International Orthopaedics (2019) 43:531–538
https://doi.org/10.1007/s00264-018-4211-5

REVIEW ARTICLE

Effect of collagen supplementation on osteoarthritis symptoms: a meta-analysis of randomized placebo-controlled trials

Juan Mario García-Coronado[1] · Lorena Martínez-Olvera[1] · Rodrigo E. Elizondo-Omaña[1] · Carlos Alberto Acosta-Olivo[2] · Félix Vilchez-Cavazos[2] · Luis Ernesto Simental-Mendía[3] · Mario Simental-Mendía[2]

Received: 18 July 2018 / Accepted: 19 October 2018 / Published online: 27 October 2018

Abstract

Purpose Osteoarthritis (OA) is one of the most common causes of disability and a prevalent chronic disease. The use of collagen is growing due to the satisfactory results in the treatment of OA. However, the possible beneficial effects of collagen for the treatment of OA are currently controversial. The aim of the present meta-analysis was to evaluate the effect of collagen-based supplements on OA symptoms.

Methods PubMed-Medline, Scopus, and Google Scholar databases were searched for randomized placebo-controlled trials evaluating the effect of orally administered collagen on OA symptoms using the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) scale and/or the Visual Analog Scale (VAS). Meta-analysis was conducted using a random-effects model and a generic inverse variance method. Heterogeneity was tested using the I^2 statistic index.

Results Collagen treatment showed a significant reduction in the score of total WOMAC index (WMD − 8.00; 95% CI − 13.04, − 2.95; $p = 0.002$). After subgroup analysis of the WOMAC subscores, the collagen supplementation revealed a significant decrease in the stiffness subscore (WMD − 0.41; 95% CI − 0.74, − 0.08; $p = 0.01$), whereas the pain (WMD − 0.22; 95% CI − 1.58, 1.13; $p = 0.75$) and functional limitation (WMD − 0.62; 95% CI − 5.77, 4.52; $p = 0.81$) subscores did not have significant differences. Finally, a significant reduction was found in the VAS score after collagen administration (WMD − 16.57; 95% CI − 26.24, − 6.89; $p < 0.001$).

Conclusion The results of this meta-analysis showed that collagen is effective in improving OA symptoms by the decrease of both total WOMAC index and VAS score.

Keywords Collagen supplementation · Osteoarthritis symptoms · WOMAC index · Visual Analogue Scale · Meta-analysis

Introduction

Osteoarthritis (OA) is a progressive disease caused by the destruction of joint cartilage and remodeling of the adjacent bone. These disturbances are consequence of stresses that may be the beginning of joint damage. In particular, the destruction of cartilage is usually located in two or more joints such as knees, hips, lower back, neck, or small joints of the fingers [1], being the knee the most frequently affected in approximately up to 83% of total OA patients [2]. Moreover, OA is the most common type of arthritis affecting over 25 million in the USA [3], with increasing prevalence among adults aged 65 years and older [4].

The current non-surgical treatment for knee OA is focused on relieving symptoms, minimizing functional impairment, and preserving quality of life. For patients with knee OA, the initial pharmacological treatment is mainly based in the use of oral non-steroidal anti-inflammatory drugs (NSAIDs) and intra-articular corticosteroids [5, 6]. Alternatively, several clinical trials have revealed the potential beneficial effects of different nutraceuticals and dietary supplements, such as glucosamine [7], chondroitin sulfate [8], hyaluronic acid [9], vitamin D [10], and collagen [11, 12] for the treatment of OA.

✉ Mario Simental-Mendía
mario.simentalme@uanl.edu.mx

[1] Department of Human Anatomy, Faculty of Medicine, Universidad Autónoma de Nuevo León, Monterrey, Nuevo León, México

[2] Orthopedics and Traumatology Service, University Hospital "Dr. José Eleuterio González", Universidad Autónoma de Nuevo León, Av. Francisco I. Madero and Av. Dr. José Eleuterio González, 64460 Monterrey, Nuevo León, México

[3] Biomedical Research Unit, Mexican Social Security Institute, Durango, Durango, México

The effect of these nutrients as a benefit for OA has been described in the literature as a different alternative to conventional pharmacological treatments such as NSAIDs [13].

