

## Collagen Supplements and Osteoarthritis Pain: How Persuasive is the Evidence?

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### Abstract

**Background:** Osteoarthritis pain- and pain-relieving strategies have been topics of great interest to clinicians, patients, and researchers for many years with no definitive consensus. In addition, the role of various supplements that may have a beneficial influence on osteoarthritis pain has generally been overlooked, despite their demonstrated potential.

**Aim:** This mini review aimed to examine support for the alternate hypothesis that collagen supplements can help to ameliorate osteoarthritis pain significantly and effectively.

**Methods:** A narrative review and analysis of all the available English language related literature housed in key data bases was undertaken in an effort to support this hypothesis.

**Results:** Although data stemming from randomized placebo controlled trials are limited, and highly diverse, cumulative findings appear to support a more favorable role than not for collagen supplements in efforts to safely reduce mild to moderate osteoarthritis pain of the hip or knee.

**Conclusion:** While likely to be more helpful than not, more carefully conceived longitudinal studies of various osteoarthritis samples using clinically relevant biomechanical, neurological, and biochemical outcome instruments and standardized doses of oral collagen administration to validate current pain associated findings are warranted and likely to prove extremely valuable.

**Keywords:** *Articular Cartilage; Collagen; Function; Osteoarthritis; Pain; Supplementation*

### Introduction

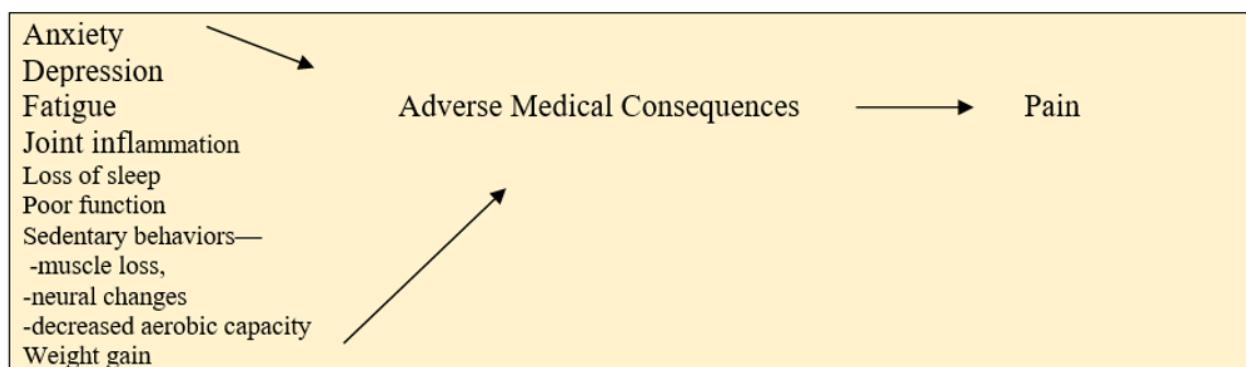
Chronic osteoarthritis, and its accompanying pain features remains a widespread reasonably intractable problem for many, if not most, older adults. A disease with no known cure and one that is commonly progressive and can spread from affecting a single joint, such as the knee, to affect others, such as the hip, commonly fails to be improved by one or more available currently advocated pharmacologic approaches. Surgery, which may be employed at some point, is also not without complications, and does not always facilitate function in the long-term.

Some evidence does suggest though that osteoarthritis may be attenuated more readily than not to some degree by the extent to which the adult with this condition enacts behaviors such as exercise, weight control, as well as recommended sleep behaviors [1]. As well, a variety of nutritional as well as supplementary approaches have been recommended, with the expectation of achieving various degrees of pain relief and enhanced joint status [2].

In this regard, Deer, *et al.* [3] have expressed the view that pain control is especially important in the context of the ongoing 2020 corona virus [COVID-19] pandemic as many adults with moderate to severe pain are found to attend emergency rooms, already overwhelmed by the virus. This group does state however, how essential it is to treat the chronic pain symptoms, and to duly allay excess suffering, especially if elective procedures are postponed, or the patient is now too fearful to undergo this form of surgery [4]. Strategies that can ameliorate pain, while improving overall health and that do not overwhelm limited hospital resources are especially indicated. This group [4] also highlights strategies that have been adopted in some countries to limit hospital visits due to non-COVID 19 situations, as well as limiting pain treatments among older persons who are excessively overweight with uncontrollable comorbid conditions, who may indeed have moderate to severe osteoarthritis, along with being at heightened COVID 19 risk, secondary infections, and complications due to anti-inflammatory drug usage, corticosteroid usage and opioids [5]. Other data reveal that persons with severe forms of arthritis may be asked to leave the hospital environment and self-isolate for at least 12 weeks as they are especially at high risk for the virus [6] and those especially at risk are cases with severe-end stage hip or knee osteoarthritis who may be suffering COVID-19 associated levels of increased anxiety [4], as well as lock down mediated outcomes of heightened pain, and reductions in physical function [7].

