

GENERAL ORTHOPAEDICS

Adipose tissue-derived injectable products combined with platelet-rich plasma for the treatment of osteoarthritis: the promising preclinical results are not confirmed by the clinical evidence

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- **Purpose:** The association of adipose tissue-derived injectable products with platelet-rich plasma (PRP) has been promoted for osteoarthritis (OA) treatment. The aim of this study was to investigate the preclinical and clinical evidence supporting the potential of this combined approach to treat OA.
- **Methods:** A systematic review was performed in January 2024 on five databases (PubMed, Embase, Scopus, Cochrane, and Web-of-Science) to identify preclinical *in vivo* and clinical studies. Safety, OA biomarker changes, and outcomes in terms of clinical and imaging results were analyzed. The quality of studies was assessed with the SYRCLÉ's tool for preclinical studies and the Downs and Black checklist for clinical studies.
- **Results:** Ten preclinical studies (223 animals) and 14 clinical studies (594 patients) were included. Preclinical results documented improvements at the cartilage histological and immunohistochemical evaluation and at the biomarkers level. Clinical studies confirmed the procedure's safety, and the case series suggested satisfactory results in different joints in terms of symptoms and function improvement, with positive findings at the biomarker level. However, the randomized controlled trials did not document any clinical benefit, nor any changes in the imaging analysis. A large heterogeneity and overall poor quality were documented in both preclinical and clinical studies.
- **Conclusions:** There is an increasing interest in the use of adipose tissue-derived injectable products associated with PRP for the treatment of OA joints, with preclinical studies showing promising results with this combined approach. However, clinical studies did not confirm the benefits offered by PRP augmentation to adipose tissue-derived injectable products in patients affected by OA.

Keywords: adipose tissue; cartilage; orthobiologics; osteoarthritis; platelet-rich plasma

Introduction

Osteoarthritis (OA) is a degenerative disease characterized by progressive deterioration and loss of articular cartilage, with concomitant structural and functional changes in the entire joint, including synovium, meniscus (in the knee), periarticular ligaments, and subchondral bone (1). Traditional conservative treatments include weight loss, physical therapies, non-steroidal anti-inflammatory drugs, and intra-articular corticosteroids or hyaluronic acid injections (2). These management strategies mainly offer symptom relief rather than disease-modifying changes to the affected joint (3). In this context, orthobiologics have been developed to offer more than just symptom reduction, showing promising results in slowing down disease progression in animal OA models (4, 5, 6). Among these, platelet-rich plasma (PRP) is demonstrated to offer higher results than other traditional products, although without reaching optimal outcomes (3). Thus, research attention has been recently focused on cell-based injectable solutions.

Adipose tissue is emerging as the source of choice to obtain mesenchymal stromal cells (MSCs), thanks to the advantages compared to other sources like bone marrow (7, 8, 9, 10, 11). Adipose tissue can be harvested with a low discomfort and it allows to obtain a high concentration of MSCs with immunomodulatory and anti-inflammatory properties (12, 13). The use of adipose tissue-derived injectable products in clinical practice is growing for the management of OA joints, with preliminary clinical studies reporting their safety and efficacy (14, 15, 16, 17, 18, 19, 20, 21). However, available comparative clinical trials did not find an overall superiority of these products over other orthobiologic approaches like PRP or bone marrow aspirate concentrate (BMAC) (22, 23). To improve the treatment potential, the combined use of adipose tissue-derived injectable products and platelet concentrates has been proposed, based on positive *in vitro* study findings (24, 25, 26, 27). Despite the promising results, the combined use of adipose tissue-derived injectable products and PRP for the treatment of OA joints remains controversial.

The aim of this systematic review was to investigate the available preclinical and clinical literature on the association of adipose tissue-derived injectable products and PRP, in order to document the evidence supporting the potential of this combined injective approach to treat OA joints.

Materials and methods

Search strategy and article selection

A systematic review of the literature was performed on the combined use of adipose tissue-derived injectable products and PRP as injective treatment for OA

joints. This study was registered on the International Prospective Register of Systematic Reviews (PROSPERO registration number: 510446). A literature search was conducted on 17 January 2024 on five electronic databases (PubMed, Embase, Scopus, Cochrane, and Web of Science), with no time limitation and without any filters, using the following string: '(PRP OR platelet-rich plasma OR plasma rich in growth factors OR PRGF OR platelet-derived growth factor OR platelet-derived OR platelet gel OR platelet concentrate OR PRF OR platelet-rich fibrin OR ACP OR autologous conditioned plasma OR APS OR autologous protein solution OR platelet lysate OR platelet supernatant) AND (adipose OR fat OR adipose-derived OR stromal vascular fraction OR SVF) AND (cartilage OR chondr* OR synov* OR osteoarthritis OR OA)'.

