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Effect of hydrolysed collagen supplementation on knee osteoarthritis: a systematic review

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ABSTRACT

Background: Knee osteoarthritis (KOA) is a burden for the modern society. One of the most important inflammatory conditions of the muscle-skeletal system, KOA is characterized by joint pain, crepitus, local inflammation, tenderness, limitation of movement and effusion with no systemic effects. Bjordal et al. (2004) in a meta-analysis, analyzed more than 13,000 patients regarding chronic inflammatory diseases and the use of non-steroidal anti-inflammatory drugs, including coxibs. In this study, the authors demonstrated that in long-term inflammatory diseases, anti-inflammatory drugs had a slightly superior effect compared to placebo. Oral supplementation with hydrolysed collagen has been proposed as an alternative to treat symptoms. The purpose of this review was to investigate the effects or oral supplementation with hydrolysed collagen in KOA. **Methods:** Randomized placebo-controlled were searched in different databases, from 2001 to 2021, using the following keywords in titles and abstracts ("knee osteoarthritis" OR "knee arthrosis") AND ("hydrolysed collagen supplementation"). **Results:** From 565 articles, only 4 fulfilled the eligibility criteria with variations on the number of subjects, collagen dose and origin, age, and gender of patients, blinding with variation also in the bias criteria. **Conclusion:** The studies are very heterogeneous but reached the same conclusion that oral collagen supplementation may be slightly effective to mitigate KOA symptoms. However, the number of studies is a limitation and no evidence of any possible mechanism is provided. Further studies are needed to investigate the hypothesis.

Keywords: Hydrolysed collagen, Knee osteoarthritis, Cartilage matrix

BACKGROUND

With the increase of the lifespan, and the aging of the populations, many chronic diseases, being osteoarthritis one of the most common, have been impacting the quality of life of thousands of people [(1-3)]. Knee osteoarthritis, specifically, is a serious health problem and affects approximately 27 million people only in North America [(4)]. The prevalence of this disease worldwide is 3,8%, however; the prevalence in some countries is significantly high such as, 12,1% in United States, 10,5% in Canada, and 6,3% Japan [(5-6-7)].

The current pharmacological treatments for osteoarthritis, are mainly oral non-steroidal anti-inflammatory drugs (NSAIDs), intra-articular corticosteroids and hyaluronic acid [(8-9-10)], which only target the symptoms. However; due to the characteristics of osteoarthritis, these medications must be used in a chronic way representing a great risk of serious adverse effects in the stomach and heart, beside the damage on liver and kidney. None of the actual treatments recommended for knee osteoarthritis acts in the cause of the disease [(11)]. Bjordal et al. [(12)] in a meta-analysis published in the British Medical Journal, analyzed more than 13,000 patients regarding chronic inflammatory diseases and the use of non-steroidal anti-inflammatory drugs, including newer drugs such as coxibs. In this study, the authors demonstrated that in long-term inflammatory diseases, anti-inflammatory drugs had a slightly superior effect compared to placebo.

In this context, the use of hydrolysed collagen supplementation, a nutraceutical, form of knee osteoarthritis treatment, may represent an option, but its effects on the healthcare need to be validated by evidence provided by reliable research methods such as more well done randomised double-blind placebo-controlled clinical trials [(14)].

Collagen supplementation has been long used in folk medicine, and its empirical uses dates to thousands of years. First, as bone broth, later as gelatin, and since the Middle Age is being used for its positive effect on the joint health [(15)]. Collagen is a fibrous protein, found in all animals, formed by peptides with a molecular structure that enables it with a unique resistance and elasticity [(16-17)]. Being the most common protein in the whole organism and the most prevalent one in the joints, collagen represents about 60% of the dry weight of cartilage [(17-18)].

The collagen fibers are arranged in the extracellular space near the surface of the cartilage and are cross-linked by covalent bonds forming a three-dimensional network, which provides tensile strength and resistance to shear [(17-18)]. A healthy cartilage is maintained due to a finely tuned turnover process of the matrix balancing synthesis and breakdown [(19-20)]. The deregulation of this balance leads to a shift towards degradation with a subsequent loss of cartilage in addition to inflammation of the surrounding tissue [(19-20)].

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Collagen is can be found in all animal products and by-products, but none of the collagen present in the food is absorbed in the gastrointestinal without being hydrolysed into peptides, mainly in di and tripeptides, at the most as pentapeptides, and then reach the circulation [21-22]. This means that all collagen used in our daily needs is synthesize in the body, and studies show that the collagen production decreases in chronological age [23], affecting the hole body, including the balance between the synthesis and breakdown process of the cartilage matrix.