In absence of any effective osteoarthritis pain remedy, and possible lack of ready access to community health centers, community based treatment options such as swimming pools, public health centers and some parks [2,8] as well as surgical delays or postponements [8], to help both patients as well as providers to focus on pain mitigating interventions that can be done safely in the home at low cost, a number of valid approaches have been put forth, such as the consistent use of exercise, education, and diet modifications [2,8]. For purposes of reducing pain, whether this is severe, or moderate, a host of dietary supplements have increasingly been proposed [10-12].

Alternately, a failure to mitigate the degree of suffering attributable to osteoarthritis of one or more joints may not only increase the risk for hospitalization and severe COVID-19 [9], but may induce the following adverse effects shown in figure 1, thus heightening the disease pathology and its manifestations and sufferer’s overall health care needs:



**Figure 1:** Schematic of health issues anticipated to exacerbate osteoarthritis if pain is not minimized effectively [3,13].

**Rationale**

Current options to promote joint comfort in the case of osteoarthritis remain limited largely to a variety of medicines that can reduce pain, but can also have adverse health effects [1]. According to Lee, *et al.* [14] a major source of osteoarthritis pain stems from collagen disruption and/or diverse cartilage defects, and hence this pain source is an important one to target. A tissue component that can potentially be maintained through careful joint usage, as well as one’s diet, particularly through meat products, as well as possibly by ingesting

its hydrolysed form extracted from a variety of animal, vegetable or fish related sources in the form known as collagen hydrolysate (CH) is said to be helpful in this respect [15]. Kumar, *et al.* [16] further affirm that recent studies do show that enzymatically hydrolysed collagen, plus collagen peptides if ingested orally, and which can be readily absorbed, can also be distributed to joint tissues where it is observed to exhibit both analgesic and anti-inflammatory properties.

As reported by Crowley [17] animal trials [18] have shown that undenatured (native) collagen type II or UC-II is similarly effective in treating osteoarthritis 'like' pain, with no observable side-effects [19]. Moreover, following UC-II withdrawal for a period of 30 days, a relapse of overall pain, exercise-associated lameness and pain upon limb manipulation was observed. In the horse, Gupta, *et al.* [20] found that compared to a glucosamine and chondroitin treated group who showed significant reductions in pain after intervention, compared with pretreated values, the efficacy was less potent when compared with that observed with undenatured collagen (UC-II). This finding was observed and reproduced in a clinical study by Crowley, *et al.* [17] suggesting type of collagen supplementation will have a bearing on outcome that is observed over time.

Mechanistic studies such as that by Dar, *et al.* [21] have further revealed that the administration of oral collagen hydrolysate in a model of posttraumatic osteoarthritis appears to safely induce chondroprotective effects that are dose-dependent. These included increases in cartilage area, chondrocyte number and proteoglycan matrix at 3 and 12 weeks post-injury. Preservation of cartilage and increased chondrocyte numbers correlated with reductions in destructive enzyme levels and cell death rates, respectively. Supplemented mice also displayed reduced synovial hyperplasia, suggesting an anti-inflammatory effect. These findings were taken to reveal the possible effect of collagen ingestion at the tissue and cellular level that may underpin its clinical efficacy in terms of relieving pain.

Liu, *et al.* [11] however, concluded that there is no long-term benefit of collagen supplementation documented in any clinical study related to osteoarthritis pain relief and potential functional improvements. However, this group did not review all relevant studies, nor other forms of oral collagen.

In short, although it can be shown that ingesting oral collagen or injecting collagen directly into an osteoarthritic joint can be of help to knee osteoarthritis sufferers [14] and that animal models of osteoarthritis appear to support a favorable role for collagen supplementation post injury or disease onset, the idea that supplements such as collagen will be effective in the clinical realm among self-help remedies, is not widespread, and accepted by all [11]. Its mechanism of action has also been questioned. It is also not listed or even apparently discussed as a recommended strategy in current osteoarthritis treatment guidelines [22].

