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Systematic Review

Orthobiologic injections for treating degenerative meniscus lesions: a matter of facts? Ten years of clinical experience in a systematic review

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ABSTRACT

Introduction: The treatment of degenerative meniscal lesions usually consists of conservative measures such as physical therapy or knee injections. Recently, the use of orthobiologics, in the form of platelet-rich plasma and cell-based therapies, gained huge popularity in orthopedic practice.
Objectives: The aim of the present systematic review is to summarize the available evidence concerning the use of orthobiologics in the treatment of degenerative meniscal lesions.
Data sources: A comprehensive search of PubMed, Google Scholar, Cochrane, and EMBASE was performed using various combinations of the following keywords: meniscus AND (platelet OR BMAC OR bone marrow OR adipose OR stromal vascular fraction OR placental OR cord OR jelly).
Study eligibility criteria, participants, and interventions: Articles were screened according to the following inclusion criteria: (1) clinical reports or randomized trials that included injections to treat degenerative meniscal lesions; (2) written in the English language; (3) published from 2012 to 2022.
Results: Nine studies were finally included in the present systematic review: 8 for platelet-rich plasma and 1 for micro-fragmented adipose tissue. All the studies reported clinical and functional improvements for degenerative meniscal lesions treated with orthobiologics.
Limitations: Included studies highlight considerable heterogeneity in methodological approaches. Differences in product choice, outcome measures, and follow-up preclude the ability to generate definitive suggestions for application in the everyday clinical practice.
Conclusions and implications of key findings: The literature suggests that the use of orthobiologics may offer a new effective therapeutic strategy for the treatment of degenerative meniscus lesions.

Introduction

Meniscal tears can be defined as interruptions in the continuity of the meniscal fibrocartilage.[1] Based on the etiology, meniscal tears can be classified as traumatic (tears that occur with trauma of sufficient energy and with sudden onset of knee pain) and degenerative (lesions with a slow progression and without a clear history of trauma).[2] In terms of location, the most commonly affected zones are the body and posterior horn of the medial meniscus.[3]

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From a clinical point a view, degenerative meniscal tears present as knee pain without a clear history of recent trauma, often in patients over 40 years of age, possibly (but rarely) accompanied by the presence of mechanical symptoms (clicking, popping).[4] On physical examination, findings that point to the presence of a meniscal lesion are joint line tenderness, pain on deep knee flexion, positive meniscal provocation tests (McMurray, Apley, Childress, Thessaly, Steinman), and an audible click during range of motion. Knee effusion may be present, but it is more commonly observed with acute traumatic meniscal tears.[5] The imaging modality of choice to support a diagnosis of a degenerative meniscal lesion is magnetic resonance imaging (MRI).[6] On MRI, degenerative meniscal lesions appear as areas of linear hyperintensity contacting the posterior and most commonly inferior surface of the meniscus (horizontal tears) or areas of hyperintensity with multiple components (complex tears).[7]

The treatment of degenerative meniscal lesions, in the absence of mechanical symptoms, constitutes primarily conservative measures,[2] while arthroscopy[8] should only be performed in the presence of knee locking or failure of conservative measures in the absence of knee osteoarthritis.[9] This is based on a course of supervised physical therapy[10] and/or knee injections.[11] These can consist of Visco supplementation with hyaluronic acid, corticosteroid injections, or "so-called" orthobiologic approaches (including autologous blood products such as platelet-rich plasma [PRP] and cell-based therapies),[12] which can be delivered intra-articularly or directly into meniscus tissue with the aid of ultrasound (ultrasound-guided intrameniscal injection). The rationale behind the use of these products in the treatment of degenerative meniscal lesions is the presence in these products of growth factors and cells that may promote angiogenesis, cell proliferation, and cell differentiation,[13,14] all characteristics that are beneficial for the healing of the torn meniscus.

While a number of studies have evaluated the literature concerning orthobiologics as an adjunct to meniscal repair[15,16]or as a treatment in preclinical studies,[17,18] we are not aware of any studies that have systematically reviewed the clinical literature concerning orthobiologics as a standalone treatment for degenerative meniscal lesions. The aim of the present systematic review is to summarize the available evidence concerning the use of orthobiologics to treat degenerative meniscal lesions.

Data sources

A comprehensive search of PubMed, Google Scholar, Cochrane, and EMBASE was performed using various combinations of the following keywords: meniscus AND (platelet OR BMAC OR bone marrow OR adipose OR stromal vascular fraction OR placental OR cord OR jelly). The search was performed on October 30, 2022 with 2 reviewers evaluating included studies independently (U.V. and A.G.).