The synthesis of collagen in our body is made in the fibroblasts [24], and studies show that one food-derived dipeptide of collagen, proline-hydroxyproline stimulates cell proliferation of fibroblasts and the synthesis of collagen and hyaluronic acid synthesis [25-26], meaning that the ingestion of these peptides can reduce the decrease of collagen production in the body.

Hydrolysed collagen used as supplementation has different origins such as, porcine collagen peptide (PCP), bovine collagen peptide (BCP), chicken sternum and marine origin such as jellyfish, and dried squid [27] Is important to know that there are two different forms of collagen supplementation, the hydrolysed collagen peptide and the undenaturated collagen type II (UCII), although both are supplements of collagen, they have different mechanisms of action [26-28].

The objective of this review is to find out if hydrolysed collagen supplementation has reliable evidence on relieving the symptoms of knee osteoarthritis, without the side effects present in other pharmacological approaches.

METHODS

Search strategy

An online systematic search was performed for eligible randomized placebo-controlled trials using the electronic databases Medline (PubMed), Cochrane Database, Google Scholar, Portal de Periódicos CAPES, SciELO and Direct Science from 2001 to September 2021, following the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) guidelines [31].

The PICO (population, intervention, comparation/control, and outcome) [32] acronym was used to develop search strategy and the inclusion/exclusion criteria. Based on that, the controlled vocabulary was applied in combination with the Boolean operators for the search in title and abstracts such as (“knee osteoarthritis” OR “knee arthrosis” AND “hydrolysed collagen supplementation”).

Study selection

The selection was restricted to randomized placebo-controlled trials evaluating the effect of hydrolysed collagen supplementation on knee osteoarthritis symptoms, associated or not with hip, using the Western Ontario McMaster Universities (WOMAC) Osteoarthritis Index. Trials with undenatured collagen, parenteral collagen administration, treatment duration less than 2 months, lack of placebo control group for collagen treatment, non-interventional studies (reviews, case control, cross-sectional, or cohort design), or incomplete data presentation on baseline or follow-up of WOMAC index sub scores were excluded.

Studies Identification

Two investigators (A.G. and C.C.) independently screened the articles by title, abstract, and full text. Inclusion of a study was decided by consensus between both investigators.

Data Extraction, Primary and Secondary Outcomes

The data was extracted as: author(s), year of publication, study period, country of origin, study design, sample size, inclusion and exclusion criteria, intervention type, description of intervention, follow-up period, primary and secondary outcomes, and dropout rate.

Methodological Quality and Risk of Bias

Methodological quality was assessed independently using the Cochrane Collaboration tool for assessing risk of bias in RCTs [33]. Disagreements were resolved through consensus.

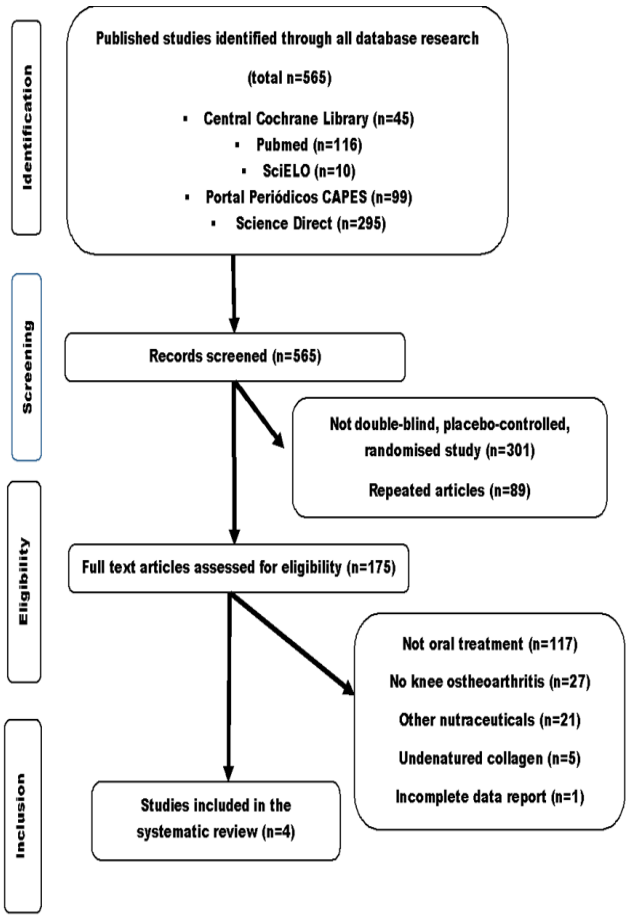
Questionnaires of articles

The articles included in this review used the Western Ontario McMaster Universities Osteoarthritis Index (WOMAC), which is a questionnaire validated in several countries. It is reliable responsive measure, and a self-report tool to measure specific three dimensions of the disease: pain, disability and joint stiffness and also quality of life [34]

