



BACKGROUND

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Glucosamine, Chondroitin and Joint Health

Introduction

Glucosamine and chondroitin dietary supplements are used, alone and in combination, to promote joint health, particularly in adults with osteoarthritis (OA) (1). There is a wide array of well-established joint health benefits for both glucosamine and chondroitin (Table 1). Onset of benefits is gradual and takes several weeks to months; consequently, benefits are maintained with regular, long-term use of these nutrients. There is a strong body of human clinical trials that supports the safe use of glucosamine, chondroitin sulfate, or their combination for significant and long-lasting decreases in joint pain and improvements in mobility (see Table 2 for recent studies). Several meta analyses have been conducted on the two nutrients, either alone or in combination, with the majority concluding that glucosamine and chondroitin are both safe and beneficial supplements for joint health (2-5).

Table 1. Benefits of glucosamine and chondroitin supplements

Benefit	Glucosamine	Chondroitin
Reduced joint space narrowing	X	X
Improved joint comfort	X	X
Improved mobility	X	X
Production of new cartilage	X	X
No adverse effects	X	X

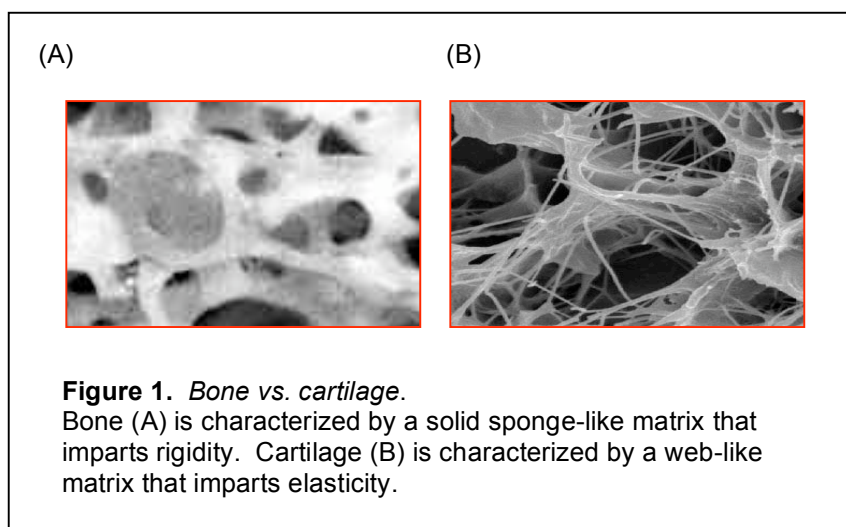
Structure and Function of Joints

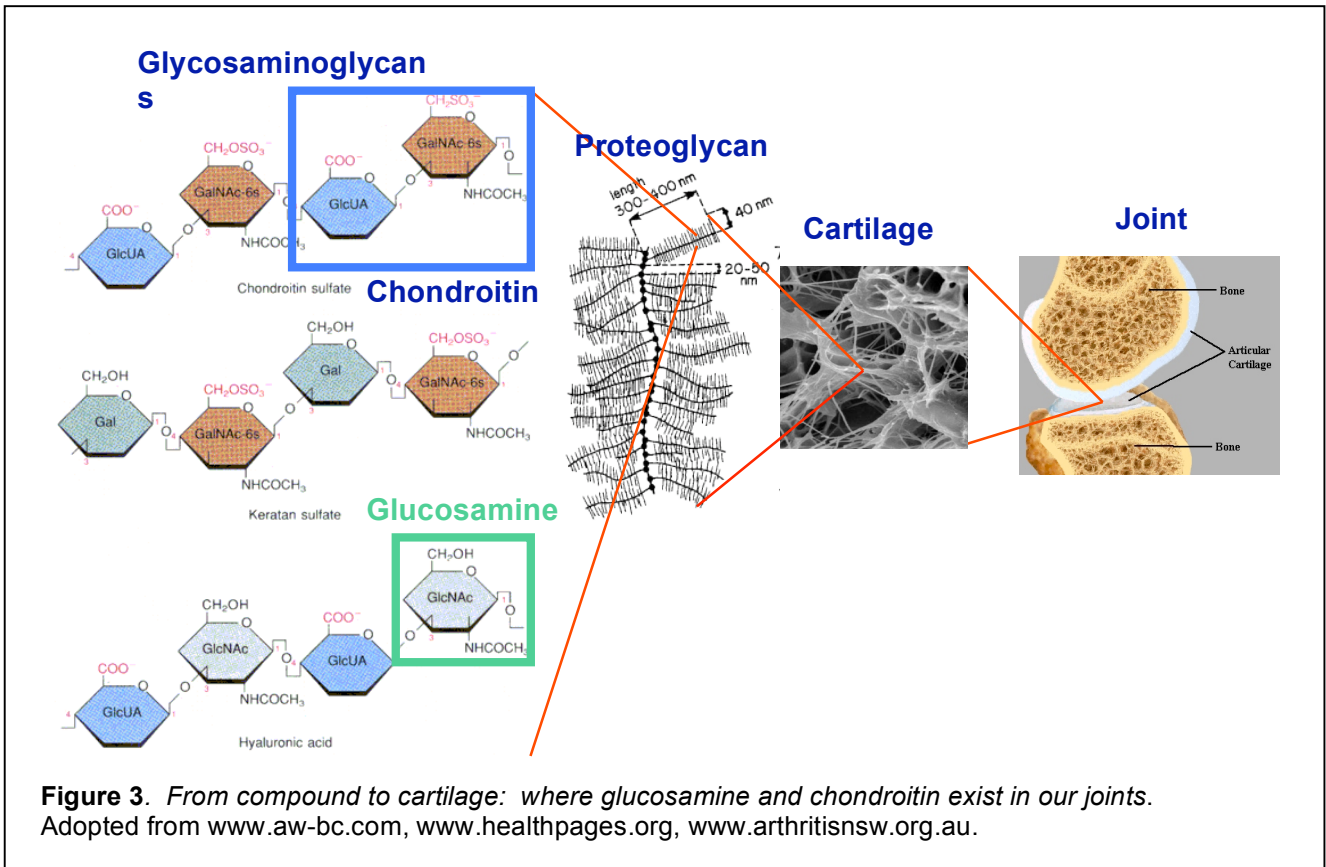
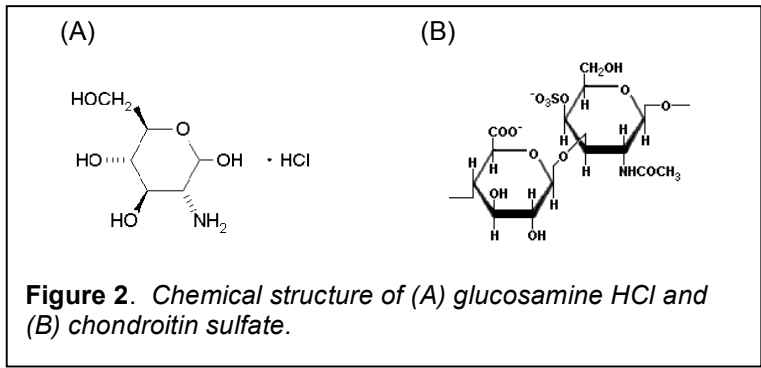
Joint cartilage is made up of a highly organized matrix that includes specialized cells, known as chondrocytes, various types of proteins, and water. Collagen protein, the most abundant protein in the body, is weaved into a matrix connected by structural compounds known as proteoglycans and glycosaminoglycans (GAGs). Together with the protein type II collagen GAGs combine to form a “web-like” structure, or flexible network of fibers that

