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HUMAN NUTRITION

RESEARCH NOTES

A COMPILATION OF VITAL RESEARCH UPDATES ON HUMAN NUTRITION

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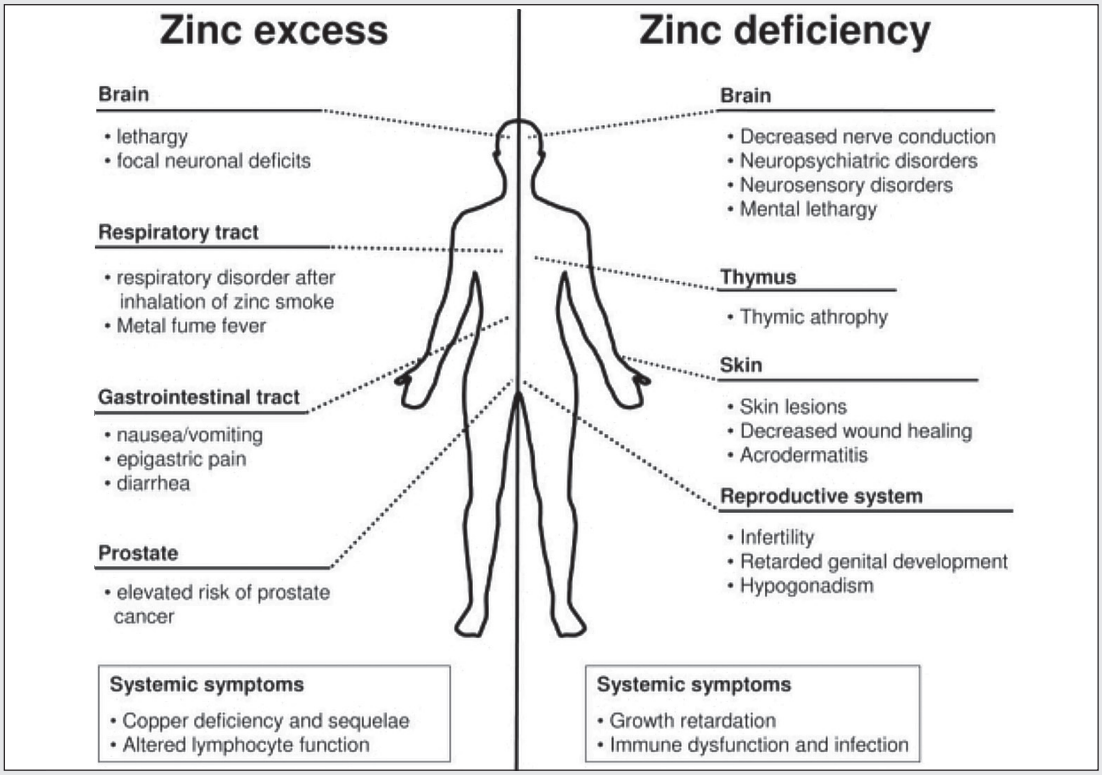
Zinc and Inflammation

Zinc is a group IIb metal, and is of critical importance. It is second only to iron in worldwide incidence of deficiency, impacting 2 billion people in developing nations. It plays many maintenance roles in cellular metabolism and gene expression. Depending on the source, it is part of between 100 and 300 biological enzymes in the body. The cellular processes regulated by zinc, include mitosis, apoptosis, secretion and signal transduction. It is critical to a diverse group of physiological processes, such as insulin release, T cell cytokine production, wound healing, vision, and neurotransmission. Given the wide range of functions impacted or regulated by zinc (See Figure 1 below), it can be seen that its deficiency, or even marginal deficiency can have serious health implications. In this issue, we are looking more specifically at areas in which the anti-inflammatory effect of zinc is of utmost importance. Involving things such as T Cell cytokine expression, NF kappaB signaling PPAR, COX-2 expression, and down regulation of pro-inflammatory markers, such as iNOS, among others.

To emphasize the impact that zinc has as an anti-inflammatory activist, the following abstracts will show a variety of pathologies in which zinc can exhibit its anti-inflammatory benefits, including things, as diverse as anti-aging effects, asthma and other airway diseases, inflammatory acne, bronchiolar allergic inflammation, autoimmune disease, sickle cell anemia, and inflammatory diseases such as atherosclerosis.

