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ASSESSING ZINC LEVELS: IS IT THE HOUR OF NEED?

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Abstract:

Zinc is an essential mineral playing a pivotal role in numerous aspects of cellular metabolism. Zinc deficiency affects all age groups, but the effect on growing children is very severe. Zinc deficiency is known to cause stunted growth and development in children. However, there are no reliable biomarkers of zinc status to assess health risk. Without a specific, sensitive biomarker to determine the zinc nutritional status, zinc intervention program is a struggle. Sensitive and specific analysis of zinc status is hence cardinal to defining optimal zinc status and setting evidence-based reference intake level. Given the lack of an accurate, sensitive zinc biomarker that reflects zinc nutrition across various populations and situations, research is needed to identify new biomarkers. Presently, the biochemical marker for measuring the zinc status is analyzing the plasma zinc. However, zinc homeostasis depends on many factors complicating the detection of marginal zinc deficiency.

Key words: *Zinc; homeostasis; markers; under nutrition; deficiency*

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INTRODUCTION:

Global estimates suggest that maternal and child undernutrition is responsible for causing diseases in children below five years at a rate of about 35% and deaths of 3.5 million per year. This is due to the deficiency of vitamin and nutrients. The ability to assess the role of nutrition in disease prevention and health promotion is predicted on the possibility of identifying precise and well-founded biomarkers that reflect nutrient exposure, status, and effect. 156 million children under age of 5 around the world are stunted [1]. Stunting and other forms of under nutrition are a major contributing factor to child mortality, disease and disability. Micronutrient deficiencies including deficiencies of vitamin A, iodine, zinc and folic acid are common factors contributing to the stunted children.

Zinc deficiency

Zinc deficiency is due to inadequate intake or mal-absorption of zinc from diet. People having the diet of plant products are limited with zinc availability and absorption due to high levels of inhibitors like fibre and phytates, compared to populations having animal products. It is estimated that zinc deficiency affects about one third of world's population according to food availability data, although severe zinc deficiency is rare, mild-to-moderate zinc deficiency is quite common around the world. The WHO and UNICEF recognise zinc deficiency as being one of the most important health issues globally. Zinc act as a regulatory ion, a catalyst or a structural element thus playing an important role [2]. Zinc deficiency affects half of the global population. Worldwide, zinc deficiency is responsible for approximately 16% of lower respiratory tract infections, 18% of malaria and 10% of diarrhoeal disease [3]. High mortality among children resulting from these infections has been reported due to zinc deficiency [4]. Prevalence of zinc deficiency is very common, and 61% of the population is at the increased risk of low dietary intake. Undernutrition has taken a heavy toll in developing countries like India, as 47% of children are enduring malnutrition and also India is one of the foremost countries with hunger situation. Zinc is vital to protein synthesis, cellular growth, and cellular differentiation. Zinc is a cofactor for the functioning of ~ 300 different proteins. The zinc status is varied during infection and inflammation. Studies in children have corroborated the important role of zinc in the modulation of immune function, growth, and development. Mild to moderate zinc scantiness makes them vulnerable to infection. Zinc or zinc-dependent proteins therefore directly affect the transcription and translation, thus regulating the expression of proteins and other metabolites [5].

Zinc is an indispensable metal vital for balanced growth and development. Zinc is the second most copious metal after iron in the human body. Zinc is a paramount cofactor for over more than 300 enzymes [5]. Around 3% of human genome encompassing 709 genes code for zinc bearing transcription factors [25]. Zinc is vital for insulin metabolism and signaling [6,7]. Zinc plays a crucial role in multitudinous biochemical and physiological pathways involving gene expression, signal transduction and antioxidant defense [8-10]. Inadequate consumption of zinc is a worldwide problem notably affecting India. About 2.1 million deaths among Indian children (<5 years) occur due to typhoid, malaria, measles and pneumonia. Evidently 1000 children die from diarrhea alone every day. All these are attributed to reduced zinc consumption. In five Indian states, current epidemiological research has revealed high extensiveness of zinc deficiency among children associated with low socioeconomic groups outlining an overall zinc deficiency of 43.8% (cut-off level (≤ 65 µg/dL) based on serum zinc levels. Orissa was the highest with (51.3%) followed by Uttar Pradesh (48.1%), Gujarat (44.2%), Madhya Pradesh (38.9%), and Karnataka (36.2%) [11,12]. One more recent cross-sectional study (n=630) confirmed low plasma zinc concentrations and substandard cognitive performance in 45% of adolescent girls in India, signifying the need to adopt dietary zinc for normal health (12). Nearly (64.6%) of pregnant women have been shown to suffer zinc deficiency in the state of Haryana, because of low intake of dietary zinc [13]. Zinc deficiency causes a metabolic and clinical deficiency that has no symptoms leading to imperfect growth, wasting and stunting. Correlation of zinc depletion to zinc status physiologically is due to an incomplete understanding of biological functions of zinc.