In particular collagen is a nutritional supplement usually contained in foods such as fish and meat. However, its absorption is low because it is not hydrolyzed, which is why collagen needs to be hydrolyzed in order to become a physiologically available supplement [14, 15]. Hydrolyzed collagen may induce cartilage regeneration by increasing the synthesis of macromolecules in the extracellular matrix [16]. On the other hand, undenatured type II collagen is derived from chicken sternum cartilage, and has been described to influence the humoral and cellular immune response, thus protecting against the onset of joint damage through the induction and migration of T regulatory cells (Tregs) and producing anti-inflammatory cytokines [17, 18]. Furthermore, Tregs may also stimulate chondrocytes to synthetize cartilage matrix components via anti-inflammatory cytokines [19, 20].

The use of collagen is growing due to the satisfactory results in the treatment of OA. Even compared to other supplements such as glucosamine, which is one of the most used, collagen has shown a greater benefit [12]. However, as part of the nutraceutical family and the lack of a standardized treatment of this relatively novel approach to treat OA, suspicion about its real therapeutic effectiveness is imminent. Hence, the objective of the present study was to evaluate the effect of collagen-based supplements on OA symptoms through a meta-analysis of randomized controlled trials (RCTs).

Methods

Search strategy

PubMed-Medline, Scopus, and Google Scholar databases were searched for randomized placebo-controlled trials using the following search terms in titles and abstracts (also in combination with MESH terms): (collagen OR collagen supplementation OR collagen supplement) AND (osteoarthritis OR knee osteoarthritis OR knee pain) AND (randomized OR placebo). The wild-card term "*" was used to increase the sensitivity of the search strategy. Three authors independently carried out the search of studies through the different databases. The search was limited to articles published in English language and studies in humans. The literature was searched from inception to May 24, 2018.

Study selection

The selection was restricted to randomized placebo-controlled trials evaluating the effect of orally administered collagen on OA symptoms using the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) scale and/or the Visual Analog Scale (VAS) and providing sufficient information on WOMAC index subscores and/or VAS at baseline and at the end of follow-up in each group or presenting the net change values. Trials with injected collagen, treatment duration of less than 2 months, lack of placebo control group for collagen treatment, non-interventional studies (reviews, case-control, cross-sectional, or cohort design), or not presenting complete data on baseline or follow-up of WOMAC index subscores and/or VAS were excluded.

Main outcome variables

Eligible studies were reviewed, and the following data were abstracted: (1) first author's name; (2) year of publication; (3) study design; (4) target population; (5) number of participants in the collagen and placebo groups; (6) type and dose of collagen administration; (7) treatment duration; (8) age, gender, and body mass index of study participants; and (9) values of WOMAC and VAS score at baseline and follow-up. Data were extracted by two independent authors, and discrepancies were resolved through discussion and authentication by a third author.

Risk of bias assessment

A systematic assessment of bias in the included studies was performed using the Cochrane criteria [21]. The items used for the assessment of each study were as follows: sequence generation, allocation concealment, blinding of participants, personnel, and outcome assessment, incomplete outcome data, selective outcome reporting, and other potential sources of bias. According to the recommendations of the Cochrane Handbook, a judgment of "yes" indicated low risk of bias, while "no" indicated high risk of bias. Labeling an item as "unclear" indicated an unclear or unknown risk of bias.

Analysis

Meta-analysis was conducted using the Review Manager statistical software (RevMan [Computer program], version 5.3. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014). For WOMAC scores all values were collated in the 5-point Likert-type; if WOMAC scores were expressed in millimeters, the values were transformed into 5-point Likert-type using a rule of three. For the VAS score, all values were collated in millimeters. When numeric values were only available in figures (results presented as graphs or charts), the data were extracted with the GetData (Graph Digitizer) software version 2.26. When only the standard error of the mean (SEM) was reported, standard deviation (SD) was estimated using the following formula: $SD = SEM \times \mathrm{sqrt}(n)$, where n is the number of subjects. Meta-analysis was conducted using a random-effects model (using the DerSimonian-

Laird method) and the generic inverse variance method. Effect sizes were expressed as weighted mean difference (WMD) and 95% CI. Heterogeneity was tested using the I^2 statistic index.

Results

Search output

After the initial database search, we identified 114 published trials. Then, the abstracts were reviewed, and 66 articles were excluded because they did not meet the inclusion criteria. Of these, 48 full-text articles were carefully reviewed for eligibility and 43 were excluded for no collagen oral treatment (n = 39), target population without OA (n = 3), and incomplete data (n = 1), leaving five eligible studies which were selected and included in the present meta-analysis. The detailed study selection process is found in Fig. 1.

