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REVIEW ARTICLE

Medical use of hydrolyzed collagen in osteoporosis

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ABSTRACT

In this narrative review, the scientific background of the use of collagen in osteoporosis is presented, drawing inspiration for a discussion on the food supplements use in medicine. The first part of the paper provides an overview on collagen and hydrolyzed collagen. The second part deals with collagen carential disease, comprising conditions ranging from nail fragility to osteoporosis. The third part focuses on osteoporosis and its treatment, the fourth on hydrolyzed collagen. The medical use of hydrolyzed collagen provides a typical example of “Green economy”, the new alliance between man and nature that is involving medicine too.

Key words

Collagen, Hydrolized collagen, Collagen carential disease, Osteoporosis, Green medicine.

Introduction

The collagen use in osteoporosis stands on a solid scientific basis, but it is confined to food supplements, which do not enjoy a good reputation. The first part of this narrative review provides an overview of collagen, its properties and use in the form of hydrolysate. The second focuses on the collagen carential disease, tracing its history from nail fragility to bone medical conditions. The third part focuses on osteoporosis and its treatments, the fourth on hydrolyzed collagen. The paper ends with a reflection on the green economy, the new alliance between man and nature that is involving medicine too.

Literature review

COLLAGEN AND HYDROLYZED COLLAGEN. After water, fats and carbohydrates, collagen is the main component of the body¹. It permeates liquids, cells, organs and systems assuming different forms and functions^{2,3}. It is elastic in skin, hard in nails, flexible in hair, fluid in mucous membranes and secretions. It provides bone both with fibrils, which provides the elasticity needed to withstand shocks, and with an organic matrix, which hardens bones by depositing mineral salts⁴. Without this matrix, calcium would flow away unused.

Like the organism to which it belongs, collagen is born, reaches the fullness of conformations and functions, then ages and disintegrates. The latter phenomenon results in a daily loss of collagen in the order of 14-18 g, which cannot be offset by assuming collagen as such. If this happened, it resulted in autoimmune reaction⁵⁻⁷. To be incorporated, collagen must hydrolyze, so as to release amino acids and peptides,

which are used for its biosynthesis according to the original inside collagen conformation⁸.

The collagen molecule includes 20 amino acids that are also present in other proteins, so that collagen could theoretically regenerate at their expenses. There is a problem, concerning the aminoacidic composition of collagen. The glycine and proline body contents, as an example, are 10-20 times higher than in food proteins. To ingest the amount of glycine corresponding to 10 grams of collagen, a person should ingest 2.8 liters of milk or 160 grams of meat. Concerning proline, the corresponding quantities are 0.4 liters and 110 grams respectively. A high protein intake could theoretically solve the problem, but it involves side effects, including excessive loss of calcium in urines, absorption of undigested proteins, toxic metabolites such as uric acid. A 2023 meta-analysis sees no evidence for the relation between high protein intake and bone health⁹. Incidentally, the same problem involves vegetarian and vegan diets.

It follows that hydrolyzed collagen is unique in providing the amino acids and peptides that are needed to offset the collagen loss. The dose is of the order of 100 mg/kg/day.

COLLAGEN CARENTIAL DISEASE.

Around the middle of last century, in the US there has been a widespread, over the counter use of gelatin against nail fragility. Incidentally, gelatin is to consider synonym for hydrolyzed collagen. The main component of nails is collagen, which is also the main component of hair. Hence the idea that gelatin worked against hair fragility too. Tested in humans and laboratory animals, hydrolyzed collagen proved effective^{10,11}. Nails and hair are appendices of the skin. Accordingly, the next

step dealt with skin conditions, ranging from wrinkles to dystrophic ulcers. Hydrolyzed collagen proved active both by oral and topical administration^{3,12,13}. By the way, the preclinical and clinical evidence concerning the above and below effects is so widespread, that the reader is referred to reviews, rather than single papers.

