ALBION®
HUMAN NUTRITION

RESEARCH NOTES

A COMPILATION OF VITAL RESEARCH UPDATES ON HUMAN NUTRITION

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Arthritis: The Role of Minerals in the Palliation of Inflammation

Osteoarthritis: The most common form of arthritis, characterized by degenerative loss of articular cartilage, subchondral bony sclerosis (hardening), and cartilage and bone proliferation at the joint margins with subsequent osteophyte (bony outgrowth) formation[1].

Rheumatoid Arthritis: A chronic syndrome characterized by nonspecific, usually symmetric inflammation of the peripheral joints, potentially resulting in progressive destruction of articular and periarticular structures1.

There are many disorders that are forms of, or related to arthritis, in addition to the two major types listed above. These include psoriatic arthritis, ankylosing spondylitis, Sjogren's Syndrome, Lyme Disease, infectious arthritis, Reiter's Syndrome, Behcet's Syndrome, neurogenic arthropathy, gout, and chondrocalcinosis.

In osteoarthritis and rheumatoid arthritis, there is a focal loss of cartilage resulting from increased activity of catabolic pathways. This catabolic activity is stimulated, for the most part, by pro-inflammatory cytokines, like interleukin-1 and tumor necrosis factor alpha. In addition, reactive nitrogen and oxygen intermediates are involved in the extracellular-matrix-degrading activity and may also be responsible for the cartilage damage occurring in osteoarthritis and rheumatoid arthritis. With this in mind, Mazzetti I, et al.[2] evaluated the oxidative stress related to reactive nitrogen and oxygen intermediates in osteoarthritic and rheumatoid arthritic patients. The results of this study suggested that nitric oxide plays a major role in altering chondrocyte (cartilage cells) function in osteoarthritis, while the harmful effects of radical oxygen intermediates are more evident in the chondrocytes from patients with rheumatoid arthritis. All of this comes from an imbalance in the ratio of oxidants to antioxidants.

Evans and Halliwell[3] state that the damaging oxidative species (reactive oxygen, nitrogen and others) arise as by-products of metabolism and as physiological mediators and signaling molecules. The levels of these oxidative intermediates are held in check by the antioxidant defense

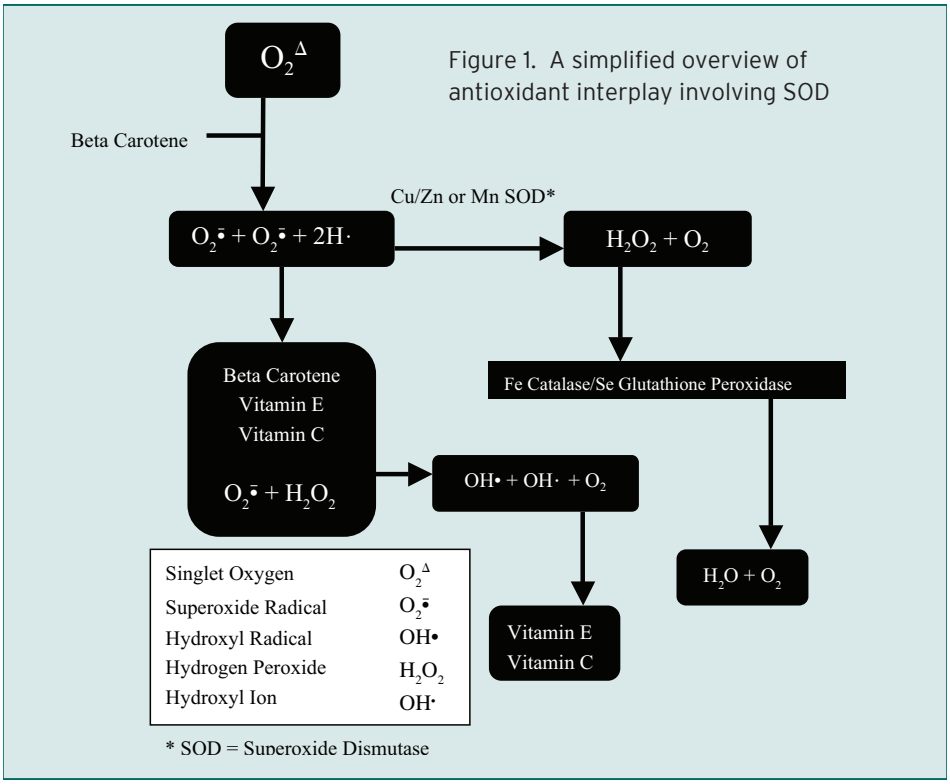

Figure 1. A simplified overview of antioxidant interplay involving SOD

system. The components of this defense system are micronutrients, like vitamins C and E, or are dependent on dietary micronutrients (e.g. Cu/Zn and Mn superoxide dismutase). The antioxidant defense is a coordinated system in which deficiencies in any one component will impact the efficiency of the others (Figure 1). A deficiency in these micronutrients leads to oxidative stress, which leaves body tissues open to the damaging effects of the oxidative intermediates seen in arthritics.

