ALBION®
HUMAN NUTRITION

RESEARCH NOTES

A COMPILATION OF VITAL RESEARCH UPDATES ON HUMAN NUTRITION

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Antioxidant Defense Systems and Trace Minerals

The amount of medical and other scientific research giving strong evidence to support the positive benefits derived from antioxidant micronutrient supplementation continues to grow.

Free radicals (the antioxidants' arch enemy), as a causative factor in the disease and aging process, have become popular focal points of clinical research. The increased interest into the negative health effects of free radicals has given rise to the term *Free Radical Pathology*. Free radicals have been implicated as a pathological factor in the following health problems: arthritis, atherosclerosis, ischemic heart disease, cancers, cataracts, emphysema and retinopathy.

The main target of free radicals is the polyunsaturated fats (PUFA) that make up the major part of the cell membranes. Free radical attacks cause the PUFA to undergo a process called peroxidation (becoming rancid in nature). This rancidity causes further free radical propagation which leads to cellular damage, enzyme deactivation, and a foothold for the health problems listed above.

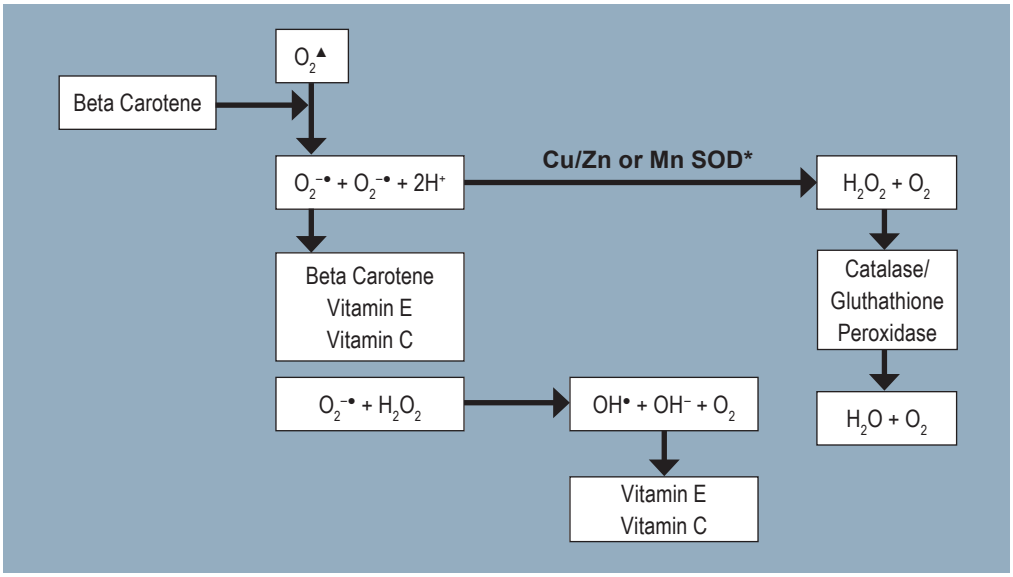
With the growth in knowledge of free radical pathology has come renewed interest in the roles of the antioxidant micronutrients. The effectiveness of vitamin E, vitamin C, and beta-carotene as potential weapons against the dangers of free radicals has been most frequently investigated. Much evidence points to their effectiveness in fighting atherosclerosis, cataracts, and enhancing the immune system.

More recently, the roles of certain trace minerals in the maintenance of the body's antioxidant defense system have produces increased interest. Selenium, iron, copper, zinc, and manganese have all exhibited antioxidant involvement.

A major player in the body's antioxidant defense system is an enzyme known as superoxide dismutase (SOD). Many supplements reportedly offer superoxide dismutase as an ingredient. Unfortunately, the molecular weights of enzymes are quite high. The copper-zinc SOD has a molecular weight in excess of 30,000 daltons, while the manganese SOD weighs more than 60,000 daltons.

