes in all these studies.

Considering the Coleman-Kon score, the evidence suggests low methodological quality in the studies evaluated. In general, the short average follow-up and the type of retrospective study are factors that lower the score. Furthermore, in many papers, because the inclusion and exclusion criteria were not well reported, the recruitment rate was not evaluated, introducing another source of bias. Moreover, although all

Table 3
Bias assessment according to the Coleman methodology score modified by Kon et al. [27].

	TOT	Study size	Foll-up	Surg proc.	Type of study	Surg proc description	Postop rehab	MRI	Histo	Outcome criteria	Assessm of CO	Selection process
Roato et al. [37]	67	0	2	10	10	5	5	10	10	5	7	3
Garza et al. [28]	61	4	2	10	15	5	0	10	0	5	7	3
Boric et al. [29]	57	0	5	10	10	5	2	10	0	5	7	3
Hudetz et al. [32]	53	4	2	10	10	5	0	10	0	5	7	0
Russo et al. [34]	51	4	5	4	10	5	5	0	0	5	5	8
Russo et al. [35]	49	4	2	4	10	5	5	0	0	5	5	8
Mautner et al. [33]	34	10	2	10	0	5	0	0	0	2	5	0
Onoi et al. [31]	37	0	0	10	10	5	2	0	0	5	2	3
Schiavone Panni et al. [38]	34	7	5	4	0	5	0	0	0	5	5	3
Yokota et al. [30]	34	0	0	10	10	5	2	0	0	2	5	0
Cattaneo et al. [39]	33	4	2	4	0	5	5	0	0	5	5	3
Peretti et al. [36]	–	–	–	–	–	–	–	–	–	–	–	–

Legend: TOT = total; Foll-up = mean follow-up; Surg proc = surgical procedures descriptions; Postop rehab = post-operative rehabilitation; MRI = magnetic resonance imaging; Histo = histological outcome; Assessm of CO = assessment of clinical outcome; - = data not available.

authors adequately described the procedure (with the exception of Peretti et al. [36]), in many studies [34–36,38,39] patients underwent concomitant surgeries such as arthroscopic debridement, microfractures, or high tibial osteotomy, thus preventing a clear understanding of the real contribution and clinical potential of stem cell-based treatment. The basic questions about the number of cells administered, the optimal number of injections to achieve the best therapeutic effect, and the superiority of one method of preparation over another still remains unanswered. Post-operative rehabilitation was described in seven studies [29–31,34,35,37,39] (but correctly defined exclusively in four papers [34,35,37,39]), while the outcomes of MRI were reported in only four studies [28,29,32,37] and the histological outcome only by Roato et al. [37].

The numeric expansion of available kits (i.e., devices) for the treatment of patients with knee OA through mechanical lipoaspirate processing is evident [24]. This could be a great opportunity to provide a concrete therapeutical chance even for a pathology still strictly limited to invasive demolition surgery. Nevertheless, an expanding market for these technologies does not always mean improving the standard of care, especially when there is a lack of comparative trials evaluating the effectiveness of a new treatment versus established ones. Comparing the proportional use of these devices in today clinical practice with the documented trials available, a substantial deficit emerges: many devices have insufficient published scientific data to certify their clinical use.

Finally, the question of inter-human variability has not yet been faced. This is a fundamental prerogative for the success of these biological therapies, because a particular “patient profile” could respond better to a specific biologic stimulus than another. This highlights the need for further research, dedicated to understanding the unique characteristics of a specific stem cell-based product and the responses of a categorized joint environment.

Expanding the number of treatment options available to patients with knee OA does not always improve the standard of care, especially when comparative trials assessing the quality of one new treatment versus others are lacking. Furthermore, the scarce use of scores such as the Coleman-Kon score prevents methodological comparison of different studies. The extraordinary clinical results obtained with the minimal non-enzymatic manipulated lipoaspirate processing should encourage research and stimulate new wide-ranging investigations to ensure strong validation and standardization of new therapeutic protocols.

5. Conclusion

This work took into consideration the potential offered by the use of technological tools for the processing of adipose tissue through minimal handling in a closed system. These devices are now widely used in clinical practice, but studies are still scarce, and few trials have been published to evaluate their efficacy in vivo. The very encouraging empirical results have provided a boost to production, saturating the market with multiple devices often lacking the published preclinical experimental standardization and with poorly defined usage protocols.

In this review, we considered 12 clinical trials, in which devices for minimal manipulation of lipoaspirate were used for regenerative purposes in the context of knee OA. It has been highlighted that, on the basis of the Coleman-Kon score, these trials are scarce quantitative and burdened by numerous methodological limitations (these evaluated by the Coleman-Kon score), which prevent an evaluation standardization and imply results that are difficult to compare. This review shows significant clinical improvement of the osteoarthritic knee after treatment in all studies (assessed with clinical scores, sometimes by MR imaging and histological evaluation), regardless of the device used. Among the devices considered, Lipogems® is the most studied in available clinical trials.

Reasonably, greater standardization of devices protocols will be desirable in the future, but only obtainable with qualitatively optimal and dedicated clinical studies for each device. In this way, the high clinical potential offered by these methods could be correctly optimized for defined patient populations.

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Author contribution statement

UL conceptualized and designed the study, searched electronic medical databases, analyzed and interpreted the data, drafted the manuscript, approved the article; SV analyzed and interpreted the data, drafted the manuscript, approved the article; SN and BM performed a critical revision of the article; AS conceptualized and designed the study, performed a critical revision of the article for important intellectual content, approved the article.

Conflict of interest statement

Authors declare no conflict of interest.

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