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Review

Zinc homeostasis and immunosenescence

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ABSTRACT

For more than 50 years, zinc is known to be an essential trace element, having a regulatory role in the immune system. Deficiency in zinc thus compromises proper immune function, like it is observed in the elderly population. Here mild zinc deficiency is a common condition, documented by a decline of serum or plasma zinc levels with age. This leads to a dysregulation mainly in the adaptive immunity that can result in an increased production of pro-inflammatory cytokines, known as a status called inflamm-aging. T cell activation as well as polarization of T helper (Th) cells into their different subpopulations (Th1, Th2, Th17, regulatory T cells (Treg)) is highly influenced by zinc homeostasis. In the elderly a shift of the Th cell balance towards Th2 response is observed, a non-specific pre-activation of T cells is displayed, as well as a decreased response to vaccination is seen. Moreover, an impaired function of innate immune cells indicate a predominance of zinc deficiency in the elderly that may contribute to immunosenescence. This review summarizes current findings about zinc deficiency and supplementation in elderly individuals.

Contents

Zinc status and immune function

In 1934 the essentiality of zinc for animals has been recognized [1], but it was not until the early 1960s that zinc was known as an essential trace element for human beings [2]. Zinc is highly important for all proliferating cells in the human body, especially for the whole immune system. Zinc is considered to be relatively non-toxic to humans and the human body contains a total amount of 2–4 g zinc [3]. The recommended daily allowance (RDA) in the United States for zinc is 11 mg/day for men and 8 mg/day for women. In the European Community and in recommendations by the WHO lower values between 9.4 and 10 mg for men and 6.5–7.1 mg for women are advised, but no specific RDA for elderly individuals exists to date [4]. An adequate daily intake of zinc is necessary to achieve a steady state for proper immune function, because there is no specialized zinc storage system in the human body. Thus zinc deficiency often occurs because of malnutrition, especially in the elderly [5]. However, many other factors may play a critical role, like decreased intestinal absorption, depending on the composition of the food, or medication like diuretics, could cause a diminished zinc availability or retention. Even diseases such as diabetes, which occur with increased frequency in older people, have been associated with zinc deficiency (see Table 1) [4,5]. Zinc deficiency manifests itself on different levels and can be subdivided into either marginal zinc deficiency, as it is observed in the elderly population, or severe zinc deficiency. Severe zinc deficiency is caused by metabolic disorders regarding zinc uptake as well as by other sources such as parenteral nutrition without zinc, and results in complex immune defects, observed in its most severe form in the zinc malabsorption syndrome acrodermatitis enteropathica, a rare autosomal recessive disorder [6,7]. Untreated, this disease is lethal within a few years, but pharmacologic zinc

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Table 1
Zinc supplementation studies.

Disease	Symptoms	Effects of zinc supplementation	Possible mechanism	References
Hepatic encephalopathy	Confusion/coma as a result of liver failure	Inceased physical component scale, reduced hepatic encephalophathy scale, reduced blood ammonia level	Increased function of hepatic ornithine transcarbamylase	Reding et al. [96] Grüngreiff et al. [97] Takuma et al. [98]
Diabetes mellitus	Weight loss, polyuria, polydipsia, and polyphagia	Reduced blood glucose level	Increased HDL, reduced TG, LDL oxidation, inhibition of insulin degradation	Hennig et al. [99] Salgueiro et al. [100] Partida-Hernandez et al. [101] Gunasekara et al. [102]
Artheriosclerosis	Focal arterial lesion, occlusion of blood vessels	Reduction of inflammatory biomarkers	Decreased oxidative stress markers, CRP, NF-κB activation, increased A20 and PPARα	Connell et al. [103] Prasad et al. [104] Bao et al. [80]
Chronic hepatitis C	Fatigue, nausea, muscle or joint pains, and weight loss	Decreased incidences of gastrointestinal disturbances, decreased body weight loss	Induction of antiviral interferon, inhibition of viral replication, reduction of aminotransferase and alanine aminotransferase level	Cakman et al. [44] Yuasa et al. [105] Himoto et al. [106] Matsumura et al. [107]
Diarrhea	Abnormally frequent discharge of semisolid or fluid fecal matter from the bowel	Reduction of incidence and prevalence	Regeneration of gut epithelium, increase level of enterocyte brush border enzymes, increased clearance of bacteria	Bettger et al. [108] Shankar et al. [109] Karamyyar et al. [110] Malik et al. [111]
Disease	Symptoms	Effects of zinc supplementation	Possible mechanism	References
Shigellosis	Abdominal discomfort, cramps, diarrhea	Increased intestinal mucosal permeability, better nitrogen absorption, increased serum zinc	Increased alkaline phosphatase activity, elevated serum antibody titers, B cells and plasma cells	Alam et al. [112] Rahman et al. [113] Raqib et al. [114] Roy et al. [115]
Diabetic Hepatho-phaty	Diffuse glomerulo-nephritis, nephrotic syndrome, Hypoalbuminemia, hyperlipidemia	Increased urinary albumin excretion, lower vLDL and HbA1c	Inhibition of LDL oxidation, reduction of inflammatory cytokines, reduction of endothelial cell adhesion markers	Henning et al. [99] Reiterer et al. [116] Khan et al. [117]

