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X. ISTERH CONFERENCE REVIEW

Zinc: An antioxidant and anti-inflammatory agent: Role of zinc in degenerative disorders of aging

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ABSTRACT

In the developed countries nearly 30% of the elderly are zinc deficient. Many chronic diseases seen in the elderly such as atherosclerosis, diabetes, neuro-degenerative disorders, Parkinson's disease and age related macular degeneration (AMD) may be due to chronic inflammation and increased oxidative stress. Zinc in human plays an important role in cell mediated immunity and is also an antioxidant and anti-inflammatory agent. Zinc supplementation studies in the elderly have shown decreased incidence of infections, decreased oxidative stress, and decreased generation of inflammatory cytokines. Decreased incidences of blindness in patients with AMD and increased atheroprotective effect have been observed in the zinc supplemented elderly. Zinc is a molecular signal for immune cells and many transcription factors involved in gene expression of inflammatory cytokines and adhesion molecules are regulated by zinc.

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Introduction

Essentiality of zinc was only recognized 50 years ago [1,2]. The clinical manifestations of zinc deficiency include growth retardation, testicular hypofunction, immune dysfunction, increased oxidative stress and increased generation of inflammatory cytokines [3–8]. Currently it is estimated that nearly 2 billion subjects in the developing world may be zinc deficient. A severe deficiency of zinc such as seen in patients with Acrodermatitis Enteropathica (AE), is fatal if not diagnosed and treated properly with zinc supplementation [9]. The patients usually die of infections.

Zinc has been used to treat and prevent diarrhea in infants and children globally very effectively resulting in saving millions of lives [10,11]. WHO (World Health Organization) has now implemented this therapy in nearly 70 countries. Zinc is an approved FDA (US Food and Drug Administration) agent for the treatment of Wilson's disease [12].

The severity and duration of common cold may be decreased significantly with the proper use of zinc acetate lozenges [13,14]. The progression of age related macular degeneration (AMD) and its complication, blindness in the elderly has been shown to be effectively managed by the use of therapeutic levels of zinc supplementation [15–18]. The studies of AREDS (age related eye diseases study) group in AMD subjects has shown that during 10 years of follow-up, the mortality due to cardiovascular events in the elderly was significantly decreased in the zinc supplemented group (see

Abbreviations: A20, zinc containing transcription factor; CRP, plasma C-reactive protein; HAE, 4-hydroxyalkenals; IL-1β, Interleukin-1β; IL- 6, Interleukin 6; MCP-1, macrophage chemoattractant protein-1; MDA, malondehyde; NF-κB, nuclear factor kappa B; ox-LDL, oxidized low density lipoprotein; PPAR-α, peroxisome proliferator-activated receptor-α; VCAM-1, soluble vascular cell adhesion molecule.

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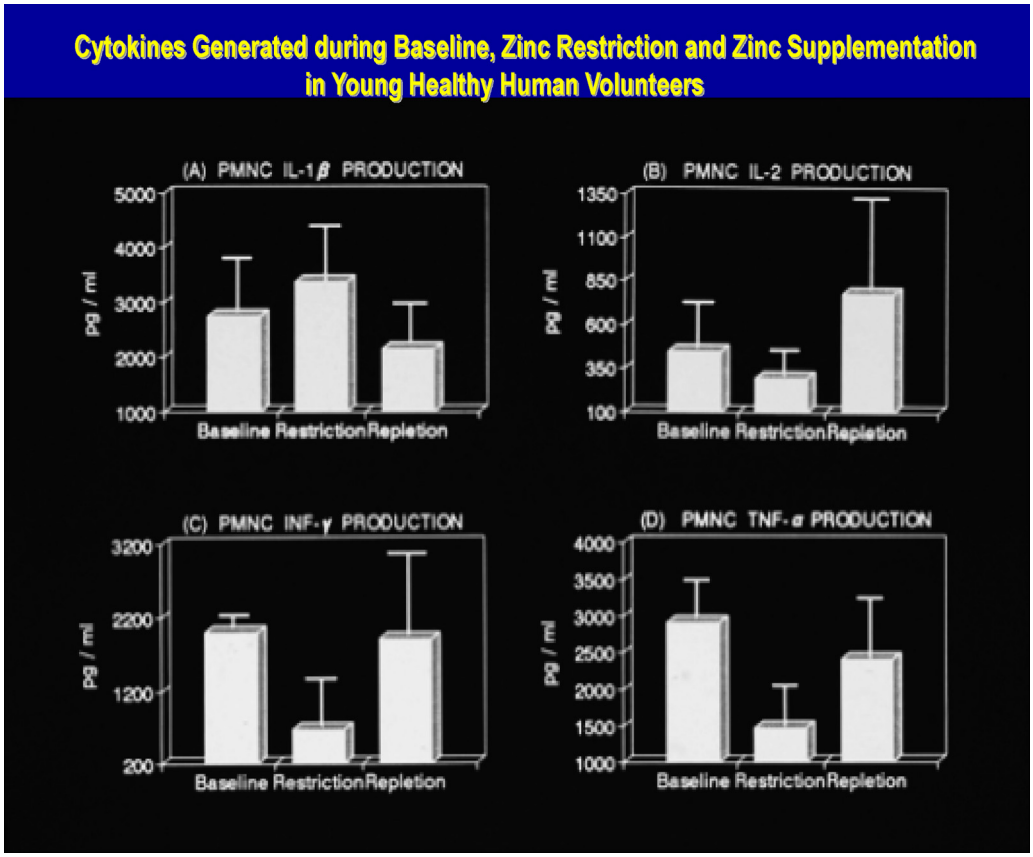

