Review

Effect of collagen supplementation on knee osteoarthritis: an updated systematic review and meta-analysis of randomised controlled trials

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ABSTRACT

Objective. *To perform a systematic review and meta-analysis to assess the clinical efficacy of collagen-based supplements on knee osteoarthritis (OA) symptoms.*

Methods. *Until October 2023, we conducted searches on the MEDLINE, EMBASE, Web of Science, and Scopus databases to identify randomised controlled trials (RCTs) that reported the effects of oral collagen-based supplements on knee OA. Quantitative data from outcomes were pooled using a random- or fixed-effects model (depending on inter-study variability) and the generic inverse variance method. The Cochrane Risk of Bias 2.0 tool was employed to assess the risk of bias.*

Results. *This systematic review incorporated information of 870 participants included from 11 RCTs, with 451 allocated to the collagen supplementation group and 419 to the placebo group. The meta-analysis revealed an overall significant improvement of both function [MD, -6.46 (95% CI -9.52, -3.40); I^2=75%; p=0.00001] and pain scores [MD, -13.63 (95% CI -20.67, -6.58); I^2=88%; p=0.00001], favouring collagen supplementation.*

Conclusion. *The results of this meta-analysis suggest that oral collagen administration relieves OA symptoms. Our findings revealed noteworthy improvements, statistically and clinically, in both functional and pain scores.*

Introduction

Osteoarthritis (OA) is a prevalent chronic joint disease and stands as one of the primary degenerative disorders with limited succeed in treatment (1–3). While OA can affect joints of various sizes, the knee is particularly susceptible, reaching an 83% of all OA cases. This condition affects approximately 13% of women and 10% of men over the age of 60 (4, 5).

There is a diverse range of non-surgical therapeutical options for knee OA, primarily focused on alleviating symptoms and reducing functional impairment to maintain a good quality of life (6). Initial treatments typically involve the use of oral or topical non-steroidal anti-inflammatory drugs (NSAIDs) and intra-articular application of corticosteroids (7, 8). However, numerous clinical trials and meta-analyses have explored the potential benefits of various nutraceuticals and dietary supplements, including glucosamine, chondroitin sulfate, vitamin D, and collagen (6, 9-13). Nevertheless, due to the limited availability of robust evidence, most guidelines do not recommend (8, 14) or consider uncertain (15, 16) the use of nutraceuticals for managing knee OA. Specifically, the evidence on collagen supplementation is currently insufficient to make any definitive recommendation.

Numerous preclinical and clinical studies suggest that collagen supplementation could be a promising option for early-onset OA patients, through reducing cartilage breakdown (17, 18). However, it is essential to note that the available evidence is of moderate to low quality due to various factors, including methodological limitations (17). In light of emerging evidence from recent randomised controlled trials (RCTs) investigating the effects of collagen supplements, we undertake an updated analysis in this field. This endeavour seeks to potentially validate the findings

from the previous meta-analysis (6). Equally important is emphasising that a new analysis should also encompass an evaluation of the clinical relevance of the observed responses, an aspect overlooked in the earlier analysis, but crucial for a more thorough understanding of the potential therapeutic impact of collagen supplementation.

Therefore, the purpose of this systematic review and meta-analysis of RCTs is to conduct an updated assessment of the clinical relevance of collagen-based supplements on knee OA symptoms.

Methods

The study protocol is registered with PROSPERO under the registration number CRD42023438898. The study adheres to the PICOS (Population, Intervention, Comparison, Outcome, Study design) criteria, encompassing patients diagnosed with knee OA established by Kellgren-Lawrence or Albhack classification (P), oral administration of collagen supplementation (I), placebo (C), and the assessment of pain relief and functional improvement using validated scales or questionnaires (*e.g.* VAS, WOMAC, KOOS, IKDC) (O) in randomised clinical trials (parallel or cross-over) (S). The review also includes the documentation of adverse events. Furthermore, this systematic review follows the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines (19).

Selection criteria and search strategy

The search strategy, collaboratively developed by an experienced librarian and the study authors, employed a combination of MeSH terms (*e.g.* knee osteoarthritis, knee OA, knee pain, collagen supplementation, collagen supplement, collagen administration, collagen hydrolysate, collagen peptides) and relevant text words. The aim was to identify original articles or abstracts in any language that included patients diagnosed with knee OA. The comprehensive search covered databases such as MEDLINE, EMBASE, Web of Science, and Scopus, spanning from inception to October 2023. Exemplar search strategies are detailed in Appendix 1.

A study was considered eligible for inclusion in the meta-analysis if it reported at least one outcome under review. Exclusion criteria encompassed inconsistencies in study design, presentation at conferences or congress meeting, or duplication. Studies with less than 9 weeks of follow-up were excluded, with no language restrictions. Additionally, studies lacking relevant data concerning the outcomes of interest were also excluded.

Study selection process

The process encompassed a two-step approach conducted by two reviewers. In the first step, titles and abstracts of studies were assessed, with inclusion of studies approved by at least one reviewer. The second step involved a full-text screening, using the same criteria from the first phase. The agreement between reviewers was gauged using the kappa statistic, adjusting for chance (20), and any discrepancies were resolved through consensus. For data management during the selection process, the Distiller Systematic Review Software (DistillerSR, Evidence Partners, Ottawa, Canada) was employed.