In either case, both structures have molecular weights that far exceed what the body can absorb intact without digestion which, in this case, results in the destruction of the SOD enzyme. Research has shown that molecules weighing 1,500

Figure 1.
Simplified Overview of Antioxidant Interplay



Singlet Oxygen = $O_2^{\blacktriangle}$
Superoxide Radical = $O_2^{-\bullet}$
Hydroxyl Radical = $OH^{\bullet}$
Hydrogen Peroxide = H_2O_2
Hydroxyl Ion = OH^-

* SOD = Superoxide Dismutase

daltons are the maximum size for intact absorption. In view of this, it becomes obvious that SOD supplements are of little or no value. Instead, we need to supplement certain components of SOD.

How do these nutrients aid the SOD defense systems? Scientific studies have shown that the proper intake of copper, zinc, and manganese are required for optimal activity of the several types of superoxide dismutase. Currently, three SOD enzymes have been identified:

- SOD-1 (Cytosolic, Copper/Zinc SOD)
- SOD-2 (Mitochondrial, Manganese SOD)
- SOD-3 (Erythrocyte, Copper/Zinc SOD)

As Shown in Figure 1, when the proper trace minerals are part of the enzyme, SOD functions enzymatically to convert toxic superoxide anion radicals to hydrogen peroxide, which is then converted to water, etc., via the action of glutathione peroxidase or catalase. All of the enzymes in the antioxidant protective systems require the presence of specific trace minerals for their activities. The superoxide anion is an unstable, reactive, and therefore chemically dangerous free radical, and if not chemically quenched via the SOD defense pathway, it can initiate lipid peroxidation, which results in the accumulation of water soluble fluorescent compounds in the liver, lungs, spleen, kidneys, heart, and brain (lipofuscin or ceroid pigments).

Henning, B., "Dietary Fat and Micronutrients: Relationships to Atherosclerosis", The Journal of Optimal Nutrition 1 (1): 21-23, 1992.

Rosenber, I., "Mutations in the Copper and Zinc Containing Superoxide Dismutase Gene are Associated with Lou Gehrig's Disease", Nutrition Reviews 51 (8): 243-45, August, 1993.

Harman, D., "Free Radical Theory of Aging: The Free Radical Disease", Age, 7: 111-31, 1984.

Halliwell, B. and Gutteridge, JML, "Free Radicals in Biology and Medicine", Clarendon Press, Oxford, 1985.

Sato, K., Niki, E., and Shimasaki, H., "Free Radical Mediated Chain Oxidation of Low Density Lipoprotein and its Synergistic Inhibition of Vitamin E and Vitamin C", Arch BioChem Biophys 279: 402-05, 1990.

Jacques, P.F., et al., "Antioxidant Status in Persons With and Without Senile Cataracts", Arch Opth 106: 337-40, 1988.

Simin, N.M., et al., "Vitamin E Supplementation Enhances Cell Mediated Immunity in Healthy Elderly Subjects", Am J Clin Nutr, 52: 557-63, 1990.

Oberly, L.W., "Superoxide Dismutase Volume I", CRC Press, Boca Raton, FL., 1982.

Copper and Zinc Status of Patients with Coronary Artery Disease (CAD)

Recent evidence has linked oxidative changes in low density lipoprotein cholesterol (LDL-C) with the development of atherosclerosis. Trace minerals, such as copper and zinc, are reported to prevent this phenomenon via their direct effect on LDL-C, or more likely, as part of the SOD enzyme which has been shown to block LDL-C oxidation.

In this study, the researchers examined the copper and zinc status of 50 patients

Longitudinal changes of Manganese Dependent Superoxide Dismutase and Other Indices of Manganese and Iron Status in Women

This study evaluated the changes in manganese superoxide dismutase (MnSOD) activity and other indices on manganese and iron status in 47 women during a 124-day supplementation period.