Figure 1. "The Essential Toxin: Impact of Zinc on Human Health", Laura M. Plum, et al., Int J Environ Res Public Health 2010; 7, 1342-1365



Abstracts of Interest

Efficacy and safety study of two zinc gluconate regimens in the treatment of inflammatory acne.

Meynadier J.
Eur J Dermatol. 2000 Jun;10(4):269-73.

(AA) This double-blind study was conducted on 67 patients with inflammatory acne who received one of two zinc gluconate regimens (Rubozinc) for three months. One was a constant-dose regimen and the other included an initial three-week loading dose, but both regimens provided the same cumulative dose at three months. The primary assessment criteria was the change with respect to baseline in the total number of superficial inflammatory lesions (papules and pustules). The two treatment groups were not statistically significantly different, with respect to this criteria, after three, five, seven or thirteen weeks of treatment. Therefore, the regimen that included a loading-dose provided no additional benefit. The results of this study are in favor of the conventional therapeutic regimen of two capsules daily for three months, as defined in the marketing authorization.

Anti-inflammatory effects of zinc and alterations in zinc transporter mRNA in mouse models of allergic inflammation.

Lang C, Murgia C, Leong M, Tan LW, Perozzi G, Knight D, Ruffin R, Zalewski P.
Am J Physiol Lung Cell Mol Physiol. 2007 Feb;292(2):L577-84. Epub 2006 Nov 3.

(AA) There is clinical evidence linking asthma with the trace element, zinc (Zn). Using a mouse model of allergic inflammation, we have previously shown that labile Zn decreases in inflamed airway epithelium (Truong-Tran AQ, Ruffin RE, Foster PS, Koskinen AM, Coyle P, Philcox JC, Rofe AM, Zalewski PD. Am J Respir Cell Mol Biol 27: 286-296, 2002). Moreover, mild nutritional Zn deficiency worsens lung function. Recently, a number of proteins belonging to the Solute Carrier Family 39 (ZIP) and Solute Carrier Family 30 (ZnT) have been identified that bind Zn and regulate Zn homeostasis. Mice were sensitized, and subsequently aerochallenged, with ovalbumin to induce acute and chronic airway inflammation. Mice received 0, 54, or 100 microg of Zn intraperitoneally. Tissues were analyzed for Zn content and histopathology. Inflammatory cells were counted in bronchoalveolar lavage fluid. Cytokine and Zn transporter mRNA levels were determined by cDNA gene array and/or real-time PCR. Zn supplementation decreased bronchoalveolar lavage fluid eosinophils by 40 and 80%, and lymphocytes by 55 and 66%, in the acute and chronic models, respectively. Alterations in Zn transporter expression were observed during acute inflammation, including increases in ZIP1 and ZIP14 and decreases in ZIP4 and ZnT4. Zn supplementation normalized ZIP1 and ZIP14, but it did not affect mRNA levels of cytokines or their receptors. Our results indicate that inflammation-induced alterations in Zn transporter gene expression are directed toward increasing Zn uptake. Increases in Zn uptake may be needed to counteract the local loss of Zn in the airway and to meet an increased demand for Zn-dependent proteins. The reduction of inflammatory cells by Zn in the airways provides support for Zn supplementation trials in human asthmatic individuals.

New insights into the role of zinc in the respiratory epithelium.

Truong-Tran AQ, Carter J, Ruffin R, Zalewski PD.
Immunol Cell Biol. 2001 Apr;79(2):170-7.