Concerning topical uses, hydrolyzed collagen displays two actions, consisting in a protective and a nourishing action. To those who have read the Aeneid, they recall the pizzas that Aeneas discovered when he landed in Lavinio. They served as food containers, which were afterward eaten without wastes. The protective action of hydrolyzed collagen is stronger than a metal sheet¹⁴. Concerning the nourishing action, it is due to amino acids and small peptides released by hydrolyzed collagen, which penetrate the skin, providing an excellent cell culture medium^{15,16}.

Next steps of this intriguing story involved both the digestive tract and the bone, involving quite a number of medical conditions, such as heartburn, gastro-intestinal erosions and ulcers, rheumatoid arthritis, degenerative osteo-articular conditions. Results were positive in both these fields^{3,12}.

Taken together, the above data support the idea of a Collagen Carential Disease, which is caused by a failure of the main protein of the organism, and responds to hydrolyzed collagen^{3,7,12}. The evidence of the working hypothesis derived from the above idea consists of the "*diagnosis ex juvantibus*" criterion, where *juvantibus* agents consist of hydrolyzed collagen. Evidence provided by controlled clinical trials does also exist, being centered on single medical conditions.

Hydrolyzed collagen is not a synthetic medicinal product burdened with unknowns, risks and dangers. It's a drug of natural origin, endowed with a history that teaches how to use it safely. The only difference from vitamins is that hydrolyzed collagen is converted into collagen in the body. In other words, it acts as a prodrug. Hydrolyzed collagen is currently used in medicine as a food supplement, which is not allowed to display a medicinal action. The Community Code is clear: "*In case of doubt, if a product taking into account its characteristics may fall simultaneously within the definition of medicinal product and that governed by another Community Directive, the provisions concerning medicinal products apply*" (Directive 2001/83/ EC of the European Parliament and of the Council of 6 November 2001). The European Court of Justice is even more explicit: "For a product which satisfies both the requirements to be a foodstuff and those to be a medicinal product, the provisions of Community law specifically concerning medicinal products apply" (Judgment of 29 April 2004, in Case C/150/00 v Austria, and C/387/99 v Germany). In other words, to be used in medicine a food supplement should be registered as a medicinal product, which is a long, complicated and expensive process.

A compromise is offered by Homeostasis,¹⁷ the document of the Council of Europe that recognizes the medicinal use of a food supplement aimed at "maintain, support or optimize specific physiological parameters". In the case of hydrolyzed collagen, the physiological parameter consists of the role of collagen in normal functions of the body. This principle is not yet fully transferred into sanitary legislation, but this is not surprising. The therapeutic action of citrus juice in scurvy was

discovered by James Lind in 1747, but it took half a century to equip the British Navy with this primitive food supplement. Meanwhile, British Navy crews suffered and, in some cases, died of scurvy.

OSTEOPOROSIS.

Osteoporosis is a skeletal disorder characterized by a low density and deterioration of bone structure, with a consequent increase of fracture risk. In Europe it affects about 75 million people, mostly aged women. Worldwide, bone fractures amount to about tens thousands per day, ten million per year. Diagnostic criteria include patient and family history, clinical examination and laboratory tests that focus on bone density. Dual-energy X-ray absorptiometry (DEXA scan) is considered the gold standard for the diagnosis. Osteoporosis is defined as a bone density of 2.5 standard deviations below that of a young adult.

Beside insufficient movement and malnutrition, etiopathogenetic factors include advanced age, genetic predisposition, cancer, diseases such as cirrhosis and rheumatoid arthritis, hyperthyroidism and hypothyroidism, hyperparathyroidism and hypoparathyroidism, corticosteroids, quite a number of medicinal products, smoking, alcohol and other substances of abuse.

Physical exercise is considered a first line treatment of osteoporosis. It should be practiced regularly, preferably for at least 30-40 minutes a day. Walking, climbing stairs, practicing bodyweight gymnastics and dancing are all effective measures. Swimming and cycling are less so, because of the reduction of gravity force. The importance of this factor is shown by astronauts that are exposed to severe osteoporosis¹⁸. Incidentally, the same risk

theoretically applies to high-altitude commercial flights, particularly for cabin crew who suffers of long-term exposures to reduced gravity.