Study appraisal and synthesis methods

The present systematic review followed Preferred Reporting items for Systematic Reviews and Meta-analysis guidelines[19] (flow chart shown in Fig). All articles identified by the initial literature search were screened according to the following inclusion criteria: (1) clinical reports or randomized trials that included injections to treat meniscal tears or degeneration; (2) written in the English language; (3) published from 2012 to 2022. Exclusion criteria were: (1) in vitro studies or review articles; (2) preclinical studies or studies not performed on human subjects (3) not evaluating treatment of meniscal tears or degeneration; (4) not written in the English language. All duplicate articles, articles from non-peer–reviewed journals and articles lacking access to the full text were excluded. Conference presentations, narrative reviews, editorials, and expert opinions were also excluded. Discrepancies between the 2 reviewers were resolved by discussion, and the final results were reviewed by the senior investigators (E.K., B.D.M.).

Results

Study selection

A total of 498 related records were identified in the initial database search. Following evaluation of titles and abstracts, 21 full-text manuscripts were included and further assessed for eligibility. As shown in the Preferred Reporting items for Systematic Reviews and Meta-analysis flowchart (Fig) 12 records were excluded for not meeting the inclusion criteria. A total of 9 studies dealing with orthobiologic injectable treatments for degenerative meniscal lesions were finally included in the present systematic review (Table).

Study characteristics

Of the 9 selected studies, only the one from Kaminski et al[20] was a randomized, double blind, controlled trial comparing placebo to PRP injections in the setting of percutaneous meniscal trephination. The remaining studies were retrospective (4) or prospective (4) single arm studies evaluating the injection of 2 different products: PRP was assessed in 7 studies while micro-fragmented adipose tissue (MFAT) was assessed in 1 study. The injection of the specific product was variably described as intrameniscal, perimeniscal or intra-articular in the different reports and the procedure was ultrasound-guided in the majority of those. Interestingly, Blanke et al[23] performed 3 weekly injections of PRP through a fluoroscopic-guided procedure stating that meniscal tissue was identified by increase and then loss of resistance. As for the study protocol, relevant variability was observed: MFAT was injected in a single administration in the setting of meniscal trephination while PRP was either evaluated after a single injection (4 studies) or in 3 (3 studies) or in 4 multiple injections (1 study).

Similarly, different clinical outcomes were reported in the evaluated studies. Özyalvaç et al[24] were the only group not reporting pain modifications (visual analog scale (VAS) or numeric rating scale (NRS)) after the injective treatment and there were no clinical

Table
List of the studies included in the systematic review.

