

The Rational Use of Collagen in Osteoarthritis: Review article

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Abstract: Osteoarthritis is a degenerative disease affecting joints that is chronic and disables the movement of patients with increasing pain and decreasing their quality of life with age. Available treatments are only symptomatic with no cure. Recent methods for managing osteoarthritis involve using pharmacological, non-pharmacological treatments or both for improving physical function in patients and alleviating pain. Clinical trials were conducted to reveal the extent of benefits obtained from different nutraceuticals and food supplements, such as collagen with growing use and fairly good results in the treatment of osteoarthritis. The goal of this study is to review the current information about the rational use of collagen in osteoarthritis

Keywords: Osteoarthritis; Collagen; Native Collagen ;Collagen Hydrolysate;Undenatured Collagen.

Introduction:

Osteoarthritis (OA) is a joint disorder characterized to be chronic and cause disability to patients. The trends of increasing life expectancy and obesity are likely to increase its prevalence. Its prevalence about 7% of the worldwide population (about 500 million people) affecting women more than men. Genetic predisposition and physical trauma are also risk factors for it.^(1,2)

OA pathophysiology involves both inflammatory and metabolic factors that leads to progressive destruction of articular cartilage. Articular cartilage is located at the end of long bones and within the intervertebral disc to provide a low friction surface and the ability to transport heavy loads. Degradation of cartilage will affect the entire joint including the joint ligaments, synovium and subchondral bone causing pain and low quality of life.⁽³⁾

Pain and movement ability are the hallmark symptoms in OA patients. These symptoms decrease functionality and subsequent impairments in work, psychological effects and even the sleep of the patients. Different scales can be used for pain measurement and quality of life estimation in OA. The Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) used for the assessment of the pain degree, stiffness degree, and the physical functionality. It consisted from 24 items each of them is scored as 0 to 4 points. In this index a score of zero means there is no pain/no limitation and a score of 1 means mild pain/limitation and so on higher scores mean severe OA.⁽⁴⁾ Pain intensity can also be evaluated by the Visual Analogue Scale (VAS) consisted from a horizontal line with 10 centimeter long that marked by the patients to represent their pain intensity.⁽⁵⁾

Many drugs that are effective in reducing pain can be used for osteoarthritis, but without improving the underlying cause or cartilage destruction. Nowadays

several alternative therapies have been used in order to decrease cartilage degradation such as nutraceuticals, chondroitin sulphate, glucosamine and hyaluronic acid⁽⁶⁾. Lately, collagen, a dietary supplement is in increasing use to improve joint health. Cartilage is composed of 10% chondrocytes and 90% extracellular matrix, which is 60-70% water and the rest, is organic material. In the cartilage organic material, the main protein found is collagen Type II. Recently, preclinical researches are essential to clarify the predicted role of collagen derivatives and how can affect the cartilage repair process. This helps in preventing unwanted multiple drug therapy and better designing of future clinical trials.⁽⁷⁾

Collagen Therapy in Osteoarthritis:

Many efforts were done previously in treatment of OA using both non-pharmacological like exercise and medications like analgesics, nonsteroidal antiinflammatory drugs (NSAIDs), opioids, and corticosteroids. These medications are symptomatic only reducing pain, inflammation and immobility but they are not disease modifying and have adverse effects. Since there are no curative medications, so supplements and nutraceuticals such as collagen and collagen derivatives are tried to be used by OA patients⁽⁸⁾. The word of nutraceuticals comes from combining words "nutrition and pharmaceutical" and refers to products used to help in the prevention and treatment of chronic diseases such as OA. Actually nutraceuticals correspond to food or products that improve health status without adverse effects. Collagen is a safe food supplement which accumulates in cartilage when properly administered. Low level of collagen in the body may result from aging or poor nutrition so supplementation with it may stimulate chondrocytes and improve the buildup of cartilage matrix⁽⁹⁾. Experimental studies revealed that peptides from oral collagen absorbed and concentrated in cartilage tissue. Preclinical studies in animal models were conducted to assess the effect of

collagen derivatives used in treating OA patients and reported daily dose of undenatured native chicken type II collagen (UC-II) when applied after injury to knees may help the mechanical function without progressive damage of the articular cartilage.⁽¹⁰⁾ These results encouraged more studies to estimate the role of collagen derivatives in alleviating disease symptoms⁽¹¹⁾. A systematic literature review about collagen hydrolysate (CH) found that there are little benefits to recommend the daily use of it.⁽¹²⁾ While other randomized placebo controlled trials evaluating the efficacy of oral collagen on disease symptoms using WOMAC scale or VAS found significant positive effect on stiffness but not on pain and functional limitation. In fact, further efforts should be made by laboratory and clinical researchers to obtain definitive results.⁽¹³⁾

Non-hydrolyzed Collagen:

Collagen is the prominent protein that found in extracellular matrix of connective tissues such as skin, tendons, ligaments, bones, cartilage with functions of building of joint cartilage, anti-inflammatory, antioxidant and signaling activity. It is a big protein, of approximately 300KDa, with a complex structure due to its quaternary structure formed by a triple-helix. Its protein sequence is unusually rich in the amino acids hydroxyproline, proline and glycine, making the motif Gly-Pro-Hyp a hallmark of its sequence⁽¹⁴⁾. Collagen derivatives are obtained from beef, pork, fish bones and skins then pass through enzymatic hydrolysis to smaller amino acids and/or peptides increase that increase their postprandial absorption and bioavailability⁽¹⁵⁾. The pre-digested and processed collagen products known as collagen hydrolysates (CHs) and found as capsules. There are many steps and manufacturing processes to make CHs products with variable molecular weight (MW) as a result of variable amino acids and peptide sequence. Lower MW peptides are more easily taken and absorbed through small intestine then blood circulation so improving their delivery to joints. Type II collagen found mostly in articular cartilage and intervertebral discs so oral collagen administration may provide support cartilage repairing but this still not proved yet. Other formulations synthesized based on hydrolysis degree that yield collagen derivatives of undenatured collagen or hydrolyzed collagen⁽¹⁶⁾. Still there are no studies that determine the absorbed amount of collagen peptides in the gastrointestinal tract then to blood. Clinical trials evaluating the oral undenatured and hydrolyzed collagen were conducted to show that their administration is associated with mild adverse effects and well tolerated by the patients⁽¹⁷⁾.

1. Undenatured Collagen (UC-II)

Many clinical trials have been conducted on humans and animals about the use of undenatured collagen type II (UC-II) that is often extracted from chicken cartilage⁽¹⁸⁾. It has a fair good safety profile with immune modulatory properties. The degree of digestion and absorption after administration to humans required to be evaluated, but the bioactive peptides have been postulated to be kept and absorbed as proline and glycine amino acids particularly that applied as important building blocks for cartilage extracellular matrix (ECM) macromolecules.^(16,19,20)

Also, UC-II play a role in decreasing body immune response towards damaging joint cartilage by multiple reactions termed oral tolerance. Oral tolerance can be defined as minimizing or suppressing the immune response by oral antigen administration which could be useful in autoimmune disease. Small doses of oral antigen are good for the suppression of cell mediated immune responses, on the other hand high doses of oral antigen that directed to peripheral tolerance⁽²¹⁾. The reason of UC-II mediated oral tolerance is due to special epitopes that occur as a part of the intact helix structure followed by immune system recognition. After recognition of these epitopes they interact with lymphoid tissue associated with gut (GALT) that result in attenuating the systemic (T cell) attack decreasing cartilage inflammation and damage.^(22,23)

There is a connection between anti-inflammatory cytokines and cartilage health. The activation of the Regulatory T cells (Tregs) after inflammation induce and stimulate chondrocytes for synthesizing cartilage components. UC-II similar to Tregs also contribute to the secretion of Interleukin 10&4 and transforming growth factor which act as anti inflammatory cytokines that minimizing the inflammatory damage and resuming collagen and ECM synthesis thus improving the functionality of the joints and decreasing pain.^(24,25)

2. Collagen hydrolysate (CHs):

Collagen hydrolysate (CHs) or hydrolyzed collagen is similar to gelatin in amino acid but differ in chemical properties. Collagen hydrolysate is well known to dissolve in water that makes its digestion and absorption easier as a free amino acids⁽²⁶⁾. Variable peptide sequences and molecular weights are produced after many processing events on native collagen. Variation between these products can affect the biological action of them on joint inflammation and subsequent effects on bone. It is well known that lower molecular weight collagen peptides are quite easily be taken to blood after absorption from small intestine and easily delivered to joints⁽²⁷⁾.

The amino acid composition of collagen peptides has a great effect on the hydrolysis and digestion process. Some peptides are not readily hydrolyzed and digested after administration resulting in low absorption. Peptides such as proline or hydroxyproline resulted from degradation of peptides, have been measured to circulate for up to four hours in blood after collagen and gelatin administration by oral route. Oral hydrolyzed collagen degraded to smaller peptides and amino acids with low molecular weight. So hydrolyzed collagen administration associated with higher level of solubility, bioavailability and higher absorption in comparison to undenatured collagen. It has been suggested that collagen derived peptides stimulate chondrocytes synthesizing ECM macromolecules, increase osteoblast activity and decrease osteoclastic activity⁽¹⁶⁾. Combined oral administration of CH with other nutritional ingredients such as calcium and vitamin D bring more beneficial effects on bone health. Improvement of body health also has been demonstrated with CH due to antioxidant activity, anti-aging, wound healing effect and reducing the risk of thrombosis-related cardiovascular diseases⁽²⁸⁾.

Conclusion:

Many efforts are being made to find new therapeutic options that can both reduce OA pain and improve the disease course. Nutraceuticals such as collagen are attractive candidates due to their safety profile and good improvement with its use. However, collagen considered to be effective in small scale clinical trials and have greater impact in early stages of OA. Also there is little evidence about the ability of collagen to ameliorate and treat advanced joint damage. More studies and collaboration at both the academic and industrial level are required to support and give a scientific explanation for the rational use of collagen, clarify the mechanism of action in OA and the development of effective products.

Conflict of Interest

There is no conflict of interest.

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