(AA) Over the past 30 years, many researchers have demonstrated the critical role of zinc (Zn), a group IIb metal, in diverse physiological processes, such as growth and development, maintenance and priming of the immune system, and tissue repair. This review will discuss aspects of Zn physiology and its possible beneficial role in the respiratory epithelium. Here we have detailed the mechanisms by which Zn diversely acts as: (i) an anti-oxidant; (ii) an organelle stabilizer; (iii) an anti-apopototic agent; (iv) an important cofactor for DNA synthesis; (v) a vital component for wound healing; and (vi) an anti-inflammatory agent. This paper will also review studies from the authors' laboratory concerning the first attempts to map Zn in the respiratory epithelium and to elucidate its role in regulating caspase-3 activated apoptosis. We propose that Zn, being a major dietary anti-oxidant has a protective role for the airway epithelium against oxyradicals and other noxious agents. Zn may therefore have important implications for asthma and other inflammatory diseases where the physical barrier is vulnerable and compromised.

Zinc metabolism in airway epithelium and airway inflammation: basic mechanisms and clinical targets. A review.

Zalewski PD, Truong-Tran AQ, Grosser D, Jayaram L, Murgia C, Ruffin RE.
Pharmacol Ther. 2005 Feb;105(2):127-49.

(AA) In addition to basic housekeeping roles in metalloenzymes and transcription factors, dietary zinc (Zn) is an important immunoregulatory agent, growth cofactor, and cytoprotectant with anti-oxidant, anti-apoptotic, and anti-inflammatory roles. These properties of Zn are of particular importance in maintaining homeostasis of epithelial tissues which are at the front line of defense. This review is about the role of Zn in airway epithelium (AE). The first part focuses on the cellular biology of Zn, and what is known about its distribution and function in AE. The second part of the review considers evidence for altered Zn metabolism in asthma and other chronic diseases of airway inflammation. Important issues arise from a potential therapeutic perspective as to the optimal ways to monitor circulating and epithelial Zn levels in patients and the most effective means of supplementing these levels.

Zinc and its specific transporters as potential targets in airway disease.

Murgia C, Lang CJ, Truong-Tran AQ, Grosser D, Jayaram L, Ruffin RE, Perozzi G, Zalewski PD.
Curr Drug Targets. 2006 May;7(5):607-627.

(AA) The dietary group IIb metal zinc (Zn) plays essential housekeeping roles in cellular metabolism and gene expression. It regulates a number of cellular processes including mitosis, apoptosis, secretion and signal transduction as well as critical events in physiological processes as diverse as insulin release, T cell cytokine production, wound healing, vision and neurotransmission. Critical to these processes are the mechanisms that regulate Zn homeostasis in cells and tissues. The proteins that control Zn uptake and compartmentalization are rapidly being identified and characterized. Recently, the first images of sub-cellular pools of Zn in airway epithelium have been obtained. This review discusses what we currently know about Zn in the airways, both in the normal and inflamed states, and then considers how we might target Zn metabolism by developing strategies to monitor and manipulate airway Zn levels in airway disease.

Zinc supplementation in the elderly reduces spontaneous inflammatory cytokine release and restores T cell functions.

Kahmann L, Uciechowski P, Warmuth S, Plümäkers B, Gressner AM, Malavolta M, Mocchegiani E, Rink L.
Rejuvenation Res. 2008 Feb;11(1):227-37.

(AA) Aging is associated with low-grade inflammation on the one hand and mild zinc deficiency on the other. These conditions contribute to decreased immune functions, resulting in increased incidences of infections and autoimmune diseases. The aim of this study was to give more insight into the question, to what extent is low-grade inflammation caused by zinc deficient status. Here we report the effect of improved intracellular zinc status on low-grade inflammatory activity in 19 healthy elderly subjects. Our experiments show that adjustment of labile zinc by moderate zinc supplementation reduces spontaneous cytokine release and defects in termination of inflammatory activity. This results in reduced amounts of unspecific preactivated T cells and leads to improved T cell response upon mitogenic stimulation. Therefore, in contrast to other anti-inflammatory drugs, zinc does not suppress, but improves immune reaction upon pathogen invasion. These results suggest that mildly zinc-deficient, healthy elderly subjects might benefit from moderate zinc supplementation due to a more balanced immune response with reduced incidences of infections and autoimmune diseases.

Zinc and inflammatory/immune response in aging.

Vasto S, Mocchegiani E, Malavolta M, Cuppari I, Listì F, Nuzzo D, Ditta V, Candore G, Caruso C.
Ann N Y Acad Sci. 2007 Apr;1100:111-22.

