https://doi.org/10.34108/eujhs.535414

SAĞLIK BİLİMLERİ DERGİSİ
JOURNAL OF HEALTH SCIENCES
Erciyes Üniversitesi Sağlık Bilimleri Enstitüsü Yayın Organıdır

Derleme 2021; 30: 83-86

ZINC, ITS FUNCTIONS AND ROLE IN THE IMMUNE SYSTEM
ÇİNKO, FONKSİYONLARI VE İMMÜN SİSTEMDEKİ ROLÜ

Burcu USLU[1], Şule AKTAÇ [2]

[1]*Yuksek Ihtisas University, Faculty of Health Sciences, Department of Nutrition and Dietetics, Ankara*
[2]*Marmara University, Faculty of Health Sciences, Department of Nutrition and Dietetics, Istanbul*

ABSTRACT

Zinc (Zn) is the essential mineral for the organism. It is a biological trace element that needs to be taken every day for optimal health. Despite the vital necessity of Zn, the body has no warehouse that can be used to maintain metal levels for a long time. Zinc is absorbed in the intestine by specific zinc-bearing proteins and distributed in the human body. Free zinc is rare in serum because albumin is highly attached on proteins such as α2-macroglobulin and transferrin. During zinc deficiency, while polymorpho nuclear cells chemotaxis and phagocytosis decreased, zinc supplementation had the opposite effect. Pathogens are destroyed by the activity of nicotinamide adenine dinucleotide phosphate (NADPH) oxidases which have been shown to be inhibited by both zinc deficiency and excess after phagocytosis.

Keywords: Immune system, zinc, zinc-binding protein

ÖZ

Çinko (Zn), organizma için temel minerallerden biridir. Optimal sağlık için her gün belirli bir miktarda alınması gereken bir eser elementtir. Hayati öneme sahip olan çinkonun vücuttaki düzeyini korumak için kullanılabilecek bir çinko depose yoktur. Çinko, spesifik çinko taşıyan proteinler tarafından bağırsakta emilir ve insane vücudunda dağıtılır. Serumda serbest çinko nadirdir; çünkü albümin, α2-makroglobulin ve transferrin gibi proteinlere büyük oranda bağlıdır. Çinko eksikliğinde polimorfo nükleer hücreler kemotaksisi ve fagositoz azalırken, çinko takviyesi tam tersi bir etkiye sahiptir. Patojenler, fagositoz sonrasında çinko yetersizliği veya fazlalığı sonucu inhibe edildiği gösterilen nikotin amidadenin dinükleotid fosfatoksidazlarının aktivitesi ile yok edilir.

A**nahtar kelimeler:** Çinko, çinko-bağlayıcı protein, immune sistem.

INTRODUCTION

Looking at the history of Zinc (Zn), it is an element known since ancient times but its production and use are not fully understood (1). Zinc (Zn) is an essential mineral for the organism.It is a biological trace element that needs to be taken every day for optimal health (2). For the immune system to function properly, zinc is needed in the body. Zinc is involved in many biological formations. Zinc is the cofactor of more than 300 enzymes that affect various organ functions with secondary effects on the immune system. It also affects nucleic acid metabolism and protein synthesis (3). The human body contains 2-3 g of zinc and approximately 57% of total body zinc is found in skeletal muscle and 29% in bone; It is known that the heart and blood plasma contain 0.1 - 0.4% zinc (4). Recent developments have revealed that structural and biochemical bases for zinc transport throughout the cell membrane. Zinc homeostasis has been demonstrated by clinical studies of immune cells such as dendritic cells, T cells, B cells, and mast cells (5).

