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REVIEW PAPER

Zinc: its impact on immune function in children

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ABSTRACT

Based on the analysis of literary sources, this review highlights the main reasons and mechanisms of zinc impact on the development of immunodeficiency conditions in children. The study outlines the importance of zinc homeostasis in the functioning of innate and adaptive immunity. The multifaceted influence of zinc on the activity of the immune system includes the regulation of maturing, differentiation, activity of innate immunity cells (neutrophils, monocytes-macrophages, mast cells, natural killers, dendrite cells) and adaptive immunity cells (T-lymphocytes and B-lymphocytes), activation of interferon synthesis, regulation of the activity of inflammation process, participation in signalling pathways of antigen presentation to the highly specific immune cells, and support of the antioxidant status in the child's organism. The role of zinc status in antiviral immunity, particularly in COVID-19 infection, is considered. A risk group for the development of zinc deficiency and immunodeficiency conditions is identified.

KEY WORDS:

zinc, children, innate immunity, adaptive immunity.

INTRODUCTION

Microelements are the chemical substances present in human organisms in tiny quantities; their total amount does not exceed 0.005% of body mass. However, they are essential for the human body's normal functioning and the proper child development because microelements participate in all life processes [1, 2]. Unlike vitamins, which can be synthesized in human organisms, microelements must be received with food and water. Insufficient intake of microelements with food and water may lead to microelement deficiency and dysfunction of some body systems.

Based on UNICEF data (The State of the World's Children, 1998), microelement deficiency costs countries, on average, nearly 5% of gross national income. Unfortunately, microelement deficiency manifests subclinically for a long time with no symptoms in both adults and children. The highest importance for maintaining human health is held by essential microelements: calcium, potassium, sodium, chloride, zinc, iodine, chromium, cobalt, manganese, molybdenum, magnesium, copper, selenium, sulphur, and iron [1]. According to the WHO (2009), in many world countries, levels of above listed essential microelements in food intake are marginal, which causes the development of microelement deficiency [3]. One of the most studied essential microelements is zinc (Zn), which is second by quantity in the body. The WHO states that different zinc deficiency stages are present in at least one-third of the world's population. Its expression and distribution depend on the population's geographic location, income, and food traditions, ranging between 10 and 80% [4]. In particular, based on WHO data, in Eastern European countries approximately 10% of the population has hypozincaemia [5].

MATERIAL AND METHODS

A literature search of the PubMed and Scopus databases, regarding the subject of the role of zinc in the human body, using the word "zinc" and the combination

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TABLE 1. Mechanism of action of zinc

No	Function	Biological role
1.	Structural	Component of numerous proteins, including multiple metalloproteins; biological membranes,
2.	Catalytic	Participate in the metabolic processes
3.	Support of reproductive function	A part of the genetic apparatus of cells, affects the processes of transcription and replication of DNA and RNA
4.	Regulation	Controls all processes of the cell cycle, provides control of gene expression in the process of replication and differentiation of cells, regulates the processes of transcription of other intracellular proteins
5.	Neuromodulator and neuromediator	Impact on formation and functioning of the central nervous system
7.	Biosynthesis of bone tissue	Increases activity of osteoblasts and inhibits osteoclasts' activity, promotes bone mineralization, affects longitudinal bone growth and skeleton formation
8.	Collagen synthesis	Promotes wound healing
9.	Insulin, testosterone, other hormones biosynthesis	Promotes the normal functioning of the endocrine and reproductive systems
10.	Heme biosynthesis	Normal functioning of erythrocytes; prevents erythrocyte hemolysis
11.	Immune response	Regulation of the processes of innate and acquired immunity
12.	Anti–teratogenic effect	Promotes growth and development of the fetus; hypozincemia in pregnant women causes a delay in intrauterine development of the embryo during the last months of gestation
13.	Antioxidative activity	Protection from oxidative damage

of the words "zinc" and "immune system", "viral infection", "COVID-19", "supplementation", and "deficiency" was conducted. We used relevant full-text articles, which were published between January 2012 and July 2021. We also used some basic articles, which were published in 1999-2011. Studies with results relating to the role of zinc in the human body, especially in providing an immune response and the possibility of its potential applicability in the prevention and treatment of COVID-19, were selected for analysis.