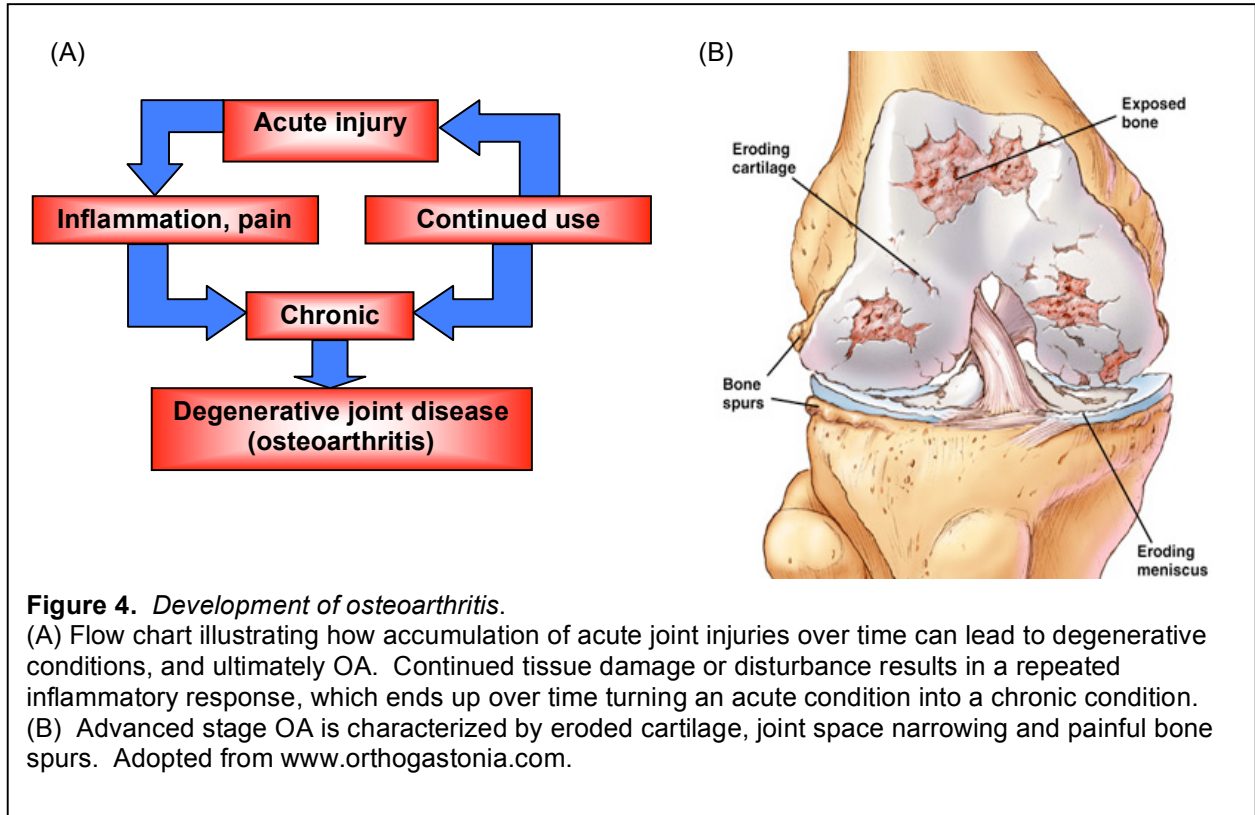
distinguish cartilage from bone, and provide the characteristic elasticity (Figure 1) (6). When combined with large amounts of water in the small joint space, this produces a tough, but compliant load-bearing surface that serves as an effective cushion between bones.

Unlike bone, cartilage generally lacks a blood supply or nerves. Therefore, the health of the joint is influenced by a variety of local factors, such as glucosamine and chondroitin, that are both biochemical and physical in nature. Glucosamine (Figure 2A) is a naturally occurring aminopolysaccharide normally produced by the body, and is the obligatory precursor for the production of GAGs (6). Chondroitin sulfate (Figure 2B) is one of the six major GAGs and is a long chain of repeating units formed from N-acetylgalactosamine sulfate and glucuronate (6). (Glucosamine is the starting material for N-acetylgalactosamine.) The GAGs formed from glucosamine and chondroitin in turn make up a large portion of the connective tissue proteins, proteoglycans (Figure 3) (7). Neither glucosamine nor chondroitin is an essential nutrient, and neither is present in any significant amount in the human diet.

As a dietary supplement, glucosamine occurs in three possible forms: as glucosamine hydrochloride, glucosamine sulfate (the most commonly studied), and N-acetyl glucosamine. The raw material for glucosamine supplements has historically been derived from extraction of chitin, a component of shellfish (shrimp, crab, and lobster). Recent technological advances have led to a more efficient means of production of a vegetarian source by fermentation (8). Chondroitin Sulfate is usually derived from bovine trachea, although other sources such as ovine or porcine trachea and shark skeletons (shark cartilage) are also used in some dietary supplements (9).







Clinical Research

Osteoarthritis (OA) is the most common degenerative joint disease, affecting 21 million Americans each year, and results from a progressive degeneration of the articular cartilage (10, 11). The large, weight-bearing joints tend to be most adversely effected – in particular, the spine, hip, and knee. Symptoms include pain, stiffness, and reduced range of motion.