Flow and characteristics of included studies

Data were pooled from five RCTs [11, 12, 22–24] comprising a total of 519 subjects, including 277 and 242 participants in the collagen treatment and placebo arms, respectively. Included studies were published between 2009 and 2016. The clinical trials used different types and/or doses of collagen. The range of intervention periods was from ten to 48 weeks. All selected trials were parallel study design. All included studies enrolled subjects affected with OA. Characteristics of the selected clinical trials are presented in Table 1.

Risk of bias assessment

According to Cochrane criteria, only one study [11] had insufficient information about random sequence generation and other trial [22] for allocation concealment. Moreover, two studies were characterized by lack of information regarding blinding of participants, personnel, and outcome assessors [11, 22]. However, all selected trials showed low risk of bias with respect to incomplete outcome data and selective outcome reporting. Complete information regarding to risk of bias assessment is shown in Table 2.

Effect of collagen supplementation on OA symptoms

Collagen treatment showed a significant reduction in the score of total WOMAC index (WMD − 8.00; 95% CI − 13.04, − 2.95; p = 0.002; Fig. 2). After subgroup analysis of the WOMAC subscores, the collagen supplementation revealed a significant decrease in the stiffness subscore (WMD − 0.41; 95% CI − 0.74, − 0.08; p = 0.01), whereas the pain (WMD − 0.22; 95% CI − 1.58, 1.13; p = 0.75) and functional limitation (WMD − 0.62; 95% CI − 5.77, 4.52; p = 0.81) subscores did not have significant differences (Fig. 3). Finally, a significant reduction was found in the VAS score after collagen administration (WMD − 16.57; 95% CI − 26.24, − 6.89; p < 0.001; Fig. 4).

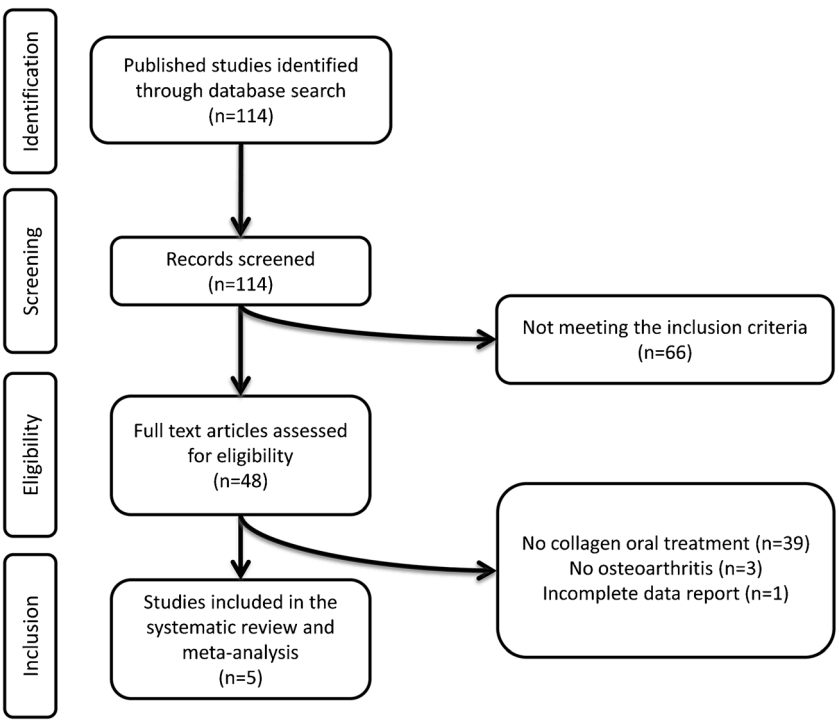

Fig. 1 Flow chart of the number of studies identified and included into the meta-analysis

