

# ALBION<sup>®</sup>

## RESEARCH NOTES

A COMPILATION OF VITAL RESEARCH UPDATES ON HUMAN NUTRITION

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### Cartilage Breakdown: Osteoarthritis

**O**steoarthritis is a progressive disease characterized by the destruction of articular cartilage. This is also known as degenerative joint disease, and it is the most common form of arthritis. Osteoarthritis can involve any joint, but most often occurs in the spine, hips, knees or hands. Osteoarthritis affects more than 20 million American adults, and its prevalence increases with age. Basically 50% of all Americans 65 years or older have some form of arthritis. It is the leading chronic medical condition and

the leading cause for disability in those over the age of 65.

Osteoarthritis is a result of the breakdown of articular cartilage. Articular cartilage (see figure 1) is the substance that provides a cushion between the bones of the joints. Healthy cartilage permits bones to glide over one another and performs as a shock absorber during physical movement. In the course of osteoarthritis, the cartilage breaks down and wears away, resulting in bone on bone

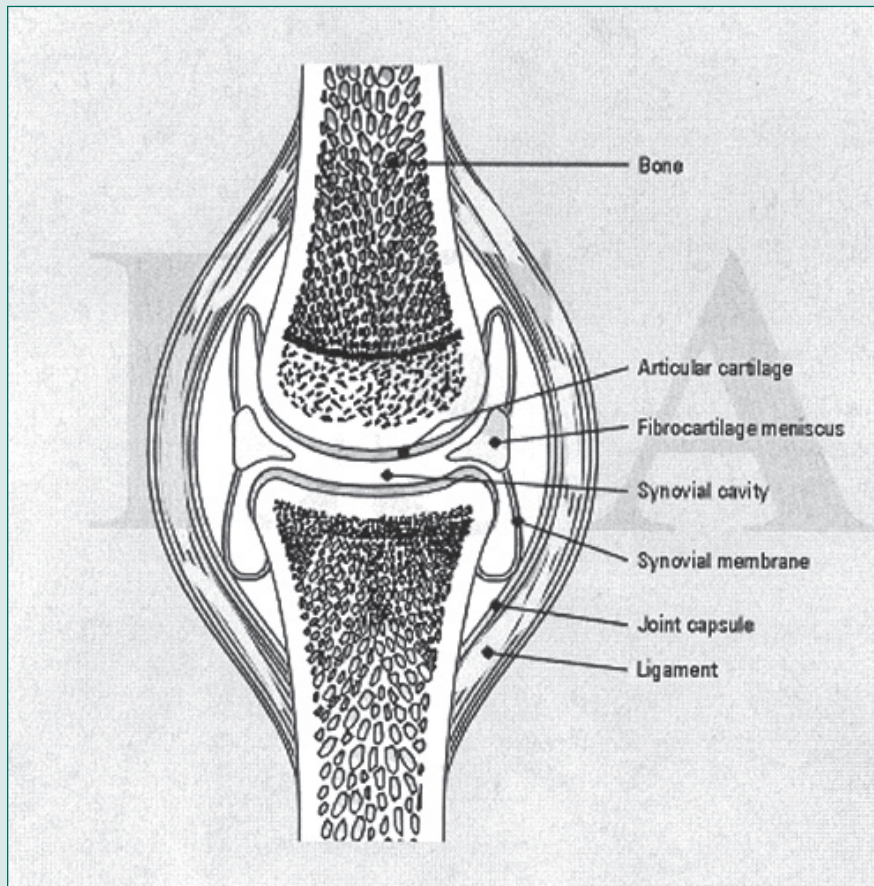
friction, which causes pain, swelling, and loss of joint mobility. This loss or breakdown of articular cartilage at load-bearing sites occurs increasingly with age, but it is not an inevitable result of age. Most articular cartilage lasts a lifetime. Age does not cause cartilage damage, but the passage of time increases ones' cumulative exposure to the risk factors of osteoarthritis.

#### Risk Factors for Osteoarthritis

1. Age – osteoarthritis is more common after the age of 45.
2. Gender – more common in women than men.
3. Hereditary conditions leading to defective cartilage and joint deformity.
4. Joint injuries incurred in sport activities, work activities or accidents.
5. Obesity.
6. Diseases that affect the structure and function of cartilage, such as rheumatoid arthritis, hemochromatosis, Paget's disease and gout.

In fact, the sequence of events in cartilage failure is not known, however, in the absence of preceding inflammation, the most critical early event is likely to be structural failure of the surface collagen, with fibrillation, fissuring and subsequent fragmentation due to repeated use. This is like the scuffing of the leather sole of a shoe (also a collagen), which will lead to a hole eventually. In some cases, the cartilage failure starts with the cartilage cracking away from the underlying bone (as

Figure 1.



in the torn cartilage seen in an athletic injury) along the line of the junction of the two, then flaking off in patches. The way in which cartilage disintegrates most likely depends on the reason for its failure.