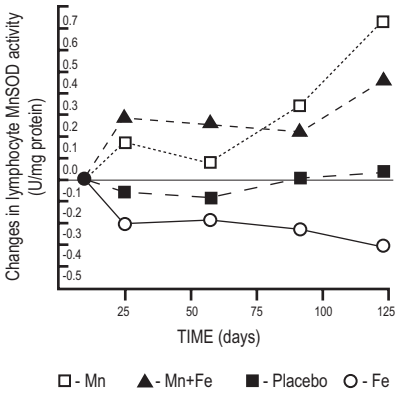
The women received one of four treatments: placebo, 60 mg of iron, 15 mg of manganese, or both mineral supplements. Due to Albion's reports of higher bioavailability, the researchers chose manganese amino acid chelate for the study.

The amino acid chelate form was reported to have an 82.3% greater rate of absorption. Both groups taking the manganese amino acid chelate supplement experienced significant increases in lymphocyte manganese superoxide dismutase (MnSOD) activity ($P<0.05$), as well as serum manganese levels over baseline values. The group taking the iron supplement alone exhibited the lowest MnSOD values as seen in Figure 2.

Davis, C.D., and Gregger, J.L., Am J Clin Nutr 1992: 55: 747-52.

Figure 2.

Changes in lymphocyte McSOD activity over time in 47 women supplemented with manganese and/or iron.



admitted to Duke Medical Center for cardiac catheterization. Twelve of the patients had insignificant CAD (blockage ≤ 50%) while the other 38 had significant CAD.

The patients with significant CAD were found to have low dietary intakes of copper and zinc. Copper intakes were inversely related to the total and LDL-C values. The researchers felt that this study suggested that adequate copper status may have a positive influence on lipid levels, in addition to the roles that the two trace minerals play in blocking LDL-C oxidation.

Bales, C.W., et al., J Am Col Nutr 1993, p. 591.

Amino Acid Chelates Increase SOD Activity in Animals

In an animal study conducted at Oklahoma State University, investigators gave cattle a supplement containing copper, manganese, and zinc as either the amino acid chelates or as inorganic metal salts. They found that when the animals received the Albion chelates, the erythrocyte Cu/Zn SOD activity was significantly increased ($P<0.05$).

Over a 60 day period, the SOD activity in the group receiving the chelates increased 11.7%, whereas the SOD activity in the group ingesting the inorganic metal salts ($CuSO_4$ and $ZnSO_4$) decreased 3.8%.

Kropp, J.R., "The Role of Copper in Beef Cattle Fertility." In Ashmead, H.D., Ed The Role of Amino Acid Chelates in Animal Nutrition (Park Ridge: Noyes) 154, 1993.

Albion's Approach to SOD System Maintenance

The body's antioxidant defense system relies on optimal nutritional support of specific nutrients. Vitamin C, beta carotene, and vitamin E are commonly taken to supply the body with key components for its antioxidant defense system. Each of these antioxidants plays a different role in the fight against free radical pathology. This is why taking just one antioxidant doesn't do the trick. In addition, the antioxidants from different sources or chemical types have shown varied abilities against free radicals. Some antioxidants have even been shown to have sparing or regenerating effects on other antioxidants (i.e. vitamin C and vitamin E).

The enzymes that make up the body's SOD system are no different. Different forms work in different areas: blood cells, liver, heart, and so on. A deficiency of any of the SOD enzymes can have negative ramifications for other antioxidant enzymes, such as atalase or glutathione peroxidase.

Due to the size of the SOD enzymes, oral administration of SOD does not enhance SOD activity. The enzymes are digested and destroyed in the GI tract. The best way to fuel the body's SOD enzyme supply is to provide an optimal supply of the individual components, such as: copper, zinc, and manganese amino acid chelates. Several studies involving these patented Albion chelated trace minerals have shown that the use of these highly absorbable chelated trace minerals results in greater SOD enzyme activity.