Data collection and risk of bias assessment

The extraction of data was conducted independently and in duplicate, utilising a standardised digital format. Eligible studies underwent a thorough review, and the following information was extracted: first author, publication year, treatment duration and follow-up, participant count, intervention arms, dosage, collagen source, OA classification, demographics of study participants, values of pain and function scores, and recorded side effects. The risk of bias for each included RCT was evaluated using the Cochrane risk-of-bias tool for randomised trials version 2 (RoB 2.0) (21). Whenever feasible, potential publication bias was explored through visual inspection of Begg's funnel plot asymmetry and Egger's weighted regression tests. To address potential missing studies and adjust for the impact of publication bias on the analysis, the Duval and Tweedie "trim and fill" method was employed (22).

Data analysis and synthesis

The meta-analysis utilised two statistical software tools: Comprehensive Meta-Analysis version 4 software and the Review Manager statistical software version 5.4.1. For each study, the summary of the intervention effect was determined through mean differences (MD) and 95% confidence intervals (CI) for both pain and functional outcomes. Calculation of net changes in measured scores was derived as follows: the measure at the end of follow-up – the measure at baseline in both the intervention and control groups. The mean change from baseline was employed for analysis. In cases where numerical values were solely presented graphically, the GetData (Graph Digitizer) software version 2.26 was used for data extraction. The standard deviation of the mean differences was computed using the intervention-specific standard deviations and an imputed correlation coefficient (R) of 0.5 (23).

The meta-analysis employed a random-effects model and the generic inverse variance method when the heterogeneity exceeded 50%. Conversely, a fixed-effects model was used if the heterogeneity fell below 50%. To assess the consistency and heterogeneity among studies, the Cochrane's Q statistic test was applied, with a significance threshold set at $p<0.05$. Additionally, the I^2 statistic was utilised, categorising 0–25% heterogeneity as unimportant, >25–50% as moderate, and >50% as important heterogeneity. A sensitivity analysis was conducted to evaluate the impact of individual studies on the overall effect size using the leave-one-out method (*i.e.* systematically removing one study at a time and re-analysing) (24, 25). Lastly, the effect sizes for each outcome were compared against established minimal clinically important difference (MCID) criteria in knee OA to gauge the clinical significance of the observed changes.

Results

Search output

The search strategy initially yielded 802 publications. Out of these, 766 studies were excluded for not meeting the inclusion criteria, and four studies

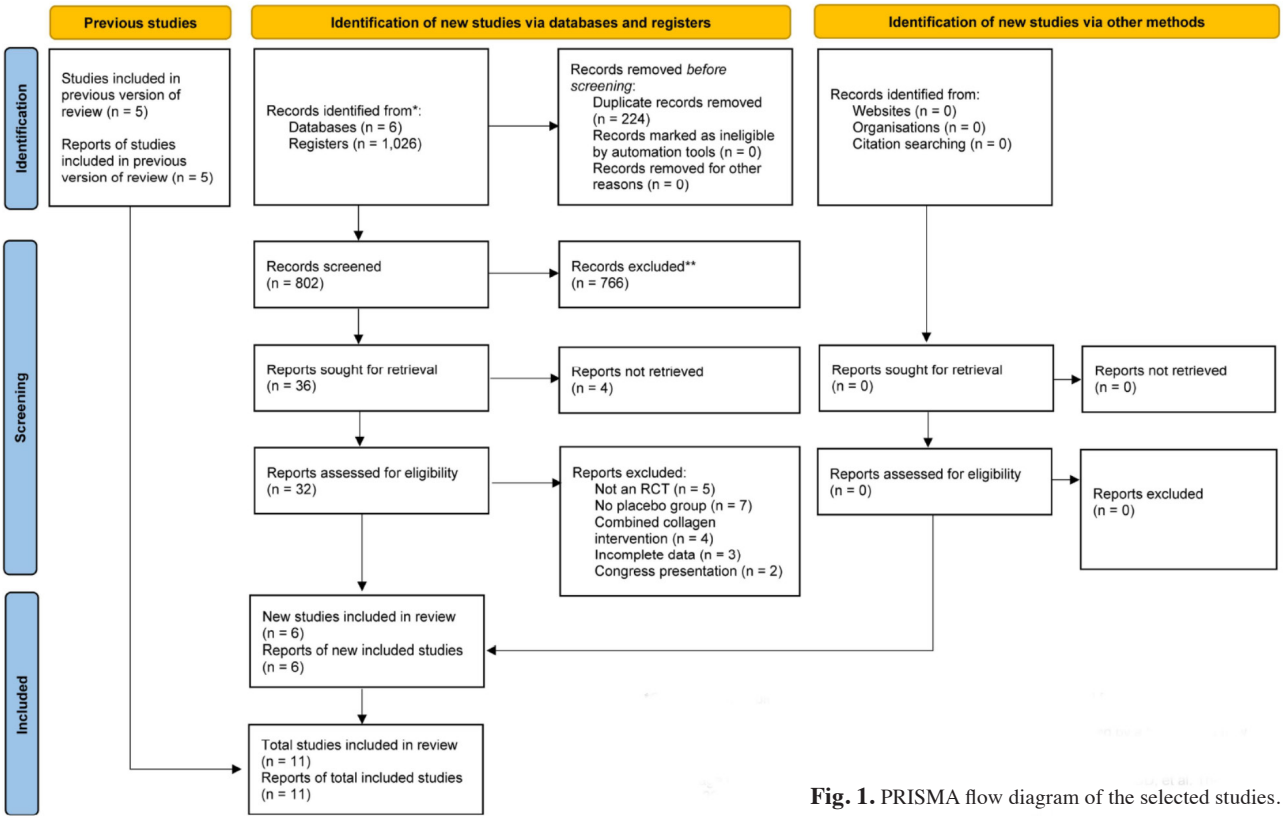

Fig. 1. PRISMA flow diagram of the selected studies.