The recognized causes for cartilage failure include:

Dysplasia ♦ Trauma ♦ Infection ♦ Other forms of preceding synovitis ♦ Osteonecrosis ♦ Osteochondritis ♦ Metabolic cartilage changes ♦ Neuropathic damage ♦ Surgical meniscectomy

### Cartilage and Its Components: A Basis for Nutritional Therapeutics

The biochemical composition of articular cartilage evolves through the various life stages. These compositional changes could likely lead to the evolution of cartilage mechanical properties. For the most part, cartilage is composed of proteoglycans, collagen, and pyridinoline crosslinks. The glycosaminoglycans (GAGs, essential components of the proteoglycans) are heteropolysaccharides. These molecules are long unbranched polysaccharides containing a repeating disaccharide unit. The disaccharide units contain either of two modified sugars, N-acetylgalactosamine (GalNAc) or N-acetylglucosamine (GlcNAc)

and an uronic acid such as glucuronate or iduronate. GAGs are highly negatively charged with extended conformation which leads to them imparting high viscosity and low compressibility to the proteoglycans, which makes them ideal for lubricating fluids of the joint. In addition, their rigidity provides structural integrity to cartilage. The GAGs of physiological importance are hyaluronates, dermatan sulfate, chondroitin sulfate, heparin and heparin sulfate, and keratan sulfate. The chondroitin sulfate and keratan sulfate (structures in Figures 2 and 3) are the GAGs most involved with articular cartilage formation.

The GAGs are most often linked to core proteins to form proteoglycans (also known as mucopolysaccharides). The GAGs extend in a perpendicular fashion from the protein core in a brush-like structure. The GAGs are linked to the protein core through a specific trisaccharide made of two galactose and one xylulose residue. The trisaccharide linkage is coupled to the protein core through a bond to a serine residue in the protein (see Figure 4).

The understanding of the formation and biochemical composition of cartilage has been looked at in the current nutraceutical cartilage repair strategies.

### Importance of Manganese

Manganese is an essential trace mineral. It has been shown to scavenge hydroxyl and superoxide radicals. Manganese is a critical component of the metalloenzyme manganese superoxide dismutase (MnSOD), which is found in the mitochondria of the lymphocytes, and is the principal constituent of the mitochondrial oxidant defense system. Animal studies have verified that animals fed a manganese deficient diet are known to have reduced MnSOD activity in the heart muscle and nervous tissue. These animals have been found to have mitochondrial abnormalities and pathological changes to the tissues mentioned, resulting from oxidative damage due to reduced MnSOD activity.

In the formation of proteoglycans, manganese has been clearly demonstrated to be a key component to the enzymatic catalyst system which is responsible for the formation of cartilage. There are at least six (6) known glycosyltransferases which require manganese as their cofactor. These enzymes, with the needed assistance of manganese, are involved in the biosynthesis of the linkage of the glycosaminoglycan chains as part of the proteoglycan biosynthesis (chondroitin, keratan, dermatan, etc.). Dietary manganese deficiency results in skeletal and cartilage malformations, which are

Figure 2.

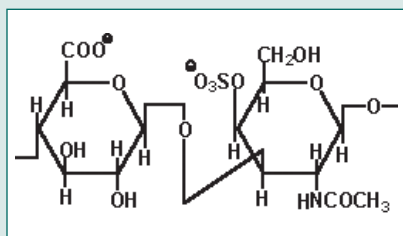


Figure 3.

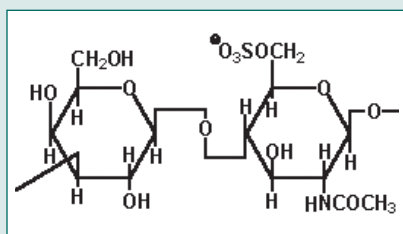
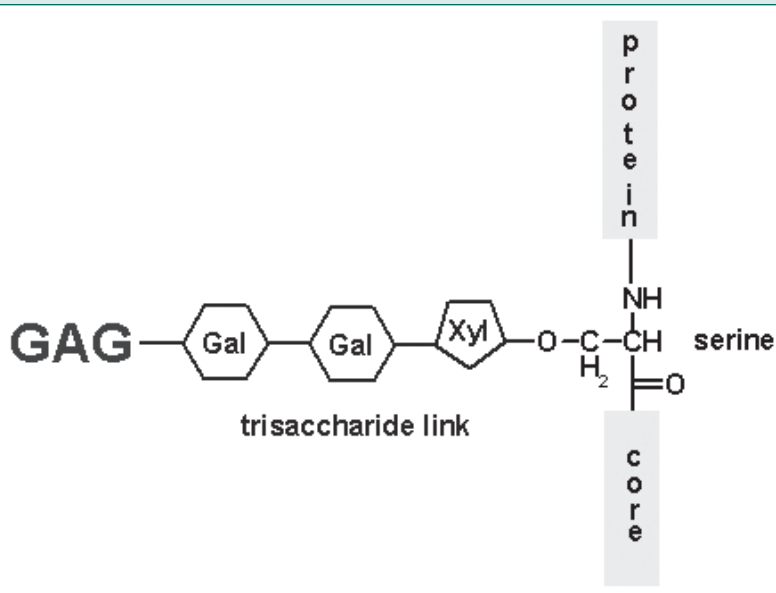


Figure 4: Structure of the GAG linkage to protein in proteoglycans



thought to be due to the decreased activity of the manganese-dependent glycosyltransferases.