Table 1 Demographic characteristics of the included studies

Author	Study design	Target population	Collagen source	Treatment duration	*n*	Study groups	Age (years)	Female (*n*, %)	BMI (kg/m^2)	WOMAC total (Likert)	VAS (mm)
Benito-Ruiz et al. (2009)	Randomized, double-blind, placebo-controlled (multicenter)	Primary knee osteoarthritis (K-L, 1–3)	Chicken	24 weeks	111, 96	Collagen hydrolysate 10-g/day, Placebo	58.7 ± 10.4 59.1 ± 11.6	103 (92.8), 89 (92.7)	27.1 ± 4.1, 28.3 ± 4.6	35.9 ± 17.3, 33.5 ± 16.6	43.1 ± 7.4, 42.1 ± 7.5
Kumar et al. (2014)	Randomized, double-blind, placebo-controlled	Knee osteoarthritis (K-L, 2–4)	Porcine/ bovine	13 weeks	19, 11, 19, 11	Collagen peptides (porcine) 10-g/day, Placebo, Collagen peptides (bovine) 10-g/day, Placebo	ND, ND, ND, ND	17 (89.5), 10 (90.9), 11 (57.9), 7 (63.6)	26.1 ± 3.8, 23.1 ± 1.9, 25.9 ± 3.3, 25.8 ± 3.3	47.2 ± 9.8, 47.3 ± 8.6, 50.3 ± 9.6, 50.1 ± 14.7	63.2 ± 10.6, 60.0 ± 6.3, 66.0 ± 12.3, 62.0 ± 14.0
Lugo et al. (2016)	Randomized, double-blind, placebo-controlled (multicenter)	Knee osteoarthritis (K-L, 2–3)	Chicken	24 weeks	63, 58	Undenatured type II collagen 40-mg/ day, Placebo	53.5 ± 7.9, 53.1 ± 7.8	30 (47.6), 30 (51.7)	25.2 ± 0.4, 24.7 ± 3.0	55.9 ± 8.1, 55.3 ± 10.2	58.4 ± 7.3, 58.2 ± 7.1
McAllindon et al. (2011)	Randomized, double-blind, placebo-controlled (pilot study)	Mild knee osteoarthritis (> 3-mm tibiofemoral joint space)	Porcine/ bovine	48 weeks	15, 15	Collagen hydrolysate 10-g/day, Placebo	58.9 ± 8.0, 60.3 ± 8.5	9 (60.0), 9 (60.0)	30.1 ± 4.6, 31.2 ± 7.0	20.3 ± 10.5, 29.2 ± 13.8	ND, ND
Schauss et al. (2012)	Randomized, double-blind, placebo-controlled	Osteoarthritis in hip and/or knee (VAS pain ≥ 4 for 3 months)	Chicken	10 weeks	35, 33	Collagen hydrolysate 2-g/day, Placebo	54.3 ± 8.7, 54.5 ± 9.8	23 (66.0), 18 (55.0)	ND, ND	54.6 ± 11.5, 54.9 ± 10.1	ND, ND

Values are expressed as mean ± SD

ND no data, BMI body mass index, K-L Kellgren-Lawrence classification, VAS Visual Analogue Scale, WOMAC Western Ontario and McMaster Universities Osteoarthritis Index

Table 2 Quality of bias assessment of the included studies according to the Cochrane guidelines

Study	Sequence generation	Allocation concealment	Blinding of participants, personnel, and outcome assessors	Incomplete outcome data	Selective outcome reporting	Other sources of bias
Benito-Ruiz et al. (2009)	U	L	U	L	L	U
Kumar et al. (2014)	L	U	U	L	L	U
Lugo et al. (2016)	L	L	L	L	L	L
McAlindon et al. (2011)	L	L	L	L	L	L
Schauss et al. (2012)	L	L	L	L	L	L

L low risk of bias, H high risk of bias, U unclear risk of bias

Discussion

Results of the present meta-analysis suggest that the administration of oral collagen decreases the symptoms of OA. This finding was supported by the reduction in both the total WOMAC index and VAS score.

The possible beneficial effects of collagen for the treatment of OA are currently controversial; while a previous systematic review of RCTs and quasi-RCTs did not find sufficient evidence to recommend the generalized use of collagen hydrolysate in clinical practice [25], other studies have reported significant between-group differences in WOMAC index and VAS scale in favour of collagen treatment as compared with the control group [11, 22], which is consistent with our results. Nonetheless, although it has been observed that collagen supplementation suppresses the development of joint damage in experimentally induced arthritis [26], the putative underlying mechanism for the positive impact of collagen on OA symptoms is not fully known. In this context, results from experimental studies have revealed that collagen is capable to reduce articular pain as well as plasma and urine levels of CTX-II (cross-linked C-telopeptide of type II collagen), a biomarker of cartilage degradation [27]. Moreover, other studies have shown that oral administration of hydrolyzed collagen significantly increases the appearance of collagen-derived peptides such as Pro-Hyp in human blood [28] which promote the synthesis of hyaluronic acid from synovial cells [29]. Furthermore, the stimulation of cultured chondrocytes by hydrolyzed collagen results in the production of type II collagen and proteoglycans [30]. However, future studies are required in order to elucidate the mechanism involved in the improvement of knee OA symptoms following oral collagen supplementation.