could not be retrieved. Upon reviewing 32 full-text, 21 were excluded for the various reasons, such as lacking a placebo group (n=7), not being RCT (n=5), involving combined collagen intervention (n=4), incomplete data (n=3), and congress presentations (n=2). Five studies were part of the previous version of this systematic review, with six new additions. Consequently, 11 clinical trials were selected and included in the meta-analysis. The complete workflow is illustrated in Figure 1.

Characteristics of the included studies

This systematic review encompassed data from 870 subjects, with 451 in the collagen supplementation arm and 419 in the placebo arm. The studies spanned publication dates from 2009 (26) and 2023 (27). Enrolled participants had diagnoses raging from mild to moderate knee OA, with only one study including patients with severe knee OA (28). The follow-up duration varied across studies, ranging from 10 weeks (29) to 48 weeks (30). The trials reported the usage of undenatured collagen and hydrolysed collagen, with chicken sternal cartilage being the most frequently used collagen source (27, 29, 31, 32). Comprehensive information on study characteristics and patients is presented in Table I.

Risk of bias assessment

In the domain of the randomisation process, two studies (11, 33) raised some concerns, while the remaining studies demonstrated a low risk of bias. Concerns in the deviations from intended interventions domain were noted in five studies (11, 26-28, 33), with the rest exhibiting a low risk of bias. All the studies demonstrated a low risk of bias in domains related to missing outcome data and measurement of the outcome. Regarding the selection of reported results, two studies (29, 32) prompted some concerns, while the remainder presented a low risk of bias. Overall, four studies were rated as low risk (30, 31, 34, 35), and seven studies were classified as having some concerns (11, 26-29, 32, 33). The complete risk of bias assessment is depicted in Figure 2.

Efficacy of collagen supplementation

A total of 11 and 5 studies reported functional (WOMAC) and pain (VAS) outcomes, respectively. The meta-analysis revealed an overall significant improvement of both pain [MD, -13.63 (95% CI -20.67, -6.58); I^2=88%; p=0.0002; Fig. 3] and functional scores [MD, -6.46 (95% CI -9.52, -3.40); I^2=75%; p<0.0001; Fig. 4], favouring collagen supplementation. The sensitivity analysis demonstrated that collagen supplementation's effects on both functional and pain outcomes remained consistent and were not influenced by any single study (Supplementary Table S1, Suppl. Table S2).

Subanalysis for the functional WOMAC score was performed including pain [MD, -1.23 (95% CI -2.08, -0.38); I^2= 62%; p=0.004; Fig. 5], stiffness [MD, -0.56 (95% CI -1.02, -0.09); I^2=52%; p=0.02; Fig. 5] and function [MD, -3.70 (95% CI -7.65, 0.25); I^2=82%; p=0.07; Fig. 5], showing a significant improvement in the domains of pain and stiffness with the use of collagen supplementation.

Clinical relevance of collagen supplementation

In all the studies that assessed pain using the VAS, an MCID of 20% (36) or more was achieved, with two studies

Table I. Characteristics of the included studies.

