Glucosamine Sulfate Use in Osteoarthritis

Osteoarthritis

Osteoarthritis (OA), commonly referred to as “wear and tear” arthritis, is the most common form of arthritis affecting almost one third of people over 45 years of age (Braham et al, 2003, p.45; Pavelka et al, 2002, p.2113; Simanek et al, 2005, p.51). The disease is characterized by focal or global loss of articular cartilage, bone changes and an imbalance in inflammatory and non-inflammatory pathways (Braham et al, 2003, p.45).

Chondrocyte insufficiency, and/or apoptosis, is thought to result in physiological loss of ability to effectively remodel the extracellular matrix, and repair local cartilage defects (Simanek et al, 2005, p.54). Increasing levels of matrix metalloprotinases, aseptic inflammation of synovial tissues and changes in joint fluid composition further impair cartilage metabolism and its wear (Simanek et al, 2005, p.54). Aging, obesity and physical injury all contribute to the degeneration of joint cartilage, resulting in symptoms such as pain, stiffness and reduced functional mobility of affected joints (Simanek et al, 2005, p.51; Braham et al, 2003, p.45).

The natural course of the disease is usually that of a slow progression, however in some cases the joint may be come severely eroded over several months. Osteoarthritis is a source of great morbidity, impaired quality of life and places a significant burden on the health care system (Simanek et al, 2005, p.51).

In the absence of a cure for OA, current treatment approaches are aimed at effectively reducing pain and improving joint function (Pavelka, 2002, p.2113). Ideally treatment should reverse or slow down progression of the disease, in order to limit long-term disability (Kelly, 1998, p.27; Pavelka et al, 2002, p.2113).

Glucosamine sulfate

Glucosamine is a naturally occurring amino sugar derived from glucose. Formed in the body as glucosamine 6-phosphate (G6-P), it is required for the production of proteoglycans, mucopolysaccharides and hyaluronic acid. These substances make up joint tissue such as articular cartilage, tendons and synovial fluid (Braun & Cohen, 2005, p.214).

Within the body glucosamine inhibits the degeneration of proteoglycans and is a primary substrate and stimulant of proteoglycan biosynthesis. Hence glucosamine plays an important role in halting or reversing joint degeneration (IMgateway: Glucosamine, 2001; Alternative Medicine Review Monograph: Glucosamine Sulfate, 1999, p.193; Kelly, 1998, p.27).

Dietary Sources: Chitin from shellfish

Supplement: Glucosamine is derived from marine exoskeletons or produced synthetically (Braun & Cohen, 2005, p.214; Simanek et al, 2005, p.52). Glucosamine sulfate is a salt form.

Composition: 2-amino-2-deoxy-D-glucose

Actions: Chondroprotective and anti-inflammatory (Braun & Cohen, 2005, p.215).

Indications: Osteoarthritis

Other uses: Inflammatory bowel disease (Braun & Cohen, 2005, p.215).

Dosage:

· Adults: 1500 mg (taken as 500 mg TID) for minimum of 6 weeks. Obese patients may require higher dose. (IMgateway: Glucosamine, 2001; Alternative Medicine Review: Monograph Glucosamine Sulfate, 1999, p.194).

· Pediatric: No known literature reports for use in pediatric populations. Not currently recommended for children (IMgateway: Glucosamine, 2001).

Mechanism of Action

Glucosamine sulfate (GS) is a supplemental form of G6-P, the starting point in the synthesis of structural proteins and other important macromolecules.

Treatment with GS is aimed at normalizing biosynthesis of the substrates required to restore the functional ability of a joint (Kelly, 1998, p.38). GS does this by stimulating proteoglycan synthesis, inhibiting the degradation of proteoglycans and stimulating the regeneration of damaged cartilage. GS may also promote the incorporation of sulfur into cartilage (Alternative Medicine Review: Monograph Glucosamine Sulfate, 1999, p.193; Kelly, 1998, p32).

Glucosamine is a small molecule and highly soluble in water, making it easily absorbed in the intestine. A significant amount however is metabolized during first-pass through the liver (Kelly, 1998, p.30; IMgateway: Glucosamine; 2001).

