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Review

Oral chondroprotection with nutraceuticals made of chondroitin sulphate plus glucosamine sulphate in osteoarthritis

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ABSTRACT

Oral supplementation of chondroitin sulphate plus glucosamine helps repair the articular surface in osteoarthritis. Chondroitin-S reduces the concentration of the pro-inflammatory cytokines and transcription factor involved in inflammation. GlcN.S enhances cartilage specific matrix components and prevents collagen degeneration in chondrocytes by inhibiting hydrolytic enzymes, and preventing the oxidation of lipids and proteins. Chondroitin-S plus GlcN.S are slow-acting drugs that alleviate pain and partly restore joint function in OA patients. Orally administered pharmaceutical-grade chondroitin-S plus GlcN.S stabilize the joint space narrowing and significantly decrease the number of patients with new erosive OA. They are safe and no adverse events have ever been reported; they are recommended by EULAR and OARSI. The cost/effectiveness of the oral chondroitin-S plus GlcN.S therapy derives from the reduction of costs for physiotherapy, and for gastroprotective and non-steroidal drugs. The synergistic association of these two world-widely preferred nutraceuticals is a step forward in the management of OA.

Contents

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1. Introduction and scope

Osteoarthritis is essentially a debilitating disease characterized by a gradual loss of articular cartilage in synovial joints, that causes painful impairment. Functional limitation gradually occurs as a result of joint stiffness and progressive loss of joint motion owing to deformities (loss of the cartilage surface and side growth of osteophytes) accompanied by inflammation of the synovial membrane.

The pharmacological therapy is directed to the prevention of pain and the improvement of function. Standard analgesic/anti-inflammatory drugs include NSAIDs, opioids, paracetamol, vitamins, COX-2 inhibitors, capsaicin and glucocorticoids, that however might exert various gastrointestinal and cardiovascular side effects; most importantly they do not correct the degenerative disorder of the connective tissue. Ideally, the therapy would be expected to preserve the articular structures, improve the quality of life, and guarantee safety.

Chondroitin-S and GlcN in various forms (scaffolds, hydrogels, injectables, dietary supplements) represent valid therapeutic alternatives because they are ubiquitous in the human body, being two components of the cartilage (Busilacchi, Gigante, Mattioli-Belmonte, Manzotti, & Muzzarelli, 2013; Goldberg, Von Feldt, & Lonner, 2002; Henrotin, Mathy, Sanchez, & Lambert, 2010; Henrotin and Lambert, 2013; Luttosch & Baerwald, 2012; Muzzarelli, 2009; Muzzarelli et al., 2012a; Ravi Kumar, Muzzarelli, Muzzarelli, Sashiwa, & Domb, 2004). In fact chondroitin-S and GlcN are amply available as dietary supplements for the prevention of cartilage loss *via* increase of their concentration in the joint: they help preserve, or even repair, the damaged articular surface in OA (Volpi, 2011).

Glucosamine in the form of GlcN.S is one of the most commonly used complementary medicines in Western countries: moreover, a considerable proportion of the Australian population aged 45 and over consumes GlcN.S. The same is reported for Korea, Russia and other countries (Noskov, Lavrukhina, Shirokova, & Pryanichnikova, 2013; Seo et al., 2013; Sibbritt, Adams, Lui, Broom, & Wardle, 2012).

The scope of this review article, the first devoted exclusively to oral chondroprotection with the aid of the association of chondroitin-S (a polysaccharide ester) with GlcN.S (an aminosugar salt), is therefore the evaluation of recent data on said dietary supplement as a slow-acting modifier of osteoarthritis for (i) oral administration of components of the cartilage, and (ii) prevention and treatment of the degeneration of the joint cartilage in the elderly. Aspects related to sources of the raw materials, analytical chemistry, pharmacokinetics, enhancement of assimilation *in vivo*, economics and recommendations made by Societies are also considered. Understanding the synergy of the two ingredients of this dietary supplement in providing safety of use and efficacy in the cartilage regeneration on the medium/long term is a further object of this work.

2. Biochemical data on chondroitin sulphate

A few extensive reviews have related the biomedical effectiveness of chondroitin-S to its origin, quality and formulation, in the light of its structural diversity and biochemical behavior (Fosang, 1999; Fosang & Beier, 2011;Fosang & Rogerson, 2010; Hochberg, 2010; Kamarul, Ab-Rahim, Tumin, Selvaratnam, & Ahmad, 2011; Vangsness, Spiker, & Erickson, 2009, among others).