In a healthy joint, the cartilage within the joint serves as a cushion, permitting the bones to rotate, glide, and roll upon each other smoothly and easily during activities like walking. Over time, acute, “micro” injuries go unnoticed, are ignored, and when not properly cared for, cause more damage that escalates the problem. The resulting chronic inflammation from repeated injury and repair (exacerbated by age, poor diet or repeated injury) can lead to elimination of the smooth matrix characteristic of healthy cartilage (Figure 4A). The result can be eroded cartilage, exposed bone, and formation of bone spurs (small calcium and tissue deposits) (Figure 4B). As erosion takes place, the joint space narrows, and with advanced forms of OA can result in “bone grinding on bone”. There are a number of established risk factors for OA, including age, overtraining with joint-loading exercises, chronic joint injury, obesity, genetics, and low estrogen levels (11).

Both glucosamine and chondroitin have been subjected to an impressive array of high-quality human clinical studies in adults with OA (Table 2). The two most recently conducted randomized, controlled trials conducted on glucosamine and chondroitin also happen to be the two largest trials conducted on these nutrients to date. The NIH-sponsored *glucosamine/chondroitin arthritis intervention trial* (GAIT) involved more than 1500 OA patients who ingested 1500 mg/day glucosamine hydrochloride, 1200 mg/day chondroitin sulfate, the combination of the two, 200 mg/day of the prescription pain medication Celebrex™, or placebo for twenty four weeks. The results after six months indicate that the glucosamine/chondroitin combination were significantly more effective at reducing moderate to severe knee pain than placebo, and slightly more so than Celebrex™ (12). The *glucosamine unum die efficacy* (GUIDE) trial conducted in Europe involved more than 300 OA patients who ingested 1500 mg/day glucosamine sulfate, 3000 mg/day acetaminophen, or placebo for twenty four weeks. Preliminary results indicate that the glucosamine sulfate was significantly more effective than acetaminophen at reducing pain (13). Both studies reported that the supplements were safe and well tolerated.

While the data are overwhelmingly supportive of glucosamine and chondroitin as effective alternative OA therapies, their effectiveness at preventing or reducing the risk of OA remains to be conclusively determined. However, the very nature of the two serving as structural components of cartilage (Figure 3) strongly supports a hypothesis of OA prevention or

delayed onset. Further, in addition to the benefits of pain reduction, research has demonstrated that alone or in combination they appear slow the progression of joint degeneration, stimulate production of new cartilage, increase joint space (or reduce joint space narrowing), have an anti-inflammatory effect, and improve mobility (14-22), all of which play an important role in the development of OA (Figure 4). These effects, rather than analgesia (the traditional treatment modality for OA), are responsible for the pain reduction conferred by glucosamine and chondroitin. Experts now agree that each of these nutrients is considered to be effective over a period of 2-6 months, with longer studies showing continued safety and benefit.

Safety

Inherent safety for long-term use of each nutrient has been extensively documented. There has been speculation that due to its chemical resemblance to glucose, high intakes of glucosamine might raise blood sugar, a possible concern for diabetics. A recent study demonstrated that the combination of daily ingestion of 1500 mg glucosamine hydrochloride and 1200 mg chondroitin sulfate over a period of ninety days had no effect on either blood sugar levels or hemoglobin A1c concentrations in diabetics (23). These findings are consistent with the results of studies conducted in healthy adults (24), and other reviews indicating that glucosamine does not have a diabetogenic effect (25). While the possibility exists for extremely high doses of glucosamine to influence blood sugar levels, there are no data to support such effects under the recommended conditions of use.

Likewise, concerns about chondroitin sulfate and interactions with anticoagulant drugs have not been found or supported. Several meta-analyses conducted and published within the past several years (2-5) and a recent risk assessment (26) have collectively concluded that both glucosamine and chondroitin supplements are as safe as placebo.

Recommended Intake

The most commonly suggested doses are 1500 mg for glucosamine (either hydrochloride or sulfate) and 1200 mg for chondroitin sulfate daily. These amounts are equally effective taken all at once or divided into two or three doses per day. Individuals with existing OA or those at high risk for developing OA, such as elderly, athletes involved in high-impact exercise, or post-menopausal women, will likely benefit the most.