The WOMAC questionnaire was originally developed to measure symptoms and physical disability of patients with OA [31]. The measure was developed to evaluate clinically relevant changes in health status of patients as a result of intervention treatment [32]. Moreover, the VAS is one of the major methods to assess treatment efficacy in OA [33]. Thus, the clinical utility of both WOMAC and VAS scales makes them the most widely used tools for the evaluation of the effectiveness of new treatments or approaches in clinical orthopaedics.

Because the VAS and WOMAC score have been recommended to evaluate global pain in patients with OA [34], we analyze these parameters in our meta-analysis which revealed that the consumption of oral collagen significantly decreased the VAS score and total WOMAC index but not the WOMAC pain subscale. This inconsistency may be explained because the WOMAC subscore assesses the pain in five different activities; meanwhile, the VAS reflects the intensity of pain through a unidimensional measure.

Interestingly, when considering the three subscales for the total WOMAC value, the collagen showed a positive

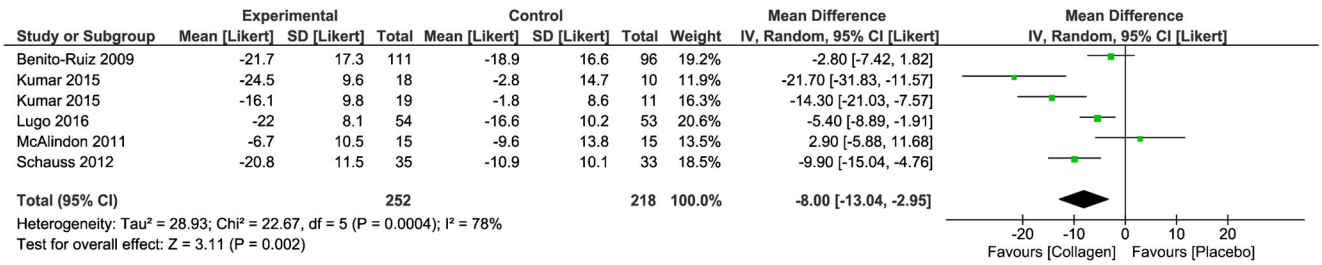

Fig. 2 Forest plot displaying weighted mean difference and 95% confidence intervals for the impact of collagen supplementation on the total WOMAC index