Thus in a disease where it is important to prevent cartilage breakdown and collagen destruction, or restore or boost collagen production, collagen supplements, made up of peptides, which may help to rebuild cartilage or reinforce it in instances where the production of collagen is impaired appears highly relevant to explore further. Moreover, in cases where undenatured collagen type II, that is collagen that is not broken down extrinsically and mechanically, is ingested, the finding that small amounts ingested over time may invoke a clinically important immune response that safely limits inflammatory destruction processes that are hard to control safely by other means at present [23], surely warrants attention.

### Aims of the Study

In light of the aforementioned arguments, and a strong desire to explore all pathways that may lead to some form of osteoarthritis pain relief and possible joint reconstruction processes, this mini review aimed to examine the processes and outcomes of all available human randomized placebo controlled osteoarthritis intervention trials regarding the specific nutraceutical, known as collagen.

In particular, the review aimed to examine the degree of support for the idea that oral collagen ingestion can help to significantly reduce osteoarthritis pain, by examining the results of published randomized placebo controlled trials conducted on adults with an osteoarthritis diagnosis and its specific impact on pain [24], rather than bone and skin health.

Collagen was chosen for study because it is a therapeutic approach that the individual can self-administer without personnel or assistance, and appears justified at this time, when management of the disease is largely that of self-management. Moreover, the possible utility of oral collagen for ameliorating osteoarthritis pain is based on a robust set of pre-clinical findings that may be masked to some degree in current comparative clinical studies that do not provide clear controls [25]. At the same time, Ragle, *et al.* [12] note that the use of collagen hydrolysates consisting of small peptides with a molecular weight lower than 5.000 Da. produced from gelatinization and subsequent enzymatic hydrolysis of native collagen which is found in rich collagenic animal tissues [24], while showing significant improvement in pain and functional indices for several subgroups of adults with osteoarthritis, may not be universal.

**Methods**

Available data located in PUBMED, were initially searched as this data base houses a majority of the most salient peer reviewed journals in the medical field. Other sites explored were Scopus, Web of Science, Science Direct, and Google Scholar. In all cases, clinical trials that did not focus on definitive osteoarthritis for example, Kanzaki, *et al.* [26] and Kwoh, *et al.* [27], those that were implemented in laboratory settings or in animal models, those that were pilot studies, study proposals, and studies that examined injection delivered collagen, plus those using multiple compounds including collagen [28], as well as comparing multiple compounds, as well as collagen with no placebo control grouping [17,28] were deemed ineligible for addressing the topic of specific current topic of interest. Since very few publications exist, regardless of data base reviewed, no differentiation was currently made in terms of the nature of the collagen product employed in the available studies that were selected for review, and all oral collagen forms tested independently of other oral supplements were deemed acceptable.

**Results**

**General findings**

Terms Applied	Number of Citations*
Collagen supplementation and cartilage	255
Collage supplementation and chondrocyte	148
Collagen supplements and osteoarthritis	120
Clinical studies	14
Randomized studies	11
Collagen supplementation and osteoarthritis	56
Clinical studies	8
Randomized studies	5
Collagen hydroxylate and osteoarthritis	36
Randomized studies	9
UC-II collagen and osteoarthritis	12

**Table 1:** PUBMED search results: 1993-2020.

*UC: Undenatured; \*many citations = abstracts, proposals, examination multiple compounds, healthy cases.*

