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## **Inflamed Joints: The Oxidative Stress Connection**

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Oxidative stress is probably not the first thing that comes to mind when you hear the word "arthritis." When your customers mention joint pain, you probably think aging, wear and tear, physical injury or maybe a food allergy. Supplementally, you might recommend chondroitin or glucosamine sulfate. However, from the field of sports nutrition - an area where musculoskeletal injury accounts for 90 percent of all injuries and every athlete has a 50 percent chance of sustaining an injury (1), we are learning that oxidative stress is a key to understanding musculoskeletal and joint health.

### **The Structure Of Joints**

Joints sound simple but they aren't. Articulations (a common medical term for joints) are places where bones come together to allow coordinated movement. There are 206 bones in the human skeleton and the vast majority of them come together in synovial articulations, where a fluid-containing cavity separates the bones from each other. The synovial cavity is lined by a synovial membrane charged with holding the synovial fluid in place. This membrane rests not against the bones, but against cartilage, a special tissue connecting the ends of the bones. Because special tissue (cartilage) forms the articular surface, it is typically called "articular cartilage."

In osteoarthritis, the most common form of arthritis, damage to the articular cartilage is visible upon X-ray. In fact, researchers have predicted that one-third of all adults in the United States over age 65 would show articular cartilage damage in the hands, feet, knees and hips upon X-ray. (2) In rheumatoid arthritis, the second most common form, the articular cartilage is compromised initially by an abnormal tissue (pannus) covering the articular cartilage. These abnormal deposits on the articular surface are understood to result from chronic inflammation of the synovial membrane. Although no one is exactly sure how joint components become dysfunctional, more and more evidence points to the role of oxidative stress in exacerbating inflammation and worsening joint health.

Once again, sports nutrition has taught us a lot about oxygen, oxidative stress and the joints. Movement requires oxygen, and exercising cells may need 15 times as much oxygen as resting cells. (3) But there are paradoxes to oxygen metabolism and it is delicately balanced: The body is much more efficient at producing energy when oxygen is around; but when it is, highly reactive

molecules (reactive oxygen species or ROS) are formed and can cause cell damage. To handle ROS, special oxygen-processing enzymes and ROS-neutralizing molecules are required. Free radicals are one type of ROS requiring special neutralizing molecules called free-radical scavengers. Oxidative stress is defined as any condition where increased ROS are not properly balanced by increased oxygen-processing enzymes and ROS-neutralizing molecules.

### **Hypoxia, Oxidative Stress and Arthritis**

One line of thinking about oxidative stress' role in joint pain involves analysis of movement and blood flow. The articular cartilage is unique because it is avascular, meaning it does not directly receive blood flow. Like some other body tissue (lymphatic tissue, for example), the cartilage depends directly on movement for nourishment. Motion of the ligaments (bone-to-bone connectors) and tendons (bone-to-muscle connectors) surrounding a joint facilitates delivery of nutrients to the cartilage in part by allowing nearby blood vessels to fully dilate. As long as pressure in the exercising blood vessels exceeds pressure in the synovial cavity, joint nourishment is enhanced. But when movement is absent and the synovial pressure becomes greater than the pressure in nearby blood vessels, the vessels can collapse and a process called hypoxic-reperfusion injury may begin. (4)

This process involves one of the great ironies of oxygen metabolism: Production of ROS and risk of damage to cells is greatest when oxygen concentrations are lowest. In rheumatoid arthritis, damage to the synovial cavity has been shown to correlate with fluctuating oxygen pressure in the joint, overproduction of ROS, lack of oxygen-processing enzymes and free-radical scavenging molecules. (5)

### **Oxidative Stress and Connective Tissue Structure**

Another line of thought about oxidative stress and arthritis involves the nature of connective tissue itself. Unlike most other tissues, connective tissue is predominantly non-cellular and is primarily composed of an extracellular matrix (ECM). Three basic components are found in this ECM: fibers (especially collagen fibers), ground substance (composed of glycosaminoglycans and glycoproteins), and fluid.

The best-studied fibers in the ECM of connective tissue are the collagen fibers. These proteins are the most abundant in the body and constitute about 30 percent of all body protein by weight. Collagen stability has been shown to be highly sensitive to levels of inflammatory messenger molecules in the synovial fluid. When levels of these inflammatory messaging molecules (like interleukin-1 or tumor necrosis factor alpha) are high, collagen damage and arthritis risk are greatly increased. (6) The debate about

estrogen levels and arthritis may be partially resolved with future research in this area. Researchers have often speculated that autoimmune forms of arthritis like lupus, scleroderma and rheumatoid arthritis in women may be greatly impacted by estrogen metabolism, but findings have been confusing. In rheumatoid arthritis, increased estrogen supply (as might be provided by oral contraceptive use, for example) has been suggested to protect against joint damage. In the case of lupus, however, flare-ups during pregnancy have suggested that upregulated estrogen metabolism may be problematic because estrogen levels can increase by almost 100 times over pre-pregnancy levels. Researchers at the University of Goteborg, Sweden, have recently shown that administration of one form of estrogen (estradiol) can greatly suppress collagen damage in cell cultures, and apparently does so by modifying oxidative metabolism with a special emphasis on lowering nitric oxide production. (7)

If the oxidative stress/connective tissue hypothesis is correct, we would expect to see supplementation with oxygen-processing enzymes and free-radical-scavenging molecules to have a protective effect on connective tissue. So far the jury is still out, but the evidence is pointing toward a favorable verdict. The antioxidant n-acetyl-cysteine (NAC) has been shown to suppress activity of the inflammatory messaging molecules like tumor necrosis factor alpha, thus blocking an inflammatory cascade resulting in overproduction of ROS. (8) Some similar effects have been shown for the reduced form of the antioxidant glutathione (GSH), and also for the oxygen-processing enzyme catalase (CAT). Interestingly, protective results were not shown for the better-known protective enzyme superoxide dismutase (SOD). (9)

