

## Efficacy of Oral Collagen in Joint Pain - Osteoarthritis and Rheumatoid Arthritis

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### Abstract

**Introduction:** Joint pain is one of the most common types of chronic pain. Osteoarthritis (OA) and rheumatoid arthritis (RA) are the two leading causes of joint pain and there are currently no prophylactic or curative treatments available. Oral collagen has been implicated in providing a potential means to treat arthritis. This review article aims to identify, evaluate and summarize the results of published animal and human clinical trials related to oral collagen in the treatment of joint pain caused by OA and RA.

**Methodology:** Articles were searched using EMBASE and Medline databases. Search terms for keywords and titles included: "osteoarthritis", "rheumatoid arthritis", "joint pain", "oral collagen". Articles containing the following are included in our search: randomized controlled trials, clinical evidence and animal models containing primary quantitative data, *in vitro* studies of oral collagen related with joint pain, joint disease, OA or RA.

**Results:** Numerous preclinical and clinical studies have been carried out to investigate the efficacy of oral collagen and both OA and RA. Oral collagen is administered either in an undenatured form or in a partially denatured form for patients with OA, and in general, has been found to be reasonably efficacious, although more trials will be required to confirm and consolidate these findings. In contrast, oral collagen has a more debatable response rate in patients with RA, especially when compared with methotrexate, an existing therapy.

**Conclusion:** There is some evidence that suggests oral collagen is effective for OA and has shown to be tolerable and safe for the patient. The clinical efficacy of oral collagen in RA remains controversial, particularly when compared with conventional therapies such as methotrexate.

**Keywords:** Oral collagen; Oral tolerance; Osteoarthritis; Rheumatoid arthritis

### Introduction

Joint pain is one of the most common types of chronic pain [1]. The leading cause of joint pain is arthritis, which is the inflammation of one or more joints. There are more than 100 different forms, with osteoarthritis (OA) being the most common type, affecting 8.75 million people in the UK [2], followed by rheumatoid arthritis (RA), affecting around 400,000 people [3]. In a healthy joint, articular cartilage covers the ends of the bones and is lubricated by the synovial fluid. OA affects the articular cartilage where the direct contact of bones results in pain, while RA is an autoimmune inflammatory disease that causes hyperplasia of the synovium resulting in painful and stiff joints [4]. OA and RA have a significant impact on the health-related quality of life and disability level of patients [5,6]. Despite the large numbers of patients affected, there are currently no prophylactic or curative treatments available.

There have been various preclinical and clinical trials conducted on the treatment of joint pain with oral collagen, in particular type II collagen, which is the principal constituent of articular cartilage and a major autoantigen of human in RA [7].

### Oral Tolerance

Oral collagen can be obtained from a product naturally or processed using enzymes. It has the potential to reduce the progression of OA and RA by inducing an oral tolerance in the arthritic patient. Oral tolerance is a state of immune suppression in response to the oral administration of an antigen. This immune response is a result of reduced systemic delayed-type hypersensitivity, the production of T-cells and cytokines, and suppressed serum antibody responses [7].

Oral collagen can be absorbed via intestinal epithelial cells, Peyer's patches and intestinal dendritic cells [8] and has shown to induce different mechanisms of oral tolerance. For example, active immune suppression using low doses is a process that involves activation of dendritic cells abundant in Peyer's patches and their subsequent induction of regulatory T ( $T_{reg}$ ) cells, most prominently the CD4+CD25+Foxp3+ T cell subset in mesenteric lymph nodes [9]. This process of dendritic cell activation may also occur in the liver following antigen dissemination via the portal venous system after passing through intestinal epithelial cells into the bloodstream [9]. The activation of anti-inflammatory IL-10 by  $T_{reg}$  cells has been shown to suppress the expression of the pro-inflammatory IL-17, a cytokine implicated in RA [10,11]. Furthermore, CD25+ has also shown to play a role in IL-2 deprivation, a cytokine responsible for modulating the differentiation of effector T cell subsets, including TH1, TH2 and TH17 [12]. IL-4 and TGF $\beta$ , suppressive cytokines, are also upregulated

[13]. Meanwhile, at higher doses oral collagen, clonal deletion and energy are thought to occur [12], thus providing a potential means to reduce inflammation in arthritis.