Fig. 1. This figure shows the increased generation of IL-1β from stimulated PMNC (peripheral blood mononuclear cells) in mildly zinc deficient human subjects. Zinc deficiency per se was responsible for this effect, inasmuch as there was no infection to account for this phenomenon. This is from Ref. [28]

Table 1). These clinical effects of zinc supplementation in humans are very impressive and have a high impact on human health.

Patients with sickle cell disease (SCD) become zinc deficient because persistent hemolysis leads to hyperzincuria and zinc deficiency [19,20]. Zinc supplementation improves growth and development, and immune functions. A recent Cochrane Review has concluded that zinc supplementation is the only therapy currently available which decreases incidence of infection and pain crisis in SCD patients [21].

During the past few decades we have also learned that over 300 enzymes require zinc for their activation or stability of structures and now there are over 2000 transcription factors that are involved in gene expression of proteins that are zinc dependent [7]. We now know that zinc is a molecular signal for immune cells and that homeostasis of intracellular Zn^{2+} levels are maintained by 14 ZIP (SLC 39A) and 10 ZNT (SLC 30A) transporters [22,23].

In this review the roles of zinc as an antioxidant and anti-inflammatory agent will be presented. Oxidative stress and chronic inflammation are considered to be important contributing factors for many chronic diseases such as atherosclerosis and related cardiac disorders, cancer, neurodegeneration, immunologic disorders and the aging process itself. The possible role of zinc in prevention of these disorders will be discussed.

Table 1
Zinc supplementation in AMD (AREDS) study.

	Decrease in risk of advanced AMD	Decrease in risk of vision loss
Vitamins	17%	10%
Zinc alone	21%	11%
Vitamins + zinc	25%	19%

Risk of mortality was reduced by 27% in only zinc group.

Mechanism of zinc action as an antioxidant

Zinc functions as an antioxidant by different mechanisms. Oxidative stress is an important contributing factor for several chronic diseases attributed to aging such as atherosclerosis and related cardiac disorder, neurodegenerative disorders and even cancer [24–26]. Together $^{\bullet}O_2^-$, H_2O_2 and $^{\bullet}OH$ are known as reactive oxygen species (ROS) and they are continuously being produced in vivo under aerobic conditions. In eukaryotic cells, the mitochondrial respiratory chain, microsomal cytochrome P450 enzymes, flavoprotein oxidases and peroxisomal fatty acid metabolism are the most significant intracellular sources of ROS. The nicotinamide adenine dinucleotide phosphate oxidases (NADPHs) are a group of plasma membrane-associated enzymes which catalyze the production of $^{\bullet}O_2^-$ from oxygen by using NADPH as electron donor (see Fig. 1). Zinc is an inhibitor of NADPH oxidase which results in decreased generation of ROS. Zinc is also a co-factor of the enzyme superoxide dismutase (SOD), which catalyzes the dismutation of $^{\bullet}O_2^-$ to H_2O_2.

Zinc competes with Fe^{2+} and Cu^{2+} ions for binding to cell membranes and protein, displacing these redox active metals which catalyze the production of $^{\bullet}OH$ from H_2O_2. Zinc also induces the generation of metallothionein which is very rich in cysteine and is an excellent scavenger of $^{\bullet}OH$. Zinc binds to sulfhydryl (SH) groups of bio-molecules protecting them from oxidation. Zinc increases the activation of antioxidant proteins, molecules and enzymes such as glutathione (GSH), catalase, and SOD, and reduces the activities of oxidant-promoting enzymes such as inducible nitric acid