(AA) Life-long antigenic burden determines a condition of chronic inflammation, with increased lymphocyte activation and proinflammatory cytokine production. A large number of studies have documented changes in zinc metabolism in experimental animal models of acute and chronic inflammation and in human chronic inflammatory conditions. In particular, modification of zinc plasma concentration, as well as intracellular disturbance of antioxidant intracellular pathways, has been found in aging and in some age-related diseases. Zinc deficiency is diffused in aged individuals in order to avoid meat and other high zinc content foods due to fear of

cholesterol. Rather, they increase the consumption of refined wheat products that lack zinc and other critical nutrients as a consequence of the refining process. On the other hand, plasma zinc concentration is influenced by proinflammatory cytokines (IL-6 and TNF-alpha) and by metallothioneins (MT) homeostasis, which is in turn affected by proinflammatory cytokines. MT increase in aging and chronic inflammation allowing a continuous sequestration of intracellular zinc with subsequent low zinc ion availability against stressor agents and inflammation. This phenomenon leads to an impaired inflammatory/immune response in the elderly. A major target of zinc is NF-kappaB, a transcription factor critical for the expression of proinflammatory cytokines whose production is regulated by extra- and intracellular activating and inhibiting factors interacting with the regulatory elements on cytokine genes. Effects of zinc on translocation of NF-kappaB have been attributed to the suppression of phosphorylation and degradation of the inhibitory proteins (A20) that normally sequester it in the cytoplasm. Moreover, this factor and A20 are regulated by specific genes involved in inflammation and by intracellular zinc ion availability. So, it is not so surprising that zinc deficiency is constantly observed in chronic inflammation, such as in old individuals. On the other hand, cytokine genes are highly polymorphic and some of these polymorphisms are associated with atherosclerosis and diabetes type 2. Therefore, zinc turnover, via MT homeostasis, in individuals genetically predisposed to a dysregulation of the inflammatory/immune response may play a crucial role in causing possible adverse events with the appearance of age-related diseases.

Zinc deficiency induces vascular pro-inflammatory parameters associated with NF-kappaB and PPAR signaling.

Shen H, Oesterling E, Stromberg A, Toborek M, MacDonald R, Hennig B.
J Am Coll Nutr. 2008 Oct;27(5):577-87.

(AA) Marginal intake of dietary zinc can be associated with increased risk of cardiovascular diseases. In the current study we hypothesized that vascular dysfunction and associated inflammatory events are activated during a zinc deficient state. We tested this hypothesis using both vascular endothelial cells and mice lacking the functional LDL-receptor gene. Zinc deficiency increased oxidative stress and NF-kappaB DNA binding activity, and induced COX-2 and E-selectin gene expression, as well as monocyte adhesion in cultured endothelial cells. The NF-kappaB inhibitor CAPE significantly reduced the zinc deficiency-induced COX-2 expression, suggesting regulation through NF-kappaB signaling. PPAR can inhibit NF-kappaB signaling, and our previous data have shown that PPAR transactivation activity requires adequate zinc. Zinc deficiency down-regulated PPARalpha expression in cultured endothelial cells. Furthermore, the PPARgamma agonist rosiglitazone was unable to inhibit the adhesion of monocytes to endothelial cells during zinc deficiency, an event which could be reversed by zinc supplementation. Our in vivo data support the importance of PPAR dysregulation during zinc deficiency. For example, rosiglitazone induced inflammatory genes (e.g., MCP-1) only during zinc deficiency, and adequate zinc was required for rosiglitazone to down-regulate pro-inflammatory markers such as iNOS. In addition, rosiglitazone increased IkappaBalpha protein expression only in zinc adequate mice. Finally, plasma data from LDL-R-deficient mice suggest an overall pro-inflammatory environment during zinc deficiency and support the concept that zinc is required for proper anti-inflammatory or protective functions of PPAR. These studies suggest that zinc nutrition can markedly modulate mechanisms of the pathology of inflammatory diseases such as atherosclerosis.

Zinc supplementation decreases oxidative stress, incidence of infection, and generation of inflammatory cytokines in sickle cell disease patients.