Publication	Study design	Patients' characteristics	Meniscus disease	Treatment	Outcome measure	Follow-up (months)	Main clinical findings	Additional findings
Di Matteo et al[21]	Prospective	12 (10 M; 2 F) Age: 51.7 ± 19.1 y	Medial degeneration K-L 0-1	3 US-guided IM and PM inj. of ACP (Arthrex, Naples, FL)	IKDC, VAS	6-12-18	IKDC* and VAS* improved 1 patient failed No severe AEs	Negative correlation with duration of symptoms
Guenoun et al[25]	Prospective	10 (7 M; 3 F) Age: 40.4 ± 13.6 y	Medial degeneration No knee OA	1 US-guided IM and PM inj. of PRP (Hy-Tissue, PRP, FIDIA)	KOOS, MRI, VAS, RTS	KOOS 3-6 At 6 month MRI (7 patients)	KOOS* and VAS improved 60% response rate 80% pain <10 min	Stable lesions at MRI 100% RTS
Popescu et al[26]	Retrospective	30 (9 M; 21 F) Age: 13.9 ± 1.43 y	Tear II acc. Reicher	1 IA inj. of PRP (PRP kit not specified)	Lysholm, NRS	3	NRS* and Lysholm* improved	77% had "excellent" or "good" outcomes
Özyalvaç et al[24]	Retrospective	15 (6 M; 9 F) Age: 33.2 ± 8.2 y	Tear II acc. Reicher Ahlback 0-1	1 US-guided IM inj. of PRP (T-LAB PRP kit, T-Biotechnology Laboratory, Istanbul, Turkey)	Lysholm, MRI	Mean: 31.9 ± 5.6 (19–39)	Lysholm* improved Correlation between Lysholm and MRI improvement	MRI improved*: 67% grade II to grade I regression
Blanke et al[23]	Retrospective	10 (6 M; 4 F) Age: 53.3 ± 13.9 y	Tear II acc. Reicher	3 weekly fluoroscopy-guided IM inj. of PRP (Arthrex ACP Double Syringe System)	NRS, MRI, RTS	6	NRS* improved 60% RTS	40% MRI improvement 40% additional surgery
Medina-Porqueres et al[30]	Retrospective	38 (30 M; 8 F) Age: 50.7 ± 9.65 y	Tear I-III acc. Reicher	3 weekly IA and PM inj. of PRP (no specific PRP kit adopted)	KOOS, NRS, Tegner	Mean: 75.92 ± 31.7 days (39–190)	KOOS*, NRS*, Tegner* improved No AEs	100% satisfaction rate
Kaminski et al[20]	Prospective RCT Double blind	72 (41 M; 31 F) Age: control 46 (27-68) y study 44 (18-67) y	Chronic horizontal lesion	Control: 1 US-guided trephination with placebo Study: 1 US-guided trephination + PRP (no specific PRP kit adopted)	VAS, KOOS, WOMAC, IKDC, MRI	3-6-12 At 33° week (MRI)	PROMs improved in both groups Higher VAS* and KOOS for symptoms* improvement in PRP group	MRI healing rate superior in PRP group Arthroscopy free survival superior in PRP group*
Alessio-Mazzola et al[11]	Prospective	69 (21 M; 48 F) Age: 52.1 ± 7.8 y	Medial grade III acc. Crues K-L 0-1	4 weekly IA inj. of PRP (no specific PRP kit adopted)	Lysholm, VAS, ROM, WOMAC, Tegner	1-3-6-12	Lysholm, VAS, WOMAC improved ROM improved No AEs	Patients <50 y had better VAS*, Lysholm*, Tegner*, WOMAC*, ROM* improvements AEs limited to adipose harvest procedure
Malanga et al[22]	Prospective	20 (11 M; 9 F) Age: 59.8 ± 6.5 y	Atraumatic tears Knee OA	1 US-guided trephination + IM and IA inj. of MFAT (Lipogems® processing kit, Lipogems International SpA, Milan, Italy)	KOOS, NRS	3-6-12	NRS* and KOOS* improved No severe AEs	

Abbreviations: acc., according to; ACP, autologous conditioned plasma; AE, adverse events; F, female; FIDIA, xxxx; IKDC, International Knee Documentation Committee Subjective Knee Form; IA, intraarticular; IM, intrameniscal; Inj, injection; KOOS, knee injury and osteoarthritis outcome score; M, male; MFAT, micro-fragmented adipose tissue; MRI, magnetic resonance imaging; NRS, numeric rating scale; OA, osteoarthritis; PM, perimeniscal; PROM, xxxx; PRP, platelet-rich plasma; RCT, randomized controlled trial; ROM, xxxx; RTS, return to sport; US, ultrasound; VAS, xxx; WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index.

* Statistically significant ($P < .05$).

