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Intra-articular injections of hyaluronic acid versus plasma rich in growth factors (PRGF) for knee osteoarthritis: a meta-analysis of randomised controlled trials

A meta-analysis

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Abstract

Introduction: The present meta-analysis compared intra-articular injections of hyaluronic acid (HA) versus plasma rich in growth factors (PRGF) in patients with knee osteoarthritis (OA). The outcome of interest was the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC).
Methods: This study was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-analyses: the 2020 PRISMA statement. All the head-to-head randomised controlled trials (RCT) comparing intra-articular HA injections versus PRGF were accessed and included in the present study. Only studies that clearly stated that injections were performed in patients with knee OA, irrespective of the severity of OA, were considered. Data concerning the WOMAC index were retrieved at baseline and last follow-up. The endpoint of interest was to investigate whether intra-articular HA injections are associated with WOMAC score improvement compared to PRGF injections at 4–6 months follow-up.
Results: Data from 432 patients were collected and 76.3% (330 of 432) of the patients were women. The mean age of the patients was 58.2 ± 1.5 years and the mean body mass index (BMI) was 28.0 ± 0.5 kg/m^2. At baseline, comparability in mean age, BMI, male:female ratio, WOMAC and related subscales were documented. The PRGF group evidenced lower values of the function subscale of the WOMAC index ($P = 0.03$). No difference was found in the overall WOMAC index ($P = 0.05$) and its stiffness ($P = 0.4$) and pain ($P = 0.07$) subscales.
Conclusion: The current level I evidence suggests that the use of PRGF might be associated with more favorable clinical outcomes than using HA.

Keywords
Orthobiologics · Degeneration · Viscosupplementation · Orthopaedic · Arthritis

Supplementary Information

The online version of this article (https://doi.org/10.1007/s00132-025-04615-w) contains supplementary material, which is available to authorized users.

