

Zinc and allergy relation

Abstract

Increase in the allergic disease prevalence worldwide has stimulated many investigations into the changes in daily life trends and/or environmental circumstances. Dietary change is one of the most important factors in these styles. Several clinical studies have reported an association between an increase in the incidence of allergic diseases and low Zinc consumption daily. Zinc is one of the primary dietary factors and of the most widely disseminated bio elements present in all organs, living tissues, and secretions. Zinc is also known as a cofactor for cellular proteins, nucleic acids, carbohydrates and lipids. Thus, it is a trace element essential for cell growth, development, and differentiation. Zinc is necessary for cellular functions in the organism, and irregular Zinc homeostasis causes different health problems consisting of growth retardation, immunodeficiency, hypogonadism, neuronal and sensory dysfunctions. Since Zinc deficiency is able to cause a variety of defects in the organisms including immune system, it could be related with increased rate of allergic diseases in children. Anti-oxidant, anti-apoptotic, anti-inflammatory and anti-allergic effects of Zinc are very important to prevent skin and airway diseases of the organism. Subsequent to losing these beneficial effects, Zinc deficiency is supposed to play a role in the pathogenesis and severity of allergic skin and respiratory tract diseases. Therefore, maintaining normal Zinc levels might lower the risk of development and progression of allergic diseases, especially in who are already hypozincemic. More research is required to establish whether Zinc deficiency is a risk factor for the development of allergic disease or a secondary outcome of these diseases.

Keywords: zinc, allergy, atopic dermatitis, asthma, airway

Volume 1 Issue 1 - 2014

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Received: May 05, 2014 | **Published:** May 13, 2014

Introduction

Zinc is one of the essential dietary factors and of the most widely distributed biometals present in all organs, living tissues, and secretions. Zinc is transported loosely bound to albumin in the circulation. The plasma Zinc pool is an insignificant pool (0.1% of total), but it is nevertheless immunologically important. The six percent of total Zinc content exists in the skin.¹ Zinc is also known to be a non-redox active ion and a cofactor for cellular proteins, nucleic acids, carbohydrates and lipids. Thus, it is a trace element essential for cell growth, development, and differentiation. And it is involved in maintaining the structure and function of ≥ 300 different enzymes. More than 2,000 transcription factors regulating gene expression require Zinc for their structural integrity and binding to DNA. The total body Zinc content of human subjects is 1.5-3 grams and it is the second most abundant trace element in the body after iron (4grams).²

Over the past 50years, many researchers have shown the important role of Zinc in a variety of physiologic processes, including body growth and development, priming and maintenance of the immune system, and in tissue regeneration. Recent studies also revealed that Zinc acts as an intracellular second messenger for transducing extracellular stimuli into intracellular signaling events in monocytes, dendritic cells, and mast cells.³ Zinc is an important regulator of caspase-3, as well as an antioxidant, microtubule stabilizer, growth co-factor, and anti-inflammatory agent.⁴ The essential trace element Zinc is extensively required in cellular functions, and abnormal Zinc homeostasis causes a variety of health problems that include growth retardation, immunodeficiency, hypogonadism, and neuronal and sensory dysfunctions. Zinc homeostasis is regulated through Zinc transporters, permeable channels and metallothioneins.⁵

The well accepted increase in the prevalence of allergic disease in developed countries has stimulated much research into the changes in lifestyle and/or environmental conditions. Changing diet is one of