Search output and flow

Initially, 565 articles were identified, and after applying the inclusion criteria only 4 remained as shown below in Figure 1. From these 565, 301 were not double-blind placebo-controlled studies, 89 were repeated articles, 117 did not use supplementation (oral administration), 27 included multiple joints, 21 used other nutraceuticals, 5 were of undenaturated collagen type II and 1 had incomplete data.

Figure 1. Overview of screening and selection process for the systematic review



Characteristics of included studies

Three of the included papers were related to food and agriculture studies and one related to food and nutrition. None came from publications related to medical, paramedical, biochemical, or pharmacological research. Two studies were funded by collagen manufacturers [35-36], the third study, at least one of the authors was an employee of this kind of industry [37] and in the fourth study one author is a medical consultant in such industry [37]. The studies took place in India, China, United States and Equator, being published in 2009; 2012; and two in 2014. All the selected papers were double-blind placebo-controlled randomized clinical studies.

The ratio between the treated group, and the placebo group was 2:1 in one study and on the others 1:0.95; 1:1; 1:0.98. Not only the group ratios were different in each study, but also the sample sizes varied from 60 to 250 subjects, adding a total of 490 individuals, and the research duration varied from 70 days to 6 months. Although the source of the hydrolysed collagen varies, in one study was a mix of bovine and pig [37], one from chicken [36], one from bovine [38] and one from non ruminant [35], it does not interfere with the research, due to the fact that hydrolysed collagen can come form many animal sources, as cattle, pig, chicken and even form marine animals as jellyfish and dried squid[27].

After the being extracted mainly by enzymatic hydrolysis[39], is reduced to di and tri peptides, it so can be absorved in the gut. Regardless of its origin, all 28 types of collagen are made of only six peptides, glycine, proline, lysine, hydroxylamine, hydroxyproline and alanine[40], and once hydrolysed are reduced to the same di and tripeptides The doses varied from 4g (2g twice daily) to 10 g in only one dose.

The total of 490 subjects were involved in the 4 studies, with 38 side effects identified after the hydrolysed collagen supplementation. One of the studies did not mention the adverse events.
The described adverse events were:

- allergic edema (01 case)
- vomiting (01 case)
- diarrhoea (01 case)
- gastrointestinal events (17 cases)
- common cold (01 case)
- respiratory events (5 cases)
- mild skin rashes (1 case)
- increase of pain (2 cases)
- migraine headache (9 cases)

There was no gender distinction in three of the articles, and in one study the purpose was to verify the effects of hydrolysed collagen supplementation in women with knee osteoarthritis. One of the articles included subjects with low grade of osteoarthritis, in the other three the inclusion criteria was patients with osteoarthritis with a pain score of 4 or more, that means moderate pain, which interferes significantly with activities of daily living (ADLs). In two articles the age group selected was from 40 to 70 years, in another article, from 30 to 65 years and one article did not mention the age of the subjects.

Risk of bias assessment

Out of the four articles, two had unclear and two low bias evaluation; however, all of them were sponsored by the companies that not only provided the collagen as they were the manufacturers of this product, as classified as high risk in other bias for the two investigators.