To illustrate, Dr. DiSilvestro, et al., at Purdue University compared 23 people afflicted with rheumatoid arthritis to 48 healthy individuals. People who have rheumatoid arthritis have low Cu/Zn SOD activity. The investigators gave the arthritic group 2 mg of copper per day, as Albion's copper amino acid chelate for 28 days. As seen in Figure 3, the SOD activity in the rheumatoid arthritis group increased 21% and was at almost the same level as the healthy control group. The increased activity was statistically significant ($P<0.001$).

Although copper has been viewed as the key factor in the activization of the copper/zinc SOD levels, zinc plays a stabilizing role. Walters, et al., have stated that alteration in copper and zinc status in diabetics leads to malfunction of the copper/zinc SOD system, resulting in lipid peroxidation and the cardiovascular complications and retinopathy associated with diabetes.

Manganese cannot be neglected any more than zinc for optimum SOD activity. Manganese activates mitochondrial SOD. In a study previously discussed, David and Greger reported that a 15 mg supplement of manganese amino acid chelate increased lymphocyte manganese SOD activity six fold in women during a 124-day study.

Albion's patented Copper, Zinc,

and Manganese Chelazomes® are the trace minerals of choice, when looking for a way to formulate an overall nutritional antioxidant program. They are scientifically tested and proven to be better absorbed than other mineral sources and gentle on the system.

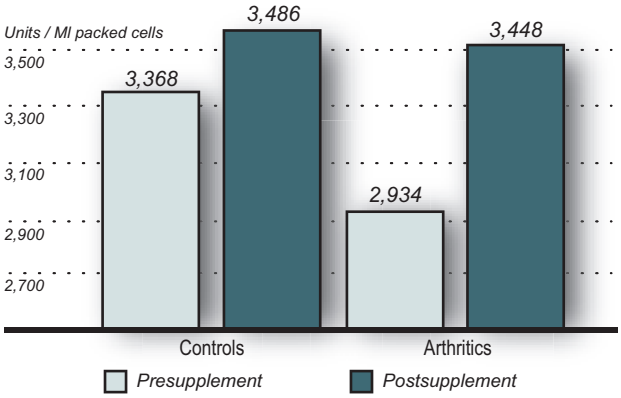
DiSilvestro, R., et al., "Effects of Copper Supplementation on Ceruloplasmin and Copper-Zinc Superoxide Dismutase in Free Living Rheumatoid Arthritis Patients", J Amer Col Nutr II (2): 177-80, 1992.

David, C.D., and Greger, J.L., "Longitudinal Changes of Manganese-Dependent Superoxide Dismutase and Other Indexes of Manganese and Iron Status in Women", Am J Clin Nutr 55: 747-52, 1992.

Walter, R.M., et al., "Copper, Manganese, and Magnesium Status and Complications of Diabetes Mellitus", Diabetes Care 14 (11) 1050-55, Nov. 1991.

Figure 3.

The effect of Copper Amino Acid Chelate on Erythrocyte Superoxide Dismutase Production.



The Antioxidant Properties of a Novel Zinc-Carnosine Chelate Compound, N – (3-aminopropioyl) – L-histidine Zinc.

A zinc-carnosine chelate attenuates gastric mucosal injury and inhibits the increase of lipid peroxide in the gastric mucosa induced by burn shock or ischemia reperfusion. The exact mechanism for its antioxidant effect remains to be elucidated.

The antioxidant properties of this zinc chelate were compared in vitro, to zinc sulfate and L-carnosine. There was only superoxide anion scavenging activity in the zinc chelate containing cells. The zinc-carnosine inhibited superoxide generation from polymorphonuclear leukocytes stimulated by opsonized zymosan, and also inhibited the generation of hydroxyl radicals by the Fenton reaction. The increase in lipid peroxides in brain and liver was also inhibited by the zinc carnosine chelate.

These findings indicate that the strong anti-ulcer and antioxidant actions of this zinc chelate in vitro are due to a combination of the antioxidant actions.

Yaashikawa, T., et al., Biochemica et Biophysica Acts 1115 (1) 15-22, Nov. 14, 1991.

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