THE ROLE OF ZINC IN THE HUMAN BODY

Zinc, being one of the essential microelements, has unique biological importance for the child organism (Table 1):

- It is a part of all enzymatic systems in the organism (zinc-containing enzymes belong to all 6 classes of enzymes, which participate in the metabolic processes and control energy metabolism, DNA and protein biosynthesis, stability of plasma membranes, proliferative processes, degree of development of oxidative stress, sexual differentiation, and physical and neuropsychological child development) [6, 7].
- It is a part of more than 300 metalloenzymes such as DNA and RNA polymerase, dehydrogenase, carboxypeptidase, phosphatase, superoxide dismutase, alcohol dehydrogenase, and pyruvate carboxylase, which directly participate in all life processes. In particular, a decrease in zinc level in the human body causes inhibition of the activity of metalloproteinases, which promote inactivation of viral, intracellular, and bacterial pathogens so that the phagocytosis process is disrupted [8].
- It is a part of the genetic apparatus of cells (zinc-containing proteins are located in the cell nucleus and zinc-containing domains, "zinc fingers", promote binding of the transcription factors to the DNA molecules and promote interaction of proteins with zinc domains with the RNA molecules and other proteins molecules, thus affecting transcription and replication processes [9].
- It controls all processes of the cell cycle (maintains control of gene expression in cell division and cell differentiation processes, so zinc deficiency during embryogenesis can cause the development of defects in the embryo) [9, 10].
- It participates in the metabolism of nucleic acids and proteins by being a part of multiple metalloproteins, which regulate transcription and translation of other intracellular proteins. In cells, zinc-dependent proteins are concentrated in the cytoplasm, nucleus, endoplasmic reticulum, Golgi apparatus, and mitochondria [11, 12].
- It participates in the stabilization and regulation of permeability of cellular and intracellular membranes, and membrane transport processes by being a part of biological membranes [9].
- It has an impact on formation and functioning of the central nervous system as a neuromodulator and neuromediator [10].
- It participates in the biosynthesis of bone tissue – it increases activity of osteoblasts and inhibits osteo-

clast activity, promotes bone mineralization and collagen synthesis, and affects longitudinal bone growth and skeleton formation [13]. Zinc deficiency promotes resistance to somatotropin in the child organism [14].

- It is essential for vitamin A metabolism, which has antioxidant properties and protects the organism from oxidative stress [15]. Zinc is a cofactor of the β-carotin-15,15-dioxygenase enzyme and affects retinol dehydrogenase activity, which both participate in the transformation of carotenoids and vitamin A into their active forms. Besides that, zinc is vital for the synthesis of the apo-retinol binding protein, which is responsible for the transportation of retinol (the active metabolite of vitamin A) to the place of its action in the body [16].
- It participates in the activity of the endocrine system by directly participating in insulin biosynthesis. Adrenocorticotropic hormone, somatotropin, and gonadotropic hormones are also zinc-dependent hormones. Zinc is a part of the nuclear receptor of triiodothyronine and mediates its activity; also, zinc is a part of superoxide dismutase enzyme, deficiency of which promotes thyroid gland hyperplasia [11].
- It plays a vital role in the normal functioning of erythrocytes. Zinc participates in heme biosynthesis, and inhibits phospholipase A2 and adenosine triphosphatase enzymes, which prevents erythrocyte haemolysis [7, 11].
- It acts as a teratogenic factor in embryonic development during the early stages of gestation hypozincaemia in pregnant women and causes a delay in intrauterine development of the embryo during the last months of gestation [17].

ANTIOXIDATIVE PROPERTIES OF ZINC

Zinc actively participates in immune system activity and maintenance of antioxidative status in the child organism [18, 19].

In human cells, a significant part (about 20%) of total intracellular zinc concentration is contained in the metallothionein (MT) proteins that are crucial for the maintenance of Zn^{2+} homeostasis and free radical oxidative processes. In particular, MT molecules contain a powerful antioxidant, cysteine, and are able to bind and utilize free radicals [6, 20]. Moreover, MT can interact with and bind other chemical elements such as copper, cadmium, mercury, and arsenic, which have oxidative and toxic properties in relation to biological structures. For stabilization of cellular membranes, it is not only essential to have zinc in their composition but also zinc participation in the protection of these structures from oxidative damage done by reactive oxygen species (ROS). Because zinc is a part of intracellular and extracellular oxidative enzyme Cu/Zn-superoxide dismutase, the synthesis intensity and catalytic activity of which depend on the level and biological accessibility of these microelements, and also inhibits nicotinamide adenine dinucleotide phosphate, which is responsible for ROS production, zinc is an essential antioxidant and plays a significant role in maintaining antioxidative status in the body, which is vital for the child organism because all systems and organs in children are functionally immature and any defects can lead to irreversible processes [11]. Also, zinc antioxidative properties are exhibited in the inhibition of syntheses of inflammatory cytokines (TNF-α and interleukin-1β), which produce ROS [18]. Thus, zinc plays a significant role in regulating the expression of the activity of the inflammatory process.