the most important factors in these trends. Several clinical studies have related an increase in the incidence of allergic diseases with low dietary Zinc intake.^{6,7} Zinc deficiency could lead to a variety of defects in the organisms including immune system, which it seems to be associated with increased rate of allergic diseases in children. Zinc deficiency can be categorized into 2 groups-a congenital form, known as acrodermatitis enteropathica, and the acquired forms. Congenital acrodermatitis enteropathica occurs universally, with a projected incidence of 1 per 500,000 children. Nutritional Zinc deficiency of varying degree has been estimated to occur in more than 2×10^9 people. Therefore, it is estimated that a substantial proportion of the developed countries is at risk of minor Zinc deficiency.¹ Since body does not store Zinc, constant dietary intake is indispensable. It is clear that Zinc deficiency is an important public health problem worldwide, with significant consequences. The problem is the increasing trend toward Zinc-poor dietary change based on processed foods and soy-based substitutes.⁸ Infants and young children are especially susceptible to Zinc deficiency because of their higher Zinc requirement for rapid growth and development; growth-limiting nutritional Zinc deficiency can exist in otherwise healthy infants.⁹ Zinc is normally obtained from red meat, and other animal proteins, which not only have high Zinc content but the Zinc is bound to ligands which facilitate its absorption. Other sources of Zinc are seafoods, dairy foods, cereals, and nuts. Diets which are low in animal protein and rich in phytate contribute to the high incidence of Zinc deficiency in many developing countries. Another cause of primary Zinc deficiency in human could be Zinc-poor soils (e.g. on which cows raised and food grown).^{1,7}

As mentioned above, nutrition and/or dietary changes amongst other factors may have played a major role in the development of allergic disease. Two hypotheses have been proposed concerning different aspects of diet and/or nutrition: I-Reduction in dietary antioxidants and/or antioxidant cofactors (e.g. Zinc) consequent to reduction in intake of fresh fruit, vegetables and increased

consumption of fast food: Seaton et al.¹⁰ observed that the increase in asthma had come first and paralleled by changes in the UK diet, particularly declining consumption of green vegetables had increased population susceptibility.¹⁰ Although Zinc is not properly considered an antioxidant, Litonjua et al.¹¹ in their cohort studies reported that low levels of Zinc in the diet of women during pregnancy were associated with an increased likelihood that their children would develop wheezing and asthma in childhood. II-Change in fatty acid intake from ω -3 to ω -6 polyunsaturated fatty acids (PUFA) because of an increase in margarine instead of animal fat consumption: In 1997, Black and Sharpe.¹² drew attention to changes in dietary fat intake that had preceded and paralleled the increase in asthma and suggested that changes in dietary fat intake may have contributed to the increase. Dietary intake of saturated animal fats (butter and lard) has decreased and consumption of ω -6 PUFA present in margarine and vegetable oils has increased. Additionally, consumption of oily fish (tuna, herring, mackerel, and trout) or derived fish oil products (cod liver oil) in diet has decreased. More ω -6 PUFA intake in the diet results in the release of proinflammatory arachidonic-acid metabolites. These metabolites increase the formation of leukotrienes and prostaglandins from arachidonic acids. Furthermore, Zinc deficiency in these individuals increases eicosanoid production, and might augment inflammation in respiratory tract as well.¹³ Nevertheless, in a study, the authors did not find a significant difference between the patient and control group when they compared groups by Zinc and ω -3 PUFA (red meat and fish, respectively) rich diet consumption. There have been several observational and supplementation studies whose results were often contradictory and non-conclusive.^{14,15}

Possible effects of zinc deficiency affecting allergic disease development

Zinc has been supposed to have anti-oxidant, anti-apoptotic, anti-inflammatory and anti-allergic effects in the organism.² Zinc deficiency is suspected to play a role in the pathogenesis, control, and severity of allergic skin and airway diseases, consequent to losing these beneficial effects of Zinc in the organism.

Anti-oxidant effect: Glutathione peroxidase and superoxide dismutase, the important anti-oxidant metallo-enzymes of the body, contain Zinc in their structure.² Therefore, Zinc is an important antioxidant element in the airway epithelium as well as skin.

Anti-apoptotic effect: Excessive and improper apoptosis of respiratory tract epithelial cells plays a role in the pathogenesis of asthma. One of Zinc's effects in airway epithelium is to inhibit apoptosis. Allergen sensitized mice where Zinc deficiency was created through diet showed three times the rate of epithelial cell apoptosis than those fed a diet containing normal amounts of Zinc. Zinc protects respiratory tract epithelial integrity by both preventing caspase 3 activation and the lysis of proteins that provide intercellular connection.¹⁶

Anti-inflammatory action: Zinc is thought to modulate the expression of a range of inflammatory cytokines known to be important for recruiting inflammatory cells into the lung. In a murine model of allergic airway inflammation, Zinc deficiency is associated with increased airway eosinophilia.¹⁷ Eosinophils located in the respiratory tract lumen are known to be highly activated, and they release a range of proinflammatory cytokines and cytotoxic proteins that further amplify the inflammatory response.¹³ Zinc supplementation significantly decreased the number of eosinophils and other inflammatory cells, resulting in a less severe inflammatory response.¹⁷

Anti-allergic responses: Although the mechanisms, by which Zinc deficiency affects the allergic response, are not fully understood; there have been proposed some effects, as summarized below.