## Nutritional Cartilage Repair Strategies

Recently, there have been several studies which examine the use of a combination of nutrients in the treatment of osteoarthritis, and other cartilage related disorders. These repair strategies have combined the use of manganese, glucosamine, and chondroitin. In certain cases, manganese, as ascorbate has also been used. The majority of these research trials have been published over the last five years. In 1977, almost 30 years ago, Dr. DeWayne Ashmead of Albion, along with Roy Nipko DVM was involved in a nutritional cartilage repair study (*Canine Disc Disease: cause, prevention, and a new approach to treatment*, Veterinary Medicine/Small Animal Clinician, August 1977, pp. 1337-1342). In this study, it was seen that the supplementation of the animals (dogs) with the Albion Manganese Amino Acid Chelate led to improvement in the animals that had the disc disease. Additionally, the data accumulated at the start of this study indicated that the animal that had disc disease contained 91% less manganese than the disc disease-free animals.

The following are four (4) examples of studies that have incorporated glucosamine, chondroitin and manganese in treatment trials to help in the repair of cartilage in a variety of degenerative joint disease disorders:

- *Glucosamine, chondroitin, and manganese ascorbate for degenerative joint disease of the knee or low back: a randomized, double-blind, placebo-controlled pilot study.*

Leffler CT, et al.

Mil Mid 1999 Feb;164(2):85-91.

Finding: This combination was found to relieve subjective and objective signs of osteoarthritis.

- *Efficacy of combination of FCHG49 glucosamine hydrochloride, TRH122 low molecular weight sodium chondroitin sulfate, and man-*

*ganease ascorbate in the management of knee osteoarthritis.*

Das A and Hammad TA.

Osteoarthritis Cartilage 2000 Sep; 8(5):343-350.

Finding: The studied nutrition combination was found to be effective for the treatment of radiographically mild to moderate osteoarthritis of the knee measured by the Lesquene Index of severity of osteoarthritis of the knee.

- *Effects of an orally administered mixture of chondroitin sulfate, glucosamine hydrochloride, and manganese ascorbate on synovial fluid chondroitin sulfate 3B3 and 7D4 epitope in a canine cruciate ligament transaction model of osteoarthritis.*

John KS, et al.

Osteoarthritis Cartilage 2001 Jan;9(1):14-21.

Finding: The administration of the combination of chondroitin, glucosamine, and manganese were observed to significantly elevate the epitope levels of chondroitin, suggesting that these compounds may act to modulate articular cartilage matrix metabolism in vivo.

- *Effect of pre-loading oral glucosamineHCl/chondroitin sulfate/manganese ascorbate combination on experimental arthritis in rats.*

Beren J, et al.

Exp Biol Med (Maywood) 2001 Feb;226(2):144-151.

Finding: This nutrient combination was seen to impart a statistically significant decrease in the prevalence of collagen induced autoimmune arthritis (as measured by arthritis index and histologic index scoring).

## Summary

Physical and chemical damage to the cartilage, including the discs of the spine, have been shown to be at the root of a wide range of musculoskeletal disorders. In many cases, people are put on a variety of anti-inflammatory drugs in an attempt to palliate the pain and inflammation that these cartilage problems give rise to. In certain situations,

physical therapy is also employed. For the more extreme conditions, surgery is often performed toward the same end. It has been commonly held that cartilage tissue was not one that could be regenerated. Too slow a building process. Research has provided a way to grow this type of tissue in the lab, and subsequently inserting this tissue into the body at the site it is needed. Interest is growing for this approach. In the studies mentioned earlier, it has been clearly shown that cartilage disorders do respond in several ways to nutritional repair strategies. The nutritional combination of manganese, glucosamine, chondroitin and ascorbate are amongst the most commonly evaluated nutritional cartilage repair strategies. All of them are involved in the biochemical building of cartilage. Unfortunately, the efficiency of absorption for glucosamine, chondroitin sulfate, and manganese are relatively low. According to research on this subject, glucosamine has a relative absorption of around 12%, while low molecular weight chondroitin is around 4.8 – 5% [Adebowale A, et al, Biopharm Drug Dispos 2002 Sep;23(6):217-225], and manganese salts have checked in at about 5% absorption efficiency (PDR Health, 2004). The studies that have shown benefits to the use of these nutritional repair strategies have done so at very high doses for the glucosamines and chondroitins.

As mentioned, manganese salts, including ascorbates have been demonstrated to be of low absorption efficiency. Albion's Manganese Chelazome® (manganese glycine amino acid chelate) has been shown to be far superior in absorption to the manganese salt forms (Davis C.D. and Gregger J.L., Am J Clin Nutr, 1992;55:747-752). The use of Manganese Chelazome® in cartilage repair strategies could result in improved manganese absorption, which theoretically could improve the effectiveness of this treatment. Albion's Research and Development Division is looking at ways to improve the relative absorption of the various components of the mentioned nutritional approaches to cartilage repair.

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