Author	Follow-up	n	Intervention arms	Dosage	Collagen source	OA classification (Kellgren-Lawrence)	Age, years	Female, n (%)	BMI (kg/m^2)	Pain score at baseline (VAS)	Functional score at baseline (WOMAC)
Benito-Ruiz *et al*. 2009	24 weeks	111	HC	10.0 g daily	Non-ruminant bones	1–3	59.4±10.6	117 (92.9)	27.2±4.3	43.1±7.4	35.9±17.3
		96	Placebo				58.8±11.4	114 (91.9)	28.2±4.4	42.1±7.5	33.5±16.6
Chen *et al*. 2023	24 weeks	38	HC-II	2.0 g daily	Chicken sternal cartilage	1–3	59.8±7.7	30 (78.9)	24.4±3.3	ND	ND
		37	EC + HC-II	2.0 g + 5.81 g daily	Chicken meat + chicken sternal cartilage	57.3±7.1	33 (89.2)	23.9±3.5			
		38	GS HCl	1.5 g daily	NA		59.1±8.2	32 (84.2)	24.6±2.6		
		38	Placebo	NA	NA		56.4±6.4	33 (86.8)	24.4±3.3		
Costa *et al*. 2020	24 weeks	20	UC-II + physiotherapy	40 mg daily	Chicken sternal cartilage	1–3	55.5±8.8	14 (70.0)	31.2±4.9	6.4±0.8	44.8±8.6
		20	Placebo + physiotherapy				57.4±11.4	16 (80.0)	30.3±5.7	5.6±1.0	42.6±9.5
		20	Physiotherapy				59.6±8.2	9 (30.0)	30.4±5.8	6.1±0.9	34.3±5.8
Costa *et al*. 2021	24 weeks	20	UC-II	40 mg daily	Chicken sternal cartilage	1–3	60.3±7.5	13 (65.0)	26.9±3.8	ND	34.9±16.2
		20	Placebo				57.6±7.0	14 (70.0)	30.0±4.5		34.9±20.6
		20	UC-II + physiotherapy				55.5±8.8	14 (70.0)	30.2±4.9		45.3±17.9
		20	Placebo + physiotherapy				57.4±11.4	16 (80.0)	30.3±5.7		43.0±20.2
		20	Physiotherapy				59.6±8.2	9 (45.0)	30.4±5.8		34.7±11.9
Hewling *et al*. 2019	12 weeks	44	Native collagen	450 mg daily	Eggshell membrane	ND	53.3±7.6	63 (72.0)	28.2±2.7	7.0±3.4 †	35.4±19.7
		44	Placebo							6.6±3.7 †	31.6±16.4
Jiang *et al*. 2014	24 weeks	46	BCP	8.0 g daily	Bovine type I collagen	1–3	60.9±8.8	46 (100)	24.5±3.1	3.4±1.7 †	15.8±3.5
		48	Placebo				60.7±6.2	48 (100)	24.0±3.3	3.9±1.4 †	15.3±5.0
Kumar *et al*. 2015	13 weeks	19	PCP	5.0 g twice a day	Pork skin	2–4	ND	17 (89.4)	26.1±3.8	63.2±10.6	47.2±9.8
		11	Placebo		NA			10 (90.9)	23.1±1.9	60.0±6.3	47.3±8.6
		19	BCP		Bovine bone			11 (57.8)	25.9±3.3	66.0±12.3	50.3±9.6
		11	Placebo		NA			7 (63.6)	25.8±3.3	62.0±14.0	50.1±14.7
Lugo et al. 2016	24 weeks	63	UC-II	40 mg daily	Chicken sternal cartilage	2–3	53.5±1.0‡	30 (47.6)	25.2±0.4‡	58.4±1.0 ‡	1398±27.9 ‡§
		65	CS				52.6±1.0‡	37 (56.9)	25.5±0.4‡	59.1±1.0 ‡	1396±31.8 ‡§
		58	Placebo				53.1±1.0‡	30 (51.7)	24.7±0.4‡	58.2±1.0 ‡	1382±34.8 ‡§
Luo et al. 2022	12 weeks	34	UC-II	40 mg daily	Chicken sternal cartilage	2–3	50.9±7.1	ND	24.7±2.6	72.7±9.6	86.1±7.6
		33	GS + CS				51.4±6.4		25.3±3.0	70.3±7.3	86.7±7.2
		34	Placebo				48.7±7.3		25.2±2.3	71.2±8.8	86.5±6.5
McAlindon *et al*. 2011	48 weeks	15	HC	10.0 g daily	Bovine hide, bone, pigskin, or fish	2–3	58.9±8.0	9 (60.0)	30.1±4.6	4.6±2.6 †	20.3±10.5
		15	Placebo				60.3±8.5	9 (60.0)	31.2±7.0	5.8±3.0 †	29.2±13.8
Schauss *et al*. 2012	10 weeks	35	HC-II	300 mg	Chicken sternal cartilage	ND	54.3±8.7	23 (66.0)	ND	ND	54.6±11.5
		33	Placebo				54.5±9.8	18 (55.0)			54.9±10.1

Data are shown as mean ± standard deviation unless otherwise indicated.
‡ Mean ± standard error; † WOMAC, pain; § WOMAC, total (range 0–2,400)
HC-II: hydrolysed type II collagen; EC: BRAND'S essence of chicken; PCP: porcine collagen peptides; BCP: bovine collagen peptides; UC-II: undernatured type II collagen; CS: chondroitin sulfate; GS: glucosamine; BMI: Body Mass Index; OA: osteoarthritis; NA: not applicable; ND: no data; VAS: visual analogue scale; WOMAC: Western Ontario and McMaster Universities Arthritis Index