Zinc is required for the proper functioning of both eukaryotic and prokaryotic cells. It is needed to grow, repair and maintain the structure and function of proteins and nucleic acids, including enzymes and transcription factors. Despite the vital necessity of Zn, no tank exists that can be used to maintain metal levels for a long time in the body. Intestinal malabsorption, kidney disease, alcoholism, cancer, aging, and pharmacological interactions, can lead to changes and deficiency of Zn carriers (6).Zinc is widely distributed in all body organs and tissues; liver, plasma and other tissues play a central role in systemic zinc metabolism by regulating a rapidly changeable zinc pool. The uptake of zinc to tissue is coordinated by multiple cellular zinc carriers divided into two groups according to their function: zinc carriers (ZnT) and Zrt- and Irt-like proteins (ZIP) (7).Two-way transport of Zn along cell membranes is tightly protected by two families of proteins: while zinc-regulated transporter (ZRT), iron-regulated transporter

Corresponding Author: Öğr. Gör. Burcu USLU, ORCID ID: 0000-0002- 6371-6562, Yüksek İhtisas Üniversitesi Beslenme ve Diyetetik Bölümü, Ankara
E-mail: burcuuslu@yiu.edu.tr
Telefon: 0 312 2851712
Doktor Öğretim Üyesi Şule AKTAÇ, suleaktac@hotmail.com, ORCID: 0000-0002-2158-5015

Makale Geliş Tarihi : 04.03.2019
Makale Kabul Tarihi: 27.10.2020

(IRT) -like proteins (ZIP; soluble carrier (SLC) 39A) facilitate the flow of zinc from the extracellular media and intracellular compartments, mediate to Zn in the movement from the cytosol to extracellular environments and intracellular compartments. Defects in Zn carriers have been associated with specific diseases such as Alzheimer's disease, diabetes, cancers, and other pathological processes (8). The majority of unstable zinc in the body is absorbed by intestinal epithelial cells through the metal carrier protein Slc39a4, which is then transported to the plasma and used by almost all cell types in the circulation. For protecting the zinc homeostasis, excess zinc is excreted through the kidneys and intestine through Slc39a5. Endogenous zinc is usually found in two forms in various organs and tissues. The majority of the zinc is in a stationary pool where zinc is firmly attached to metalloenzymes and zinc finger transcription factors. The remaining small amount of zinc is in a variable pool of varying amounts of free zinc ions (9).

This review was conducted to assess the functions of zinc and its role in the immune system.

Functions of Zinc

Red meat and oysters are a rich source of Zn in the diet. Foods made from unrefined cereals, legumes, or phytate -rich plant parts effectively reduce the bioavailability of Zn by binding. Zinc is absorbed in the intestine by specific zinc-bearing proteins and distributed in the human body. Free Zn is rare in serum; because albumin is highly attached to proteins such as α2-macroglobulin and transferrin. Albumin binds zinc to a relatively low and medium affinity α2-macroglobulin and its high-affinitytransfer. Intracellularly, Zn is disintegrated between the nuclei(~ 30-40%) and the specific zinc-storing vesicles(~50%) called zinosomes, and the remainder disintegrated between the cytoplasm and other organelles (10). Approximately 5-15% of the cytosolic zinc pool is bound by metallothioneins having four isoforms designated MT-1, MT-2, MT-3 and MT-4. MT-1, MT-2 and MT-3 are all synthesized in the central nervous system (CNS), but MT-1 and MT-2 are expressed in all tissues, and in the CNS it is primarily expressed by astrocytes. Similarly, while MT-3 is mainly expressed in the CNS, it is small metallothionein localized in MT-4 layered epithelial cells (11). The biochemistry of both MTF-1 and MTs indicates that the control of zinc homeostasis interacts with many other cellular systems. Several factors induce MT expression not only to sequester any zinc residue but also to provide sufficient metabolically available zinc for cellular processes (12).

In addition, zinc ions regulate synaptic transmission in the hippocampus and cortex or act as neurotransmitters by modulating many ligands and voltage-gated ion channels. The deterioration of zinc homeostasis in these regions causes many disorders in cognitive, behavioral, and emotional regulation through the mechanisms of decreased neurogenesis and neuronal plasticity (13).

Zinc and Immune System

A large number of diseases - particularly inflammatory disease - are associated with aging, pregnancy, lactation, and Zn deficiency in vegetarian or vegan lifestyles. Therefore, as mentioned earlier, zinc can be assumed to play an important role in the development of diseases. This emphasizes the importance of deep understanding of the various functions of zinc in the immune system and thus in health and disease (14).