A conspicuous feature of OA is the gradual loss of aggrecan from cartilage. Aggrecan, the main space-filling compound in the ECM of the articular cartilage, is a large proteoglycan made of a central protein core to which numerous chondroitin-S and keratan sulphate chains are covalently attached. Aggregate formation is through the N terminus globular domain (G1) of the aggrecan core protein which binds non-covalently to decameric units of HA and to the link protein to form stable complexes. The release of aggrecan from the complex involves enzymatic hydrolysis of the core protein. The inter-globular domain between G1 and G2 was found to be sensitive to proteolysis by MMP and aggrecanase. The C terminus G3 domain is missing from one half of the cartilage aggrecan, as a result of extracellular processing. The GAG attachment region between G2 and G3 comprises a keratan-S domain and two chondroitin-S subdomains; aggrecanase can truncate aggrecan molecules at this position. The overall carbohydrate content is therefore variable and can amount to 95%.

Although it is clear that MMP-13 (collagenase-3) is the major cartilage collagenase, and that a disintegrin and metalloproteinase with thrombospondin motifs (ADAMTS-4 and/or -5) are the main aggrecanases in human cartilage, it is not clear how their zymogens are activated, nor how their activities are modulated *in vivo*. Based on their activities *in vitro*, these serine proteinases are thought to act indirectly, by activating MMP-3 (stromelysin) and MMP-2 (gelatinase A), which can subsequently activate collagenases. At the moment it can be said that 1 = Aggrecan is degraded by many proteinases under physiological conditions; 2 = Aggrecanases cleave at multiple sites in the aggrecan core protein; as a point of difference, the collagenase cleavage is at a single site in the collagen-II triple helix. 3 = IL-1 stimulation induces active aggrecanase in cartilage; 4 = Aggrecanases are constitutively active in synovium. 5 = Extensive aggrecanolysis is reversible *in vivo*. 6 = Aggrecan half-life in cartilage is *ca.* 3.4 years.

The anionic nature of aggrecan makes it osmotically active, thereby imparting resilience and allowing the cartilage to deform reversibly under load. It has been confirmed by Bali, Cousse, and Neuzil (2001) that the anti-inflammatory and chondroprotective properties of chondroitin-S result from enhanced biosynthesis of connective tissue components like hyaluronan, and higher viscosity of the synovial fluid at the afflicted sites. Aggrecan, as well as collagen-II, is a typical chondrogenic marker that reveals the cartilage regeneration (Remya & Nair, 2013).

Chondroitin-S is formed by a repeated disaccharide unit consisting of D-glucuronic acid (GlcA) and N-acetyl-D-galactosamine (GalNAc) with MW in the range 20–50 kDa (Collins, 1987). The structure of chondroitin is written in shorthand either as [GlcA β(1–3)-GalNAc β(1–4)] or as -4)-[βGlcA-(1–3)-βGalNAc]-(1-. When the linear chain of these disaccharide structural units is sulphated either in the 4 or the 6 position of GalNAc, the polysaccharides are called chondroitin-4-sulphate (C4S) and chondroitin-6-sulphate (C6S) respectively. Besides the micro-heterogeneity mentioned above, further micro-heterogeneity occurs when differently sulphated dimeric units are located within the polymeric chains: this inherent characteristic and the number of dimeric units forming the polymer exert influence on the pharmacological activity.

Human proteoglycans having chondroitin-S chains are abundant in cartilage, aorta, skeletal muscle, eye, lung and brain (David G et al., 1989; David CL et al., 1998; Kimata et al.,1974; Oohira et al.,1994; Zako, Shinomura, Miyaishi, Iwaki, & Kimata, 1997). They are synthesized intracellularly starting from glucose or glucosamine precursors (Scheme 1) and are secreted by chondrocytes as a macromolecular complex to be released to the extracellular matrix or to remain localized at the cell surface. The biosynthesis of the chondroitin-S chain of proteoglycans occurs in the Golgi apparatus simultaneously with the sulphate ester formation catalyzed by sulfotransferases at the positions of their respective competence (Habuchi, 2000; Prydz & Dalen, 2000). A need for detailed structural information on cartilage extracellular matrix molecules has been generated by interest in their pathological degradation. Posttranslational modifications are believed to play a role in determining the susceptibility to proteolytic degradation during the development