Specific study findings

Authors	Sample	Strategy	Results	Conclusion
Benito-Ruiz., <i>et al.</i> [15]	250 knee osteoarthritis cases	Subjects were given 10g collagen hydrolysate daily for 6 months	There were significant improvements in knee joint comfort Subjects with the greatest joint damage, and lowest meat protein intake benefited most	Collagen hydrolysate is safe and effective in relieving osteoarthritis pain and warrants further consideration as a food ingredient
Hewlings., <i>et al.</i> [2]	88 osteoarthritis cases randomized to an active or control situation	The impact of a 450 mg daily dosage of a water-soluble chicken eggshell membrane hydrolysate dietary supplement was examined in the terms of function, mobility, general health and well-being	After 12 weeks, normalized analysis showed the poorest initial performers benefited the most by day 5 in walking endurance, with the rest of the population showing significant improvement over placebo by week 12 Stiffness was also significantly improved by day 5	Walking distance and ability, reduced stiffness benefits were attained safely and maintained over a 12 week period A similar collagen based dietary supplement may offer a safe option for relief from symptoms and increased mobility for adults with osteoarthritis
Kumar., <i>et al.</i> [16]	The effectiveness of orally supplemented collagen peptide to control the progression of knee osteoarthritis	Improvements were assessed via the WOMAC, VAS and quality of life (QOL) change scores from baseline-13 weeks (Visit 7) Safety and tolerability were also evaluated	There was significant reduction from baseline to Visit 7 in the primary end points scores and in QOL Subjects in the placebo group remained unaltered	The study demonstrated that collagen peptides may have significant potential for advancing the management of osteoarthritis
Lugo., <i>et al.</i> [30]	191 knee osteoarthritis cases randomized to 3 groups	The 3 groups received daily doses of undenatured collagen UC-II (40 mg), glucosamine and chondroitin sulphate (1500 mg G & 1200 mg C), or placebo for 180-days Primary endpoints for all groups were the change in total WOMAC scores from baseline-day 180 Secondary endpoints included the Lequesne Functional Index, the VAS and WOMAC pain subscales	At day 180, the collagen group showed a significant reduction in overall, scores of pain, stiffness, and function compared to placebo and GC groups Safety was similar among the groups	UC-II improved joint knee pain symptoms in cases of knee osteoarthritis to a greater degree than placebo and glucosamine chondroitin treatments Additional studies to uncover the mechanism for this positive result are duly warranted
McAlindon., <i>et al.</i> [31]	Single center prospective pilot study of 30 cases with mild knee osteoarthritis	10 g porcine or bovine collagen hydrolysate sources along with permitted analgesics for 48 weeks	Cartilage MRI was assessed, as was WOMAC pain, and functional capacity, analgesic consumption, protocol adherence	Non conclusive - groups had differing baseline features, and used analgesics, and no VAS pain scores, and both groups tended to improve clinically

Moskowitz, <i>et al.</i> [32]	389 knee osteoarthritis cases in 3 countries were examined	Experimental groups received 10 g collagen hydrolysate daily for 24 weeks	Changes in WOMAC and VAS scores were recorded	Only certain groups improved, WOMAC pain, function, global assessment score changes were greater in collagen than placebo group
Shauss, <i>et al.</i> [1]	80 patients with progressive hip or knee osteoarthritis and at least 3 months of modest joint pain that was physician-verified were studied	Subjects were divided into two groups and administered either 2g of collagen compound or placebo for 70 days Other outcome measurements included the VAS for pain and the WOMAC scores taken on days 1, 35, and 70	The tolerability profile of the treatment group was comparable to that of the placebo Intent-to-treat analysis showed the treatment group, as compared to placebo, had a significant reduction in pain on day 70 WOMAC scores on days 35 and 70 were significant The experimental group showed higher physical activity scores than the placebo group on days 35 + 70	The collagen supplement, a low molecular weight dietary supplement of hydrolyzed chicken sternal cartilage extract] is well tolerated and effective in managing osteoarthritis symptoms, and in improving the patient's daily living abilities Supplementary collagen appears to have the potential for complementing current osteoarthritis therapies

**Table 2:** Randomized placebo controlled clinical study summaries of the effects of oral collagen on osteoarthritis pain and their results and implications.

**Other relevant findings**

Compared with placebo, collagen peptide supplementation in combination with resistance training further improved the participant's body composition by increasing their fat free muscle components, their muscle strength and their fat mass loss [33].

As well, even though more firm recommendations on their clinical utility remain, Tack, *et al.* [34] demonstrated a tentative and positive role for vitamins and amino acid supplements in the process of facilitating multilevel changes in musculotendinous healing.

Dressler, *et al.* [35] similarly support the view that specific forms of collagen peptide supplementation in athletes with chronic ankle instability will yield significant improvements in subjective perceived ankle stability, and a reduction in the re-injury rate of ankle sprains.