Level of evidence: level I

Supplementary material online – scan QR code

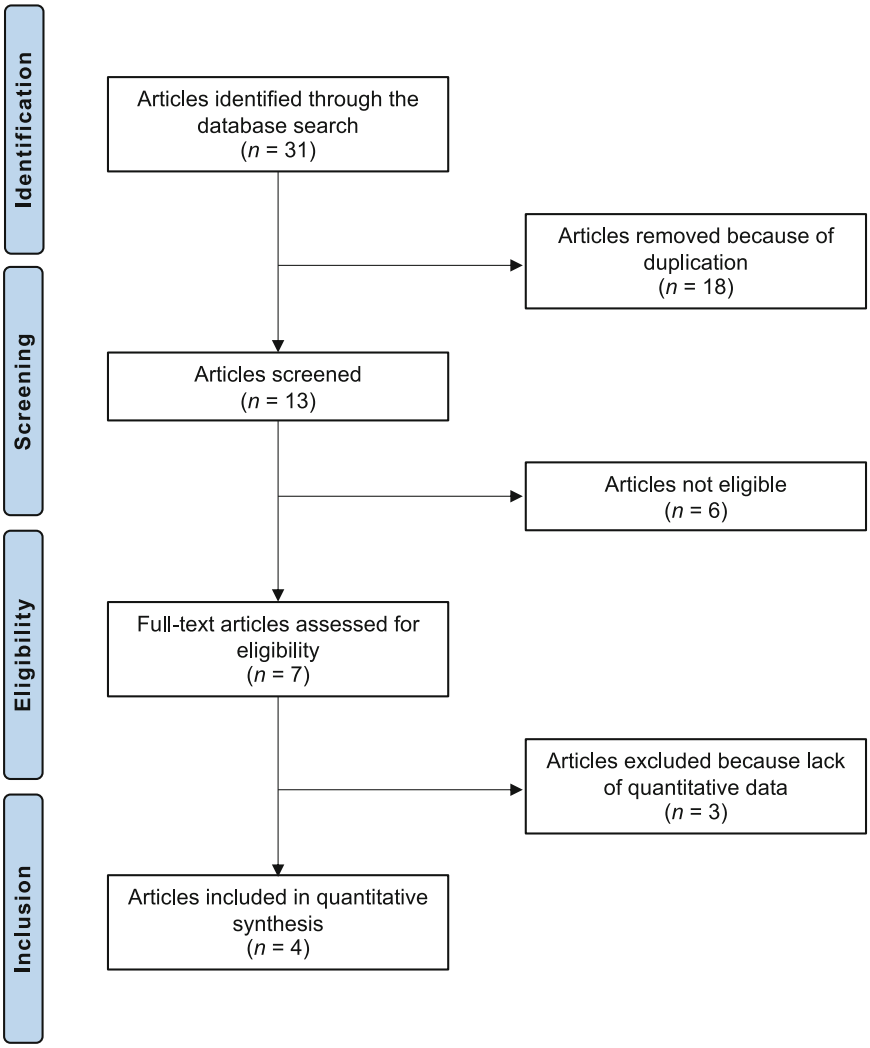


Fig. 1 ▲ PRISMA flow chart of the literature search

Introduction

Knee osteoarthritis (OA) is a prevalent chronic condition that primarily affects older people, significantly impairing mobility and quality of life caused by pain, stiffness and functional decline [1–3]. The pathology of OA involves the progressive degeneration of joint components, including cartilage, joint lining, ligaments and bone [4, 5]. This deterioration contributes to the substantial personal, social and economic burdens associated with the condition [4, 6]. Among nonsurgical treatment options, intra-articular injections of hyaluronic acid (HA) and plasma rich in growth factors (PRGF) are frequently employed, given their potential to provide symptom relief and possibly alter the course of OA [7, 8]. The HA is a major component of synovial fluid and cartilage and facilitates joint lubrication and cushioning [9–11]. Injections of HA improve joint mechanics and alleviate pain based on their viscoelastic properties by increasing the HA levels in osteoarthritic knees [12–14]. Conversely, PRGF uses autologous blood-derived growth factors to foster the natural healing processes and tissue regeneration [15–17]. This latter approach targets symptom management and proposes a regenerative solution by enhancing the biological repair of joint tissues [18, 19]. Despite the therapeutic promise of HA and PRGF, their comparative efficacy and the duration of their benefits are topics of ongoing debate and investigation [20–22].

The literature reveals varied results concerning the effectiveness and sustainability of these forms of treatment. While HA is widely recognized for its ease of use and minimal side effects, the extent and longevity of its benefits are contested [21, 23]. Some studies reported diminishing efficacy with continued use, suggesting a potential plateau effect [24, 25]. In contrast, PRGF has shown promising outcomes in pain reduction and functional improvement, occasionally surpassing the results achieved with HA [26, 27]; however, the broader application of PRGF remains limited, partly resulting from the need for more extensive data on its long-term effects and safety profile [28]. Comparative analyses are crucial in clarifying these aspects, yet they often yield inconsistent findings. Some meta-analyses have indicated that PRGF might outperform HA in improving joint function and pain management [29, 30] but these conclusions vary depending on the study design, sample size and treatment protocols. Moreover, while both treatments generally have low-risk profiles, comprehensive long-term data concerning their adverse effects are scarce [31, 32]. Another critical gap in the current research landscape is the inconsistent use and interpretation of patient-reported outcome measures (PROM). This variability can obscure the actual efficacy of the treatment, complicating the ability to draw clear conclusions from the data. Furthermore, most studies have concentrated on short-term results or have been hampered by small sample sizes and heterogeneous patient demographics, limiting the generalizability of these findings. Addressing these knowledge gaps is essential to optimize treatment strategies for knee OA.

The present meta-analysis compared intra-articular injections of HA versus PRGF in patients with knee OA. The outcome of interest was the Western Ontario and

Abbreviations

CI	confidence interval
HA	hyaluronic acid
MD	mean difference
OA	osteoarthritis
PRGF	plasma rich in growth factors
RCT	randomised controlled trials
RoB	risk of bias
WOMACA	Western Ontario and McMaster Universities Osteoarthritis Index