Markers for Zinc status

There are several reported methods of identifying zinc deficiency, and each method has its advantages and disadvantages. According to BOND zinc expert panel, serum or plasma zinc concentration values act as a biomarker for dietary zinc consumption and stunting acts as a functional indicator of zinc status [14]. Plasma zinc concentration levels have been proposed as a reliable marker to measure zinc status as they react positively to acute dietary zinc restriction or zinc addition stimulus. Zinc status can be measured in people at the peril of zinc insufficiency by estimating the plasma zinc concentration. Plasma zinc status cannot be considered as gold standard as they have their own constraints. Foods rich in zinc and foods which are added with zinc respond differently when their plasma levels are quantified, and they are also affected by the physiological condition of the person. At the same time, not enough information is available about whether blood cells, urine, nails, and hairs can be used as a source of zinc to predict zinc levels [14]. Bui (2013) [15] reported zinc intake was inconsistently associated with markers of serum zinc concentration. The associations between zinc intake was assessed with serum zinc, alkaline phosphatise and serum albumin as the biomarkers. Lowe [16] has elaborately reviewed on 32 potential biomarkers from 46 publications. Using plasma zinc concentration as a biomarker is reliable during an effective response to zinc to intervention such as growth in children or immune response. Modulation of plasma zinc

concentration occurs in response to zinc intake or depletion. But using plasma zinc as biomarkers has several pitfalls. The factors affecting zinc status are bioavailability, physiological state of the person, the possibility of zinc being metabolized when consumed as food or a supplement and analytical considerations such as contamination of plasma by hemolysis of blood and equipment used to collect blood. Measuring hair zinc concentration has several drawbacks as the level measured does not reflect the current zinc concentration. Because zinc is incorporated in the hair follicle during growth and as the hair matures it undergoes keratinization resulting in trapping of zinc in the protein structure of hair. Hence, the amount of zinc estimated in hair represents the quantity of zinc available during the time of hair growth. Urinary zinc could be used as a biomarker for predicting zinc status, but it has many drawbacks as zinc levels can only be estimated if there is acute zinc depletion. Apart from this, protein catabolism, starvation, strenuous exercise, diabetes, and trauma will result in elevated levels of zinc excretion. The use of nails to quantify zinc concentrations is limited as there is a lack of sensitive equipment to measure nail zinc concentration. More than 300 enzymes possess zinc as a cofactor for their function. So these bound zinc proteins may be secreted or leaked into the surrounding circulation. These proteins might act as biomarkers reflecting the status of zinc. Metallothionein is one of the markers which can serve as biomarker as it expression is highly modulated by a transcription factor know as MTF-1, which in turn is regulated by cellular zinc concentration [17]. Metallothionein levels increase with increasing cellular zinc concentration and might reflect zinc status, but using metallothionein as a biomarker has some issues, because it has been reported that there is a negative correlation plasma zinc status and metallothionein expression in blood mononuclear cell. This indicates that stress or inflammation raises the metallothionein concentration with concurrent depletion of plasma zinc levels thereby complicating the use of metallothionein expression has a biomarker of zinc levels [18,24] . Alterations in cellular zinc status affect the exporting and importing of zinc. It has been observed the zinc deficiency causes decreased expression of zinc efflux transporters (ZnT1 or ZnT2). In a human trial of severe zinc deficiency (< 2 mg dietary zinc/d), the expression of ZnT1 was found to be significantly downregulated after ten days in the blood cells [19,20]. But it is not clear if the mild to moderate deficiency of zinc affects the ZnT1 expression. A cytoskeletal protein named dematin has been recognized as a marker of zinc status during a clinical trial of acute zinc deficiency, but