According to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) and Cochrane guidelines (28), the article selection (Fig. 1) and data extraction process were conducted separately by two authors (SO and LA). The initial title and abstract screenings were made using the following inclusion criteria: preclinical *in vivo* and clinical studies of any level of evidence, written in the English language, without time limitation, and evaluating the intra-articular combined use of adipose tissue-derived products and PRP for the injective treatment of joints affected by OA. Exclusion criteria consisted of articles written in other languages, literature reviews, basic science *in vitro* articles, congress abstracts, studies without the combined use of the two orthobiologics, and studies on joint diseases different from OA. In the second step, full texts of the selected articles were screened, with further exclusion according to the previously described criteria. Additionally, all references from the selected papers and previously published relevant reviews were also screened. Two investigators reviewed each article (SO and LA), and any discrepancies between them were resolved by discussion and consensus with a third author (AB).

Data extraction, outcome measurement, and quality assessment

For the included studies, relevant data were extracted from article texts, tables, and figures, and then summarized and analyzed according to the purpose of the present study. In particular, the following data were collected for preclinical studies: year of publication, treatment type and schedule, details of the injected products, number of evaluated animals, OA models, follow-up length, and main results. For clinical studies, the following data were collected: year of publication, study design, treatment type and schedule, details of the injected products, number of evaluated patients, patient characteristics including sex, age, and body mass index, follow-up length, clinical scores used, main results, failures, and adverse events. The efficacy of the combined use of adipose tissue-derived injectable

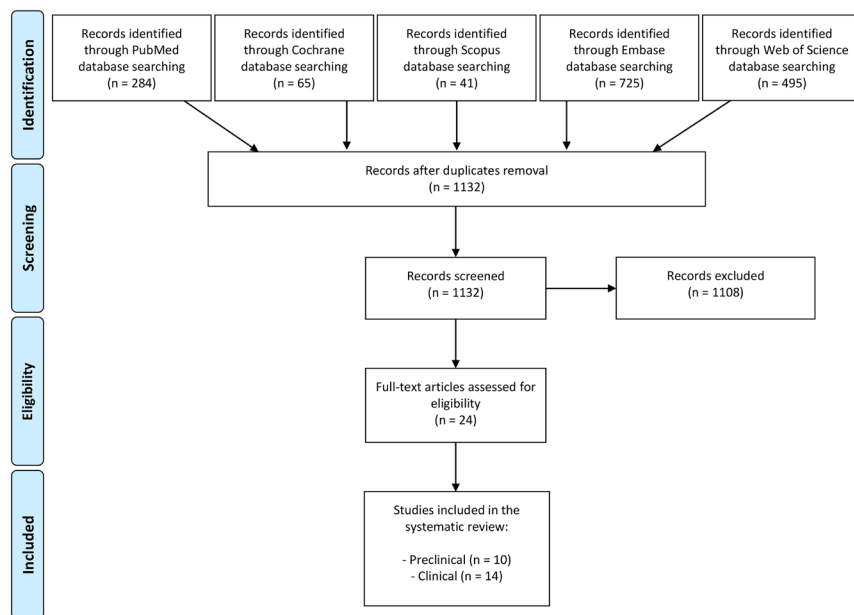


Figure 1
 Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flowchart of the study selection.

products and PRP was evaluated by summarizing the reported benefits through the scores used, while the safety of the procedures was explored by identifying the reported side effects.

The risk of bias in the included studies was assessed independently by two authors (SO and MS) with disagreements resolved by consensus with a third author (AB). The Systematic Review Centre for Laboratory animal Experimentation (SYRCLE)’s tool was used for preclinical studies (29), while the Downs and Black checklist was used for clinical studies (30).