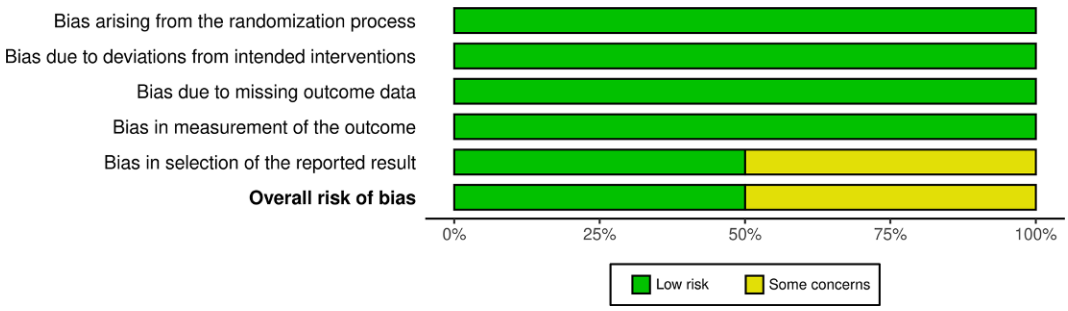


Fig. 2 ◀ Cochrane risk of bias tool. (RoB2)

McMaster Universities Osteoarthritis Index (WOMAC). It was hypothesized that intra-articular PRGF injections would improve the WOMAC scores to a greater extent than HA injections in patients with knee OA, particularly over a 4–6 months follow-up period.

Methods

Eligibility criteria

All the head-to-head randomized controlled trials (RCT) comparing intra-articular injections of HA versus PRGF were accessed. Only studies published in peer-reviewed journals were considered. According to the author's language capabilities, English, German, Italian, French and Spanish articles were eligible. Only studies with level I evidence, according to the Oxford Centre of Evidence-Based Medicine [33], were considered. Only studies that clearly stated that injections were performed in patients with knee OA, irrespective of the severity of OA, were considered. Studies which evaluated intra-articular injections augmented with other biologically active compounds were not considered. Studies that were regarded as comparators of other noninfiltrative treatments were not eligible.

Search strategy

This study was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses: the 2020 PRISMA statement [34]. The PICODT algorithm was preliminarily established:

- P (problem): knee OA.
- I (intervention): intra-articular injections.
- C (comparison): HA vs. PRGF.
- O (outcomes): WOMAC.
- D (design): RCT.
- T (timing): 4–6 months follow-up.

In December 2024 the following databases were accessed: PubMed, Web of Science and Embase. No time constraint was set for the search. The medical subject headings (MeSH) used for the database search are reported in the "Appendix". No additional filters were used in the database search.

Selection and data collection

The database search was performed independently by two authors (MJ and NJ). All the resulting titles were screened by hand and, if suitable, the abstract was accessed. The full text of the abstracts which matched the topic was accessed. If the full text was not accessible or available, the article was not considered for inclusion. A cross-reference of the bibliography of the full-text articles was also performed for inclusion. Disagreements were debated and mutually solved by the authors. In further disagreements, a third senior author (**) made the final decision.

Data items

The data extraction was performed independently by two authors (MJ and NJ). The following data at baseline were extracted: author, year of publication and journal, number of patients with related mean age and body mass index (BMI). Data concerning the WOMAC [35] were retrieved at baseline and last follow-up. Data were extracted in Microsoft Office Excel version 16.72 (Microsoft Corporation, Redmond, USA). Concerning the WOMAC index score, 24 health-specific items covering pain (5 items), stiffness (2 items) and function (17 items) were assessed. The subscale scores for pain, stiffness and function are summed to produce the total score. Scores range from 0 (no pain) to 20 (highest pain) for pain, 0 (no stiffness) to 8 (greatest stiffness) for stiffness, 0 (best function) to 68 (worst function) for function and 0 (best health) to 96 (worst health) for the total score. Higher scores represent worse pain, stiffness, and functional limitations. The endpoint of interest was to investigate whether intra-articular HA injections are associated with WOMAC score improvement compared to PRGF injections at 4–6 months of follow-up.

Methodological quality assessment and quality of the recommendations

The risk of bias was evaluated following the guidelines in the *Cochrane Handbook for Systematic Reviews of Interventions* [36]. The risk of bias in the extracted studies was independently assessed by two reviewers (MJ and NJ). Disagreements were solved by a third senior author (FM). The RCTs were evaluated using the revised risk of bias assessment tool (RoB2) [37, 38] of the Cochrane tool for assessing the risk of bias in randomized trials (RoB). The following endpoints were evaluated: bias arising from the randomization process, bias based on the deviations from intended interventions, bias because of missing outcome data, bias in the measurement of the outcome and bias in the selection of the reported result.