Table 1. Studies included in the Systematic Review

Author	P.Benito Ruiz,et al.	Schauss AG, et al.	Jiang J, et al.	Kumar S, et al
Year of publication	2009	2012	2014	2014
Paper	Int.j.Food Sci.Nut.	j.Agric.Food Chem	Agro Food Industry Hi Tech	J.Sci.Food Agric.
Study period	6 months	70 days	6 months	14 weeks
Country of origin	Equator	United States	China	India
Conflict of interest	The study was funded	One of the authors was na	One of the authors was a	Two of the autors were
	by Protein S.A. (Girona)	employe of BioCell Technology	Medical consultant of Rousselot AP	employers of Nielatin
Study design	Randomized double blind	Randomized double blind	Prospective single centre randomized	Double blind placebo controled
	controled multicentre trial	placebo controled stuy	double blind placebo controled trial	randomized clinical study
Ratio	01:0.98	01:01	01:0.95	02:01
Sample size	250	80	100	60
Gender	Male and female	Both sexes	Women	Both sexes
Group age	No age description	Age betwen 40-70	Woman age betwen 40 and 70	Age betwen 30 and 65
		with knee and/or hip ostheoarthritis	with knee osteoarthritis	with knee osteoarthritis
Inclusion criteria	Primary osteoarthritis of the knee	Knee ostheoartthritis with VAS> 4	Knee ostheoartthritis with VAS> 4	Knee ostheoartthritis with VAS> 4
Exclusion criteria	Secondary ostheoarthritis	Serious or cronic medical condition	Stage IV of severe osteoarthritis/ anormal kidney and liver function	Visual analogic pain scale < or = 4
Collagen origin	Non ruminant	Chicken	Bovine	Bovine (BCP) and Pig (PCP)
Intervention	Once daily administration	Oral dose of two 1 g capsules	Daily oral dose of 8g	Oral dose of 5g
description	of 10 g dose	twice daily		twice daily
Questionnaire used	WOMAC	WOMAC	WOMAC	WOMAC
Follow up period	Examined at baseline and after 3 and 6 months	Three visits day 0, day 35 and day 70	Examined at basline; 3 and 6 months	Seven visits with na interval of 15 days
Primary outcomes	There was a reducion in	Strongly suggested that collagen	The values of the WOMAC scores	Significant reduction in the
	overall WOMAC scores	is effective in Osteoarthritis	decreased significantly	scores leves of WOMAC
Secondary outcomes	Also were reported placebo effect	Significant placebo effect	More investigations should be iniciated to confirm the efficacy	Similar results using bovine and pig collagen
Adverse events	Migrane headache - 9 cases	Mild skin rashes - 1 case	Unclear	CP allergic edema/BCP - 1 case
	Gastrointestinal -17 cases	Increase in VAS-WOMAC -2 cases		Vomiting - 1 case
	Respiratory - 5 cases			Common cold - 1 case
				Diarrhes - 1 cas
Dropout rate	Placebo group - 18	Placebo group - 7	Placebo group -2	Unclear

Table 2. Main Outcomes of the Studies included in the Systematic Review

Main Outcomes Variables	P. Benito Ruiz, et al.	Kumar S, et al.	Schauss AG, et al.	Jiang J., et al.
Randon generation	unclear	Low	low	unclear
Allocation concealment	low	Nuclear	low	unclear
Blinding participants	unclear	Low	low	unclear
Blinding Care Providers	unclear	Nuclear	unclear	unclear
Blinding assessors	unclear	Nuclear	low	unclear
Incomplete outcome data	low	High	low	low
Group similarity at baseline	low	Low	low	low
Selective reporting	low	High	low	low
Co-interventions	low	High	low	low
Compliance	low	Nuclear	low	low
Intention to treat	low	Nuclear	low	unclear
Timing	low	Low	low	low
Others	high	High	high	high
Total	low	Nuclear	low	unclear

WOMAC results

In Benito Ruiz et al.(2009) study [35] the WOMAC index score overall reduction of 27.1 ± 18.1 (60%) of the hydrolysed collagen was not statistically different of the placebo group of 18.9 ± 16.1 (56%), a diference of 4%, however the WOMAC pain subscore improvement in the hydrolysed collagen was 64% while in the placebo group was of 53%, a diference of 19% (P=0,044) which is significantly greater in favor of hydrolysed collagen. In the same study, WOMAC function subscore the results were a improvement of 59.30% in hydrolysed collagen group and 57.21% in the placebo group,a diference of 2.09% not statisticaly diferent.

Also in Benito Ruiz study, the WOMAC stiffness subscore the results were 60.90 hydrolysed collagen and 58.31% in the placebo group.In the study of Schauss A G et al.(2012) [37] the WOMAC scores of pain, stiffness, and physical difficulties were compared between groups. In Schauss A G study the hydrolysed collagen group a WOMAC pain score in day 0 of 9.88 ± 2.93 to 6.13 ± 2.66 on day 70 while the placebo group had WOMAC pain score in day 0 of 10.53 ± 2.71 to 7.48 ± 3.40 with a difference between groups close to statistical significance (P=0.052). The WOMAC stiffness subscore in Schauss A G was in day 0 to hydrolysed collagen group was of 4.30 ± 1.36 and in day 70 was 2.48 ± 1.15, the placebo group had the WOMAC stiffness subscore in day 0 of 4.28 ± 1.34 and on day 70 of 3.00 ± 1.68 not having a statistically difference between groups.