The immune response includes two mechanisms; innate and adaptive immunity. The first cells that encounter and destroy invasive pathogens are natural immunity cells. The innate immune system is a collection of cells and proteins that are functionally diverse and defending against the invasion of foreign organisms. At the sites of infection, epithelial cells function as the first and highly effective barrier layer. However, if they break, a rapid flow of phagocytes, such as neutrophils and macrophages, will help prevent the initial progression of the infection. Interruption of pathogens by these phagocytes helps to activate adaptive immunity, leading to a permanent dissolution of the infection (15). Polymorphonuclear cells, macrophages and natural killer cells are some of the first responders. During zinc deficiency, while PMN chemotaxis and phagocytosis decreased, zinc supplementation had the opposite effect. Pathogens are destroyed by the activity of NADPH oxidases which are inhibited by both zinc deficiency and excess after phagocytosis (16). Furthermore, Zn promotes monocyte adhesion to endothelial cells in vitro and is important for the production of pro-inflammatory cytokines such as interleukins IL-1, IL-6, and tumor necrosis factor α (TNF-α) (17). Monocytes are an important cell of innate immunity and migrate to infected tissue immediately after PMN and differentiate into macrophages.Together with PMN, they mediate host defense through phagocytosis and oxidative burst. In addition, they present antigen-presenting cells (APCs) and secrete pro-inflammatory cytokines to regulate the immune response. During zinc deficiency in vitro, phagocytosis and cytotoxicity of monocytes increase, and thus oxidative stress increases. In addition, further maturation was observed in macrophages after zinc depletion, suggesting that low zinc status promotes the differentiation of monocytes (18). Zn also alters the response of natural killer cells by the reduction and recognition of MHC-class I expressions. In addition, Zn supplementation increases the differentiation and cytotoxicity of CD34 + cells to natural killer cells (19). They recognize and kill infected and transformed cells through naitotoxic mechanisms. Similar to other natural immune cells, natural killer cell activity and function depend on zinc. In humans with zinc deficiency and zinc chelator, the degraded natural killer cell-cell function has been reported after in vitro treatment (20). Other important leukocytes in natural immune defense are dendritic cells, described as a linker between the natural and adaptive immune system. They are necessary for the secretion of cytokines (IL-2, IL-6, IL-10, IL-12, TNF-α) for the natural immune system and activation of natural killer cells. Intracellular zinc concentrations play a critical role in dendritic cell function and activity (21).

Adaptive immune cells that are similar to T and B lymphocytes are highly specific but requirelonger time to become fully active. Each cell has a receptor called the B cell receptor (BCR) or T cell receptor (TCR) and has specificity for a particular antigen (22). The differentiation of immature T-cells depends on zinc. Because thymule, a hormone that plays a role in T-cell differenti-

ation, depends on zinc as a common factor. The thymule is produced by the thymus and released by thymic epithelial cells. It induces differentiation markers in immature T cells by binding to high-affinity receptors on T cells and supports T cell function, including allogeneic cytotoxicity, suppressive functions and IL-2 production (23). The maturation of T cells is affected by zinc status. On the one hand, a deficiency leads to altered rates of Th1 and Th2 cells, the apoptosis rate of increased immature T-cells, and consequently a decrease in total T-cells. On the other hand, it has been shown that zinc supplementation promotes regulatory T-cell development and suppresses maturation of Th17-cells, thus has a preventive effect on Th17-mediated autoimmune diseases. In addition, zinc induces IL-2 cytokine secretion and $CD8^+$ cell proliferation. The beneficial effects of zinc supplementation have been observed in studies on autoimmune diseases caused by zinc and TH17. Zinc supplementation has led to a decrease in the number of TH17 cells, which is an experimental model for multiple doses of zinc in multiple sclerosis, and a decrease in the severity of encephalomyelitis in mice with experimental autoimmune encephalomyelitis (24).