Synthesis methods

The main author (FM) performed the statistical analyses following the recommendations of the *Cochrane Handbook for Systematic Reviews of Interventions* [39]. The IBM SPSS software version 25 (IBM Corporation, Armonk, NY, USA) was used for descriptive statistics. The arith-

Table 1 Generalities and demographics of the included studies

Author, year	Journal name	Interventions	Patients (*n*)	Mean age (years)	Women (%)	Mean BMI (kg/m^2)
Raeissadat et al. [40]	*Clin Med Insights Arthritis Musculoskelet Disord*	PRGF	41	57.0	82	28.6
		HA	36	59.5	82	27.5
Raeissadat et al. [41]	*J Pain Res*	PRGF	60	57.1	72	27.9
		HA	59	58.6	71	28.7
Sanchez et al. [42]	*Arthroscopy*	PRGF	89	60.5	52	27.9
		HA	87	58.9	52	28.2
Raeissadat et al. [43]	*BMC Musculoskelet Disord*	PRGF	60	57.9	76	27.5
		HA	59	56.1	75	27.4

BMI body mass index; *PRGF* plasma-rich in growth factors; *HA* hyaluronic acid

Table 2 Baseline comparability

Endpoints	*P*
Mean age (years)	0.9
Women (%)	1.0
Mean BMI (kg/m^2)	0.9
WOMAC overall	0.9
WOMAC pain	0.9
WOMAC stiffness	0.9
WOMAC function	0.7

BMI body mass index, *WOMAC* Western Ontario and McMaster Universities Osteoarthritis Index

metic mean and standard deviation were used. The Review Manager software version 5.3 (The Nordic Cochrane Collaboration, Copenhagen, Denmark) was used for the meta-analyses. The paired t-test was performed with values of $P < 0.05$ considered statistically significant. The inverse variance method with mean difference (MD) effect measure was used for continuous data. The confidence interval (CI) was set at 95% in all the comparisons. Heterogeneity was evaluated through Higgins-I^2 and χ^2-tests. If $P_{\chi 2} > 0.05$, no statistically significant heterogeneity was found. If $P_{\chi 2} < 0.05$, the heterogeneity was assessed following the values of the Higgins-I^2. Suppose in the Higgins-I^2 test >70% high heterogeneity was found. A fixed effect model was set as default. If high heterogeneity was detected, a random model effect was used. Overall values of $P < 0.05$ were considered statistically significant.

Results

Study selection

The systematic literature search resulted in 31 articles. A total of 18 articles were identified as duplicates and therefore excluded. A further six investigations were discarded as they did not meet the defined inclusion criteria. In particular, the reasons for ineligibility include inadequate study design or low level of evidence ($N = 3$), evaluating intra-articular injections augmented with other biologically active compounds or considering other noninfiltrative treatment as comparators ($N = 2$), and language limitations ($N = 1$). After full-text evaluation, three additional investigations were excluded because they did not offer quantitative data on the outcomes of interest. In conclusion, four RCTs were available for inclusion. The results of the literature search are shown in **Fig. 1**.

Methodological quality assessment

The risk of bias analysis indicated a low risk of bias arising from the randomization process because all studies included were RCTs. All authors reported a high-quality allocation concealment, resulting in a low risk of bias based on deviations from intended interventions. The lack of information on the blinding of investigators and patients during treatment and follow-up in most studies resulted in a moderate risk of selecting the reported results. Incomplete data from study dropout during study enrolment or analysis occurred in none of the included studies, resulting in low risk based on missing outcome data and measurement of the reported results. In summary, the risk of bias graph indicates a good to moderate quality of the methodological assessment of RCTs (**Fig. 2**).

Study characteristics and results of individual studies

Data from 432 patients were collected and 76% (330 of 432) were women. The mean age of the patients was 58.2 ± 1.5 years and the mean BMI was 28.0 ± 0.5 kg/m^2. The generalities and demographics of the included studies are shown in **Table 1**.

Baseline comparability

At baseline, comparability was observed in mean age and BMI, male:female ratio, WOMAC and related subscales (**Table 2**).