Results

The database search identified 1610 records. After duplicate removal, the articles (n = 1132) were evaluated according to the inclusion/exclusion criteria. Thus, a

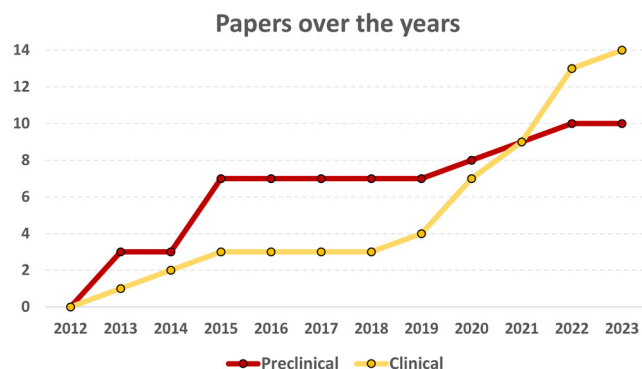


Figure 2
 Cumulative number of preclinical (red) and clinical (yellow) studies on the combined use of adipose tissue-derived injectable products and PRP as injective treatment for OA joints.

total of 24 full-text articles were included in the analysis: ten preclinical studies and 14 clinical studies focused on the combined use of adipose tissue-derived injectable products and PRP as injective treatment for OA joints (Fig. 2).

Preclinical studies

Ten preclinical studies analyzed the combined use of adipose tissue-derived injectable products and PRP as injective treatment for OA joints for a total of 223 animals evaluated. In detail, four studies were on small animals (three on murine models, one on rabbits) and six studies were on large animals (five on dogs, one on horses). The treated joints were knees in six articles, hips in two articles, and two articles focused on more joints (elbow, carpus, hip, and fetlock). OA was naturally occurring in five studies and induced in five studies (surgically induced in four studies through meniscectomy and/or anterior cruciate ligament transection or cartilage injury, and chemically induced in one study through collagenase injection).

Expanded adipose tissue-derived MSCs were analyzed in seven studies, stromal vascular fraction (SVF) in two studies, while one study evaluated a minimally manipulated adipose tissue injectable product. The adipose-derived MSCs dose was described in eight studies and ranged from 1.0×10^6 to 3.4×10^8 . Platelet concentration of the injected PRP was reported in five studies and ranged from $0.8 \times 10^6/\mu\text{L}$ to $1.2 \times 10^6/\mu\text{L}$. Only three studies described the type of injected PRP in relation to leukocyte presence: two studies used a leukocyte-rich PRP, while one study used a leukocyte-poor PRP. The PRP activation method was reported in seven studies, with two studies using calcium gluconate, two studies using calcium chloride, one study using a biophysical activation, one study using a not specified

activator solution, and one study used a not activated PRP. The adipose tissue-derived products were mixed with PRP before the injections in nine studies, while one study did not specify how the two products were combined. The amount of injected volume was reported in eight studies and ranged from 0.2 mL to 10 mL. The most common injection protocol was a single injection (six studies), while two studies performed two injections (10 min intervals), one study performed four injections (1-week interval), and one study did not state the number of injections. The final follow-up ranged from 1 month to 12 months after the injective procedure. Further characteristics of the included studies are reported in [Table 1](#).

Preclinical results

Four studies compared the effects of adipose-derived products combined with PRP vs the adipose tissue-derived treatment alone. The remaining studies evaluated the effects of the combined orthobiologic treatment vs OA controls (saline injections) in three studies and vs healthy controls (one study), while two studies did not have a control group. A synthesis of the effects provided by the combined use of adipose-derived products and PRP is reported below.

- At the cartilage level, the histological analysis documented an overall improvement in three out of four studies. In detail, in one study a significant improvement in the proteoglycan content as well as a higher percentage of type II collagen-positive cells were reported compared to adipose-derived mesenchymal stem cells (ADSCs) alone, but no differences were found in terms of Mankin's score (31). In one study, a larger area of regenerated cartilage was found compared to ADSCs alone (32). Finally, one study found better histological findings following the treatment with ADSCs + PRP compared to both PRP or ADSCs alone (33).
- Two articles evaluated the expression of specific inflammatory biomarkers, finding reduced Interleukin (IL)-6 serum and TNF- α levels in the synovial fluid following the combined treatment vs both single treatments (31, 34) and one article found an increased expression of extracellular matrix (ECM)-related genes in the combined group compared to single treatments (33).
- With regard to the clinical examination, a superiority was reported for the co-treatment in reducing the recovery time of hind-limb movement over ADSCs alone (32) and in increasing the focal compressive strength over PRP or ADSCs alone (33). Two other studies found an overall improvement but no differences among groups in terms of lameness score or Liverpool Osteoarthritis in Dogs and Canine Brief Pain Inventory scores as well as in radiographic scores (34, 35).