Th1/Th2 imbalance: Both asthma and Zinc deficiency are known to favor the Th2 inflammatory cytokine profile. Asthmatic rats with systemic Zinc deficiency were also found to have additional decrease of Th1 cytokines (IFN- γ), while the levels of Th2 cytokines (IL-4) were unaffected.¹⁸ Prasad¹⁹ studied the effects of mild nutritional Zinc deficiency for 4 weeks in human volunteers. Of particular interest was diminished functional activity of the Th1 cells but unaffected activity of Th2 cells, by this means causing a relative Th1 deficiency.¹⁹ These might be due to an imbalance between Th1 and Th2 cell functions — a switch from the Th1-dependent cellular immune response to a Th2-dependent humoral immune response. Because both asthma and Zn deficiency are associated with a skewing toward an upregulation of the production and release of various proinflammatory cytokines through the Th2 response, asthmatics who are also Zinc deficient are probably to have amplified inflammation.²⁰ Considering the previous findings that Zn deficiency worsens allergic inflammation, and Th2-dependent response is a feature of allergic inflammation in whole.

Regulatory T cells: The experiments in mice support the hypothesis that Zinc deficiency induces the Th1/Th2 imbalance not by downregulating the function of CD4⁺- CD25⁺ regulatory T cells in particular, but by suppressing various kinds of immune responding cells.²¹

Zinc and allergic diseases

Zinc may have an important protective role in the airway epithelium and Zinc deficiency may enhance inflammation and epithelial damage in the respiratory tract. Significant decreases in serum, plasma, erythrocyte or hair Zinc levels have also been reported in some of allergic individuals. Di Toro et al.²² showed that 35% of allergic children had low hair Zinc levels. Furthermore, Soutar et al.²³ noted that there was an increase in the presence of atopy, bronchial reactivity, and the risk of allergic-type symptoms in adults with the lowest consumption of dietary Zinc. Here, Zinc and allergy relation is briefly evaluated in just two major allergic disorders, atopic dermatitis and asthma, under the current literature data.

Atopic dermatitis: The cause of atopic dermatitis (AD) is multifactorial involving immunological and physiological abnormalities as well as biochemical defects of the skin barrier structure. The phenotypic expression of AD depends on a complex interaction between individual's genetic background and environmental factors, including nutrition. Inflammation and oxidative stress are considered as the main problems in AD patients. However, Zinc has anti-oxidative and anti-inflammatory effects, as mentioned above. Zinc deficiency is known to induce apoptosis of keratinocyte and is associated with refractory eruption and poor healing of skin wounds.²⁴ Consistently; animal models show that mice fed with a Zinc-deficient diet developed AD-like skin lesions.²⁵ A limited number of reports in human compare Zinc levels in patients with AD to those of healthy individuals, and the results are contradictory: some authors reported lower Zinc levels, whereas others found no differences.²⁶ For instance: Di Toro et al.²² found no differences in serum levels, although Zinc levels in hair were lower in patients with AD.