Results syntheses

The PRGF group evidenced lower values of the function subscale of the WOMAC (MD −2.43; 95% CI −4.65 to −0.21; $P = 0.03$). No difference was found in the overall WOMAC ($P = 0.05$) and its stiffness ($P = 0.4$) and pain ($P = 0.07$) subscales. The forest plots are reported in **Fig. 3**.

Discussion

Osteoarthritis (OA), particularly of the knee, is a prevalent degenerative disease that markedly impacts the quality of life from pain and functional impairment [44–46]. Among the myriad of therapeutic options, intra-articular injections such as PRGF and HA have emerged as effective nonsurgical interventions [21, 47–49]. According to the main findings of the present meta-analysis, the current level I of evidence suggests that PRGF might be associated with better outcomes than

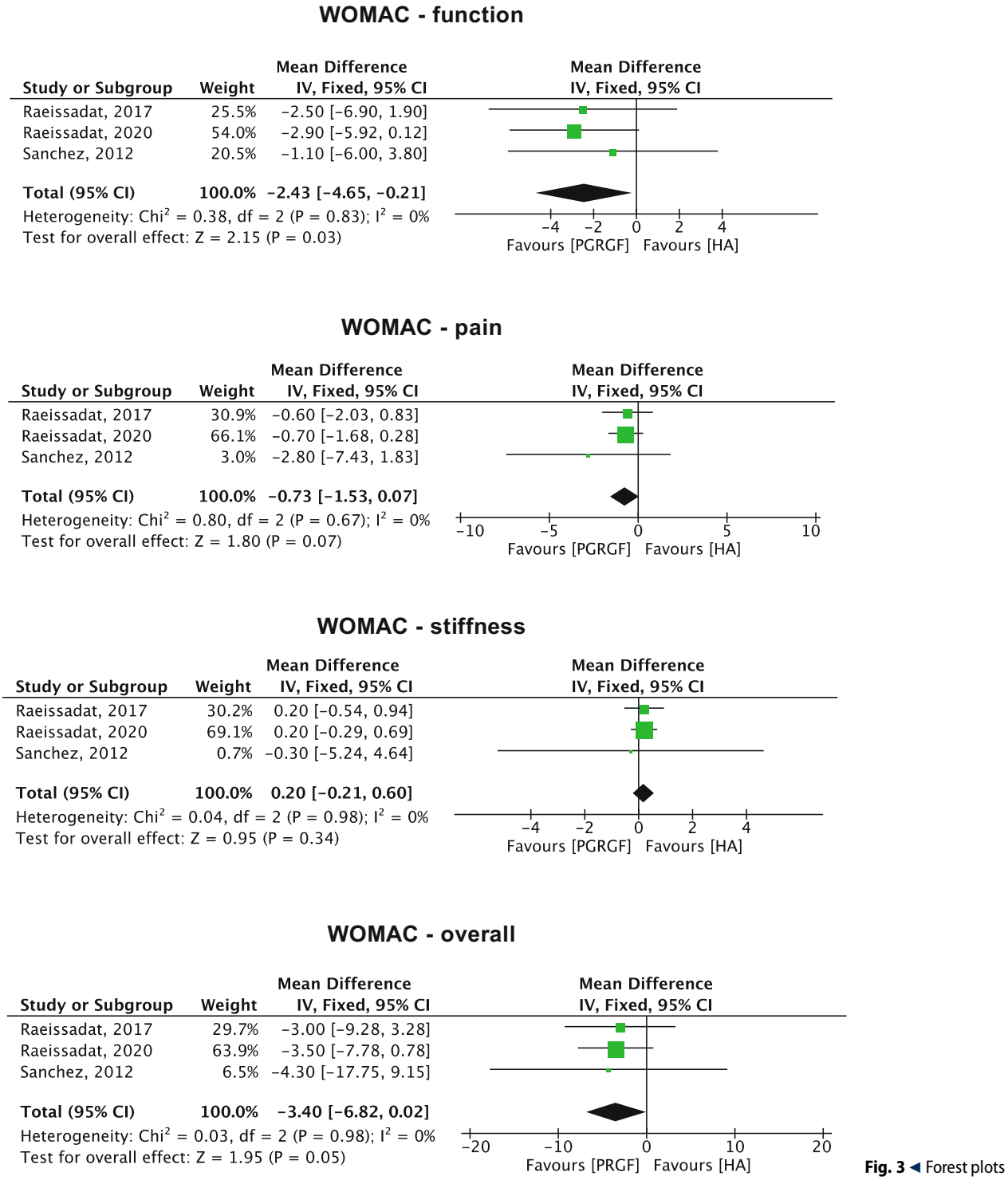


Fig. 3 ◀ Forest plots

HA. Indeed, the function subscales of the WOMAC resulted statistically significantly in favor of the PRGF group. Although not statistically significant, the WOMAC overall scale and pain and stiffness subscales indicate a clear trend favoring the PRGF group.