Therefore, zinc deficiency is manifested by a decrease in the activity of antioxidant defence processes and the development of oxidative stress in the body.

THE ROLE OF ZINC IN PROVIDING AN IMMUNE RESPONSE

Zinc plays a critical compartmentalizing role in the functioning of both innate and adaptive immunity. Zn^{2+} ions actively participate in the normal development, maturing, differentiation, and functioning of myeloid and dendrite cells [20, 21] and intensification of the cytotoxic and killer activity of NK-cells [22]. Zinc deficiency inhibits some neutrophil functions, such as phagocytosis, oxidative burst, synthesis of defensins, cation antimicrobial peptides, proteolytic enzymes, and metal chelators, chemotaxis, and formation of extracellular neutrophil trap. It also decreases the production of cytokines [23, 24]. Zinc deficiency also causes mast cell degranulation, which plays a significant role in antiparasitic immunity by releasing histamine, TNF-α, and proteases. Hence, it is clear, and evident in multiple studies, that there is incomplete phagocytosis of pathogens by neutrophils during hypozincaemia, which causes infection persistency in the child organism [23, 24].

Zinc can block the replicase enzyme of multiple viruses and thus stop the reproduction of the virus in the cells and the development of infection in the human body. In particular, experimental studies in vitro proved that Zn^{2+} cations, especially in combination with zinc ionophore pyrithione (zinc transporter through the cellular membrane), inhibit the activity of RNA coronavirus RNA polymerase by decreasing its replication [25, 26]. An important role in destroying intracellular pathogens and transmission of signals to immunocompetent cells belongs to monocytes and macrophages, for differentiation of which zinc is essential. Macrophages can regulate their intracellular zinc level depending on the pathogen, and thus zinc can exhibit a cytotoxic effect on the pathogen (in high concentrations) or stimulate ROS synthesis (during hypozincaemia) and activate free radical oxidation processes towards the pathogen [27, 28].

In studies *in vitro and ex vivo,* it is evident that zinc can induce production of interferon α and γ, which increases the antiviral activity of innate immunity. Zinc ions prevent cell apoptosis by inhibiting caspases 3, 6, and 9 and increasing the Bcl-2/Bax ratio. Moreover, zinc ions decrease local signs of inflammation (swelling, exudation, and mucus secretion) by inhibiting the transcapillary movement of plasma proteins to the inflammation site. Multiple studies *in vitro and ex vivo* showed that extracellular MT exhibits immunomodulatory effects, in particular, increased chemotaxis activity of leucocytes and immunocompetent cells, but as of today, the exact mechanisms of their action are not known. Zinc sequestration done by the human immune system helps to fight extracellular pathogens by expressing pro-inflammatory acute-phase proteins, including IL-6, which increases regulation of expression of zinc-binding peptides – MT and α2-macroglobulins – and stimulates zinc transporter ZIP14, which is embedded into the plasma membrane and facilitates zinc transportation into the cells [29]. Specifically, during the acute phase of inflammation, the biometal blood level decreases because zinc is deposited in tissue cells where inflammation is located, so it is crucial to maintain adequate zinc status in the child organism to ensure the proper response of innate immunity. Besides adequate immune response, zinc is necessary for RNA transcription, DNA synthesis, and cell stabilization [30, 31]. Thereby, disruption of zinc homeostasis leads to the development of immunodeficiency status in the child, which in the long run will lead to the development of secondary immunodeficiency.

