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Mini Review

Mutual Interaction between Obesity and Zinc Deficiency

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Abstract

Obesity and overweight are booming public health crises. Micronutrient deficiency, at all ages, is a world health issue too. High incidence of trace element deficiencies, especially zinc (Zn), in obese individuals has been reported. In addition, obesity-related consequences such as inflammation and oxidative stress affect zinc metabolism. Interestingly, with multi-protective function in obesity, the consumption of zinc in the management of obesity-associated metabolic disturbances is practical and effective. Moreover, research on zinc deficiency as a risk factor for overweight/obesity or obesity-related conditions has not yet been reported. This mini-review tries to highlight some of new findings and updates about obesity and zinc deficiency.

Keywords: Obesity; Overweight; Zinc Deficiency; Micronutrient; Inflammation; Oxidative Stress; Supplementation

Introduction

Obesity and overweight are considered as booming public health crises of the current millennium. According to a report from the World Health Organization (WHO), 1.4 billion adults in the world are overweight, and 200 million male and 300 million female adults over 20 years of age are obese [1]. Obese people are at increased risk for a myriad of serious diseases and conditions, including diabetes, dyslipidemia, cancer, hypertension, cardio-vascular disease, stroke, osteoarthritis, sleep disturbances, difficulty with physical activities, mental illness, low quality of life, mortality and so many others [2].

Nutritional deficiency in the case of extra bodyweight may seem contradictory at first, but a number of micronutrient deficiencies appear to higher in overweight and obese populations. Causes are multi-factorial, such as intake of high calorie and nutritionally poor-quality foods, lower consumption of fruits and vegetables, and increased adiposity which may affect the availability and storage of some nutrients [3,4]. Micronutrient deficiency (a silent pandemic), at all ages, is a world health problem too. Insufficient intake of micronutrients is now affecting more than 2 billion people worldwide [5]. Also, high incidence of trace element deficiencies in obese subjects has been revealed recently (table 1), for instance, mild Zinc (Zn) deficiency is rather common in European countries [6]. Newly, a notable association between low levels of Zn and obesity has affirmed [7]. About 55 years ago, human Zn deficiency was first introduced in the Middle East, in adolescent males of Iran by Prasad et al. [8]. Today, approximately 1:4 of Iranian households are zinc deficient [9]. Additionally, almost 1:3 of Iranians are overweight and/or obese [10]. Given the stated facts, evaluating associations between obesity and Zn deficien-

cy is of much importance and offers an appealing but controversial subject.

Deficiencies
Iron [11, 12] Common in overweight and obese, following bariatric surgery Obesity causes impaired iron absorption, inflammation, high hepcidin levels Anemia, extreme fatigue, shortness of breath, dizziness, headache, frequent infections
Copper [13] Common in overweight and obese, following bariatric surgery Cytochrome oxidase, superoxide dismutase, involved in the uptake of iron Anemia, lipid abnormalities, myelopathy
Selenium [14] Common in overweight and obese, following bariatric surgery Antioxidant Hypothyroidism, goiter, fatigue, mental slowing, low immunity, hair loss
Zinc Common in overweight and obese, following bariatric surgery Chronic fatigue, infertility, anorexia, anemia, dysgeusia, dysosmia, diarrhea, dermatitis, skin rash, arthritis, slow wound healing, nerve dysfunction, poor immunity

Table 1. Trace Element Deficiencies, Obesity, Roles and Symptoms.

Zinc a crucial micro-mineral, has significant catalytic, structural, anti-inflammatory and anti-oxidative roles in human body (table 2). Because of the lack of specific Zn storage in the body, daily intake of Zn is essential to reach a steady-state, maintain it and support all its functions [15]. Naturally, hypozincemia is caused by inadequate intake or absorption, elevated Zn excretion, or high bodily need. Its symptoms include growth and development complications, eye and skin issues, hair loss, delayed wound healing, loss of appetite, taste changes, diarrhea, impotence, and mental slowness [16]. In addition, Zn deficiency has been recognised to be linked with many diseases and comorbid conditions such as type 2 diabetes, metabolic syndrome and cardiovascular disease [17]. Imbalance of zinc metabolism is typical in obesity [18,19].

This mini-review tries to highlight some of new findings and updates about the association between obesity and zinc deficiency.