Several clinical trials have demonstrated the comparative efficacy of PRGF and HA in managing knee OA [50–54]. The randomized controlled trial by Sánchez et al. [42] indicated that PRGF-Endoret provided a significantly better response rate in alleviating symptoms than HA. Specifically, it achieved a 50% reduction in knee pain as measured by the WOMAC, with a noteworthy difference in response rates of 14.1 percentage points (95% CI 0.5–27.6; $p = 0.044$) between the 2 groups [42]. This study underlines the potential of PRGF to provide superior short-term benefits in pain reduction and thus improve the quality of life for patients with mild

to moderate knee OA [42]. Raeissadat et al. [40] reinforced these findings, with PRGF treatment leading to higher patient satisfaction rates and better outcomes in both pain and function over 12 months. Significant improvements were noted in both WOMAC and Lequesne index scores, which measure the severity and impact of OA [40]. These outcomes suggest that PRGF can induce more pronounced and sustained improvements in joint health than HA.

Raeissadat et al. [43] expanded the comparison by including PRGF, HA, platelet-rich plasma (PRP) and ozone therapies in a randomized clinical trial. While ozone therapy showed the best results at 2 months, PRGF and PRP maintained better outcomes at 12 months [43]. This underlines the potential of PRGF and PRP in managing knee OA beyond the immediate relief often associated with HA and ozone therapies [41, 43]. The sustained effectiveness of PRGF could be particularly beneficial in delaying the need for more invasive treatments such as knee arthroplasty [42, 55]. Regarding safety, both PRGF and HA have been generally well tolerated [40–43]. Minor complications such as injection-induced pain and swelling were reported but were comparable across both treatments, ensuring a similar safety profile [40, 41]. This aspect is crucial for the acceptability of these treatments in clinical settings given the chronic nature of OA and the potential need for repeated treatment over time [56].

While both PRGF and HA effectively reduce pain and improve function, the choice between the two may be influenced by various factors, including cost, availability, or patient preference regarding treatment administration and side effects [40, 57]. Notably, the HA group reported significantly lower immediate postinjection pain, which might be a decisive factor for some patients [40]. Clinically, the studies highlight the importance of individualized patient care in OA management [40–43]. While PRGF may provide better long-term relief and higher satisfaction in some patients, HA could be preferred for its potentially lower immediate postinjection discomfort [40, 58]. Treatment choices should be tailored to individual patient needs, considering factors such as treatment accessibility and the clinical experience of healthcare providers.

Examining the existing studies on the efficacy of PRGF and HA in managing OA reveals several methodological shortcomings that necessitate a cautious interpretation of the results. These limitations include the absence of a placebo group in some studies, which is critical to assess the true efficacy of interventions [42, 43]. Variations in the experience level of the physicians administering the injections also present a further substantial limitation. These variations can lead to inconsistencies in the treatment application, potentially influencing the reported efficacy and safety outcomes. In addition, the reliance on the WOMAC score alone as the outcome measure and the assessment at a single time point are significant limitations. While commonly used, the WOMAC score only captures some dimensions of OA symptoms and treatment effects and assessing outcomes at only one point in time may not accurately reflect the duration and sustainability of treatment benefits [59]. The studies employed PRGF and HA with differing molecular weights and for different indications, which can lead to heterogeneity in the results. Using other protocols and sessions to administer PRGF further compounds this variability, challenging the ability to draw generalized conclusions from the data. These methodological issues highlight the need for carefully designed studies to better ascertain the efficacy and safety of PRGF and HA treatments in OA. Future research should address these limitations by including placebo controls, ensuring blinding, standardizing treatment protocols and using multiple, diverse outcome measures over extended periods to provide more robust and generalizable data.