The regulatory function of zinc in adaptive immunity, first of all, is mediated by the thymus hormone thymulin, which contains zinc. Thymulin is necessary for the maturing and differentiation of T-lymphocytes in the thymus. It has been proven that thymulin also affects the proliferation and activation of T-cells in the blood and body tissues [11]. Hypozincaemia leads to the decrease in the number of T- and B-lymphocytes in the thymus and bone marrow, and a change in the Th1- and Th2-lymphocyte ratio in favour of allergic reactions caused by Th2, so maintenance of adequate zinc status will lead to a decrease in allergic reactions in children [32]. Moreover, zinc deficiency decreases allogeneic cytotoxicity and production of IL-2 by T-cells [33-35] and increases B-cell proliferation due to the intensified phosphorylation of STAT3 [36]. Modulation of zinc inhibits MHC-II expression and enhances expression of PD-L1 та PD-L2 ligands, which causes a skew in the Treg/Th17 in favour of Treg cell development and a decrease in pro-inflammatory action of Th17 [37]. Hypozincaemia leads to a decrease of lymphoid tissue in the child organism, including premature accidental involution of the thymus, resulting in the development of immunodeficiency of T- and B-cells [11].

In general, zinc promotes the general regulation of immune cell functioning of innate and adaptive immunity by affecting several signalling pathways [23, 35, 38].

The adequate immune response is provided by the coordinated action of innate immune cells, which are the first to react on any microorganism and highly specified adaptive immune cells. Innate immune cells (neutrophils, monocytes, NK-cells, mast cells, and dendrite cells) recognize general pathogen-associated molecular structures with cell-surface recognition receptors, such as Toll-like receptors (TLR), which activate signalling pathways, which induce antigen presentation to highly specific adaptive immune cells and cytokine synthesis and also regulate subsequent antimicrobial actions of naïve cells, such as degranulation, phagocytosis, and pathogen destruction [19, 22, 39]. Transduction of initial signal from the microorganism, detected by the cell-surface receptor of naive cells to the gene expression in the nucleus, is mainly carried out by the phosphorylation processes, which involve the transfer of phosphate groups from one signalling molecule to another through the chain of molecules within a signal transduction pathway. Phosphorylation reactions are catalysed by protein kinases, which are zinc metalloenzymes, so in this way zinc participates in the transformation of extracellular signal into the intracellular signalling event [40]. So, in the absence of zinc signalling, the lytic activity of NK-cells is decreased due to a decrease in recognition of MHC-I antigens on the target cells [11, 41, 42].

One of the main options for triggering the signal of activation of inflammation in the reactions of both innate and adaptive immunity is the NF-κB factor, activity of which is regulated by phosphorylation reactions and degradation of its specific inhibitor IκB. It should be noted that zinc-fingered protein A20 causes inhibition of NF-κB and inhibition of expression of IL-1β, TNFα, C-reactive protein, and other inflammation mediators and thus decreases the level of signalling in the signalling pathways with modulation of zinc status [43-44]. One more zinc-fingered protein, PPARα, changes binding of NFκB with DNA and thus prevents the induction of pro-inflammation cytokines and adhesion molecules and decreases inflammation signs [45]. Hence, maintaining zinc homeostasis in the human body is an essential factor in preventing cytokine storm during the inflammation process.

Considering zinc compartmentalization mechanisms, it should be summarized that zinc is vital for an adequate immune response [46], and its deficiency in the child or adult organism is associated with an immunodeficiency condition [47]. Disruption of zinc status in the blood and/or body cells is observed both during primary (it is part of the metalloenzymes, regulates the production and maturing of immune cells, cytokines, etc.) and secondary immunodeficiencies. For example, we will consider primary immunodeficiency disease – Bruton's disease,

which is caused by mutations in the gene that codes for Bruton tyrosine kinase and leads to agammaglobulinaemia. As of today, more than 1000 mutations of this gene are known. Due to its functions, Bruton tyrosine kinase belongs to the class of tyrosine protein kinases, which are zinc-containing enzymes that participate in signalling pathways and play an essential role in maturing and functioning of B-lymphocytes. By being a part of this enzyme, zinc participates in maintaining the activity and stability of tyrosine kinase [48]. The absence of Bruton tyrosine kinase is manifested by the significant decrease or total absence of B-lymphocytes, plasma cells, and respectively antigens, leading to severe clinical manifestations of this disease [49-51].

Hypozincaemia causes premature involution of the thymus, a decrease in the mass of lymphoid tissue, lymphocytopaenia, and inhibition of the activity of metalloproteinases, which facilitate inactivation of viral (intracellular) and bacterial (extracellular) pathogens, which in turn can lead to incomplete phagocytosis and microorganism persistency [11, 23, 24, 40, 41, 47].