B cells play an important role in the humoral immune response by producing antibodies. Zinc carrier ZIP10 regulates B cell function and plays an important role in humoral immunity by modulating BCR signals and preventing apoptosis in B cells (25). Compared with T-cells, the number of decreased pre-B cells in cases with zinc deficiency depends on glucocorticoid metabolism and increased apoptosis (26).

ZINC DEFICIENCY AND IMMUNITY IN DISEASES

Zinc status is strictly regulated by zinc-bearing proteins ZIP and ZnT. Malfunction of ZIP or ZnT causes immunological deterioration. Since T cell maturation, proliferation, differentiation and function depend on zinc; all these processes deteriorate with zinc deficiency. Schizophrenia can be triggered due to Th cell function, Th differentiation and malfunction (27). In a study, there was an increase in proinflammatory cytokine concentrations such as IL-1, IL-6, and IFN IL in patients suffering from depression. Interestingly, zinc application showed antidepressant-like effects when tested for antidepressant activity when depressive therapy was applied, IL-1β levels were reduced simultaneously, while Treg cells were induced (28). A possible hypothesis in the progression of Multiple Sclerosis (MS) is believed to be due to T cell infiltration into the central nervous system-enhancing inflammation. Interestingly, T cell function is strictly regulated by the concentration of zinc, and zinc deficiency causes an unstable immune response, leading to disorders and unchanged T cell differentiation. Indeed, failures in zinc homeostasis are associated with the development of MS. In this context, In addition to dietary zinc deficiency, increased zinc intake is associated with increased risk of MS and the development of pathogenic pro-inflammatory T cells in experimental autoimmune encephalomyelitis (29). Zinc signals act anti-inflammatory during sepsis by attenuating the pro-inflammatory response due to cellular zinc uptake by ZIP14. Therefore, zinc signals and the appropriate function of ZIP14 are important in pro-inflammatory responses, and zinc deficiency is strongly associated with high risk for exaggerated inflammation and mortality due to sepsis (30). In diabetes, zinc plays a critical role in the formation of insulin crystals in β-cells. In addition, both insulin and zinc released from B-cells are thought to have significant paracrine and / or autocrine effects leading to modulation of various molecular mechanisms (31).

REFERENCES

1. Özdemir Ö, Tabanlı G. Çinko eksikliğinin alerjikhastalıklardaki rolü. Sakarya Med J 2016; 6 (4):267-273.
2. Belgemen T,Akar N. Çinkonun yaşamsal fonksiyonları ve çinko metabolizması ile ilişkili genler. Ankara Üniversitesi Tıp Fakültesi Mecmuası 2004; 57(3):161-166.
3. Tanzer F. Çinko ve sağlığa etkileri. Turkiye Klinikleri J Pediatr Sci 2006; 2(11):68-78.
4. Choi S, Liu X, Pan Z. Zinc deficiency and cellular oxidative stress: prognostic implications in cardiovascular diseases. Acta Pharmacol Sin 2018; 39 (7):1120-1132.
5. Bin BH, Seo J, Kim ST. Function, structure, and transport aspects of zıp and znt zinc transporters in immune cells. J Immunol Res 2018; 9365747.
6. Sapkota M, Knoell DL. Essential role of zinc and zinc transporters in myeloid cell function and host defense against infection. J Immunol Res 2018; 4315140.
7. Chu A, Petocz P, Samman S. Zinc status at baseline is not related to acute changes in serum zinc concentration following bouts of running or cycling. J Trace Elem Med Biol 2018; 50:105-110.
8. Takatani-Nakase T. Zinc transporters and the progression of breast cancers. Biol Pharm Bull 2018; 41(10):1517-1522.
9. Frederickson CJ. Neurobiology of zinc and zinc-containing neurons. Int Rev Neurobiol 1989; 31:145-238.
10. Wessels I, Maywald M, Rink L. Zinc as a gatekeeper of immune function. Nutrients 2017; 9(12):1286-1330.
11. Portbury S, Adlard P. Zinc signal in brain diseases. Int J Mol Sci 2017; 18(12):2506-2519.
12. Maret W. Zinc in cellular regulation: The nature and significance of "zinc signals". Int J Mol Sci 2017; 18(11):2285-2297.
13. Wang J, Um P, Dickerman BA, et al. Zinc, magnesium, selenium and depression: A review of the evidence, potential mechanisms and implications. Nutrients 2018; 10(5):584-603.
14. Maywald M, Inga W, Lothar R. Zinc signals and immunity. Int J Mol Sci 2017; 18(10):2222-2256.
15. Djoko KY, Cheryl-lynn YO, Walker MJ, et al. Copper and zinc toxicity and its role in innate immune defense against bacterial pathogens. J Biol Chem 2015; 290:18954-18961.
16. Gammoh N, Lothar R. Zinc in infection and inflammation. Nutrients 2017; 9(6): 624.
17. Bonaventura P, Benedetti G, Albarède F, Miossec P. Zinc and its role in immunity and inflammation. Autoimmunity Reviews 2015; 14(4):277-285.
18. Dubben S, Hönscheid A, Winkler K, et al. Cellular zinc homeostasis is a regulator in monocyte differ-