**Discussion**

Osteoarthritis, a chronic, highly prevalent and disabling disease and one expected to increase in prevalence secondary to longer life expectancy and a disproportionately large aging population remains an enormous challenge to treat effectively. Indeed, multiple forms of treatment to address pain accompanying this disease, as well as attempts to restore various degrees of associated articular cartilage damage, remain only marginally effective, despite decades of research. These approaches have commonly included, but are not limited to, weight control, exercise, nonsteroidal anti-inflammatory drugs, acetaminophen, intra-articular steroids or viscosupplementation, topical analgesics, and joint replacement surgery. The use of nutraceuticals in the treatment of osteoarthritis, while not mainstream, and reasonably controversial, is increasingly common, however [12].

In this regard, this current mini review elected to specifically examine the efficacy and known safety of collagen as a novel nutraceutical for the ameliorating osteoarthritis pain, due to its purported impact on collagen synthesis, a key cartilage component [36].

As outlined in 2000 by Moskowitz [32], a form of oral collagen known as collagen hydrolysate is of particular interest as a therapeutic agent in efforts to treat osteoarthritis more effectively due to its high safety level, even when used for long periods. Although disputed by Bongers, *et al.* [37] who found collagen peptide did not reduce pain in active middle aged to healthy subjects with knee pain complaints, Bakilan, *et al.* [28] found collagen added to acetaminophen to improve the efficacy of this painkiller in a similar sample.

Moreover, most of the available randomized placebo controlled trials of osteoarthritis cases are found to benefit in the short term as noted in table 1. Work by Oessler and Siefert [36] who investigated the effect of degraded collagen on the formation of type II collagen by mature bovine chondrocytes in a cell culture model that led to a dose-dependent increase in type II collagen secretion further support a possible role for collagen in favorably influencing cartilage collagen synthesis in the case of osteoarthritis as indicated by Qi, *et al.* [38]. Other preclinical studies have revealed that hydrolysate collagen not only stimulates collagenic tissue regeneration and collagen synthesis, but the production of minor cartilage components such as glycosaminoglycans and hyaluronic acid [24].

Indeed, as discussed by Bello, *et al.* [39], it appears more authors than not imply that ongoing and future research will in all likelihood prove fruitful in this sphere, especially if efforts to clarify how collagen hydrolysate or UC-II provides its clinical effects in the case where inflammation is not the main clinical concern is forthcoming. As well, which osteoarthritis populations or subgroups are most likely to be helped by one or more oral collagen derivatives, and the optimal dosages and durations that are needed to achieve structural as well as functional impacts, which requires both study and clarification, will predictably be highly beneficial.

Importantly, it appears, its usage is not only safe in the long term, but that prolonged collagen ingestion may produce a stimulating effect that may indeed be important in efforts to develop more efficacious slow acting compounds that can alter key structural tissue associated joint changes associated with osteoarthritis as suggested by work conducted by Dar, *et al.* [21] in osteoarthritic induced mice subjected to an oral collagen derivative.

De Cezare Manneelli, *et al.* [40] examining the efficacy of porcine native type II collagen administered daily for 13 days starting from the day of artificially inducing arthritis in a rat model further observed this approach to specifically reduce postural imbalance, as well as motor activity. Moreover, an associated decrease in the plasma and urine levels of CTX-II (Cross Linked C-Telopeptide of Type II Collagen), a biomarker of cartilage degradation, suggested a collagen-dependent decrease of the structural joint damage that would normally ensue.

Other work has shown that the oral administration of collagen hydrolysates in a guinea pig osteoarthritis model increased the proteoglycan content found in the bone region of the joint that absorbs load. It also reduced the morphological changes associated with osteoarthritic cartilage destruction of the knee joint [41].

As such, and as outlined by McAlindon, *et al.* [31], almost 10 years ago, as well as de Campos [42] who currently argue against the widespread tendency to discount possibly valuable adjunctive treatments for osteoarthritis, even when promising, and safe, such as collagen in various oral forms, we urge researchers and clinicians to keep the door open on this topic and examine the evidence base carefully, while adding to this insightfully before rejecting a possible valuable treatment approach. The vagaries in the current literature, possibly attributable to their low numbers, their heterogeneity, the limited samples studied, and other factors and the failure to capture structural changes, especially those pertaining to cartilage [46], as well as valid data concerning joint loading effects, inflammatory responses, and muscle function, as demonstrated in animal models [47,48] are among the gaps that need to be addressed. The role of adherence, and shortcomings as identified here and previously by Garcia-Coronado, *et al.* [43], and listed below are only some of the key issues needing future attention:

- Study duration
- Collagen production, dosage, and delivery methods

- Sampling strategies
- Age, body mass, and gender
- Disease presentation/severity/extent/duration
- Co-occurring chronic diseases
- Possible drug interactions
- Almost exclusive use of subjective outcome measures
- The continued use of painkillers/other meds in most studies
- Use/nature of any co-interventions
- Poor research design
- Unknown instructions to patients
- Level and mode of participant's daily activities.