Function	example/mechanism
Catalytic	control of metabolism (breakdown of carbohydrates, lipolysis, protein synthesis)
Structural	proteins, cell membranes, connective tissue, teeth, bones, nails, hair and skin
Growth and development	cell division, cell growth, DNA synthesis and regulation
Anti-inflammatory	reducing cytokine production
Anti-oxidative	decreasing ROS and oxidative stress
Regulating	blood glucose, insulin, leptin and steroid hormones

Table 2. The Functions of Zinc.

Micronutrient Deficiency and Obesity

Nutritional literature on obesity often focuses on factors other than micronutrients. However, National Health and Nutrition Examination Survey (NHANES) 2001-2008 shows that obese adults compared to the normal weight have lower micronutrient intake and higher prevalence of micronutrient inadequacy. Additionally, micronutrient deficiencies have been observed in obese individuals in many parts of the world, and it is obvious that these may influence several physiological body functions, impair the immune system and elevate the risk of comorbidities [1,2]. Some studies represent high percentage of zinc deficiency in obese adults and children. For example, zinc concentrations of serum and red blood cells in obese subjects are reduced [18,19].

Zinc, Insulin Resistance and Leptin

Obese subjects with low plasma values of Zn have higher insulin resistance and leptin, compared with those who have healthy bodyweight [20-22]. Given the fact that obese people generally have hyperinsulinemia, the level of circulating leptin is directly proportional to the total amount of fat in the body, excessive calorie intake is a fast track to leptin resistance [23,24] as well as Zn is remarkably involved in regulating insulin and leptin, zinc can have an inverse association with insulin resistance index and leptin [19,25,26]. Moreover, in obesity, zinc-alpha-glycoprotein (ZAG is encoded by the AZGP1 gene, which stimulates lipolysis, induces a reduction in body fat, is associated with cancer cachexia and rises with the onset of type 2 diabetes [27] is markedly reduced in subcutaneous adipose tissue. Cellular and molecular evidence suggest that ZAG has a crucial role in modulating fat tissue insulin sensitivity [28].

Inflammation, Oxidative Stress, Cytokines and Zinc Transporters

Chronic inflammation and elevated oxidative stress are common complications of obesity [29]. Besides, high leptin and lower plasma or intracellular Zn concentrations are extremely pro-inflammatory which can upregulate IL-1, IL-6, IL-8 and TNF-α levels in obese people [23,30]. For instance, in one study, obese individuals had higher amounts especially copper/zinc superoxide dismutase which in turn may contribute to obesity-related metabolic disturbances [34,35].of inflammatory markers including C-reactive protein (hs-CRP), interleukin-6, and homocystein, especially levels of hs-CRP and IL-6 increased in the abdominally obese [31]. As noted, obesity (a chronic inflammatory state) is associated with altered zinc metabolism. One research showed that changes in zinc transporters (ZnTs and ZIPs), which are involved in the control of metabolism, may also be connected to the inflammatory state of obesity [32,33]. It seems that TNF-α, leptin, CRP and IL-6 downregulate the transporters of Zn. However, the exact mechanisms involved remain debatable. Furthermore, obesity may be relevant to changes in gene expression of zinc transporters [32]. Obesity and overweight are associated with decreased total antioxidant capacity and enzyme (SOD, GPX, CAT) activities,

Recent research has reported the importance of zinc status in the improvement of weight-related complications. For instance, surveys show that zinc is an antioxidant and anti-inflammatory agent, very effective in decreasing reactive oxygen species (ROS) [36], and may have a favourable effect on obesity-related inflammation in adults [37]. Antioxidant-rich foods are effective in the control of obesity and overweight [29]. Diets low in zinc can cause considerable reductions in the activity of the immune system. Likewise, a zinc-deficient state appears to surge cytokine production [20]. Thus, dietary zinc intervention for obese patients is effective with decrease of inflammation and ROS that lead to the redistribution of zinc in erythrocytes, plasma, saliva and urine [38]. Intriguingly, zinc monotherapy improves mood and depressive symptoms in obese subjects [39].

Factor	Mechanism
Inflammation	cytokine hyper-production
Oxidative stress	decreased total antioxidant capacity
Downregulation of zinc transporters	gene expression of transporters, raised methylation
Zinc malabsorption	impairment of intestinal uptake

Table 3. Factors causing Zinc deficiency in obese patients.