entiation of HL-60 cells by 1α, 25-dihydroxyvitamin D3. J Leukoc Biol 2010; 87 (5):833-844.
19. Muzzioli M, Stecconi R, Donnini A, et al. Zinc improves the development of human CD34+ cell progenitors towards natural killer cells and induces the expression of GATA-3 transcription factor. Int J Biochem Cell Biol 2007; 39(5):955-965.
20. Allen JI, Perri RT, McClain CJ et al. Alterations in human natural killer cell activity and monocyte cytotoxicity induced by zinc deficiency. Translational Research 1983; 102(4):577-589.
21. Sarhan D, Palma M, Mao Y, et al. Dendritic cell regulation of NK-cell responses involves lymphotoxin-α, IL-12, and TGF-β. Eur J Immunol 2015; 45 (6):1783-1793.
22. ten Hacken E, Burge JA. Molecular pathways: targeting the microenvironment in chronic lymphocytic leukemia-focus on the B-cell receptor. Clin Cancer Res 2014; 20(3):548-556.
23. Saha AR, Elba M, John WH. Zinc induces thymulin secretion from human thymic epithelial cells in vitro and augments splenocyte and thymocyte responses in vivo. Int J Immunopharmacol 1995; 17(9):729-733.
24. Kitabayashi C, Fukada T, Kanamoto M, et al. Zinc suppresses Th17 development via inhibition of STAT3 activation. Int Immunol 2010; 22(5):375-386.
25. Miyai T, Hojyo S, Ikawa T et al. Zinc transporter SLC39A10/ZIP10 facilitates antiapoptotic signaling during early B-cell development. Proc Natl Acad Sci USA 2014; 111(32):11780-11785.
26. Fraker PJ, Osati-Ashtiani F, Wagner MA, et al. Possible roles for glucocorticoids and apoptosis in the suppression of lymphopoiesis during zinc deficiency: a review. J Am Coll Nutr 1995; 14(1):11-17.
27. Girgenti MJ, Joseph JLT, Brady JM. ZNF804a regulates expression of the schizophrenia-associated genes PRSS16, COMT, PDE4B, and DRD2. PloS one 2012; 7(2):e32404.
28. Himmerich H, Milenović S, Fulda S, et al. Regulatory T cells increased while IL-1β decreased during antidepressant therapy. Journal of Psychiatric Research 2010; 44(15):1052-1057.
29. Wong Jr EK, Enomoto H, Leopoldet IH, et al. Plasma zinc levels in multiple sclerosis. Metab Pediatr Syst Ophthalmol 1980; 4(1):3-8.
30. Wessels I, Robert JC. Zinc dyshomeostasis during polymicrobial sepsis in mice involves zinc transporter Zip14 and can be overcome by zinc supplementation. Am J Physiol Gastrointest Liver Physiol 2015; 309(9):768-778.
31. Rungby J. Zinc, zinc transporters and diabetes. Diabetologia 2010; 53(8):1549-1551.