In addition to addressing the abovementioned issues and others, researchers are strongly encouraged in our view to examine whether vitamin C levels impact oral collagen supplementation intervention outcomes, given that a persistent vitamin C deficiency might undermine the process of collagen regeneration and maintenance in its own right [44]. As well, collagen supplementation and its favorable impact on joint inflammation [23], and muscle strengthening exercise outcomes is highly relevant to explore further in our view [45]. As per Ragle and Serwize [12], since oral collagen ingestion is an area of great promise as far as osteoarthritic pain amelioration goes, future studies that can more clearly examine samples with similar symptomatic and objectively derived structural deficits and derangements, as well as more extensive features known to influence osteoarthritis pathology such as laxity, body mass, pain duration and intensity will undoubtedly help to potentially identify important clinically applicable observations. Ensuring comparable placebo controls are employed in clinical oriented comparative studies, and that they are not exposed to therapies that differentiate them from the experimental group, and that all participants adhere to the recommended protocol over an extended time period, may undoubtedly help to consolidate the evidence base in this promising relatively uncharted realm. In the meantime, while many pieces of the current puzzle appear promising, their collective contributions will probably continue to be underutilized and omitted from current global self-help recommendations for osteoarthritis even if usage appears safe and can be managed by most able adults without excess health resource utilization. This will be especially so, if little is done to explain or explore the mechanisms of action of either undenatured collagen or collagen hydrolysate ingestion as regards key osteoarthritis disease indicators.

### Conclusion

Collagen supplements and derivatives ingested in an array of formulae, and which have been examined for a protracted period in various animal models, as well as humans, appear to hold great promise as a possible adjunctive or stand alone conservative approach for purposes of intervening in the osteoarthritis pain cycle [23].

More generalizable evidence of the long-term benefits or risks of oral collagen are needed however, along with data that demonstrate possible mechanisms of action for this therapeutic approach. In particular, given the profound implications of affirming that oral collagen not only increases collagen synthesis, but the synthesis of other minor cartilage matrix components such as glycosaminoglycans and hyaluronic acid, more work in this area may have profound implications for advancing the treatment of this disease. Clinical studies that further show that undenatured collagen type II impacts arthritic inflammation favorably [23] and that various forms of collagen hydrolysate and its continual ingestion helps to reduce and prevent joint pain, bone density loss and skin ageing are equally compelling and should be replicated in larger more diverse osteoarthritis samples [24].



The question of whether one or more oral supplementary collagen formulae used either alone or in combination with other neutralising or pharmacologic interventions is a potentially useful self-help approach for adults with osteoarthritis of various ages living in the community, while promising, must however, await further study, in the author's view. Given that current medical and surgical treatments can be costly, have limited efficacy, and often produce serious side effects [1], and standard therapies or surgery or both may not be accessible to all during 2020 and its pervasive pandemic lock downs of the older adult, resolving this current issue should receive high priority in our view.

In particular, the impact of oral collagen hydrolysate derivatives and their potential collagen building and remodeling effects should be studied carefully given that food sources alone do not appear as efficacious as hydrolyzed collagen formulae for this purpose [49] and the fact that undenatured collagen type II derivatives, may not be indicated for all osteoarthritis cases. As per Simon., *et al.* [50], and based on current data, more cases with osteoarthritis than not would be expected to experience some form of pain relief through the effective administration of optimal collagen supplementary doses, especially those with more severe, rather than less severe disease. The promising observations reported here and elsewhere [51,52] also imply that research to tease out responsive or non-responsive osteoarthritis patient subgroupings, along with efforts to examine the impact of oral collagen supplements on the osteoarthritis disease processes in all affected joint tissues [54], including muscle and bone [55] will undoubtedly help to advance practice options. The careful analysis of the current data in the interim tends to imply that well designed insightful research of oral collagen supplements in the future might strengthen the case for why this possible therapeutic approach should not be discarded as one that is clinically irrelevant, especially on the basis of very weak evidence [56].

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