Unbound glucosamine is rapidly incorporated into articular cartilage, creating the largest structural tissue concentration of glucosamine in the body (Kelly, 1998, p.30; Pavelka et al, 2002, p.2121). Its effect is to stimulate the synthesis of physiological proteoglycans and decrease the activity of catabolic enzymes including metalloproteases (Pavelka et al, 2002, p.2121).

Interlukin-1b (IL-1b) and TNF-alpha are considered to be the most prominent inflammatory cytokines to participate in osteoarthritic progression (Simanek et al, 2005, p.54). IL-1b down regulates the expression of galactose-b-1,3-glucuronosyltransferase I (GlcAT-I), a pivotal enzyme of glycosaminoglycans (GAG) polysaccharide chain biosynthesis. Such activity may contribute to the loss of proteoglycan synthesis elicited by the cytokine (Gouze et al, 2001, p.359).

Glucosamine inhibits IL-1b and TNF-alpha-induced nitric oxide (NO) and PGE2 production in normal articular chondrocytes, which suggests possible anti-inflammatory action (Shikhman et al, 2001, p.5158; Gouze et al, 2001, p.359; Gouze et al, 2006, p.186). By reversing some of the negative effects of IL-1b on cartilage metabolism, glucosamine is also thought to be responsible for the long-term effects on joint structure changes (Pavelka et al, 2002, p.2121; Gouze et al, 2001, p.351).

Pharmacokinetics

· Oral bioavailability: Approximately 90% of glucosamine administered as oral dose is absorbed from digestive tract (Alternative Medicine Review: Monograph Glucosamine Sulfate, 1999, p.193). Bioavailability is approximately 20-26% after first-pass metabolism (Braun & Cohen, 2005, p.214; IMgateway: Glucosamine, 2001).

· Metabolism: After oral dose, glucosamine concentrates in the liver and is either (1) incorporated into plasma proteins; (2) degraded into smaller molecules; or (3) utilized for other biosynthetic processes (Alternative Medicine Review: Monograph Glucosamine Sulfate, 1999, p.193). Unbound glucosamine is concentrated in the articular cartilage (Braun & Cohen, 2005, p.214).

· Half Life: 70 hours

· Elimination: Primarily through the urine, small amount eliminated in the feces and as CO2 in expired air (Braun & Cohen, 2005, p.214; Alternative Medicine Review: Monograph Glucosamine Sulfate, 1999, p.193).

Precautions

· Pregnancy: Insufficient reliable information to advise on safety in pregnancy (Braun & Cohen, 2005, p.216).

· Children: No studies exist for use in children. Use with caution.

· Shellfish Allergy: Although glucosamine is made from shellfish, it is not extracted from the protein component. Caution is advised in patients with shellfish allergy (Braun & Cohen, 2005, p.216; IMgateway: Glucosamine, 2001).

· Type II Diabetes: Animal studies suggest that glucosamine may raise insulin resistance, however this link has not been clearly demonstrated in human trials (Reginster et al, 2001, p.255; Pavelka et al, 2002, p.2122). Monitor blood sugar levels (Braun & Cohen, 2005, p.216; IMgateway: Glucosamine, 2001).

· Restricted Diet or Diuretics: Glucosamine sulfate may contain high levels of sodium or potassium. Individuals on a salt- or potassium-restricted diet, or using potassium-sparing diuretics should check labels before taking glucosamine sulfate (IMgateway: Glucosamine, 2001).

Interactions

· NSAIDs: Glucosamine may enhance anti-inflammatory activity of NSAIDs. Modify drug dosage as required (Braun & Cohen, 2005, p.216; IMgateway: Glucosamine, 2001).

Benefits and weaknesses of glucosamine sulfate treatment in osteoarthritis

GS is the first agent to meet current requirements, as defined by scientific organizations and acknowledged by regulatory agencies, to be classified as a symptom- and structure-modifying drug in the treatment of osteoarthritis (Pavelka et al, 2002, p.2119). The ability to improve pain and function, and retard joint space narrowing, suggests disease-modifying properties (Kelly, 1998, p.27; Reginster et al, 2001, p.251; Richy et al, 2003, p.1514).