Malnutrition treatment primarily deals with calcium, vitamin D and other essential food elements ingredients. Hydrolyzed collagen, which provides amino acids and peptides necessary for collagen biosynthesis, is not considered in osteoporosis Guidelines nor Pharmacopoeias. Let's express the opinion that its use is bioethically correct in the light of the above discussed Homeostasis document¹⁷.

Apart from physical exercise and proper food supplementation, the pharmacologic armamentarium of osteoporosis is rich and varied. Bisphosphonates are typically represented by alendronic, etidronic, clodronic and zoledronic acids. They harden the bone and reduce the risk of fractures, but are bordered by worrying side effects. For example, they may harden the bone too much, exposing it to atypical fractures. Moreover, side effects include gastro-intestinal and systemic troubles, as well as malabsorption of various medicines. In conclusion, bisphosphonates are to use in severe osteoporosis. SERMs, typically represented by Raloxifene, are selective modulators of estrogen receptors. Teriparatide reproduces the effects of parathyroid hormone on calcium. Strontium Ranelate is accredited with anti-resorption and anabolic effects. Denosumab, a monoclonal antibody counteracts the necrotizing and osteolytic fractions that are involved in rheumatoid arthritis and myeloma. In essence, osteoporosis lacks fully satisfactory treatments in terms of safety and efficacy.

HYDROLIZED COLLAGEN.

The use of hydrolyzed collagen in osteoporosis takes shape at the end of last century, thanks to

the use of animal model,¹⁹⁻²⁴ flanked by *in vitro* studies concerning the role of collagen amino acids and peptides in its biosynthesis^{25,26}. Clinical evidence is relatively recent^{27,28}. Animal models consist of ovariectomized laboratory animal and have documented the ability of hydrolyzed collagen, as such or as a mixture of collagen amino acids¹⁹ to increase bone strength and accelerate fracture repair. *In vitro* studies have shown collagen peptides to be a marker of collagen biosynthesis in bone²⁵, as well as the relation of bone collagen with the bone strength²⁶. The clinical evidence consists of double blind and observational studies documenting effects of hydrolyzed collagen in post menopausal women^{27,28}. It is relatively recent and limited, but should be considered in the previously discussed frame of Homeostasis¹⁷.

The idea of a reversible collagen loss at the base of osteoporosis dates 2005, being resumed in 2020^{29,30}. It has been described as a precise nosography entity in 2019³ and was subsequently expanded from a physio-pathological and medical point of view^{12,23}.

Conclusion.

Collagen is an invention of nature, not man. It belongs to bone structure and composition, consisting of about 70 percent hydroxyapatite [(Ca₅(PO₄)₃(OH))], and 30 per cent collagen organic matrix, mainly composed of fibrils.⁴ Hydroxyapatite guarantees the hardness that sustains the rest of the body, while collagen plays two distinct roles: on one hand, it provides the bone with the elasticity required to resist the tensional and torsional forces; on the other hand, it absorbs the mineral salts dissolved in the blood and catalyzes their deposit as a solid precipitate.

The bone conglomerate resembles the reinforced concrete of building constructions, consisting of elastic iron rods embedded in rigid concrete, except that the bone is a living tissue, capable of regenerating itself and repairing the damages. Regeneration prevails over degeneration during growth and is stimulated by motor activities, including sport, which strengthen the osteoarticular system. Degeneration prevails over regeneration in senescence and degenerative diseases, including osteoporosis.

This approach biological inspires the treatment of osteoporosis described in this paper. It should not substitute the current, prevailing treatments of osteoporosis. The latter are and remain necessary where and when nature and nature-inspired treatments do not arrive. In this sense, the medical use of hydrolyzed collagen in osteoporosis provides a tiny, but significant lesson of Green economy, the new alliance between man and nature.³¹

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