The evaluation of the risk of bias through the SYRCLE's tool ([Fig. 3](#)) showed that most items were rated as unclear (48%), while the low and high risk of bias was observed in 41% and 11%, respectively.

Clinical studies

Fourteen clinical studies analyzed the combined use of adipose tissue-derived products and PRP as injective treatment of OA joints for a total of 594 patients evaluated (370 treated with the combined use of the two orthobiologic products). Six studies were prospective case series, four were randomized controlled trials (RCTs), two were prospective comparative studies, one was a retrospective comparative study, and one was a retrospective case series. Nine studies focused on knee OA, two on radiocarpal OA, one on hip OA, and one on the trapezio-metacarpal joint, while the last study described several joints affected by OA (knee, hip, and ankle). Regarding adipose tissue-derived products, seven studies used SVF (enzymatic in four studies and non-enzymatic in three studies), six studies used minimally manipulated adipose tissue products, while only one study used expanded ADSCs.

The adipose tissue harvest site was abdomen subcutaneous fat in 11 studies, the inner side of the knees in one study, and thigh in one study, while one study obtained the adipose tissue from the abdomen subcutaneous fat or the inner side of the knees. The amount of harvested adipose tissue was reported in six studies and it goes from 30 mL to 200 mL. The adipose-derived MSCs dose was described in three studies ranging from 7.5×10^6 to 5.0×10^7 . Regarding PRP, only eight studies specified the type of PRP in relation to the leukocyte presence: seven studies used a leukocyte-poor PRP, while only one study used a leukocyte-rich PRP. The PRP activation method was reported in five studies (three using calcium chloride and two using calcium gluconate), while the platelet concentration was reported only in one study.

The most common injection schedule was the single injection administration (12 studies), while one study performed five injections (1-week interval), and one study performed an injection at baseline and other injections at 2, 3, and 4 months of follow-up. All studies mixed PRP and the adipose tissue-derived product before the injection, although further PRP injections were performed later in two studies (weekly or monthly, respectively). The total injected volume was reported in 12 studies, ranging from 1.5 mL (trapezio-metacarpal joint) to up to 37 mL (knee). Ultrasound guidance for the injection was used in 4 studies, fluoroscopy in one study, while one study used a real-time X-ray-guided injection. An arthroscopy before the injection was performed in one study. Further characteristics of the included studies are reported in [Table 2](#).

Table 1 Preclinical studies on the combined use of adipose tissue-derived injectable products and PRP for the treatment of OA joints.

Study	Animal	OA model	Joint	Characteristics of			Treatment groups		Final FU (months)	Results
				AT	PRP	Group	n			
(34)	Dog	Sp. OA	Stifle joint	ADSCs	NR (NAC vs biophysically AC, 1 inj.)	OA + ADSCs OA + PRP OA + PRP + ADSCs OA + bio-PRP OA + bio-PRP + ADSCs OA + Saline	6 6 6 6 6 6	3	PRP + MSCs combination results were more effective in all parameters, although positive progress was achieved in all groups as seen in the evaluation of the clinical scoring, radiological and pressure analysis, and cytokine measurement results.	
(35)	Dog	Sp. OA	Elbow, hip, stifle, hoch joints	ADSCs	LR-PRP	OA + PRP + MFAT	28	6	ADSCs and PRP showed a significant improvement in pain and functional scores and lameness.	
(31)	Rat	ACLT + MM	Knee	ADSCs*	NR (AC, 1 inj.)	OA + ADSCs OA + PRP OA + PRP + ADSCs Untreated OA Healthy	10 10 10 10 10	1	PRP potentiates the effects of ADSCs on the repair of damaged articular cartilage.	
(36)	Horse	Sp. DJD	Carpus, fetlocks	MF-AT	LR-PRP (NAC, 1 inj.)	OA + PRP + MFAT	9	5–10	The combined treatment significantly improved the lameness score in the carpus or the fetlock joint of sport horses presenting degenerative joint disease.	
(37)	Rabbit	Coll inj.	Knee	ADSCs†	-(AC, 1 inj.)	OA + PRP + ADSCs OA + PRP + diff ADSCs OA + PRP OA + Saline	6 6 6 6	2	ADSCs and PRP were associated with beneficial effects. No difference between undifferentiated and differentiated ADSCs.	
(33)	Dog	ACLT	Knee	ADSCs	NR (1 inj.)	OA + ADSCs OA + PRP OA + PRP + MSC OA + PBS	6 6 6 6	3	ADSCs and PRP have a synergistic effect on OA via the ECM synthesis and chondrocyte proliferation and via the anti-inflammatory reaction.	
(38)	Dog	Sp. OA	Hip	SVF	NR (1 inj.)	OA + PRP + SVF OA + Saline	10 12	6	For dogs with hip OA treated with SVF and PRP, improvements in CBPI and PVF were evident compared with results for the control group.	
(32)	Mouse	Joint destruction	Knee	ADSCs‡	NR (AC, 2 inj., 10-min interval)	OA + PRP–ADSCs OA + ADSCs OA + PBS	4 4 4	1.5	PRP-treated ADSCs transplantation significantly improves cartilage formation in murine models compared with ADSCs alone.	
(39)	Mouse	Joint destruction	Knee	SVF	NR (AC, 2 inj., 10-min interval)	OA + PRP + SVF OA + PBS	5 4	1.5	Combined SVF and PRP have a positive effect on the stimulation of proliferation, differentiation, and regeneration of cartilage in a mouse model.	
(40)	Dog	Sp. OA	Hip	ADSCs	PRGF (AC, 4 inj.)	OA + PRP + ADSCs Healthy	8 5	6	ADSCs + PRGF shows significant in terms of efficacy in objectively improving the dogs' gait and ability, and the absence of side effects.	