Conclusion

This meta-analysis underlines the potential therapeutic benefits of PRGF over HA in managing knee OA, as evidenced by improvements, particularly in the function subscale of the WOMAC score. The current level I evidence suggests that PRGF might be associated with greater outcomes than HA. The use of PRGF demonstrated superior outcomes in joint function and a trend towards better pain and stiffness management performance, albeit not statistically significant. The findings advocate PRGF as a viable nonsurgical intervention that can provide enhanced and prolonged relief in knee OA symptoms compared to HA. Nevertheless, the current evidence is constrained by a limited number of high-quality RCTs and methodological variances that may affect the consistency and generalizability of the results. Future research should address these limitations through well-designed placebo-controlled trials incorporating diverse and repeated measures over extended periods. This approach will help establish more definitive conclusions about the comparative effectiveness and safety profiles of PRGF and HA, ultimately guiding optimized treatment strategies for knee OA.

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Author Contribution. All authors have agreed to the final version being published and agree to be accountable for all aspects of the work.

Availability of data and material. The datasets generated during and analyzed during the current study are available throughout the manuscript.

Declarations

Conflict of interest. F. Migliorini, N. Maffulli, G. Pipino, M. Jeyaraman, S. Ramasubramanian and N. Jeyaraman declare that they have no competing interests.
Ethical standards. For this article no studies with human participants or animals were performed by any of the authors. All studies mentioned were in accordance with the ethical standards indicated in each case.

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Zusammenfassung

Intraartikuläre Injektionen von Hyaluronsäure im Vergleich zu plasmareichen Wachstumsfaktoren (PRGF) bei Kniearthrose: eine Metaanalyse von randomisierten kontrollierten Studien. Eine Metaanalyse

Einleitung: In der vorliegenden Metaanalyse wurden intraartikuläre Injektionen von Hyaluronsäure (HS) mit wachstumsfaktorreichem Plasma (PRGF) bei Patienten mit Gonarthrose verglichen. Als Ergebnis wurde der Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) herangezogen.
Methoden: Diese Studie wurde gemäß der PRISMA-Erklärung (Preferred Reporting Items for Systematic Reviews and Meta-analyses: the 2020 PRISMA statement) durchgeführt. Es wurden alle randomisierten und kontrollierten Head-to-Head-Studien (RCT) zum Vergleich von intraartikulären HS-Injektionen mit PRGF herangezogen. Dabei wurden nur Studien berücksichtigt, aus denen eindeutig hervorging, dass die Injektionen bei Patienten mit Gonarthrose durchgeführt wurden, unabhängig vom Schweregrad. Die Daten zum WOMAC wurden bei der Erstuntersuchung und beim letzten Follow-up erhoben. Als Endpunkt sollte untersucht werden, ob intraartikuläre HS-Injektionen mit einer Verbesserung des WOMAC-Scores im Vergleich zu PRGF-Injektionen bei der Nachuntersuchung nach 4 bis 6 Monaten verbunden sind.
Ergebnisse: Es wurden Daten von 432 Patienten gesammelt, von denen 76,3% (330 von 432) Frauen waren. Das Durchschnittsalter der Patienten lag bei 58,2 ± 1,5 Jahren und der mittlere Body-Mass-Index (BMI) bei 28,0 ± 0,5 kg/m2. Bei Studienbeginn wurde eine Vergleichbarkeit von Durchschnittsalter, BMI, Verhältnis von Männern zu Frauen, WOMAC-Score und den entsprechenden Subskalen dokumentiert. Die PRGF-Gruppe wies niedrigere Werte in der Subskala „Funktion" des WOMAC-Index auf ($p = 0,03$). Beim Gesamt-WOMAC ($p = 0,05$) und seinen Subskalen Steifigkeit ($p = 0,4$) und Schmerz ($p = 0,07$) wurde kein Unterschied festgestellt.
Schlussfolgerung: Die aktuelle Evidenzstufe I deutet darauf hin, dass die Verwendung von PRGF mit günstigeren klinischen Ergebnissen verbunden sein könnte als die Verwendung von HS.

Schlüsselwörter
Orthobiologika · Degeneration · Viskositätssupplementierung · Hyaluronsäure · Orthopädie · Arthritis

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