## Method

Articles were searched using EMBASE database from 1947 to present, and Medline from 1946 to present. Search terms for keywords and titles included: “osteoarthritis”, “rheumatoid arthritis”, “joint pain”, “oral collagen”. Articles containing the following are included in our search: randomized controlled trials, clinical evidence and animal models containing primary quantitative data, in-vitro studies of oral collagen related with joint pain, joint disease, OA or RA. Articles containing non-oral collagen studies, non-joint disease or those that were not related to OA or RA are excluded. Only the clinical studies involving animals or humans were selected for analysis and review. In order to determine efficacy, it was ensured that clinical assessment of the OA response to oral collagen was achieved via WOMAC (Western Ontario McMaster Osteoarthritis Index), whilst that of RA was done primarily through measuring the ACR criteria (American College of Rheumatology). Both WOMAC and ACR are widely employed as means of which to determine changes in the state of patients’ OA or RA respectively.

## Results

### Oral collagen in OA

Orally administered collagen to treat OA may come in two forms; undenatured type II collagen (UC-II) and partially hydrolysed collagen. The former preserves the collagen’s normal biological activity whereas the latter involves enzymatic, heat or pH degradation of collagen [13].

**Undenatured type II collagen:** At present, available literature has reported preclinical and clinical data for the use of oral collagen in the form of both UC-II and Enzyme hydrolysed collagen (EHC). In the preclinical investigation, Gupta et al. (2009) studied the effects of UC-II therapy in comparison to glucosamine and chondroitin (G+C, nutraceuticals used to treat lower arthritic pain, at 5.4 g and 1.8 g respectively) in horses displaying moderate OA.

Treatment received by the group of horses	Maximal reduction in overall pain by day 150 (%)	Maximal reduction in pain after limb manipulation by day 150 (%)
Active UC-II in 80 mg (Group-II)	79	71
Active UC-II in 120 mg (Group-III)	88	78
Active UC-II in 160 mg (Group-IV)	91	80
G+C (Group-V)	68	69

**Table 1:** Results of trial on osteoarthritic horses treated with UC-II and G+C [16].

They reported a significant lowering in overall pain within 30 and 150 days with peak pain reduction of 79%, 88% and 91% respectively at daily dosages of 320, 480 and 640 mg of UC-II (containing 80, 120,

and 160 mg of bioactive UC-II); the latter two doses appeared to be twice as effective versus glucosamine plus chondroitin. In addition, no adverse effects were reported based on subsequent analyses of physical and biochemical investigations. The authors recognised the lack of a universal equine assessment for pain, which in this study was evaluated through assessing mobility following limb manipulation (Table 1) [14,15].

Bagchi et al. (2002) oversaw a clinical pilot study exploring the response of 5 patients displaying symptoms of OA to 10 mg/day of UC-II, and reported an average of 26% reduction in pain after 42 days in 4 of the 5 test subjects [6]. Crowley et al. (2009) similarly investigated clinically the daily intake of 40 mg UC-II (n=26) containing 10 mg of bioactive UC-II, in comparison to 1,500 mg glucosamine and 1,200 mg chondroitin (n=26) for OA of the knee in 52 patients, whereby the efficacy of the oral collagen supplement was assessed via the Western Ontario McMaster Osteoarthritis Index (WOMAC) that explored patient pain, stiffness, and ability to carry out physical activities. It was found that after 90 days, WOMAC scores in the UC-II cohort were lowered by 33%, as opposed to a 14% reduction in the glucosamine and chondroitin cohort. However, at 30, 60, and 90 days post-therapy, the reductions in WOMAC scores in the UC-II group versus the G+C group were not statistically significant. In terms of safety and tolerability, there were 58 adverse events recorded in patients receiving G+C, in comparison to 35 of those receiving UC-II, although once again there was no statistical significance between the results [17].