Bao B, Prasad AS, Beck FW, Snell D, Suneja A, Sarkar FH, Doshi N, Fitzgerald JT, Swerdlow P.
Transl Res. 2008 Aug;152(2):67-80.

(AA) Zinc deficiency is common in adult sickle-cell disease (SCD) patients. We previously demonstrated that zinc supplementation to adult SCD patients decreased the incidences of infections and hospital admissions. We hypothesize that zinc supplementation improves T-helper cell function and decreases vascular endothelial cell activation, oxidative stress, and nuclear factor-kappa B (NF-kappaB)-

DNA binding in mononuclear cells (MNCs) in SCD patients. To test this hypothesis, 36 SCD patients were recruited and randomly divided into 2 groups. One group (n = 18) received 25-mg zinc orally thrice a day for 3 months. The other group (n = 18) received placebo. The results indicate that the zinc-supplemented group had decreased incidence of infections compared with the placebo group. After zinc supplementation, red blood cell, hemoglobin (Hb), hematocrit, (Hct), plasma zinc, and antioxidant power increased; plasma nitrite and nitrate (NOx), lipid peroxidation products, DNA oxidation products, and soluble vascular cell adhesion molecule-1 decreased in the zinc-supplemented group, compared with the placebo group. Zinc-supplemented patients exhibited significant decreases in lipopolysaccharide-induced tumor necrosis factor-alpha (TNF-alpha) and IL-1beta mRNAs, and TNF-induced nuclear factor of kappaB-DNA binding in MNCs, compared with the placebo group. Ex vivo addition of zinc to MNCs isolated from the placebo subjects decreased TNF-alpha and IL-1beta mRNAs. Zinc supplementation also increased relative levels of IL-2 and IL-2Ralpha mRNAs in phytohemagglutinin-p-stimulated MNCs. These results suggest that zinc supplementation may be beneficial to SCD patients.