Influences of zinc supplementation on different diseases. High-density lipoprotein (HDL), very low-density lipoprotein (vLDL), c-reactive protein (CRP), nuclear factor kappaB (NF-κB), peroxisome proliferator-activated receptor (PPARα), glycated hemoglobin (HbA1c).

supplementation of 1 mg/kg body weight can reverse all symptoms [8].

The majority of free zinc is located within the cells and additional zinc can be taken up from the plasma. This zinc pool has an average concentration of about 90 μg/dL and represents merely less than one percent of the total body content. Nevertheless, it is highly important for proper immune function. The immune system has a fast turnover of cells, making a high rate of proliferation necessary. In this connection as well as in processes like apoptosis and differentiation zinc plays a major role. This is not surprising, since zinc is enclosed in about 400 enzymes, and even over 2000 proteins are identified to contain zinc [9]. The zinc proteome consists of two major groups of comparable size, which are enzymes and transcription factors. Together, these form over 90% of the zinc proteome, indicating that the vast majority of zinc is required for catalysis and transcriptional regulation [10].

For proper zinc uptake and distribution a balanced expression of zinc transporter, namely hZIP (human Zrt-, Irt-like protein, solute carrier family SLC 39A) and hZnT (human zinc transporter, SLC30A), is the crucial factor for regulation of the cellular, biologically effective zinc content [11,12]. Alterations in zinc uptake, retention or secretion can quickly lead to zinc deficiency and thus to malfunction of cellular processes [5]. For instance zinc homeostasis has been demonstrated to affect dendritic cells (DC), particularly the involvement of zinc transporter proteins during lipopolysaccharide (LPS)-induced upregulation of major histocompatibility complex (MHC) proteins and co-stimulatory molecules [11].

Altered immune function during aging

Aging is associated with changes in the immune response (see Fig. 1). This is also due to declined serum or plasma zinc levels. Aging is related to a decreased capacity to mount an adequate response referred to as immunosenescence, resulting in increased susceptibility to infectious diseases, autoimmunity, and cancer [13]. These changes mainly affect the adaptive immunity especially the T cell-mediated cellular immune response [14]. It has been demonstrated that even with healthy aging important functions of T cells are altered. Despite the fact that the exact causes are still unknown, several phenomena are named as participating factors: the involution of the thymus [15], a reduced thymulin level [16], a shift in T cell subpopulations favoring $CD8^+$ memory T cells, the reduction of T helper cells activity, and NK cell activity [17]. Furthermore T cells of elderly individuals display a non-specific pre-activation, e.g., shown by an increased number of $CD25^+$ T cell [18], leading to impaired immune functions and responses to vaccination [19].

For T cell activation antigen presenting cells (APC) like monocytes/macrophages, and DCs are a necessary factor by taking up and presenting antigens. They coordinate the immune response by producing cytokines regarding to a sufficient stimulation that leads to an activation of both cell types. A well-known activator is LPS, which is sensed by Toll like receptor (TLR)-4. TLR-4 signaling leads to secretion of pro-inflammatory cytokines, maturation, and antigen presentation in DC and macrophages. Maturation of macrophages is calcitriol-dependent and is enhanced by zinc sequestration, which can be observed in an enhanced CD11b/CD14 surface expression. This indicates a negative regulatory role for zinc [20], depending on an altered zinc homeostasis. As it is observed in the elderly population zinc deficiency augment TLR-4-mediated production of pro-inflammatory cytokines. Furthermore, interferon (IFN)-β synthesis is increased under zinc deficient conditions and subsequent synthesis of inducible nitric oxide (NO) synthase and production of NO [21].

Another important cell population for adequate immune function are polymorphonuclear leukocytes (PMN), which are the largest population among the cells of the innate immunity and