WOMAC function subscore to hydrolysed collagen group in Schauss A G study was in day 0 40.35 ± 8.51 decreasing in day 70 to 26.65 ± 8.62 , the placebo group WOMAC function subscore in day 0 was 39.20 ± 8.75 and in day 70 was 32.90 ± 10.03 a significant difference (P<0.001)

WOMAC index score overall reduction of hydrolysed collagen group showed a greater reduction on day 70 compared with the placebo group in Schauss A G study (P<0.001). In the third study Jiang J et al. [38] the difference between of the WOMAC scores of the hydrolysed collagen group and the placebo group was significant for all three WOMAC subscales.

Results of WOMAC pain score in Jiang J study of hydrolysed collagen group in baseline were 3.41 ± 1.68, after 6 months 2.33 ± 1.55, placebo group in baseline 3.94 ± 1.42, after 6 months 3.67 ± 1.48 a difference with statistical significance (P<0.001).

Jiang J study WOMAC stiffness subscore in collagen group in baseline 1.27 ± 1.36, after 6 months 0.71 ± 0.87, placebo group in baseline 1.40 ± 1.38, after

6 months 1.29 ± 1.27 also a difference with statistical significance (P= 0.012).

WOMAC function subscore to hydrolysed collagen group in Jiang J study was in baseline 10.6± 3.5, after 6 months 8.24 ± 3.14 , the placebo group WOMAC function subscore in baseline was 10.5 ± 3.3 after 6 months was 9.96 ± 3.3 a significant difference (P=0.010). The Jiang J. study WOMAC index score overall reduction of hydrolysed collagen group in relation to the placebo group is significant (P<0.001). The results of Kumar S et al. (2014) [36], comparing the baseline of hydrolysed collagen BCP and PCP with placebo group were:

WOMAC total score points in baseline to BCP group 50.3 ± 9.6 , to placebo group WOMAC total score points in baseline 50.1 ± 14,7, in the last visit (visit 7) WOMAC total score points to BCP group of 25.8 ± 11.3, WOMAC total score and in the last visit (visit 7) to placebo group of 47.3 ± 19.4 showing a prominent downward trend in the hydrolysed BCP collagen group.

Still in Kumar study, the PCP hydrolysed collagen group WOMAC total score points in baseline 47.2 ± 9.8, to placebo group in baseline WOMAC total score points of 47.3 ± 8.6, after the 7th visit the PCP hydrolysed collagen group WOMAC total score points 31.1 ± 9.8, , WOMAC total score and in the last visit (visit 7) to placebo group was 45.5 ± 9.4 a prominent downward trend in PCP hydrolysed collagen group similar of the BCP hydrolysed collagen group. There were no data in Kumar study discriminating the WOMAC subscores.

The WOMAC pain subscore had a statistically significant reduction in three studies and in the fourth the reduction was in the WOMAC total score, the function score with some reduction and stiffness score with minor reduction.

Table 3. WOMAC Evaluation of the Studies included in the Systematic Review

WOMAC	Benito Ruiz et al	Schauss AG et al.	Jiang J et al.	Kumar S et al. BCP	Kumar S et al. PCP
Total score baseline	**35.9 ± 17.3**	**54.87 ± 10.11**	**no data**	**50.3 ± 9.6**	**47.2 ± 9.8**
Total score final	**14.2 ± 12.6**	**44.03 ± 13.81**	**no data**	**25.8 ± 11.3**	**31.1 ± 9.8**
Pain score baseline	**7.6 ± 3.5**	**9.88 ± 2.93**	**3.41 ± 1.68**	**no data**	**no data**
Pain score final	**2.8 ± 2.8**	**6.13 ± 2.66**	**2.33 ± 1.55**	**no data**	**no data**
Stiffness score baseline	**3.0 ± 1.8**	**4.30 ± 1.36**	**1.27 ± 1.36**	**no data**	**no data**
Stiffness score final	**1.2 ± 1.3**	**2.48 ± 1.15**	**0.71 ± 0.81**	**no data**	**no data**
Function score baseline	**25.2 ± 13.0**	**40.35 ± 8.51**	**10.6 ± 3.5**	**no data**	**no data**
Function score final	**10.3 ± 9.7**	**26.65 ± 8.62**	**8.24 ± 3.14**	**no data**	**no data**

DISCUSSION

The findings of the present review show the results of double-blind randomized placebo-controlled trials, which evaluated the effect of hydrolysed collagen supplementation on knee osteoarthritis symptoms searched in different databases, from 2001 to 2021. These studies concluded, supported by the reduction of the overall WOMAC scores, the hypothesis that hydrolysed collagen supplementation decreases the algic symptoms, with very few actions on the stiffness of knee osteoarthritis and a questionable benefit in function.