Figure 2

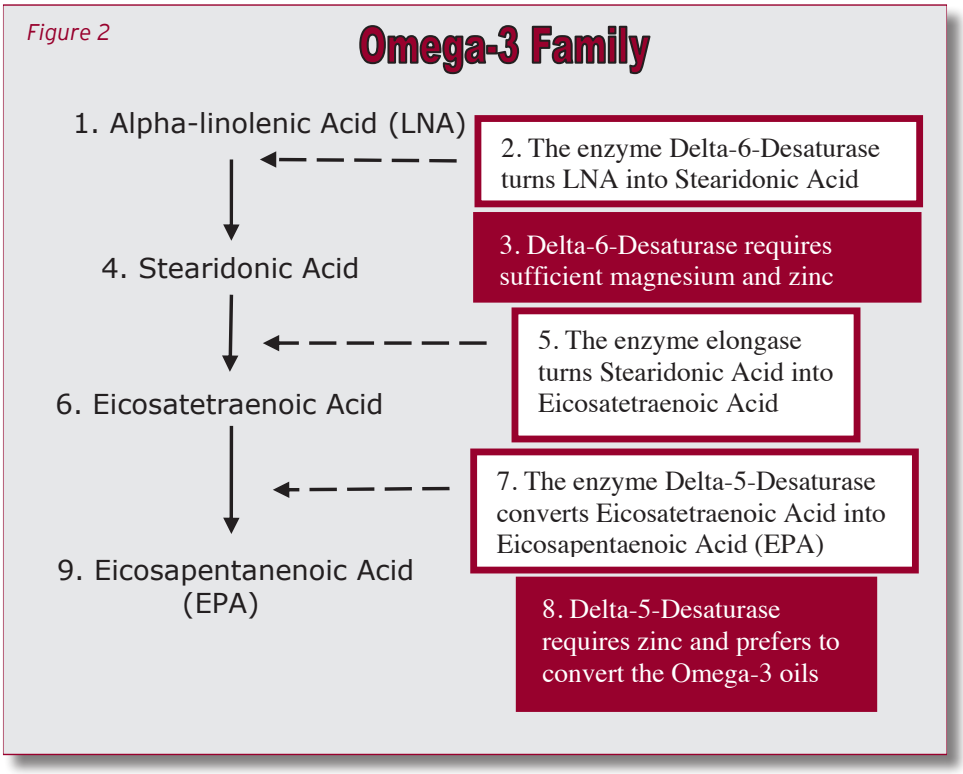
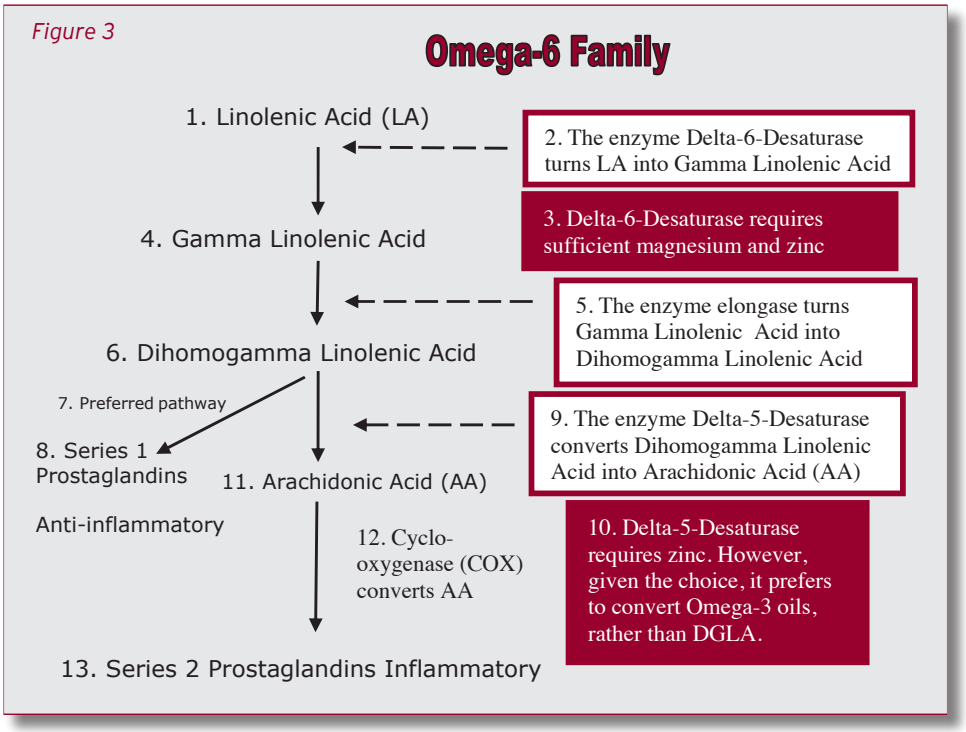


Figure 3



Concluding Comments:

As these abstracts indicate, zinc has definite anti-inflammatory effects that have been exhibited in a wide variety of physiological situations. Much of the anti-inflammatory involvement for zinc can be traced to its role as an enzymatic catalyst or regulator of delta 5 and delta 6 desaturase enzyme activity, as depicted (see figures 2 & 3), in the prostaglandin cascade associ-

Figure 4. Comparison of Four Commercially Available Zinc Supplements for Performance in a Zinc Tolerance Test"; Swan M, Disilvestro RA; The Ohio State University, Human Nutrition, Columbus, Ohio USA. Laura M. Plum, et al., Int J Environ Res Public Health 2010; 7, 1342-1365