*Preconditioned with Vitamin E; †Undifferentiated or differentiated into chondrocytes; ‡Pretreated with PRP. AC, activated; ACLT, anterior cruciate ligament transection; ADSCs, adipose-derived mesenchymal stem cells; AT, adipose tissue; CBPI, canine brief pain inventory; Coll inj., collagenase injection; DJD, degenerative joint disease; ECM, extracellular matrix; FU, follow-up; LR, leucocyte-rich; MF-AT, micro-fractured adipose tissue; MM, medial meniscotomy; MSC, mesenchymal stem cell; NAC, not activated; NR, not reported; OA, osteoarthritis; PBS, phosphate-buffered saline; PRGF, platelet rich in growth factors; PRP, platelet rich in growth factors; PVF, peak vertical force; SVF, stromal vascular fraction; Sp., spontaneous.

Clinical results

The clinical studies investigated several aspects, including safety, clinical outcome, as well as biomarkers, and imaging findings after the combined treatment.

- Safety was documented by 10 of the included studies, with no severe adverse events related to the injective procedures and no evidence of neoplastic complications or infections. The most commonly reported adverse effects were temporary pain or joint swelling, generally improved after 24 h, or harvesting site pain resolved within the first week after the procedure.
- The combined use of adipose tissue-derived products and PRP provided an overall clinical improvement in pain and function in OA patients, with similar results obtained for the different joints evaluated. Nevertheless, the included RCTs (four studies) were not able to prove the superiority of this combined injective approach compared to the use of adipose tissue-derived injectable products alone (41, 42, 43, 44). In particular, the two RCTs on knee OA of Schweich-Adami *et al.* and Louis *et al.* did not find benefits offered by PRP augmentation in terms of the Western Ontario and McMaster Universities Arthritis Index, Visual Analogue Scale for pain, range of motion (ROM), and SF-36; the RCT of Heidari *et al.* on hip OA did not find differences in terms of VAS for pain and Oxford Hip Score; and the RCT of Winter *et al.* on trapeziometacarpal OA did not find differences in terms of Quick Disabilities of Arm, Shoulder, and Hand (Quick-DASH) score, Kapandji Score, ROM, pinch, and power grip. Simunec *et al.* (45) investigated the combined use of SVF and PRP vs SVF alone in 12 knee OA patients, analyzing their results based on the OA severity according to the Kellgren–Lawrence classification. These authors reported better results of both treatment approaches in patients with grade 3 compared to patients with grade 4,

without showing significant benefits offered by PRP augmentation in terms of Knee Injury and Osteoarthritis Outcome Score.