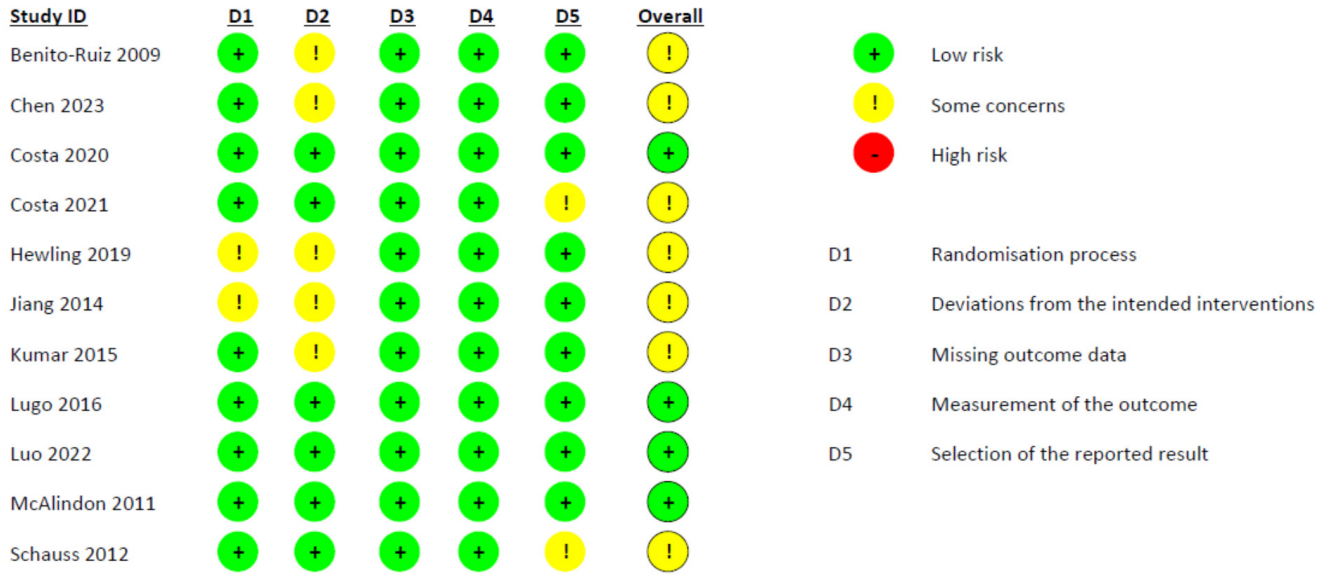

Fig. 2. Quality evaluation of studies through risk of bias assessment.

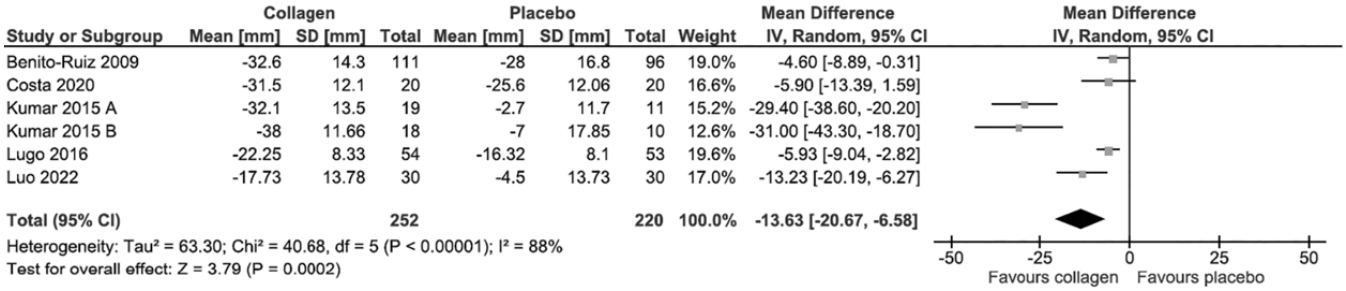

Fig. 3. Forest plot displaying weighted mean difference and 95% confidence intervals for the effect of collagen-based supplementation on pain.

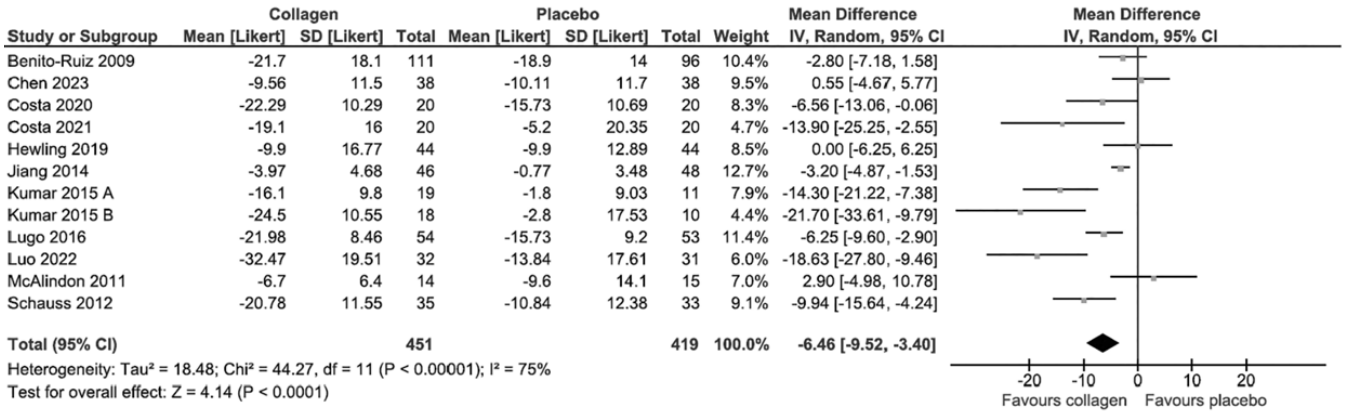

Fig. 4. Forest plot displaying weighted mean difference and 95% confidence intervals for the effect of collagen-based supplementation on the total WOMAC score.