In total, were scanned 565 articles, which only 4 articles fulfilled the inclusion criteria stablished on this review. The findings came from the analysis of a total of 490 subjects, aging from 30 to 70 years using different sources of hydrolysed collagen.

The reduced number of studies fulfilling the stablished criteria was also present in the other few reviews, all posterior 2006, about the use of collagen supplementation:

- Bello AE, Oesser[41] – 2006 – total of 7 studies, 5 before 2001
- Van Viven JPJ, et al. [42] – 2012 – total of 8 studies, 4 before 2001
- Garcia-coronado, et al. [43] -2018 – total of 5 studies[41]
- Liu X, et al. [44] -2019 – included all dietary supplements with 69 included trials with only 1 of hydrolysed collagen
- Honvo G, et al. [45]– 2019 – include not only hydrolysed collagen - total of 13[43]

- Honvo G, et al. [46]– 2020 – total of 15 clinical trials, not all randomized.

Is relevant to notice that in the WOMAC scores became patent that pain scores had the most significant reduction and the pain relieve was an important improvement in the symptoms, followed by the improvement of the function, with minor reduction in the stiffness, but this finding are limited by the few reliable trials in the subject.

CONCLUSION

The results of this review showed that hydrolysed collagen supplementation decreases the pain symptoms of knee osteoarthritis and might be a pharmacological therapy acting in osteoarthritis with minor side effects, although the reduced number of reliable trials. Based on this conclusion, furher reliable clinical trials are required to support the evidence of the beneficial effects of hydrolysed collagen supplementation on knee osteoarthritis.

Authors' contribution: Alexandre Guerreiro da Fonseca – Literature Search and critical Reading of the paper. Carly de Faria Coelho – team leader of the stuides selection and review. Patrícia Sardinha Leonardo and Rodolfo de Paula Vieira – Critical reviewers of the selected studies. Rodrigo Alvaro B. Lopes-Martins – General Coordinator and Chief of the Research Group

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REFERENCES

1. Unter DJ, Schfield D, Callander E. The individual socioeconomic impacto f ears lived wuth disability (YLDs) for sequeostheoarthritis.. Lancet Nat. Ver Rheumatol 2014; 437-441 –Pubmed
2. Global burden of Disease Study 2013 Colaborators: Globla, and national incidence, prevalence, and years lived with disability for 301 acute and chronic diseases and injuries in 188 conuntries, 1990-2013: A systematic analisis of the Global Burden of Disease Study.Lancet 2013; 386;743-800 – Pubmed
3. Vos T, Flaxman AD, Naghavi M, et al. Years lived with diasbility (YLDs) for 1160 of 289 diseaes and injuries 1990-2010. A systematic analysis for the Global Burden of Disease study. Lancet 2012;380:2163-2196 – Pubmed
4. Lawrence RC, Felson DT, Helmick CG, Arnold LM, Choi H, Deyo RA, et al. Estimates of the prevalence of arthritis and other rheumatic conditions in the United States. Part II. Arthritis Rheum 2008;58:26e35
5. Muraki S, Tanaka uraki S, Tanaka S Yoshimura N. Epidemiology of knee osteoarthritis OA Sports Medicine 2013; 1:2
6. Cross M, Smith E, Hoy D, Nolte S, Ackerman I, Fransen M, et al. The global burden of hip and knee osteoarthritis: estimates from the global burden of disease 2010 study. Ann Rheum Dis 2014; 73:1323-30
7. Cunningham LS, Kelsey JL. Epidemiology of musculoskeletal impairments and associated disability. Am J Public Health 1984; 74:574-9
8. 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.
9. 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.
10. Payne, M. W., & Petrella, R. J. (2000). Viscosupplementation effect on proprioception in the osteoarthritic knee. Archives of Physical Medicine and Rehabilitation, 81(5), 598–603.
11. Yusuf E. Pharmacologic and nonpharmacologic treatment of osteoarhtirits, Curr Treat Options Rheumatol. 2016;2:11-25.
12. Bjordal JM, Ljunggren AE, Klovning A, Slørdal L. Non-steroidal anti-inflammatory drugs, including cyclo-oxygenase-2 inhibitors, in osteoarthritic knee pain: meta-analysis of randomised placebo controlled trials. BMJ. 2004 Dec 4;329(7478):1317.
13. 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.
14. García-Coronado JM; Martínez-Olvera L; Elizondo-Omaña JRE; Acosta-Olivo; Vilchez-Cavazos F; Simental-Mendía LE; M. Simental-Mendía Effect of collagen supplementation on osteoarthritis symptoms: a meta-analysis of randomized placebo-controlled trials. International Orthopaedics (SICOT) 43: 531–538 (2019)
15. Walker, Amélie A. "Oldest Glue Discovered". Archaeology. © 1998 by the Archaeological Institute