it needs validation before it can used as a biomarker [20]. Oxidative stress generates reactive oxygen species, which causes many diseases and zinc has been termed as pro-antioxidant as zinc indirectly stimulates the cellular antioxidant machinery. Zinc deficiency and zinc overload can cause oxidative stress and production of free radicals [21].This warrants further studies to identify markers of oxidative stress and inflammation during mild to moderate zinc deficiency with caution as many other factors alter the redox state and might give false positives during zinc deficient conditions. Zinc deficiency also has been shown to affect eicosanoid production in rodents. Zinc deficient rat had higher plasma concentrations of $PGF_{2\alpha}$ and PGE_2 compared to control rats which were fed with adequate zinc [22]. It has been suggested the ratio of linoleic acid and dihomo-γ-linoleic acid could be a potential marker to assess zinc status as deficiency affects the conversion of linoleic acid to dihomo-γ-linoleic acid [23]. Zinc insufficiency impacts innate and adaptive immunity thereby influencing host defence and immune response in particular. Zinc depletion causes impaired immune cell development, compromised T-cell mediated immune reaction and elevated oxidative burst. Zinc supplementation can mitigate all these, which suggests that zinc has anti-inflammatory and immunomodulatory function. Zinc consumption levels, serum or plasma levels of zinc, and below average growth are being used as a yardstick for zinc evaluation in population [14] (Janet et al 2016). The measurement of zinc nutritional levels by laboratory methods is burdensome due to sweeping dispensation of zinc all through the body as an integral component of numerous proteins and nucleic acids. Plasma zinc concentration (PZC) are used recurrently as a directory assessing zinc shortage, but one strong drawback of PZCs is that they do not represent zinc cellular levels for the most part due to rigorous homeostatic regulatory mechanisms[16]. However, considerable research is required before those biomarkers can be used to evaluate the zinc status of individuals or populations. There are, at present, no preventive zinc programmatic activities at the national or international levels. The WHO has not established guidelines for large-scale zinc interventions that are designed to prevent inadequate zinc nutrition. Furthermore, without a sensitive, specific zinc biomarker, program planners struggle to assess the need for preventive zinc interventions and how to measure their impact.

Identification of zinc deficiency is a tough task. There are no dependable biomarkers of zinc status to judge health risk. Without an unambiguous and responsible biomarker to evaluate the zinc nutritional status, zinc intervention program is a struggle. Sensitive and precise analysis of zinc status is hence cardinal to defining optimal zinc status and setting evidence-based reference intake level. Presently, the biochemical marker for measuring the zinc status is quantifying the plasma zinc. Due to the paucity of information, active indicators like enzymes and proteins which are modulated by zinc levels cannot be used to quantify zinc status both in clinical or field studies. However, zinc homeostasis depends on many factors complicating the detection of marginal zinc deficiency. The emerging omics technology could be put good use in identifying a reliable marker which will become a fruitful aid to diagnose zinc inadequacy in populations.

CONCLUSION:

Development of evidence-based clinical guidance and effective programs for achieving global health promotion depends on the availability of valid and reliable biomarker. Zinc deficiency is highly prevalent in the human population in under developed or developing countries and, at the same time sensitive analytical techniques are not yet available to assess zinc status in humans. Delicate and specific analysis of zinc status is cardinal to delineating optimal zinc status. Zinc deficiency causes sweeping changes in metabolism affecting many proteins, lipids, and microRNAs. The question is could these specific proteins, lipids or miRNAs be identified and serve as sensitive biomarkers to assess during acute, mild to moderate and chronic zinc deficiency.

Disclosure Statement

The authors declare that there are no conflicts of interest.

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