(26, 28) reaching a satisfactory clinical improvement by decreasing <32.3 points (37) at the end of the intervention period. An overall clinically relevant improvement of 9 mm change on a 0-100 mm VAS score has been proposed for oral glucosamine-chondroitin supplementation (38), which was achieved with collagen supplementation according to our results (13.6 mm). Similarly, in studies evaluating pain through the WOMAC subscale, an MCID of 20% or more was consistently observed, and two studies (26,35) attained an MCID of at least 4.2 points. Moreover, seven studies (26, 28, 29, 31, 32, 34, 35) achieved an MCID of at least 16.1 points on the WOMAC scale (39), while one study (35) met an MCID of at least 1.9 in the stiffness subscale. Additionally, three studies (26, 29, 35) obtained an MCID of at least 10.1 points in the function subscale of WOMAC. Nevertheless, the overall effect size recorded for the total WOMAC score (6.46) did not achieve the MCID threshold of 16.1 points.

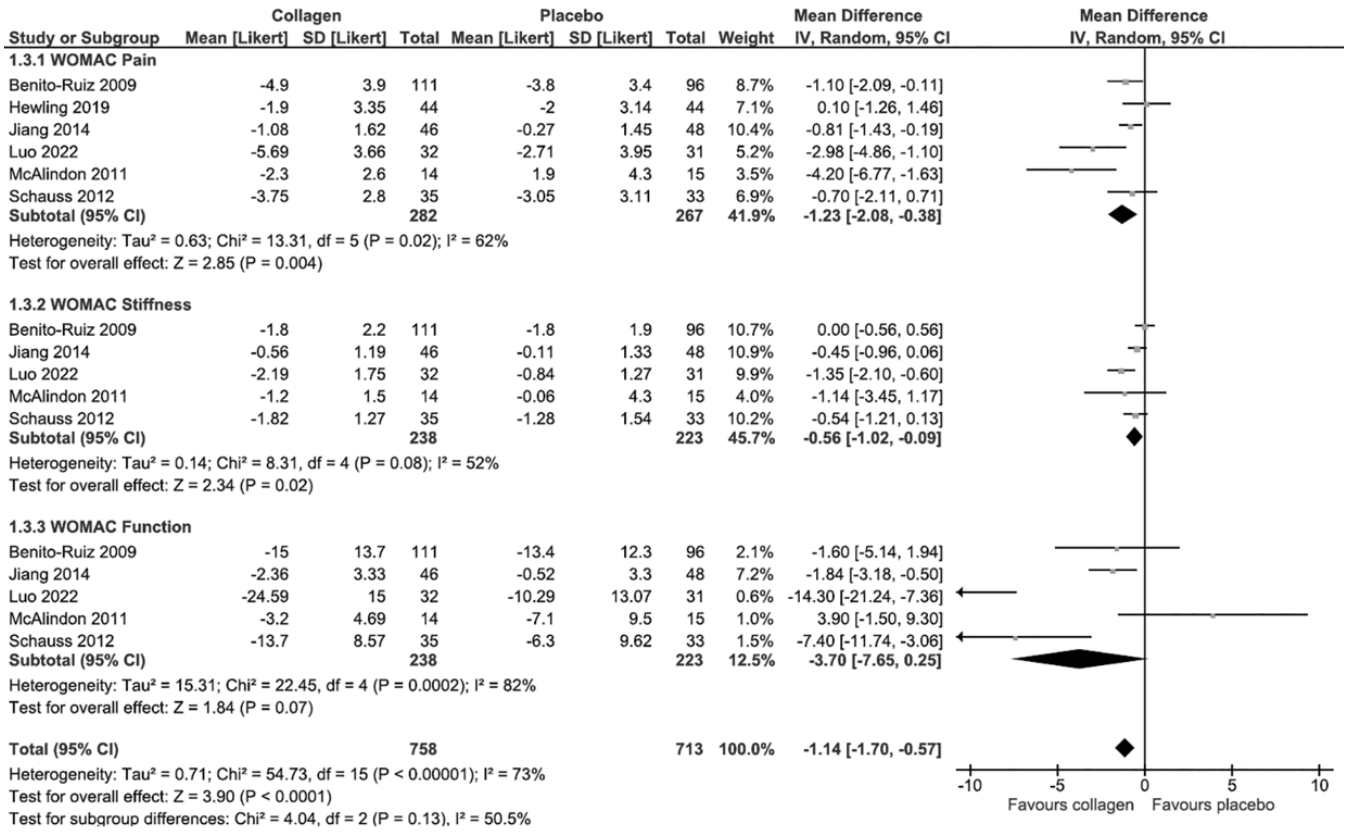

Fig. 5. Forest plot displaying weighted mean difference and 95% confidence intervals for the effect of collagen-based supplementation on the WOMAC subscores.

Adverse events

Out of the studies included in the analysis, 7 reported adverse events (11, 26, 29, 30, 34, 35). These events were generally categorised as non-severe. Only one study suggested a potential link between collagen supplementation and side effects such as headaches and poor-quality sleep (11). In the remaining studies, there was no apparent association between the treatment and the observed adverse events. Supplementary Table S3 shows a detailed breakdown of the reported adverse events.

Publication bias

An examination of publication bias revealed an asymmetric funnel plot, indicating potential bias in the functional outcome. To address this asymmetry, the "trim and fill" method was employed to impute potentially missing studies (Fig. 6). Egger's regression test (95% CI, [-3.89, 0.35]; p=0.046) and Begg and Mazumdar rank correlation test (Kendall's Tau, -0.455; z value, 2.057; p=0.023) both suggested the presence of publication bias in the meta-analysis for the functional score. Following Cochrane Handbook recommendations for Systematic Reviews of Interventions, a funnel plot for pain score was not generated due to the absence of RCTs reporting data on this outcome (40).