Table 2. Recent Randomized-Controlled Clinical Trials on Glucosamine, Chondroitin and Joint Health[†]

Study and population	Features	Dosage and study design	Duration (days)	Relevant outcomes
GLUCOSAMINE				
Herrero-Beaumont et al. 2005 (13) <i>n</i> = 318	Adult osteoarthritis patients	1500 mg/d glucosamine sulfate, 3000 mg/d acetaminophen; randomized, controlled	24 weeks (168 d)	Significant improvement in knee pain scores vs. acetaminophen and placebo
Bruyere et al. 2004 (16) <i>n</i> = 414	Osteoarthritic post-menopausal women	1500 mg/d glucosamine sulfate; randomized, controlled	3 years (1095 d)	Significant difference in joint space narrowing (no change) vs. placebo (decrease); significant improvements in pain scores vs. placebo
Braham et al. 2003 (27) <i>n</i> = 46	Adults with unspecified knee pain	2000 mg/d glucosamine HCl; randomized, controlled	12 weeks (84 d)	Significant improvement in quality of life and knee pain scores vs. placebo
Pavelka et al. 2002 (17) <i>n</i> = 202	Adult osteoarthritis patients	1500 mg/d glucosamine sulfate; randomized, controlled	3 years (1095 d)	Significant difference in joint space narrowing (no change) vs. placebo (decrease); significant improvements in pain, function and stiffness scores vs. placebo
Reginster et al. 2001 (19) <i>n</i> = 212	Adult osteoarthritis patients	1500 mg/d glucosamine sulfate; randomized, controlled	3 years (1095 d)	Significant difference in joint space narrowing (no change) vs. placebo (decrease); significant improvements in pain, function and stiffness scores vs. placebo
Thie et al. 2001 (28) <i>n</i> = 40	Adult osteoarthritis patients	1500 mg/d glucosamine sulfate, 500 mg/d ibuprofen; randomized, controlled	90 days	Significant improvement in knee pain scores vs. ibuprofen and placebo
CHONDROITIN				
Michel et al. 2005 (14) <i>n</i> = 300	Adult osteoarthritis patients	800 mg/d chondroitin sulfate; randomized, controlled	2 years (730 d)	Significant difference in joint space narrowing (no change) vs. placebo (decrease)
Uebelhart et al. 2004 (15) <i>n</i> = 120	Adult osteoarthritis patients	800 mg/d chondroitin sulfate; randomized, controlled	6 months* (168 d)	Significant difference in joint space narrowing (no change) vs. placebo (decrease); significant improvements in pain scores vs. placebo
Mazieres et al. 2001 (18) <i>n</i> = 130	Adult osteoarthritis patients	3000 mg/d chondroitin sulfate; randomized, controlled	3 months (84 d)	Significant improvements in pain, function and stiffness scores vs. placebo
Busci et al. 1998 (29)	Adult osteoarthritis	800 mg/d chondroitin sulfate;	6 months	Significant improvements in pain, function and stiffness

<i>n</i> = 80	patients	randomized, controlled	(168 d)	scores vs. placebo
Bourgeois et al. 1998 (21) <i>n</i> = 127	Adult osteoarthritis patients	1200 mg/d chondroitin sulfate (two different forms); randomized, controlled	3 months (84 d)	Significant improvements in pain and mobility scores vs. placebo (no difference between CS forms)
COMBINATION				
Clegg et al. 2005 (12) <i>n</i> = 1583	Adult osteoarthritis patients	1500 mg/d glucosamine hydrochloride + 1200 mg/d chondroitin sulfate (alone or in combination), 200 mg/d celecoxib; randomized, controlled	24 weeks (168 d)	Combination resulted in significant improvement in pain scores vs. placebo
Das and Hammad 2000 (30) <i>n</i> = 93	Adult osteoarthritis patients	2000 mg/d glucosamine hydrochloride, 1600 mg/d chondroitin sulfate, 304 mg/d manganese ascorbate	6 months (168 d)	Significant improvements in function and stiffness scores vs. placebo
Leffler et al. 1999 (31)	Navy soldiers with degenerative joint disease	1500 mg/d glucosamine hydrochloride, 1200 mg/d chondroitin sulfate, 228 mg/d manganese ascorbate	16 weeks (112 d)	Significant improvements in pain and mobility scores vs. placebo

†For all studies, reported adverse effects were not significantly different from placebo

*Equivalent to two, 3 month treatment periods

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