ZINC AND COVID-19

Considering the presence of the coronavirus pandemic at this time, it is worth mentioning the experimental data, which proves that zinc in micromolar concentrations decreases expression of ACE2 zinc-containing metalloenzyme in the lungs with the assistance of which SARS-CoV2 and SARS-CoV can enter the cell [52-53]. As of today, it is well known that in the pathophysiology of most clinical manifestations of COVID-19 active contributions are made by the renin-angiotensin and kinin-kallikrein systems, and that zinc deficiency leads to a decrease of regulation of ACE2, which promotes the accumulation not only of angiotensin II but also of des-Arg-9-bradykinin and Lys-des-Arg9-bradykinin, and causes strengthening of pro-inflammatory reaction, vasoconstriction, and prothrombotic events [54]. Hypozincaemia also promotes dysfunction of cathepsin L, which provokes the development of bradykinin deficiency at the inflammation site and decreases its vasodilatation activity. These effects possibly favour an increase in inflammatory mediator production and a change in anticoagulation parameters in patients with COVID-19. Also, in studies, it was shown that zinc in physiological concentration increases the number, length, and mobility of cilia of mucociliary clearance, which prevents viruses from entering the lower respiratory tract and decreases the risk of secondary bacterial infection, which is crucial for prevention of frequent respiratory tract infections in children [52-54].

Recent results confirm that among women in all trimesters of pregnancy, the blood serum zinc level of pregnant women with COVID-19 was lower than in healthy pregnant women. It negatively correlated with acute-phase inflammatory markers such as IL-6, ESR, procalcitonin, and CRP and correlated with the disease's severity [25].

Conducted studies show that hypozincaemia is considered a risk factor of severe COVID-19 illness [54- 55] and is interpreted as a consequence of zinc deficiency at the level of different metabolic systems that participate in the manifestation of the mentioned disease [56].

For optimization of an adequate zinc level, it is recommended that a daily dose of zinc lower than the permissible upper limits (< 7 mg for children aged 1-3 years, up to 10 mg at age 4-8 years, up to 15 mg at age 9-14 years, and up to 22 mg at age 15-17 years) be taken together with nutrition correction. In adults, the recommended daily dose of zinc is 50 mg [57]. However, randomized

TABLE 2. Groups of children at risk of zinc deficiency

Condition
Premature babies and babies with low body mass or intrauterine growth retardation
Recurrent illnesses (secondary immunodeficiencies)
Low-income families
Vegetarian families and have nutrients deficiency
Born from mothers with zinc deficiency
Chronic diseases of gastrointestinal and urinary systems
Cystic fibrosis or tuberculosis
Dermatologic diseases, including allergic dermatitis
Delayed physical development and puberty
Pathologies of the musculoskeletal system
Pathology of the nervous system, including attention deficit hyperactivity disorder
Excessive physical and/or psychoemotional load
Consumption of water with high iron content
Helminthiasis

clinical studies did not show any significant decrease in duration of symptoms associated with COVID-19 during treatment of high doses of zinc gluconate, ascorbic acid, and their combination when compared to regular treatment [58]. So, the doses mentioned above are directed to decrease the level of zinc deficiency. It is important to note that the administration of zinc supplementation is based on the presence of zinc deficiency in the blood, and not just belonging to a risk group.

Despite the lack of substantiated recommendations for zinc supplementation for prevention of COVID-19, there are data on the use of zinc for both prevention and treatment of respiratory infections [59, 60]. The study reported a reduction of the infectious rate after daily zinc intake at a dose of 10-20 mg for 6-12 months [61], so the effectiveness of zinc in the prevention of COVID-19 can be predicted.

RISK GROUPS FOR ZINC DEFICIENCY

To prevent negative consequences of hypozincaemia, which lead to the development of immunodeficiency in children, it is necessary to measure the zinc concentration in blood in the paediatric population that belong to the risk group. Taking into account the literature data [6-19], we identified categories of children that should be included in the risk group for the development of hypozincaemia (Table 2).

CONCLUSIONS

A review of literary sources showed the multifaceted influence of zinc on the activity of the immune system, which includes the regulation of maturing, differentiation, and activity of innate immunity cells (neutrophils, monocytes-macrophages, mast cells, natural killers, dendrite cells) and adaptive immunity cells (T-lymphocytes and B-lymphocytes), activation of synthesis of interferon, regulation of expression of the activity of inflammation process, participation in signalling pathways of antigen presentation to the highly specific immune cells, and support of the antioxidant status of the organism.

DISCLOSURE

The authors declare no conflict of interest.

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