Discussion

The results of this updated meta-analysis endorse the administration of oral collagen for decreasing pain and improving function in patients with knee OA, as indicated by previous meta-analysis (6). The primary approach for addressing knee OA typically involves the use of NSAIDs for pain relief. However, it is essential to note that NSAIDs do not modify the natural course of the disease, nor do they enhance knee functionality (41). Moreover, the use of NSAIDs may result in adverse effects, including gastrointestinal complications (42). Consequently, nutraceuticals and dietary supplements have emerged as valuable alternatives in the treatment of knee OA.

Within the domain of nutraceuticals and dietary supplements, collagen maintains a significant research interest. Depending on its source, molecular weight, and type, collagen can be fundamentally categorised into two primary groups: hydrolysed collagen (HC) and undenatured collagen (UC) (43-45). The key distinction between these two lies in their molecular weight, HC possesses a lower molecular weight, allowing it to be readily absorbed in the small intestine, thus reaching the cartilage of the joints, and resulting in a chondroprotective effect. On the other hand, UC is not absorbed as is within the intestine. Instead, it triggers a specific immune response, known as oral tolerance, which actively inhibits inflammation and mitigates tissue breakdown at the joint level (46, 47).

A noteworthy observation to consider derived from our analysis is that in studies where HC collagen (26, 27, 30) was employed, the results exhibited a greater degree of variability. However, the one consistent trend was the beneficial effect of collagen over a placebo, specifically in terms of pain relief, assessed using VAS or the pain domain within the WOMAC tool.

Conversely, in studies where PCP/

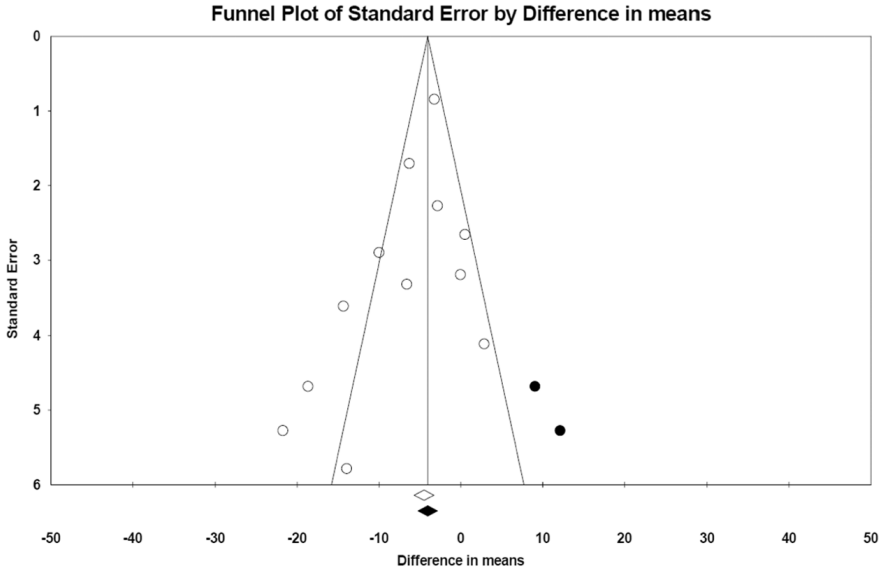

Fig. 6. Funnel plot detailing publication bias in the studies reporting the effect of collagen-based supplementation on the total WOMAC functional score.

BCP (28) or UC (31-35) were utilised, a consistent improvement for collagen over the placebo was evident across all WOMAC domains as well as the VAS score. This observation can potentially be attributed to the substantial presence of autoantigens related to type II collagen in OA patients (48, 49). As a result, the induction of oral tolerance may have an anti-inflammatory effect by reducing the plasma concentration of cytokines such as TNF-α and IL-1β (46). Oral tolerance is characterised by the deliberate suppression of specific immune reactions to antigens initially encountered in the gastrointestinal tract (50). This mechanism plays a crucial role in preventing immune responses to innocuous antigens, including food proteins.

Oral collagen supplements are believed to provide the necessary building blocks for cartilage repair and maintenance by supplying amino acids that are critical for the synthesis of cartilage proteins. The aggressive phenotype of synovial fibroblasts involves the production of cytokines and proteases that contribute to cartilage degradation.(51) Collagen supplements might help modulate the activity of these fibroblasts by reducing inflammation and providing the structural proteins necessary for cartilage repair. Also, by potentially reducing inflammation in the joints, collagen supplements can indirectly modulate pain pathways influenced by inflammatory mediators, including those interacting with nerve growth factors (52). Reduced inflammation can lead to decreased activation of pain receptors in the joint. Reducing inflammation through collagen supplements could potentially slow the progression of OA.

To determine whether an outcome has clinical relevance, in 1989 Jaeschke *et al*. (53) introduced the concept of minimum clinically important difference (MCID) which stands as "the smallest difference in score in the domain of interest which patients perceive as beneficial and which would mandate, in the absence of troublesome side effects and excessive cost, a change in the patient's management." In the context of knee OA, it appears that a reduction in pain of 10–20% as measured by either the WOMAC pain subscale or VAS, meets the criteria for a MCID (54). Furthermore, patients consider a score of 32.3 mm or less on the 1–100 mm VAS a satisfactory state (37). The information needed to establish the MCID for the complete WOMAC scale and its subscales is available in invasive knee OA studies. Therefore, we draw upon the findings of Kim *et al*. (39), which involve high tibial osteotomy with a medial opening wedge for knee OA treatment. Their study has determined that a significant MCID for knee OA includes an improvement of 16.1 points on the WOMAC scale, as well as 4.2, 1.9, and 10.1 points for the pain, stiffness, and function subscales of WOMAC, respectively.