Airway disorders: Zinc may also influence fetal lung and airway development in rats. Maternal Zinc deficiency during pregnancy is associated with abnormal fetal lung development, smaller lungs and smaller lumina of alveolar ducts, in the pups born to Zinc deficient

rats.²⁷ Several important airway matrix metalloproteinases (MMP-3, MMP-9, ADAM33) are Zinc dependent and maternal Zinc consumption during pregnancy could influence lung and respiratory tract development by modulating the activity of these proteins.^{28,29} Two birth cohorts have now reported decreased maternal intake of vitamin E, vitamin D, and Zinc during pregnancy to be associated with increased asthma and wheezing episodes in children up to 5 years of age. Although Zinc is not considered to be an antioxidant, Project Viva and the Scottish studies reported reduced maternal Zinc intake during pregnancy to be related with an increased chance of wheezing and asthma during childhood.^{11,30} Evaluation of 1,290 children at 2 years showed that low maternal consumption of vitamin E, Zinc and vitamin D during pregnancy were independently associated with an increased possibility of 'ever wheeze' and 'recurrent wheeze' during the first 2 years of life. There was no association with eczema.¹¹

Several studies reported an association between asthma and low hair and serum or plasma Zinc levels, suggesting that asthmatic children were at risk of Zinc deficiency.³¹⁻³³ Schwartz and Weiss.³⁴ performed a large scale American study (n=9074) in the 1990s that found a negative relationship between wheezing and serum Zn:Cu ratio.

Conclusion

In conclusion: no studies thus far indicate whether Zinc deficiency is preexisting factor in allergic disease (due to low dietary consumption or an anomalous Zinc transport), whether it is a secondary outcome of the allergic disease, or whether it plays any role in the development of allergic diseases. The significance of the relation between allergic-type symptoms, low serum, plasma, hair and erythrocyte Zinc levels, and low dietary Zinc consumption is not so far fully understood. Clinical investigations and epidemiological studies have suggested Zinc deficiency as a complicating or risk factor in the development of allergic disease.

Zinc supplementation's role in the treatment of allergic diseases

Of potential curiosity in the treatment of allergic disease is the anti-inflammatory, anti-allergic and anti-oxidant dietary metal Zinc. Eriksen and Kare.³⁵ found out that AD patients consuming Zinc, vitamin E, and ω -3 and ω -6 fatty acid supplements had a decreased SCORAD index within 16 weeks. In contrast, in a double-blind, placebo-controlled trial by Ewing et al.³⁶ showed no improvement in disease severity after oral Zn supplementation.

Hair Zinc levels were found to be lower in wheezy infants than in healthy controls, suggesting that Zinc deficiency may influence the recurrence risk and persistence of wheezing in early childhood.³⁷ Zinc supplementation was recommended to these hypozincemic patients in order to correct their disturbances especially the Zinc deficiency which could lead to exaggeration of their allergic conditions.³⁸ A recent study also advocated Zinc substitution in the diet of those with hypozincemia and asthma.³⁹ Constantly, the available epidemiologic data is weak but supportive regarding Zinc and a Mediterranean diet for the prevention of asthma.⁷

Research in mouse asthma models showed that Zinc deficiency was associated with inflammation in the respiratory tract, which was attenuated by Zinc supplements.^{32,40} Whether Zinc deficiency plays a similar role in the human respiratory tract has remained controversial, with studies demonstrating both high and low plasma Zinc concentrations in asthmatic patients. Nonetheless, a new study

in human demonstrated that increased wheezing frequency and asthma severity was found to be associated with significantly lower labile sputum Zinc.⁴¹

As a result: First, maintaining airway Zinc levels might lower the risk of persistence in wheezing, development and progression of asthma. Second, repleting airway Zinc levels in those hypozincemics who already have airway disease (asthma) may lessen the inflammation severity in respiratory tract.

Future expectations

The Zinc metabolism and homeostasis especially in the airways and lung, its specific functions in the various tissues and its associations to respiratory tract disease remain largely unknown. One priority is to find out a better biomarker to reflect the correct Zinc level in human tissues since its level changes due to different internal and external factors.⁴² Although serum Zinc level has been accepted generally as a biomarker for Zinc status in humans, the difficulty now is to develop non-invasive techniques enabling to reliably monitor Zinc levels in the airway. Further research is also necessary to establish whether Zinc deficiency is a risk factor for the development of allergic disease or a secondary outcome of the disease. Although oral Zinc supplementation is safe and economical, does it need to be thought in the long-term treatment of allergic disease patients such as AD, asthma, etc.? And what dose and what time it ought to be used?

Acknowledgements

None.

Conflicts of interest

Author declares there are no conflicts of interest.

Funding

None.

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