Improvement in pain and function, as measured by the algo –functional indexes of Lequesne and WOMAC (Western Ontario and McMaster Universities) was comparable to conventional NSAID use in the first four weeks of treatment (Pavelka et al, 2002, p.2121). By twelve weeks significant improvements (40 – 50%) relative to basal conditions were evident. The symptomatic effects of GS developed steadily over the first year and thereon remain constant throughout the 3-year treatment period (Pavelka et al, 2002, p.2121; Reginster et al, 2001, p.253).

Changes in radiographic minimum joint space width, measured in the medial compartment of the tibiofemoral joint, indicated prevention of joint space narrowing after the first and second year of treatment (Pavelka et al, 2002, p.2121; Reginster et al, 2001, p.253). After 3-years, glucosamine showed no joint space narrowing (on average) while patients receiving placebo experienced significant narrowing of approximately 0.2 mm (Pavelka et al, 2002, p.2117). A minimal treatment period of 3 years is recommended to slow the degenerative process of osteoarthritis (Richy et al, 2003, p.1521).

Prevention of joint space narrowing translates to a 50% reduction in the incidence of OA-related surgery of the lower limbs during a 5-year period following treatment withdrawl (Reginster et al, 2005, p.31).

Glucosamine sulfate has a tolerance record comparable to placebo, over both short and long-term administrations. No peculiar toxic effect patterns have been identified, and there is no evidence of altered glycaemic homeostasis (Pavelka et al, 2002, p.2122; Reginster et al, 2001, p.255; Richy et al, 2003, p.1521; Hughes & Carr, 2002, p.283).

Other considerations

Several studies have produced results suggesting GS has an analgesic effect in mild to moderate OA (Pavelka et al, 2002, p.2116) but not in patients with more severe disease (more pronounced joint pathology) (Hughes & Carr, 2002, p.283; Ridone et al, 2000, p.93). This implies that older patients, with a longer history of OA may find reduced effect due to increased cartilage damage (Ridone et al, 2000, p.94; Hughes & Carr, 2002, p.282).

Sponsorship and Publication Bias

Of the numerous studies evaluating GS use for symptomatic treatment of knee osteoarthritis, the majority reported benefits (Pavelka et al, 2002, p.2113; Reginster et al, 2001, p.251; McAlindon et al, 2000, p.1469; Gouze et al, 2006, p.R173). Comments however have been made regarding methodological issues such study design, and exaggerated results due to sponsorship or publication bias (Cibere et al, 2004, p.739; McAlindon et al, 2000, p.1473). Independent funding from governmental or non-for-profit organization is rare (McAlindon et al, 2000, p.1473). Despite such criticisms, the overall consensus is that GS is a safe product with some efficacy in treating osteoarthritis (McAlindon, et al, 2000, p.1474; Reginster et al, 2005, p.34).

Quality Issues

Discrepancies have been found between trials using a patent-protected formulation of GS, distributed as prescription drug by Rottapharm, and over-the-counter supplements (Reginster et al, 2005, p.31; Reginster et al, 2001, p.255; Pavelka et al, 2002, p.2122).

Rottapharm crystalline GS is the original formulation described by most literature and the form consistently reporting positive results (Pavelka et al, 2002, 2114; Reginster et al, 2001, p.251). It is available as an approved prescription drug for the treatment of osteoarthritis in Europe and a nutritional supplement in the United States (Pavelka et al, 2002, p.2114).

Extrapolating conclusive results based on a single preparation of GS to the many over-the-counter formulations requires caution (Reginster et al, 2005, p.31; Reginster et al, 2001, p.255; Pavelka et al, 2002, p.2122). Actual glucosamine content of products not subject to strict quality control may vary from 59 % to 138% when expressed as sulfate (Russell et al, 2002, p.2407).

Conclusion

Clinical studies support the use of glucosamine sulfate (1500 mg daily) as a safe and effective disease-modifying treatment for osteoarthritis. It exhibits slow acting analgesic activity, requiring approximately 4-weeks to improve pain and function. Long term administration over 3-years has the potential to stop, or at least slow, the progression of OA of the knee.

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