In our results, it can be observed that collagen is an effective treatment for pain relief, including clinical significance. This aligns with the findings by Liu *et al*. (55), where the only dietary supplements achieving this clinical outcome were UC-II and green-lipped mussel. Clinical significance was also observed overall with the WOMAC score, even when its stiffness subscale did not achieve either clinical or statistical significance.

Given that most studies found minimal adverse effects in patients treated with collagen (26, 29, 30, 34, 35), it can be considered as a safe therapeutic option for knee OA. This is consistent with previous clinical trials that have used collagen as a dietary supplement in other joint disorders or even in healthy subjects (56-58).

The present study has some limitations that warrant consideration. Firstly, considering the occurrence incidence of knee OA, the population can still be considered small; although we have increased the number of included studies (and subjects) compared to previous reports. Secondly, the included studies utilised different collagen formulations, which may have influenced our findings. Lastly, four of the RCTs had a treatment duration of 13 weeks or less, which might be insufficient to achieve the therapeutic effects of collagen supplementation on knee OA symptoms. However, it is important to consider that the samples of subjects, their demographic characteristics, and the results evaluated were very similar, minimising the possible influence of the inter-study heterogeneity.

In conclusion, the findings of this meta-analysis indicate that oral collagen administration can effectively alleviate knee OA symptoms, as demonstrated by statistical and clinically significant reductions in both pain and functional scores. However, further extended clinical trials involving larger study populations with longer follow-up are necessary to corroborate the potential therapeutic benefits of collagen supplementation in individuals with knee OA.

Appendix:
Examples of search strategies

Ovid MEDLINE-Embase

1. exp knee osteoarthritis/
2. ("arthrosis, knee" or "femorotibial arthrosis" or "gonarthrosis" or "knee arthrosis" or "knee joint arthrosis" or "knee joint osteoarthritis" or "knee osteo–arthritis" or "knee osteo-arthrosis" or "knee osteoarthrosis" or "gonarthrosis" or "osteoarthritis, knee" or "osteoarthrosis, knee" or "knee osteoarthritis").mp. [mp=ti, ot, ab, fx, sh, hw, kw, tx, ct, tn, dm, mf, dv, kf, dq, bt, nm, ox, px, rx, an, ui, sy, ux, mx]
3. collagen suplementation.mp. [mp=ti, ot, ab, fx, sh, hw, kw, tx, ct, tn, dm, mf, dv, kf, dq, bt, nm, ox, px, rx, an, ui, sy, ux, mx]
4. exp collagen/
5. ("biocor" or "collagel" or "collagen horm" or "collastypt" or "collistat" or "lyostypt" or "medistat" or "novacol" or "phonogel" or "collagen").mp. [mp=ti, ot, ab, fx, sh, hw, kw, tx, ct, tn, dm, mf, dv, kf, dq, bt, nm, ox, px, rx, an, ui, sy, ux, mx]
6. exp placebo/
7. ("placebo" or "placebo gel" or "placebos").mp. [mp=ti, ot, ab, fx, sh, hw, kw, tx, ct, tn, dm, mf, dv, kf, dq, bt, nm, ox, px, rx, an, ui, sy, ux, mx]
8. 1 or 2
9. 3 or 4 or 5
10. 6 or 7
11. 8 and 9 and 10
12. from 11 keep 1-117
13. from 11 keep 118-124
14. from 11 keep 125-298
15. from 11 keep 299-370

SCOPUS

TITLE-ABS ("arthrosis, knee" OR "femorotibial arthrosis" OR "gonarthrosis" OR "knee arthrosis" OR "knee joint arthrosis" OR "knee joint osteoarthritis" OR "knee osteo−arthritis" OR "knee osteo−arthrosis" OR "knee osteoarthrosis" OR "gonarthrosis" OR "osteoarthritis, knee" OR "osteoarthrosis, knee" OR "knee osteoarthritis") AND ("biocor" OR "collagel" OR "collagen horm" OR "collastypt" OR "collistat" OR "lyostypt" OR "medistat" OR "novacol" OR "phonogel" OR "collagen") AND ("placebo" OR "placebo gel" OR "placebos")

Web of Science

TS=(("arthrosis, knee" OR "femorotibial arthrosis" OR "gonarthrosis" OR "knee arthrosis" OR "knee joint arthrosis" OR "knee joint osteoarthritis" OR "knee osteoarthritis" OR "knee osteo-arthrosis" OR "knee osteoarthrosis" OR "gonarthrosis" OR "osteoarthritis, knee" OR "osteoarthrosis, knee" OR "knee osteoarthritis") AND ("biocor" OR "collagel" OR "collagen horm" OR "collastypt" OR "collistat" OR "lyostypt" OR "medistat" OR "novacol" OR "phonogel" OR "collagen") AND ("placebo" OR "placebo gel" OR "placebos"))

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