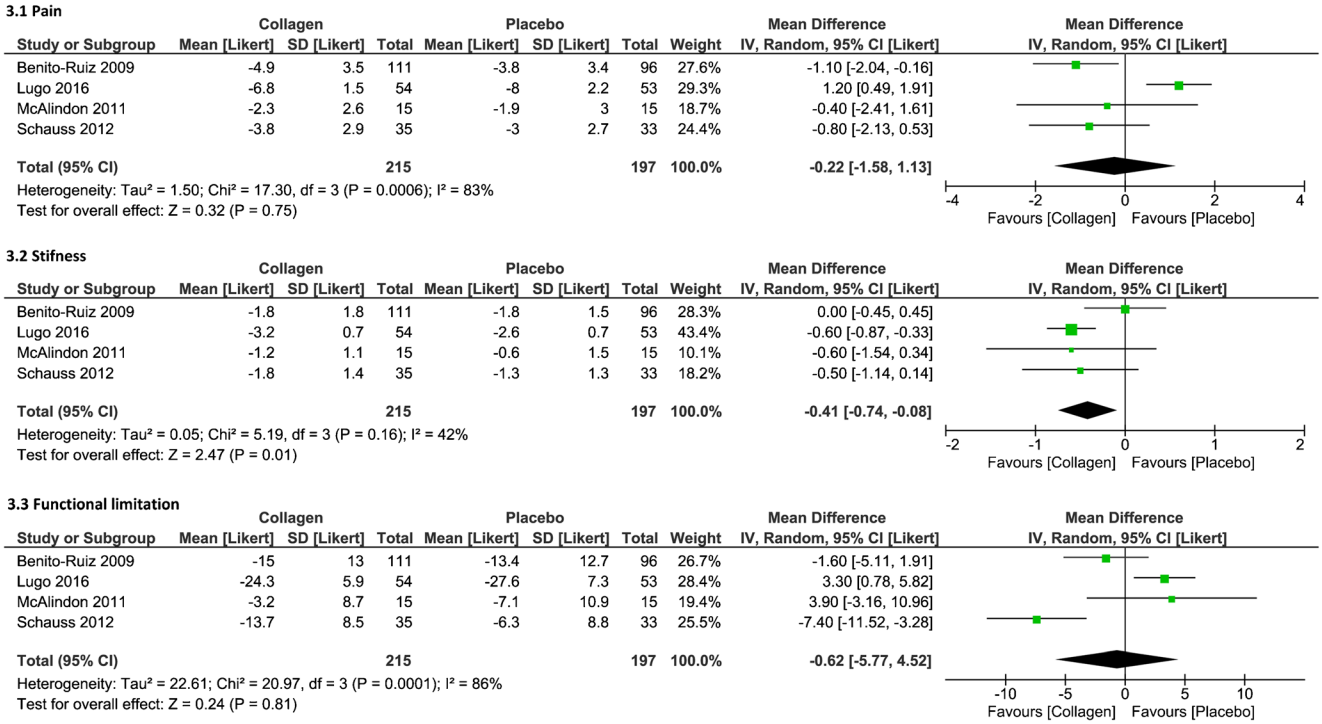

Fig. 3 Forest plot displaying weighted mean difference and 95% confidence intervals for the impact of collagen supplementation on the WOMAC Pain, Stiffness, and Functional limitation subscores

impact for the treatment of OA symptoms. Although the WOMAC pain and function subscales did not have a positive impact, the overall WOMAC score did, suggesting a global enhancement of OA symptoms following oral administration of collagen. Two factors that could be related to the inefficacy of collagen on the WOMAC subscales are the small sample and the short intervention period of some selected studies. Also, it is noteworthy that the validity and reliability of these subscales in orthopaedic patients, including OA, should be consider carefully because the evidence comes from only a few studies [35]; therefore, further clinical trials are warranted in this field. Perhaps the above-mentioned may explain why some clinical trials [22] only report the total WOMAC score and not the subscales.

There are different formulations of collagen supplementation but the hydrolyzed collagen has shown stronger therapeutic benefits for the management of OA [22], probably due to its greater absorption [24]. However, it is important to mention that although the collagen presentation and doses used by the included studies were different, both collagen hydrolysate and undenatured collagen exhibited a positive effect in the relief of OA symptoms.

The present study exhibits some limitations that should be considered. First, because few RCTs were selected for this meta-analysis and these included a limited number of participants, the total study population was small. Second, the included studies used different formulations of collagen which could have affected our results. Finally, two RCTs were conducted during a treatment period equal or less than 13 weeks, which may be insufficient to achieve the therapeutic effect of collagen supplementation on OA symptoms.

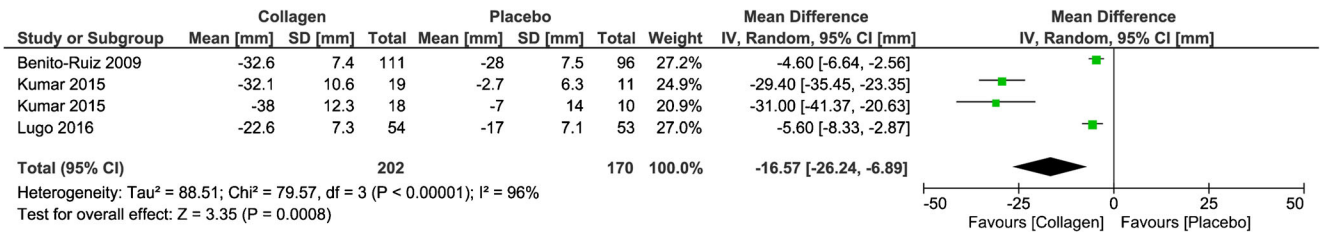

Fig. 4 Forest plot displaying weighted mean difference and 95% confidence intervals for the impact of collagen supplementation on the VAS score

The results of this meta-analysis showed that collagen is effective in improving OA symptoms by the decrease of both total WOMAC index and VAS scale. Nevertheless, further longer clinical trials in larger populations are required in order to corroborate the potential beneficial effects of collagen supplementation in patients with symptomatic OA.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