- Beyond clinical improvement, in the RCT conducted by Schweich-Adam *et al.* (41) on 26 patients with knee OA, the authors performed a synovial fluid biomarker analysis after treatment with ADSCs with or without PRP, reporting benefits offered by PRP augmentation in terms of pro-inflammatory biomarkers reduction including IL-6 and TNF.
- The RCT conducted by Winter *et al.* (44) assessed the MRI outcome in 30 patients with knee OA. The authors did not demonstrate a significant change in the value of cartilage relaxation time in T2 mapping sequences between baseline and 6 months after treatment, with no differences between the groups of minimally manipulated adipose tissue with or without PRP. Molnar *et al.* (46) evaluated 16 patients with mild to moderate knee OA treated with a non-enzymatic SVF combined with PRP using the delayed gadolinium-enhanced MRI of the cartilage indices at baseline and 6 months, showing no significant changes after the injective treatment. On the other hand, Bui *et al.* (47) performed an MRI evaluation in 21 patients with grade 2 or 3 knee OA and treated with a combined injection of SVF and PRP, reporting a cartilage thickness increase at 6 months.

The Downs and Black checklist showed an overall poor quality of the included studies, with an average score of 16.6 ± 5.1 (range: 10–26). The four RCTs included had a higher score (22.8 ± 2.8) compared to the other clinical studies (14.1 ± 3.4). More details are reported in Table 2.

Discussion

The main finding of this systematic review of the literature is that there is an increasing interest in the association of adipose tissue-derived injectable products with PRP for the injective treatment of OA joints, with

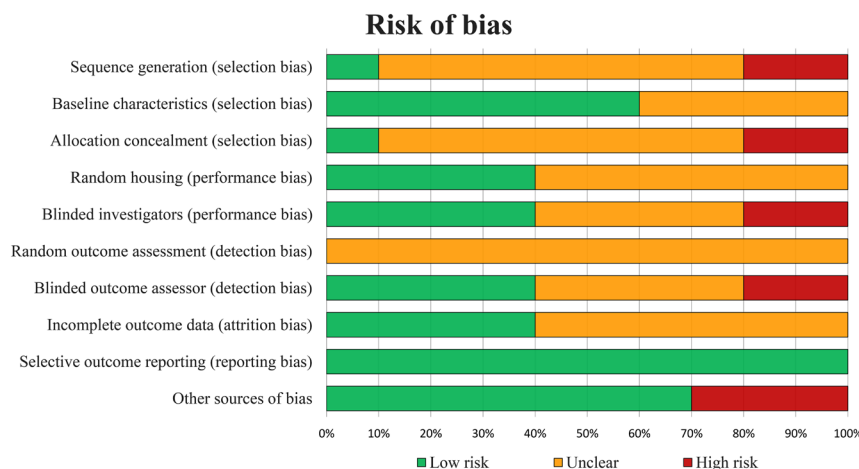


Figure 3
 SYRCLE's risk of bias assessment of the included studies. The bar chart shows the percentage of all studies that met each quality item, scored as 'Low risk', 'High risk', or 'Unclear'.

Table 2 Clinical study on the combined use of adipose tissue-derived injectable products and PRP for the treatment of OA joints.

Study design	Joint	ATDIP characteristics			PRP characteristics			Patient characteristics				Final FU, months	D&B checklist
		Type	Cell count	Type	Activation	Cell count	Treatment groups	n (M/F)	Mean age	OA grade			
(44) RCT	TMC joint	MM-AT	NR	LP-PRP	Ca chloride	NR	MM-AT; MM-AT + PRP; SALINE; PRP	95 (15/80)	64	E-L stages I-IV	24	26	
(42) RCT	Hip	MF-AT	NR	LP-PRP	Ca chloride	NR	MM-AT + PRP	90 (37/53)	60	1-4 KL [†]	12	20	
(48) PCS	RC joint	MF-AT	NR	NR	No activation	PLT: 741 ± 162 × 10 ⁶ ; WBC: 1.2 ± 1.3 × 10 ⁶	MM-AT	57 (36/21)	60	1-4 KL [†]	12	18	
(46) PCPS	Knee	N-E SVF	NR	LP-PRP	NR	NR	SVF + PRP; HLA	16 (8/8)	NR	2-3 KL	6	17	
(41) RCT	Knee	ADSCs	1 × 10 ⁷	NR	Ca gluconate	NR	ADSCs + PRP; PRP; ADSCs; CONTROL	28 (NR)	40-75	2-4 KL	6	21	
(43) RCT	Knee	MicroFat	NR	LP-PRP	Ca chloride	NR	MM-AT + SALINE	10 (5/5)	49.6	2-4 KL	6	24	
(49) PCS	Knee	SVF	NR	NR	NR	NR	MM-AT + PRP	10 (5/5)	46.4	2-4 KL	12	14	
(50) RCPS	Knee	MM-AT	NR	LR-PRP	NR	NR	LD	10 (7/3)	44.5	2-4 KL	12	19	
(45) PCPS	Knee	SVF	NR	NR	NR	NR	MM-AT + PRP	33 (11/22)	62.2 (45-75)	NR	12	14	
(51) PCS	Knee	N-E SVF	NR	LP-PRP	NR	NR	PRP	89	NR	3-4 KL	12	16	
(52) PCS	RC joint	MM-AT	NR	LP-PRP	LTA	NR	SVF + PRP; SVF	12 (NR)	61 (51-80)	3-4 KL	12	14	
(53) PCS	Knee	SVF*	NR	NR	NR	NR	SVF + PRP	15 (10/5)	43-75	2-3 KL	12	10	
(54) PCS	Knee	SVF	NR	NR	Ca chloride	NR	MM-AT	3 (1/2)	62	4 KL	12	10	
(55) RCS	Knee, hip, low back, ankle	SVF	NR	NR	Ca gluconate	NR	SVF + PRP	4 (2/2)	51.5	NR	6	10	
							SVF + PRP	21 (NR)	NR	2-3 KL	30	13	