**Denatured Collagen:** An interesting alternate form of oral collagen used against OA is partially denatured collagen, also known as pharmaceutical-grade collagen hydrolysate (PCH) which is derived from the breakdown of gelatin. However, rather than inducing oral tolerance, Ohara et al. (2014) found that a collagen-hydrolysate derived peptide stimulated greater hyaluronic acid production in-vitro by synovial cells. The group also reported that in a guinea pig model, administration of collagen hydrolysate attenuated morphological changes associated with cartilage damage that occurs in OA [18].

Clinically, a randomised, double-blinded multi-national study conducted across three countries - the UK, US, and Germany, investigated the response of patients with OA of the knee to 10 g of PCH per day versus a placebo control, in total involving 389 patients. Overall, after 24 weeks, it was found that there was no statistical significance in WOMAC pain dimension and physical function scores in favour of PCH, although a subset of 92 patients with severe baseline patient global assessment was identified as being relatively consistently more responsive to PCH than to the placebo. Nevertheless, it was concluded that PCH was well tolerated and safe to consume by patients [19]. Meanwhile, Kumar et al. (2014) reported in their randomised double-blinded clinical trial of 5 g daily twice collagen peptide’s effects on patients with knee OA a statistically significant reduction in WOMAC scores when compared to a placebo after 13 weeks [20].

EHC was also studied in a separate investigation that looked at the response of patients with OA of the knee to daily doses of 10 g of EHC (n=47), in comparison to glucosamine sulphate (1,500 mg), for 90 days (n=46). It was found that EHC, versus GS, lowered average pain level significantly at day 90 of testing, and furthermore there was a significant reduction in the WOMAC scores (P<0.05) between the two groups. Once again, EHC was generally well tolerated as well [20].

Early research into the efficacy of oral collagen for OA in the form of UC-II and partially denatured collagen has shown promise in terms of preclinical and clinical studies alike. It has been shown to be an analgesic agent, and thus symptom-reliever, to those suffering from OA. However, there is still relatively limited data available in this field, particularly large scale and longer term studies, which may not have captured certain heterogeneous phenotypes of OA (coupled with various comorbidities) may not have been factored in the currently concluded investigation [21], as illustrated by the more responsive subset of patients in Stoess' trial to PCH [19]. Furthermore, it would be beneficial to initiate a clinical study to correlate the patient response to oral collagen of elevating dosages, in order to explore the dose-dependent efficacy of oral collagen.

### Oral collagen in RA

Numerous studies, in comparison to OA, have been performed to investigate the efficacy of oral collagen supplements in preclinical and clinical subjects with RA. In a preclinical study, rats with collagen-induced arthritis (CIA) were found to show a decline in levels of pro-inflammatory IL-2 and IL-17, along with a concomitant rise in the proportion of CD4+CD25+ Treg cells following oral treatment with chicken type II collagen (10, 20, and 40 µg per kg per day, for 7 days). Furthermore, significant reductions in paw swelling were also noted [10]. This data serves to reinforce the concept of Treg-mediated oral tolerance, induced by the ingestion of oral collagen, against inflammatory arthritis. In another trial, rats with adjuvant arthritis (rheumatoid arthritis-like experimental condition brought about by injection of certain bacterial cell wall components [22]) and concomitant meloxicam (NSAID)-induced intestinal lesions were administered 20 µg/kg oral and nasal chicken type II collagen. The authors reported very minimal efficacy of oral type II collagen on arthritis in rat models with AA and concomitant intestinal lesions, thus further supporting the role the gastrointestinal system, in particular the ileal Peyer's patches, in the process of successful oral tolerance [23].