Copper, zinc and manganese are key components of the two major superoxide dismutase enzymes which have been shown to fight against the reactive intermediaries that are linked to the joint damage in arthritis. Mitochondrial manganese superoxide dismutase (Mn-SOD) is the primary cellular defense against damaging superoxide radicals generated by aerobic metabolism and as a consequence of inflammatory disease. Elevated levels of Mn-SOD provides potent cytoprotective advantage during acute arthritic inflammation[4]. The trace elements copper, zinc and selenium are linked together in cytosolic defense against reactive oxygen and nitrogen species. Copper/zinc superoxide dismutase (Cu/Zn SOD) catalyzes the conversion of superoxide to oxygen and hydrogen peroxide. The hydrogen peroxide and other hydroperoxides are subsequently reduced by the selenium containing enzyme, glutathione peroxidase (GPX)[5].

Nitric oxide is a highly reactive nitrogen intermediate involved in extracellular-matrix degrading activities that destroy cartilage (as seen in degenerative arthritis). Animal research[6] has shown that selenium dietary supplements inhibit the generation of nitric oxide, and are useful in the treatment of chronic inflammatory diseases, like arthritis. Recent studies[7,8] have shown that low selenium status has been associated with the risk for rheumatoid arthritis. A human research trial[8] indicated that patients with rheumatoid arthritis (RA) had significantly lower red cell selenium levels, and that supplementation with selenium lead to improvement in the symptoms associated with RA.

Figure 2.

Enzymes requiring zinc as a cofactor.
These are representative of the many requiring zinc for activity.

Alcohol dehydrogenase	δ-Aminolevulinate dehydrase
Lactate dehydrogenase	Fructose-1,6-bisphosphatase
Alkaline phosphatases	Transcarboxylases
Angiotensin converting enzyme	Reverse transcriptase
Carbonic anhydrase	Leukotriene hydrolase
Carboxypeptidase A, B, and DD	Phosphodiesterase
Cytoplasmic superoxide dismutase (also requires copper)	Elastase
DNA and RNA polymerases	Adenosine deaminase
Pyruvate dehydrogenase	5´Nucleotidase
Proteases and peptidases	Glyoxalase
Aspartate transcarbamylase	Transcription factor Sp 1
Thymidine kinase	Thymulin

Carolyn D. Berdanier, Advanced Nutrition Micronutrients, CRC Press 1998.

Related Albion Chelate Research

Copper Supplementation in Young Adult Women: Effects on Collagen Crosslinks and Oxidant Stress.
DiSilvestro R, Human Nutrition Ohio State University. FASEB, Spring 2003.

Copper status could affect bone breakdown in young adult women via at least two mechanisms: 1) lysyl oxidase activity, a copper enzyme which crosslinks collagen, which is involved in bone structure: and 2) superoxide dismutase 1 activity, which eliminates superoxide radical, thus stimulating bone resorption. This study was done on young adult women who were screened for copper status based on erythrocyte superoxide dismutase activity. Women with Cu/Zn SOD activities <65% of typical maximal values (this was the case in the majority of women screened) were admitted into the study. These women were supplemented with copper (2 mg/day as copper glycine amino acid chelate-Albion) or a placebo for 6 weeks. The copper, but not the placebo, raised superoxide dismutase activities as well as urinary ratios of collagen crosslinks to collagen protein. The copper glycine amino acid chelate also decreased values for two oxidant stress markers: urinary 8-isoprostane and LDL oxidation. Although the latter marker is more relevant to heart disease than bone, the improvement is indicative of better defense against free radicals.

The researcher concluded that a high percentage of young women have submaximal copper enzyme erythrocyte SOD activity, and that supplementation with copper glycine amino acid chelate has a positive impact on para-meters relevant to bone health and oxidant stress.

Figure 3.

Eznymes Requiring Copper as a Cofactor

Cytochrome c oxidase
Lysyl oxidase
Tyrosinase
Dopamine-β-hydroxylase (DOPA-4-monoxygenase)
Tyrosine oxidase
Cytoplasmic superoxide dismutase (Cu/Zn SOD)
Amine oxidase
Diamine oxidase
Monoamine oxidase
α-Amidating enzyme
Ferroxidase II
Ascorbate oxidase
Phenylalanine-4-monooxygenase
Metallothionein
Ceruloplasmin

Carolyn D. Berdanier, Advanced Nutrition Micronutrients, CRC Press 1998.