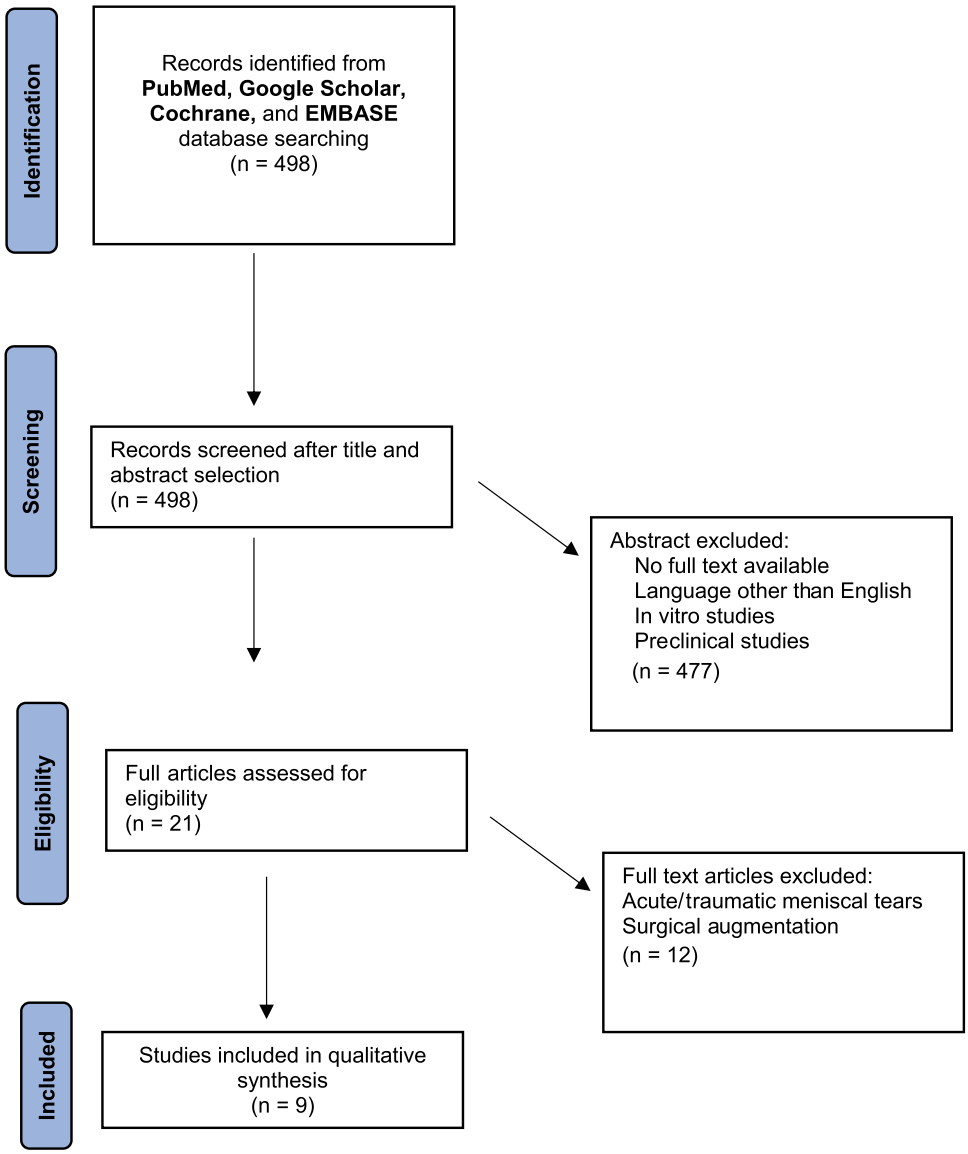

Fig. Preferred Reporting Items for Systematic Review and Meta-Analysis flowchart of the systematic literature review.

outcomes reported equally in all the 9 examined studies. The most reported clinical outcome was the knee injury and osteoarthritis outcome score (KOOS) scale (4 studies), while Lysholm, International Knee Documentation Committee Subjective Knee Form (IKDC), Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC), and Tegner scales were described only in a small portion of the selected reports. Return to sport was reported only by Guenoun et al[25] and Blanke et al[23] for a total of only 20 patients. Alessio-Mazzola et al[11] were the only authors to report specific results on range of motion variation after treatment. The possible onset of treatment-related adverse effects was reported only in 5 studies out of the 9 examined.

Posttreatment MRIs were performed and evaluated in 4 studies for a total of 68 patients: Özyalvaç et al[24] performed MRIs with a 1.0T device at a mean of 32 months follow up while all other 3 groups used a 1.5T device at 6 months of follow up. Interestingly, Kaminski et al[20] performed MRI arthrography and considered meniscal healing as the reduction of meniscal tissue contrast filling.

Study population

In the present systematic review, clinical data from 276 patients were retrieved for a total of 141 males and 135 females. The mean follow-up of the included studies was 12 months and the mean age of included patients was 44.4 years. Popescu et al[26] examined a younger cohort of 30 adolescents aged 12 to 17 years presenting lesions that were classified as grade 2 according to Reicher[27] (intrasubstance meniscal degeneration [IMD]). The Reicher classification was also used to classify meniscal lesions as “degenerative” in 3 other studies. In contrast, the Crues classification[28] was adopted by Alessio-Mazzola et al[11] and the Stoller classification[29] by

Guenoun et al,[25] but the remaining 3 studies generally described the lesions as "degenerative meniscal lesions" without reporting a specific grading system.