In the clinical setting, numerous randomised, double-blinded patient studies on the effects of oral consumption of type II collagen have been reported. Trentham et al. (1993) noted in an early trial involving 60 patients, that at the end of three months, there were significant reductions ( $P < 0.05$ ) in the number of swollen joints and the number of tender joints in patients treated with oral type II collagen (at daily doses of 0.1 mg for the first month, then 0.5 mg for the second and third months), in comparison to the placebo group [24]. Meanwhile, a later study explored the efficacy of oral type II collagen on 274 patients with active RA, based on three sets of diagnostic criteria - the Paulus criteria, the American College of Rheumatology (ACR) criteria, and a  $\geq 30\%$  reduction in the number of swollen and tender joints. Of the four doses (20, 100, 500, 2,500 µg/day) tested for 24 weeks, it appeared that a dosage of 20 µg/day produced the most positive responses in all three criteria, although only the Paulus criteria response was statistically significant when compared with a placebo. In addition, the study noted no adverse events associated with the treatment, thus promoting the safety and tolerability of oral collagen in humans [25]. Barnett made a valid hypothesis that in contrast to the Trentham study, the latter required their subjects to discontinue ongoing immunosuppressive and disease-modifying therapies, which may possibly explain the differences in the perceived optimal dosage of oral collagen between the two studies [26].

Zhang et al. [26] and Wei et al. [27] reported similar findings in their respective Phase II and III clinical trials involving 236 and 503 RA patients respectively [25,26]. In both studies, the efficacy and safety of orally taken type II collagen (0.1 mg/day for 24 weeks) were measured against the response when treated with methotrexate (10 mg/week). Both concluded a statistically significant reduction in the incidence of adverse events when oral collagen was administered; however, at 24 weeks, ACR-20 and ACR-50 response rates for oral collagen were significantly lower ( $P < 0.05$ ) than that brought about by methotrexate. Nevertheless, it is undeniable that oral collagen attenuated signs and symptoms of RA, and is thus to a certain degree effective against the disease, although whether its efficacy exceeds that of methotrexate remains questionable, despite the fact that it is highly efficacious against a placebo. In both trials, treatment was administered in association with diclofenac sodium, an NSAID known to bring about common gastrointestinal symptoms.

Overall, oral collagen supplementation has shown a degree of efficacy against RA in preclinical and clinical studies, as well as proving to be a far safer and more tolerable option versus existing immunosuppressive therapies such as methotrexate. Versus a placebo, oral collagen has shown to be highly efficacious in patients with RA; in contrast, it remains debatable whether oral collagen is in fact more effective than methotrexate. Through dose-escalating studies, it appears that a lower dose of oral collagen (between 20 and 100 µg/day) induces the most optimal response, of which activation of Treg cells has been widely implicated [27,28]. On the other hand, high doses of oral antigen are associated with lymphocyte anergy and/or deletion [8]. Although longer term trials involving larger cohorts have been carried out, it remains an area of debate as to whether simultaneous administration of NSAIDs, used a pain relievers, actually synergise or attenuate the effects of oral collagen, given their well-documented (detrimental) impacts on the gastrointestinal system. Indeed, Zhang and Wei both reported that diclofenac sodium may have overlapping roles with oral collagen [25,26]. Thus, an area to pursue in future may perhaps be to establish whether it is beneficial to administer oral collagen in RA in combination with, or without, simultaneous usage of NSAIDs.

### Conclusion

Developing more effective therapies for OA and RA represents a major challenge. At present, available treatments serve to ameliorate symptoms of the diseases, rather than act in a curative manner. Recent interest in oral collagen supplements has sparked preclinical and clinical studies into its efficacy. Preclinical studies have confirmed that the primary mechanism of action of undenatured oral collagen centres on a process of oral tolerance, whilst that of partially denatured collagen may potentially involve stimulation of production of extracellular matrix components. In general, oral collagen has been shown too efficacious against OA when administered as an undenatured or partially denatured form, although insufficient large scale, longer term trials have been conducted to consolidate current findings. Oral collagen's efficacy against RA is to a certain extent still questionable, given that it has shown a better response in comparison to a placebo control, but perhaps not so when compared with methotrexate, an existing therapy for RA. However, oral collagen stands out in its superior tolerability and safety for patients, thus making it a potentially more attractive therapy in the future.

Oral collagen clearly has a role to play in the treatment of OA and the large number of patients affected by the condition would certainly

justify further research. With modern day pressures on national health services and funding being withdrawn for joint replacements, an oral treatment with a low side effect profile would be an attractive alternative option.

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