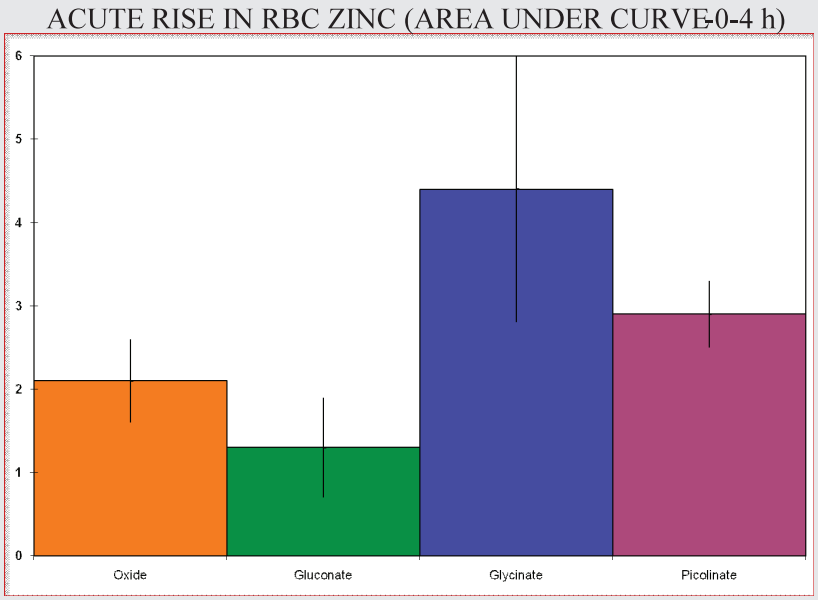
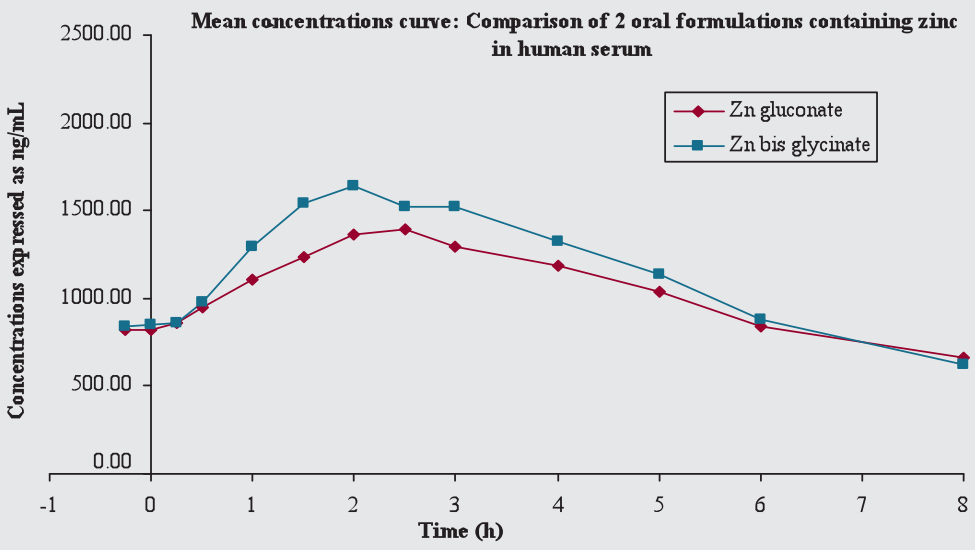


Figure 5. "A Bioavailability Study Comparing Two Oral Formulations Containing Zinc (Zn BisGlycinate vs. Zn Gluconate) After a Single Administration to Twelve Healthy Female Volunteers", Peggy Gandia, et al.; Int. J. Vitam. Nutr. Res., 77 (4), 2007, 243–248



ated with the omega 3 and omega 6 fatty acids.

The key to gaining the positive anti-inflammatory benefits from zinc lies in its bioavailability. Albion's Zinc Bisglycinate Chelate has been shown to have the highest bioavailability. Countless studies have demonstrated the great bioavailability of Albion chelates. Recent studies by (DiSilvestro RA and Swan M, submitting for publication, and Maurette J-M, et al [Int J Vitamin Res, 77<4>, 2007, 243-248) have shown the Zinc Bisglycinate Chelate to be superior to other zinc forms in absorption. In the DiSilvestro work (see Figure 4), the Zinc Bisglycinate Chelate increased the RBC level by a large margin over the other 3 zinc forms in the study. The data showed that the glycinate form of zinc was absorbed at rate about 3 times that if zinc picolinate. In the Maurette study results (see Figure 5) indicate that the Zinc Bisglycinate Chelate was absorbed at a 43% higher rate than the gluconate form. Other studies have demonstrated glycinate chelates freedom from negative dietary interactions, which is another contributing factor in their superior bioavailability.

Albion's Zinc Bisglycinate Chelate (#3506) is 20% elemental zinc.

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