Zinc Supplementation

Micronutrient supplementation could be effective for bodyweight regulation [40]. Zn supplementation significantly reduces total cholesterol, LDL cholesterol and triglycerides, therefore, it may have the potential to minimize obesity-related consequences [41]. For example, zinc supplementation enhances serum zinc significantly and decreases fasting glucose, insulin and HOMA-IR. Conflicting results in different studies could be due to variation in doses, supplementation period, difference in chemical form of zinc, as well as the supplementations have been conducted in different population groups [42]. Besides, zinc supplements could restore ZnTs expression and reduce not only the production of inflammatory cytokines but also that of oxidative stress markers, in obese populations [43,44].

Zinc Deficiency and Bariatric Surgery

Micronutrient deficiencies (iron, copper, selenium and zinc) are the most likely long-term adverse events after bariatric surgery and can result in wide range of symptoms, most commonly anemia, fatigue and neurological dysfunction (table 1). Low serum zinc concentrations have been reported in both pre- and post-operative bariatric patients [3]. One study showed a high incidence of zinc deficiency in the morbidly obese, and suggested the evaluation of zinc status in cases undergoing bariatric surgery as well as treatment of Zn deficiency before the surgery [45].

Discussion

On the one hand, according to the previous research, gaining extra weight could be a risk factor for Zn deficiency. On the other hand, we suggest that lack of zinc may cause overweight and obesity. Therefore, zinc-insufficient obese people will be caught in a vicious cycle. As mentioned earlier, obese individuals have hyperinsulinemia, hypozincemia and hyperleptinemia [26]. Apparently, there is an interrelationship among obesity, insulin, leptin and Zn metabolism. In addition, we presume that high levels of leptin in obesity may be related to increase urinary Zn loss. Considering the contribution of Zn in carbohydrate, lipid and protein metabolism, Zn-deficient individuals are liable to metabolic disorders, for this reason, zinc-sufficient obese people are less likely to develop diabetes and metabolic syndrome. In view of the fact that Zn improves insulin sensitivity and protein synthesis, it should be emphasized in weight-loss dieting.

Chronic inflammation associated with excessive bodyweight elevates cytokines, which may have the effect of reducing Zn absorption into our body. Inflammatory markers are significantly high in obese individuals, and obesity adversely affects the oxidant-antioxidant balance of the body [29,30]. On the one hand, adequate level of zinc is essential in maintaining the immune system functions, on the other, a condition of less

inflammation must exist in order that zinc can work properly in the body [32]. It is reported that the root cause of the link between immune defects and zinc-deficient state might be the raised methylation of zinc transporters (ZnTs and ZIPs), causing them not to function correctly [33,37]. This results in lower zinc concentration inside immune cells and heightened inflammatory response and cytokine expression, in fact, a vicious circle is formed. Subsequently, this trace element of ample amount could have multi-protective functions in obesity.

Insufficient intake of micronutrients may be contributing to fat deposition and obesity, and could lead to further weight gain or development of associated metabolic diseases [29]. Since zinc finger proteins (ZFPs) are important functional contributors to the regulation of adipogenesis [46], therefore, dysfunction of ZFPs might impact adipocytes negatively and develop obesity. As mentioned earlier, a combination of insulin and/or leptin resistance and Zn deficiency might result in obesity. Thus, Zn deficiency could be considered as a risk factor for overweight/obesity or obesity-related conditions. Micronutrient supplementation can induce significant reductions in bodyweight, fat mass, waist circumference, as well as increased resting energy expenditure, and have a positive effect on lipid profiles [40,47]. Consequently, the consumption of zinc supplements in the management of inflammatory and oxidative status of overweight/obese individuals seems imperative. Finally, a correction of zinc deficiency (dietary or supplemental) is more likely to have a great impact on the complications caused by excess bodyweight.

We suggest that micronutrient sufficiency is crucial in the fight against obesity, and the control of zinc status seems important in prevention, treatment and follow-up of metabolic disturbances resulted from obesity. Future research should study novel biomarkers for hypozincemia and establish the RDA of zinc (per kg of bodyweight) for obese and overweight persons. In addition, we propose conducting clinical trials on the effects of different doses of zinc supplements on obese/overweight subjects. All in all, care should be taken to optimize food intake to provide adequate intake of zinc.

Conclusion

It should be emphasized that zinc deficiency is of much importance in the etiology of obesity/overweight, and is a consequence of excessive bodyweight as well. Hypozincemia exacerbates metabolic, immune and oxidative statuses in obesity. Taken altogether the above data lead to the conclusion that enhancing zinc intake through diet and/or supplementation could be a viable strategy for reducing obesity-associated disturbances or conditions. Therefore, zinc status (serum and urine) should be monitored in obese individuals.

The authors have no conflict of interest to declare.

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