of America. www.archaeology.org/online/news/glue.html
16. Histologia básica I L.C.Junqueira e José Carneiro. - [12 . ed]. - Rio de Janeiro: Guanabara Koogan, 2013.
17. Silva TF;Penna ALB.Colágeno: Características químicas e propriedades funcionais. Rev. Inst. Adolfo Lutz (Impr.), São Paulo, v. 71, n. 3, 2012
18. Eyre DR, Weis MA, Wu JJ. 2006. Articular cartilage collagen: An irreplaceable framework? Eur Cell Mater 12:57-63
19. Creamer P, Hochberg MC. 1997. Osteoarthritis. Lancet 350(9076):503-508
20. Eyre DR. 2004. Collagens and cartilage matrix homeostasis. Clin Orthop Relat Res (Suppl) 427:S118-S122
21. Cao, C., Xiao, Z., Ge, C., & Wu, Y. (2021). Animal by-products collagen and derived peptide, as important components of innovative sustainable food systems—a comprehensive review. Critical Reviews in Food Science and Nutrition, 1–25.
22. Mienaltowski, M. J., & Birk, D. E. (2013). Structure, Physiology, and Biochemistry of Collagens. Progress in Heritable Soft Connective Tissue Diseases, 5–29. doi:10.1007/978-94-007-7893-1_2
23. Varani J, Dame M K, Rittie L, S E G Fligiel , Kang S, Fisher G J, Voorhees J J. Decreased Collagen Production in Chronologically Aged Skin. Am J Pathol. 2006 Jun; 168(6): 1861–1868.
24. Gay S, Martin G R, Muller P K, Timpl R, Kuhn K. Simultaneous synthesis of types I and III collagen by fibroblasts in culture (ascorbic acid/connective tissue/heritable diseases). Proc. Natl. Acad. Sci. USA Vol. 73, No. 11, pp. 4037-4040, November 1976 Cell Biology
25. Shigemura Y.; Iwai K.;Morimatsu F.;Iwamoto T.;Mori T.; OdaC.; Taira T.; Prk E.Y.;Nakamura Y.;Sato K. Effect of Prolyl-hydroxiproline (Pro-Hyp), a food-derived collagen peptide in human blood on growth of fibroblasts from mouse skin 2009 J.Agric. Food Chem. 57,444-449.
26. Ohara H.;Ichikawa S.; Matsumoto H.; Akiyama M.; Fujimoto N.; Kobayashi T.; Tajima S. Collagen-derived dipeptide, proline-hydroxyproline stimulates cell proliferation and hyaluronic acid synthesis in cultured human dermal fibroblasts. J.Dermatol. (2010) 37, 330-338.
27. Changwei Cao, Zhichao Xiao, Changrong Ge & Yinglong Wu (2021): Animal by-products collagen and derived peptide, as important components of innovative sustainable food systems—a comprehensive review, Critical Reviews in Food Science and Nutrition,
28. Weiner HL, da Cunha AP, Quitanda F, Wu H. Oral tolerance. Immunol. Rer 2011; 241(1);241-59 Review.
29. Tong T, Zhao W, Wu YQ, et al. Chicken type II collagen induced imune balance of main subtype of helper T cells in mesenteric lymph node lymphocytes in rats with collagen-induced arthritis. Inflamm Res. 2010; 59(5); 369-772010; 59(5); 369-77.
30. Kyung-Su Park; Min-Jung Park; Mi-La Cho; Seung-Ki Kwok; Ji Hyeon Ju; Hyeok-Jae Ko; Sung-Hwan Park; Ho-Youn Kim (2009). Type II collagen oral tolerance; mechanism and role in collagen-induced arthritis and rheumatoid arthritis. , 19(6), 581–589.
31. Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71.
32. Santos CMV, Pimenta CAM, Nobre MRC. A estratégia PICO para a construção da pergunta de pesquisa e busca de evidências. Rev Latino-Am Enfermagem 2007;15(3):508-11.
33. Higgins P T j et al.The Cochrane Collaboration's tool for assessing risk of bias in randomized trials. Research Methodos & Reporting.BMJ 2011;343:d5928. Doi: 10.1136/bmj.d5928.
34. Bellamy N, Buchaman WW, Goldsmith CH, Campbell J, Stitt LW: 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: 1833-40, 1998.
35. P.Benito-Ruiz; M.M.Camacho-Zambrano; J.N.CarrilhoArcentales, M.AMestnanza-Peralta;C.A. Valejo-Flores, S.V. Varga-lopes, R.A Villacis-Tamayo &Zurita Gavilanes(2009) A randomized contolled trial on the efficacy and safety of a food ingridient, collagen hydrolysate, for improving joint confort, Journal of Food Sciences and Nutrition, 60:sup,99-113, DOI 10.1080/09637480802498820.
36. Kumar S, Sugihara F, Suzuki K, Inoue N, Sriraam VT. (2014)A Double Blind Placebo Controlled Randomized Clinical Study on the Effectiveness of Collagen Peptide on Ostheoarthritis. J Sci Food Agric 95:702–707. Doi10.1002/jsfa.6752 23.
37. Schauss, A.G.; Stenehjem, J.; Park j.; Endres J.R.; Clewell A.(2012) Effect of the novel low molecular weight hydrolyzed chicken sternal cartilage extract, Biocell Collagen, on improving ostheoarthritis—elated symptons: a randomized, double blind, placebo-controlled trial. J.Agric. Food Chem. 2012, 60, 4096-4101