*Obtained by ultrasonic cavitation; †Median : 3.

ADSCs, adipose-derived stem cells; D&B, Downs & Black; E-L, Eaton-Littler; HLA, hyaluronic acid; KL, Kellgren-Lawrence; LP-PRP, leukocyte-poor platelet-rich plasma; LR-PRP, leukocyte-rich platelet-rich plasma; LTA, light transmittance aggregometry; MF-AT, micro-fragmented adipose tissue; MM-AT, micro-fragmented adipose tissue; MM-AT minimally manipulated adipose tissue; N-E, non-enzymatic; NR, not reported; OA, osteoarthritis; PCS, prospective case series; PCPS, prospective comparative case study; PLT, platelets; PRP HD, high-density platelet-rich plasma; PRP LD, low-density platelet-rich plasma; PRP, platelet-rich plasma; RC, radiocarpal; RCPS, retrospective comparative study; RCS, retrospective comparative case series; RCT, randomized-controlled trial; SVF, stromal vascular fraction; TMC, Trapezio metacarpal.

preclinical studies documenting promising results with this combined approach. However, clinical studies did not confirm the benefits offered by PRP augmentation to adipose tissue-derived injectable products in patients affected by OA.

This systematic review documented a growing interest in the combined use of adipose tissue-derived injectable products and PRP, with an increasing number of preclinical and clinical studies published over the years. This trend can be explained by the potential to combine PRP and cell therapies from adipose tissue to exploit the therapeutic effects of both orthobiologic products with a possible synergistic effect. The main rationale for this combined approach relies on *in vitro* studies documenting the positive benefits offered by PRP when combined with cells contained in the adipose tissue. PRP was shown to be able to stimulate the chondrogenic differentiation of ADSCs and to improve their immunogenic, immunomodulatory, and anti-inflammatory capabilities (24, 56, 57). In particular, Mardani *et al.* (56) demonstrated that PRP may be considered a natural and easily obtainable source of growth factors to promote the chondrogenic differentiation of human ADSCs, documenting that cells in the presence of 10% PRP produced markedly higher amounts of GAG and DNA in comparison to the control group. Moreover, PRP also increased chondrogenic markers in these cells, such as SOX-9, aggrecan, and type II collagen. Similarly, Hesari *et al.* (24) confirmed the chondrogenic impact of PRP on ADSCs, observing a high GAG production, an enhanced SOX9 transcription, an up-regulation of miRNAs, and a lowered TNF- α and vascular endothelial growth factor. Shen *et al.* (57) also reported that ADSCs cultured in a threedimensional PRP scaffold were able to form neocartilage, with positive staining of safranin O, confirming the positive effects of PRP on ADSCs in an *in vitro* setting.

These results encouraged researchers to investigate the combined use of PRP and adipose tissue-derived products also *in vivo*. To this aim, animal OA models are useful because they play a crucial role in understanding the structural effects of therapeutic interventions, allowing to evaluate macroscopic, histological, and immunohistochemical findings after the injective treatment (58). This systematic review found ten preclinical *in vivo* studies focused on the augmentation of PRP to adipose tissue-derived products, documenting positive data confirming the benefits offered by PRP augmentation, as previously documented *in vitro*. In particular, the combined use of adipose tissue-derived products and PRP demonstrated a synergistic activity in animal OA models leading to protective effects at the cartilage level with enhanced chondrocyte proliferation as well as collagen and proteoglycan content (31, 32, 33).