Longitudinal Changes of Manganese-dependent Superoxide Dismutase and Other Indexes of Manganese and Iron Status in Women.
Cindy D Davis and JL Greger.
Am J Clin Nutr 1992; 55:747-52.

Prior to the following study, the effect of dietary factors on manganese dependent superoxide dismutase (MnSOD) in humans had not been studied. In this study, the researchers evaluated the changes in MnSOD activity and other indices of manganese and iron status in women during a 124 day supplementation study. The women were placed into one of four groups: placebo, iron treated – 60mg of iron from ferrous fumarate, manganese treated – 15mg of manganese from manganese glycine amino acid chelate (Albion), and a combination of both manganese and iron. The manganese glycine amino acid chelate supplementation led to significant increases in MnSOD activity and serum manganese concentrations, and this was true for the group on manganese alone, as well as for the group on the combination of manganese and iron.

Short-term Zinc Supplementation in Women with Non-Insulin-Dependent Diabetes Mellitus; Effects on Plasma 5´-Nucleotidase Activities, Insulin-like Growth Factor 1 Concentration, and Lipoprotein Oxidation Rates in Vitro.
Blostein-Fujii A, et al.
Am J Clin Nutr 1997; 66:639-42.

Non-insulin-dependent diabetes mellitus (NIDDM) may cause vulnerability to moderate zinc deficiency. In the following study, a short term zinc supplementation (30mg/day of zinc as zinc glycine amino acid chelate-Albion) elevated plasma zinc and activities of 5´ nucleotidase, a zinc dependent enzyme, in 20 post menopausal women with NIDDM. The placebo treated group of women with NIDDM showed no effects on these indexes, nor any others taken in this study. The zinc supplementation doubled the mean values for 5´-nucleotidase activity. Plasma insulin-like growth factor 1 concentrations increased with the zinc glycine amino acid chelate treatment, when concentrations were <165mcg/L. The researchers conclude that moderate zinc deficiency is a frequent occurrence in subjects with NIDDM.

Figure 4.

Selenoproteins of Biological Importance

Cytosolic glutathione peroxidase
Phospholipid hydroperoxide glutathione peroxidase
Gastrointestinal glutathione peroxidase
Extracellular glutathione peroxidase
Selenoprotein W
Selenoprotein P
Iodothyronine deiodinase
Sperm capsule selenoprotein

Carolyn D. Berdanier, Advanced Nutrition Micronutrients, CRC Press 1998.

Summary

Research has clearly demonstrated that several trace minerals play a role in controlling or decreasing inflammation. Copper, zinc, manganese, and selenium each promote antioxidant activities that have positive effects on countering the impact of the oxidant stress that is seen in a variety of inflammatory health problems. Oxidant stress is a key causative factor in the joint damage that occurs in arthritis. The supplementation of these trace elements would be a rational suggestion for inclusion in a program to help control or treat arthritic conditions.

Clinical studies on Albion's zinc, copper, and manganese glycine amino acid chelates have clearly demonstrated that they are highly bioavailable and that they, in fact, improve the levels of the antioxidant enzymes known to have beneficial effects in arthritic conditions.

In the October 2000 (Vol, 9, No. 3) issue of the Albion Research Notes, many positive effects were documented for the amino acid glycine. Subsequently, more investigation into the effects of glycine have taken place. In a recent animal study[10], glycine was shown to be involved in the prevention of reactive arthritis through its ability to blunt the cytokine release associated with arthritis.

Albion's patented Zinc, Manganese, and Copper Chelazome® all use glycine as their chelating ligand, and were the chelates used in the above studies which demonstrated their positive impact on the antioxidant enzyme activities. Albion's Selenium Amino Acid Complex is selenium glycine complex.

In formulating nutritional supplements, as part of an overall program for arthritis, the following should be included as key components:

- Copper Chelazome®
- Manganese Chelazome®
- Zinc Chelazome®
- Selenium Amino Acid Complex

Figure 5.

Enzymes Requiring Manganese

Pyruvate carboxylase
Acetyl CoA carboxylase
Isocitrate dehydrogenase
Mitochondrial superoxide dismutase
Arginase
Glucokinase
Galactose transferase
Hydroxymethyl transferase
Superoxide dismutase

Carolyn D. Berdanier, Advanced Nutrition Micronutrients, CRC Press 1998.

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