38. Jiang J-X; Yu S; Huang QI-R; Zhang X-L; Zhang CQ, Praitt J. Collagen Peptides improve knee osteoathritis in elderly women. AgroFood Industry HiTech 25(2), 19-23
39. Changwei Cao, Zhichao Xiao, Changrong Ge & Yinglong Wu (2021): Animal by-products collagen and derived peptide, as important components of innovative sustainable food systems—a comprehensive review, Critical Reviews in Food Science and Nutrition,
40. Ferreira da Silva T, Barretto Penna. Colágeno: Características químicas e propriedades funcionais. Rev. Inst. Adolfo Lutz (Impr.), São Paulo, v. 71, n. 3, 2012
41. Bello AE, Oesser S. 2006. Collagen hydrolysate for the treatment of osteoarthritis and other joint disorders: A review of the literature. Curr Med Res Opin 22(11):22212232.
42. Van Vijven JPJ, Luijsterburg PAJ, Verhagen AP, van Osch GJVM, Kloppenburg M, Bierma-Zeinstra SMA. Symptomatic and chondroprotective treatment with collagen derivatives in osteoarthritis: a systematic review. Osteoarthr Cartil. 2012;20:809–21.
43. García-Coronado, J. M., Martínez-Olvera, L., Elizondo-Omaña, R. E., Acosta-Olivo, C. A., Vilchez-Cavazos, F., Simental-Mendía, L. E., & Simental-Mendía, M. (2018). Effect of collagen supplementation on osteoarthritis symptoms: a meta-analysis of randomized placebo-controlled trials. International Orthopaedics.
44. Liu X, Machado GC, Eyles JP, Ravi V, Hunter DJ. Dietary supplements for treating osteoarthritis: a systematic review and meta-analysis. Br J Sports Med. 2018;52:167–75.
45. Honvo G,Reginster JY, Rabenda V, et al. Safety of symptomatic slow-acting drugs for osteoarthritis: outcomes of a systematic review and meta-analysis. Drugs Aging. 2019;36:65–99. 31. Garcı´a-Coronado JM, Martı´nez-Olvera L, Elizondo, Oman˜a RE, et al. Effect of collagen supplementation on osteoarthritis symptoms: a meta-analysis of randomized placebo-controlled trials. Int Orthop. 2019;43:531–8. 32. Kloppenburg M, Kroon FPB, Blanco FJ, et al. 201.
46. Honvo, G., Lengelé, L., Charles, A., Reginster, J.-Y., & Bruyère, O. (2020). Role of Collagen Derivatives in Osteoarthritis and Cartilage Repair: A Systematic Scoping Review With Evidence Mapping. Rheumatology and Therapy, 7(4), 703–740.