References

1. Lane NE, Brandt K, Hawker G et al (2011) OARSI-FDA initiative: defining the disease state of osteoarthritis. Osteoarthr Cartil 19: 478–482. https://doi.org/10.1016/j.joca.2010.09.013
2. Vos T, Flaxman AD, Naghavi M et al (2012) Years lived with disability (YLDs) for 1160 sequelae of 289 diseases and injuries 1990–2010: a systematic analysis for the global burden of disease study 2010. Lancet 380:2163–2196. https://doi.org/10.1016/S0140-6736(12)61729-2
3. Sacks JJ, Luo YH, Helmick CG (2010) Prevalence of specific types of arthritis and other rheumatic conditions in the ambulatory health care system in the United States, 2001-2005. Arthritis Care Res 62: 460–464. https://doi.org/10.1002/acr.20041
4. Lawrence RC, Felson DT, Helmick CG et al (2008) NIH public estimates of the prevalence of arthritis and other rheumatic conditions in the United States, Part II Reva. Arthritis Rheum 58:26–35. https://doi.org/10.1002/art.23176.Estimates
5. Nelson AE, Allen KD, Golightly YM et al (2014) A systematic review of recommendations and guidelines for the management of osteoarthritis: the chronic osteoarthritis management initiative of the U.S. bone and joint initiative. Semin Arthritis Rheum 43:701–712. https://doi.org/10.1016/j.semarthrit.2013.11.012
6. Hochberg MC, Altman RD, April KT et al (2012) American College of Rheumatology 2012 recommendations for the use of nonpharmacologic and pharmacologic therapies in osteoarthritis of the hand, hip, and knee. Arthritis Care Res (Hoboken) 64:465–474. https://doi.org/10.1002/acr.21596
7. Kwoh CK, Roemer FW, Hannon MJ et al (2014) Effect of oral glucosamine on joint structure in individuals with chronic knee pain: a randomized, placebo-controlled clinical trial. Arthritis Rheumatol 66:930–939. https://doi.org/10.1002/art.38314
8. Zegels B, Crozes P, Uebelhart D et al (2013) Equivalence of a single dose (1200 mg) compared to a three-time a day dose (400 mg) of chondroitin 4&6 sulfate in patients with knee osteoarthritis. Results of a randomized double blind placebo controlled study. Osteoarthr Cartil 21:22–27. https://doi.org/10.1016/j.joca.2012.09.017
9. Tashiro T, Seino S, Sato T et al (2012) Oral Administration of Polymer Hyaluronic Acid Alleviates Symptoms of knee osteoarthritis: a double-blind, placebo-controlled study over a 12-month period. Sci World J 2012:1–8. https://doi.org/10.1100/2012/167928
10. Hussain S, Singh A, Akhtar M, Najmi AK (2017) Vitamin D supplementation for the management of knee osteoarthritis: a systematic review of randomized controlled trials. Rheumatol Int 37: 1489–1498. https://doi.org/10.1007/s00296-017-3719-0
11. Benito-Ruiz P, Camacho-Zambrano MM, Carrillo-Arcentales JN et al (2009) A randomized controlled trial on the efficacy and safety of a food ingredient, collagen hydrolysate, for improving joint comfort. Int J Food Sci Nutr 60:99–113. https://doi.org/10.1080/09637480802498820
12. Lugo JP, Saiyed ZM, Lane NE (2016) Efficacy and tolerability of an undenatured type II collagen supplement in modulating knee osteoarthritis symptoms: a multicenter randomized, double-blind, placebo-controlled study. Nutr J 15:14. https://doi.org/10.1186/s12937-016-0130-8
13. Akhtar N, Haqqi TM (2012) Current nutraceuticals in the management of osteoarthritis: a review. Ther Adv Musculoskelet Dis 4: 181–207. https://doi.org/10.1177/1759720X11436238
14. Oesser S, Adam M, Babel W, Seifert J (1999) Oral administration of (14)C labeled gelatin hydrolysate leads to an accumulation of radioactivity in cartilage of mice (C57/BL). J Nutr 129:1891–1895
15. Sibilla S, Godfrey M, Brewer S et al (2015) An overview of the beneficial effects of hydrolysed collagen as a nutraceutical on skin properties: scientific background and clinical studies. Open Nutraceuticals J 8:29–42. https://doi.org/10.2174/1876396001508010029
16. Adam M (1991) WelcheWirkung Haben Gelantineparaprate? Therapie Der Osteoarthrose Therapiewoche 41:2456–2461
17. Castrogiovanni P, Trovato FM, Loreto C et al (2016) Nutraceutical supplements in the management and prevention of osteoarthritis. Int J Mol Sci 17:2042. https://doi.org/10.3390/ijms17122042
18. Broere F, Wieten L, Klein Koerkamp EI et al (2008) Oral or nasal antigen induces regulatory T cells that suppress arthritis and proliferation of arthritogenic T cells in joint draining lymph nodes. J Immunol 181:899–906
19. Müller RD, John T, Kohl B et al (2008) IL-10 overexpression differentially affects cartilage matrix gene expression in response to TNF-α in human articular chondrocytes in vitro. Cytokine 44:377–385. https://doi.org/10.1016/j.cyto.2008.10.012
20. van Meegeren MER, Roosendaal G, Jansen NWD et al (2012) IL-4 alone and in combination with IL-10 protects against blood-induced cartilage damage. Osteoarthr Cartil 20:764–772. https://doi.org/10.1016/j.joca.2012.04.002
21. Higgins J, Green S (2009) Cochrane handbook for systematic reviews of interventions Version 5.0.2. London
22. Kumar S, Sugihara F, Suzuki K et al (2014) A double-blind, placebo-controlled, randomised, clinical study on the effectiveness of collagen peptide on osteoarthritis. J Sci Food Agric 95:702–707. https://doi.org/10.1002/jsfa.6752
23. McAlindon TE, Nuite M, Krishnan N et al (2011) Change in knee osteoarthritis cartilage detected by delayed gadolinium enhanced magnetic resonance imaging following treatment with collagen hydrolysate: a pilot randomized controlled trial. Osteoarthr Cartil 19: 399–405. https://doi.org/10.1016/j.joca.2011.01.001
24. Schauss AG, Stenehjem J, Park J et al (2012) Effect of the novel low molecular weight hydrolyzed chicken sternal cartilage extract, biocell collagen, on improving osteoarthritis-related symptoms: a randomized, double-blind, placebo-controlled trial. J Agric Food Chem 60: 4096–4101. https://doi.org/10.1021/jf205295u
25. Van Vijven JPJ, Luijsterburg PAJ, Verhagen AP et al (2012) Symptomatic and chondroprotective treatment with collagen derivatives in osteoarthritis: a systematic review. Osteoarthr Cartil 20: 809–821. https://doi.org/10.1016/j.joca.2012.04.008
26. Nagler-Anderson C, Bober LA, Robinson ME et al (1986) Suppression of type II collagen-induced arthritis by intragastric administration of soluble type II collagen. Proc Natl Acad Sci U S A 83:7443–7446. https://doi.org/10.1073/pnas.83.19.7443
27. Di Cesare Mannelli L, Micheli L, Zanardelli M, Ghelardini C (2013) Low dose native type II collagen prevents pain in a rat osteoarthritis model. BMC Musculoskelet Disord 14:228. https://doi.org/10.1186/1471-2474-14-228