In these same studies conducted on cell cultures at the Rush Medical College in Chicago, researchers emphasized that antioxidant protection only seems to work in conjunction with the body's immune messaging systems. In other words, the antioxidants may not be working directly on the damaged cartilage and connective tissue, but may instead be shifting the balance of cytokine messaging molecules that drive the inflammatory process. If this theory is correct, and connective tissue damage is "cytokine driven," future research might focus more specifically on the known modifiers of cytokine balance. These modifiers would include branched-chain amino acids, sulfur-containing amino acids, many carotenoids, vitamin E, essential fatty acids, isoflavones found in soybeans, lipoic acid, curcumin (in the spice tumeric) and other phytochemicals from commonly consumed beverages like green tea, or common culinary herbs like rosemary (*Rosmarinus officinalis*).

### **Glycosaminoglycans**

Two major families of molecules are present in the ground substance portion of connective tissue. The best researched are the glycosaminoglycans, or GAGS. Sometimes these substances are also referred to as mucopolysaccharides. The

GAGs are classified as linear polysaccharides because they are composed of a central, repeating disaccharide (two-sugar) unit strung out in a long chain. This disaccharide unit usually consists of a sugarlike unit called a uronic acid and a second sugarlike unit called a hexosamine. Glucuronic acid is the most common uronic acid in the GAGs, and glucosamine and galactosamine are the most common of the GAGs' hexosamines. With the exception of hyaluronic acid, all GAGs are sulfated meaning they are connected to a chemical group containing one atom of sulfur.

In addition to the GAGs critical role in determining the structure, viscosity and permeability of the ground substance in all connective tissue, they also play important metabolic roles in the health of connective tissue and joints. Transport of ions, diffusion of nutrients, retention of water, binding of growth factors, intercellular signaling and collagen synthesis all depend on GAG function. (10)

Hyaluronic acid (HA), which contains glucosamine and glucuronic acid, is a critical GAG in synovial joints because it is the predominant GAG in the articular surface and is also a key component of the synovial fluid. Orally supplemented glucosamine has been shown to be readily incorporated into hyaluronic acid synthesized by fibroblast cells. (11) Availability of glutamine appears to be an important factor in the manufacture of HA's other key component, glucuronic acid.

Oral supplementation with glucosamine sulfate has been examined in numerous studies of arthritis with repeatedly impressive results. Daily dose ranges have varied between 750 and 1,500 mg, usually administered in three to six equally divided amounts. In comparison with non-steroidal anti-inflammatories like ibuprofen, glucosamine sulfate has been shown to be slower acting but of greater effectiveness over an eight-week period. (12) In Portugal, a large multi-center trial involving 252 physicians and 1,208 arthritic subjects found oral glucosamine to be more effective in reducing pain from exertion and decreasing limitations on active and passive movement than any previously attempted treatment with the exception of glucosamine injection. (13)

The exact connection between GAGs and oxidative stress is not entirely clear. We know hyaluronic acid can itself be oxidized by ROS, and the hypoxia-reperfusion hypothesis discussed earlier may directly relate to oxidative damage of the articular surface through oxidation of the GAGs. (14) We also know from studying endothelial tissue in the lungs that there is a decrease in cellular proteoglycans (proteoglycans are GAGs linked together) upon exposure to oxidized fats. The decrease is caused by dysfunction in proteoglycan metabolism. (15) If similar mechanisms are at work in the joint, many of the considerations involving oxidized lipids, plaque formation and atherosclerosis--which we have been considering primarily in the area of cardiovascular health--will become considerations in understanding arthritis.

## Essential Fatty Acids

One critical aspect of diet for regulating oxidative stress and inflammation in the joints is essential fatty acid (EFA) intake. Quality of fat has a dramatic impact on inflammatory events, and, in particular, the ratio of omega 3 to omega 6 fatty acids in the diet should be a focal point for all of your arthritic customers. Only when the 3:6 ratio falls into the 1:1 or 1:2 range (as it does when compared to other diets around the world, such as the Mediterranean diet) do we get inhibited synthesis of the pro-inflammatory messaging molecules made from arachidonic acid. (16)

In the United States, 3:6 ratios have been estimated to fall into the 1:10 to 1:25 range - exponentially higher than the worldwide average. To make matters worse, virtually all public health recommendations in the last 10 years have created further obstacles for a balanced ratio. By focusing on intake of omega 9 fatty acids (i.e., recommendations for increased olive oil in the diet) and by encouraging use of plant oils high in omega 6 (i.e., recommendations for increased consumption of canola, safflower and sunflower oil), consumers have been given a blueprint for maintaining highly imbalanced 3:6 ratios. In addition to the well-known cold water fish (like salmon and halibut) and their oils, there are also omega 3-rich sources in the plant world. Flax seed, pumpkin seed and their carefully processed oils are examples of supplements that can help balance 3:6 ratios in an arthritis-preventive diet.

The list of oxidative stress-related conditions has been growing steadily in the past 10 years. Now included on this list are neurodegenerative diseases like Parkinson's and Alzheimer's (17), cardiovascular conditions like atherosclerosis (18), gastrointestinal problems like inflammatory bowel disease (19), lung cancer (20), AIDS (21) and, as argued in this article, arthritis. While this oxidative stress connection might complicate our approach to nutritional support for the joints, it also may simplify our customers' understanding of diet and health because it moves toward a unified theory of many common disorders and focuses attention on an increasingly well-recognized group of antioxidant supplements.

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