The benefits of PRP augmentation were observed also in terms of changes in biomarkers related to cartilage metabolism or inflammation. Biomarkers can reflect dynamic quantitative changes in joint remodeling,

thus indicating disease progression or response to a specific treatment (59). The combined use of PRP and adipose tissue-derived products induced a higher expression of ECM-related genes and a lower expression of inflammatory biomarkers compared to the adipose tissue treatment alone, confirming the therapeutic potential of PRP augmentation (31, 34). Moreover, this systematic review documented that the addition of PRP to adipose tissue-derived products also resulted in better symptoms in the treated animals, in terms of recovery time of hind-limb movement or focal compressive strength (32, 33, 38). This is particularly important, considering that the placebo effect is not present in the animal models (60), while it can influence instead the clinical results in the human setting.

These positive preclinical findings, however, were not confirmed by the clinical evidence. The current systematic review also investigated the therapeutic potential of the combined use of adipose tissue-derived products and PRP in clinical trials. This approach demonstrated a good safety profile with few adverse events in the treatment of different joints affected by OA, such as knee, hip, ankle, radio-carpal joint, and trapezio-metacarpal joint. This combined approach also induced a reduction of pro-inflammatory biomarkers including IL-6 and TNF- α , confirming the anti-inflammatory activity seen in preclinical results (41). Nevertheless, despite these findings and the positive results suggested by the case series, comparative studies showed a different scenario. Analyzing the four RCTs comparing the combined approach to the adipose tissue-derived product alone, PRP augmentation did not provide any significant improvement, neither in terms of clinical scores nor imaging outcomes (41, 42, 43, 44). PRP augmentation did not offer a further clinical improvement perceivable by the patients. In this light, to date, there is no clinical evidence of the superiority of this combined injective approach over the single adipose tissue treatment, which does not appear justified in the clinical practice for the injective treatment of OA joints. Future high-level studies are necessary to optimize and further explore the potential of this combined approach.

This systematic review underlined an important area of improvement in this field: the high heterogeneity in both preclinical and clinical settings raises a call for standardization. Many differences were documented in terms of treatment protocols and outcome measures. Different features of adipose-tissue-derived injectables have been analyzed, such as different kinds of products like ADSCs, SVF, or MM-AT. Similarly, PRP characteristics were different regarding platelet and leukocyte concentrations or activation methods. In addition, application modalities were often different, both in terms of injected volume and injection schedule. Moreover, different joints and OA grades have been analyzed, with preclinical studies also differing in terms of the type of animal models, ranging from small to large ones and from naturally occurring to surgically or chemically induced OA. Finally, different

scoring systems at different follow-ups have been used with a consequent difficulty to merge and compare results, thus impairing the possibility to perform a meta-analysis. The large heterogeneity of the field calls for further research efforts to promote a better standardization of these products, both platelet-derived and adipose tissue-derived approaches (61), and future studies will need to identify the most suitable products and understand if optimized combinations could lead to greater clinical benefits.

This systematic review has several limitations that reflect those of the included studies. In addition to the heterogeneity, the low number of included studies and the small sample size of animals and patients evaluated represent limitations of the current literature. This heterogeneity did not allow us to perform a meta-analysis and draw clear conclusions on the real benefits offered by the augmentation of PRP to adipose tissue-derived products. Moreover, the overall level of evidence is low, with most studies being case series or comparative studies and only four RCTs available. These limitations underline that the current knowledge on the combined use of adipose tissue-derived products and PRP is still preliminary, and many aspects remain to be clarified to understand the real potential of this combined injective approach. Preclinical studies are still needed as well as high-level controlled clinical trials to better understand the real potential of PRP augmentation to adipose tissue-derived injectable products, before justifying the use of this combined approach in the clinical practice for the treatment of patients affected by OA.

Conclusions

This systematic review of the literature documented an increasing interest in the use of adipose tissue-derived injectable products associated with PRP for the injective treatment of OA joints, with preclinical studies showing promising results with this combined approach. However, clinical studies did not confirm the benefits offered by PRP augmentation to adipose tissue-derived injectable products in patients affected by OA.

ICMJE Conflict of Interest Statement

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the study reported.

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