28. Iwai K, Hasegawa T, Taguchi Y et al (2005) Identification of food-derived collagen peptides in human blood after oral ingestion of gelatin hydrolysates. J Agric Food Chem 53:6531–6536. https://doi.org/10.1021/jf050206p
29. Ohara H, IidaA H, Ito K et al (2010) Effects of pro-Hyp, a collagen hydrolysate-derived peptide, on hyaluronic acid synthesis using in vitro cultured synovium cells and Oral ingestion of collagen hydrolysates in a Guinea pig model of osteoarthritis. Biosci Biotechnol Biochem 74:2096–2099. https://doi.org/10.1271/bbb.100193
30. Oesser S, Seifert J (2003) Stimulation of type II collagen biosynthesis and secretion in bovine chondrocytes cultured with degraded collagen. Cell Tissue Res 311:393–399. https://doi.org/10.1007/s00441-003-0702-8
31. Bellamy N, Buchanan W, Goldsmith C et al (1998) Validation study of WOMAC: a health status instrument for measuring clinically important patient relevant outcomes to antirheumatic drug therapy in patients with osteoarthritis of the hip or knee. J Rheumatol 15: 1833–1840
32. Bellamy N (1995) Outcome measurement in osteoarthritis clinical trials. J Rheumatol Suppl 43:49–51
33. Bolognese JA, Schnitzer TJ, Ehrich EW (2003) Response relationship of VAS and Likert scales in osteoarthritis efficacy measurement. Osteoarthr Cartil 11:499–507. https://doi.org/10.1016/S1063-4584(03)00082-7
34. Saleh KJ, Davis A (2016) Measures for pain and function assessments for patients with osteoarthritis. J Am Acad Orthop Surg 24: e148–e162. https://doi.org/10.5435/JAAOS-D-16-00303
35. McConnell S, Kolopack P, Davis AM (2001) The Western Ontario and McMaster universities osteoarthritis index (WOMAC): a review of its utility and measurement properties. Arthritis Rheum 45: 453–461