Reported clinical results

Patients undergoing PRP and MFAT injections reported a statistically significant reduction in pain, evaluated with either an NRS or VAS scale, in all studies with the exception of the study be Guenoun et al[25] where improvements in reported pain did not reach statistical significance. The mean decrease in pain from the pre-injection levels to final follow up in the considered studies was of 3.29 points (on a 1-10 scale). In the randomized controlled trial (RCT) conducted by Kaminski et al,[20] a significant difference level in the percentage of patients who exceeded minimum clinically important difference (MCID) for VAS score for PRP (65%) and placebo (39%) was detected ($P = .046$).

As previously mentioned, considerable variation in different functional scores was noted in this systematic review. Nevertheless, statistically significant improvements in patient reported knee function were found in all the 9 studies regardless of the patient reported outcome measure adopted (KOOS, IKDC, Lysholm, WOMAC) and the type of treatment (MFAT, PRP).

In the only RCT available, patients treated with either PRP or placebo experienced an improvement in functional outcomes measured with IKDC, WOMAC, and KOOS subscales. Furthermore, a statistically significant difference in the percentage of patients exceeding the MCID for KOOS for symptoms subscale in the PRP (76%) and placebo (48%) group was detected ($P = .028$).

Clinical results were generally reported up to 6 or 12 months follow up. However, Di Matteo et al[21] reported clinical outcomes at 18 months after percutaneous needling plus autologous conditioned plasma (ACP) injection in 12 patients: after a significant improvement in IKDC and VAS score from pretreatment to 12 months follow up, both results appeared stable between 12 and 18 months suggesting a persistence of the clinical effect. Furthermore, a negative correlation was found between duration of symptoms and IKDC score: patients with a longer history of pain reported significantly lower IKDC values after injection ($P = .035$, Pearson correlation coeff: -0.54). In addition, Özyalvaç et al[24] examined the clinical results at a mean 32 months follow up and reported a statistically significant improvement in mean Lysholm score from 71.1 to 91.9 after PRP treatment.

Return to sport rate after the injective treatment was described in 2 studies. Guenoun et al[25] reported a 100% return to competition or training activities in the 6 patients that used to practice sports regularly before the treatment. Similarly, Blanke et al[23] stated that 60% of the patients in their cohort increased their sports activity compared to the pre-injection situation and returned to previous athletic levels.

In the study from Medina-Porqueres et al,[30] 38 patients with stable meniscal injuries were treated with 3 weekly intra-articular and perimeniscal injections of PRP. In addition to the aforementioned statistically significant improvement in KOOS score, all patients were either very satisfied or satisfied with the outcome and none of the patients were reported to state that they would not undergo the same procedure again. In the same cohort, there was a significant improvement in the Tegner scale indicating a moderate level of sports participation after the treatment, in accordance with the improvements in Tegner scale ratings reported by Alessio-Mazzola et al.[11]

Of note, in the RCT from Kaminski et al,[20] the rate of patients that underwent arthroscopy because of failure of the injective treatment was monitored. The authors stated that 10 patients (8 in the placebo group and 2 in the PRP group) underwent subsequent arthroscopic meniscectomy or meniscal repair, resulting in a statistically significant difference in the arthroscopy free survival rate in the 2 groups favoring PRP ($P = .032$).

Only 5 studies reported that they monitored possible adverse effects of the injective treatments. Malanga et al[22] described minor complications in 52% of cases, all of which were related to morbidity at the adipose harvest site including an uncomplicated cellulitis successfully treated with antibiotics. Similarly, Guenoun et al[25] described that 80% of patients reported pain immediately following ultrasound-guided intrameniscal and perimeniscal injection of PRP with a mean VAS of 50 ± 31. In all patients pain resolved within 10 minutes.

Reported radiological results

Only 4 studies, totaling of 68 patients, included a posttreatment MRI to evaluate possible meniscal healing. MRIs were performed at 6 months following treatment in 85% of the patients. All the studies including posttreatment MRIs evaluated PRP injection while no MRI data was available on MFAT.

The biggest cohort of patients assessed using MRI were part of the RCT by Kaminski et al[20]: half of the 72 patients in the RCT were treated with a single PRP injection in the context of percutaneous meniscal trephination and compared to patients treated with placebo injection. In this specific study, MRI arthrography was performed at 33 weeks. The meniscal healing rate (defined as a reduction in meniscal tissue contrast filling), was reported to be superior in the PRP augmented group than in the control placebo-augmented group, although this did not reach statistical significance. Indeed, 60% of the menisci treated with PRP were considered either fully or partially healed on posttreatment MRI arthrography.

Özyalvaç et al[24] performed MRIs at a mean 32 months follow up after a single intrameniscal PRP injection in 15 patients with IMD (grade II according to Reicher). Interestingly, they reported a significant regression of MRI grades of meniscal degeneration: 10 patients changed from grade II to grade I IMD, 4 patients showed no radiological changes, and only 1 patient progressed to a grade III lesion. Furthermore, a statistically significant correlation between the decrease in MRI grades and increase of Lysholm score was reported.

The 10 patients treated with 3 weekly injections of PRP by Blanke et al[23] had a similar evolution: 4 of them showed a decrease of meniscal lesion, 4 remained stable, and 2 presented a progression of the baseline grade II lesions.

Lastly, Guenoun et al[25] reported stability of the meniscal tears and similar Stoller grades in all the 7 patients of their cohort that underwent MRI 6 months after a single injection of PRP.

As already mentioned, posttreatment imaging data was limited to patients undergoing PRP injection while there was no available data evaluating the morphological effect of MFAT on degenerative meniscal lesions.

Limitations

The results of the present systematic review should be evaluated in the context of its limitations. Indeed, the use of orthobiologics intended as PRP and cell-based therapies have gained tremendous popularity in multiple fields of medicine. [31,32] In vitro data indicates that autologous growth factors present in these preparations may contribute to lowering inflammation while inhibiting catabolic distress.[32] Factors with anabolic properties, present in autologous preparations of blood and fat, may promote cartilage anabolism, type II collagen deposition, and extracellular matrix remodeling justifying the rationale for the application of orthobiologics to the degenerative meniscus.[14,33] Despite this clear rationale, the clinical evidence for these strategies is limited to small studies with considerable variation in the treatments delivered and in the patients studied. Firstly, the definition of "degenerative meniscus" was heterogenous, with different classifications adopted, highlighting the need for consistency in classification systems applied. Secondly, the majority of the included studies adopted a single injection strategy (5 of 9 articles), 3 repeated the injection 3 times, 1 study performed 4 injections, with similar disparities in the follow up periods used. Moreover, the injection itself was subject to differences in terms of localization with injectate delivered inside the meniscus, in the perimeniscal region or simply within the joint space. It is intuitive that the location of delivery may critically influence effect, with delivery of factors locally to the damaged tissue potentially offering advantages over those simply injected intra-articularly where only a minimal fraction may reach the target tissue. To minimize inaccuracies in injection location, 5 out of 9 studies performed injections under ultrasound-guidance, with 1 study adopting a fluoroscopy-based technique. Studies on cadaveric human specimens have shown that the administration of substances through intrameniscal or perimeniscal approaches are feasible and do not require special equipment. As such this may be the primary choice of strategy when addressing a meniscus-only degenerative pathology.[34,35]

Heterogeneity in the data collected in the present systematic review precluded the ability to draw definitive conclusions from the data presented. Indeed, the small samples sizes of included studies and the different outcome measures adopted made it impossible to directly address the primary question as to whether the biologic agents would be of value in the treatment of degenerative meniscus lesions or not. Accordingly, the overall level of evidence of the studies is low, with almost half of the data collected retrospectively, and significantly different methodological approaches accompanied by the lack of control group. Conversely, only one of the studies conducted a prospective randomized analysis with a control group but the concurrent use of trephination, which may have a therapeutic effect itself, impedes a clear assessment of the contribution of the orthobiologic. Despite the abovementioned limitations, the data presented in the present systematic review indicate that orthobiologics may represent a valuable therapeutic strategy in the treatment of degenerative meniscal lesions. Studies with longer follow up and more uniform methodology are needed to more definitively evaluate the value of these approaches in clinical practice.

Conclusions and implications of key findings

Orthobiologic injections are increasingly utilized in the treatment of degenerative meniscal lesions. Exisiting literature evaluating these approaches are limited to a small number of studies with significant methodological limitations, with inadequate reporting of factors that may critically influence outcome. Well-designed prospective clinical trials with uniform methodological approaches are required to definitively evaluate the value of these approaches.

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Declaration of competing interest

The authors declare no competing financial interests or personal relationships related to this article.

Authorship contributions

P.C. and G.A. wrote the draft of the article. U.V. and A.G. conducted the literature review and contributed to the data collection and interpretation. B.D.M. and M.M: contributed to the conception of the article and critically revised the draft of the article. E.K. was responsible for the conception of the paper and critically revised the final draft of the article. All authors read and approved the final article.

Ethics approval

This was not applicable since this article is a Systematic Review.

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