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REVIEW PAPERS

ZINC IN MEDICINE AND TREATMENT

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Abstract

Zinc is an essential and the second most abundant trace element in humans. It is critical for the growth, development and differentiation of cells, as well as for RNA transcription, DNA synthesis, cell division and cell activation. Zinc deficiency affects mainly functions of the immune system, but other consequences include inferior sperm activity, skin lesions, growth retardation, impaired wound healing, anemia and gastrointestinal disorders. Zinc supplementation protects against the hepatotoxic effects of alcohol, enhances the transport of water and electrolytes across the intestinal mucosa and improves immune and anti-inflammatory responses. Zinc is also known as an essential mineral for normal mobilization of vitamin A from the liver to the plasma. Besides, it increases the promoter response to 1,25-dihydroxyvitamin D in osteoblasts. On the other hand, excessive amounts of free zinc in tissues are toxic and accelerated zinc accumulation of zinc is a potent killer of neurons and glial cells.

Over 300 signaling molecules and transcription factors contain zinc as a cofactor. Free zinc in immune and tumor cells is regulated by 14 distinct zinc importers (ZIP) and transporters. An elevated amount of zinc transporters LIV-1, a subfamily of ZIP zinc transporters, appears in estrogen receptor–positive breast cancer and has been used as a reliable breast cancer marker. However, the fact that malignant cells are unable to accumulate zinc is an important factor in the development and progression of malignancy of prostate cancer.

Keywords: zinc deficiency, innate and adaptive immunity, neurodegenerative diseases, breast cancer, prostate cancer.

CYNK W MEDYCYNIE I LECZNICTWIE

Abstrakt

Cynk to drugi pod względem ilości w organizmie mikroelement niezbędny dla ludzi. Jest konieczny do wzrostu, rozwoju i podziału komórek, ich różnicowania i aktywacji, a także do syntezy DNA i transkrypcji RNA. Niedobór cynku wpływa głównie na funkcjonowa-

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nie układu immunologicznego, ale i na aktywność plemników, zmiany patologiczne na skórze, opóźnienie wzrostu, nieprawidłowe gojenie ran, anemię i zaburzenia układu pokarmowego. Suplementacja cynku chroni przed hepatotoksycznością alkoholu, poprawia transport wody i elektrolitów w śluzówce jelit, polepsza zarówno działanie układu odpornościowego, jak i odpowiedź przeciwzapalną organizmu. Cynk jest niezbędny w mobilizacji witaminy A z wątroby do osocza i zmniejsza odpowiedź promotora 1,25-dihydroxywitaminy D w osteoblastach. Nadmiar wolnego cynku jest toksyczny dla tkanek, a także dla neuronów i komórek glejowych.

Cynk jest kofaktorem ponad 300 mediatorów i czynników transkrypcyjnych. Jego aktywność w komórkach układu immunologicznego i nowotworowych jest regulowana przez 14 odmiennych cynkowych transporterów (ZIP). Zwiększone ilości transportera LIV1, należącego do rodziny transporterów cynkowych, odnotowano w receptorze estrogenowym raka piersi, i dlatego jest używany jako marker nowotworowy. Z kolei niezdolność komórek nowotworowych do akumulacji cynku jest ważnym czynnikiem w rozwoju i postępie choroby nowotworowej raka prostaty.

Słowa kluczowe: niedobór cynku, odporność wrodzona i nabyta, choroby neurodegeneracyjne, rak piersi, rak prostaty.

INTRODUCTION

Zinc was first mentioned in ancient Egypt, in the Smith Papyrus from 2000 BC. The use of zinc in medicinal skin cream which it described continued through the Roman times until our day (Jae-Yong Koh 2010). Zinc is the second most abundant trace metal, with 2-4 grams in humans. Normal blood plasma zinc levels range from 0.7 mg l^{-1} to 1.3 mg l^{-1} (Pasternak et al. 2010). It is an essential trace element, critical for the cell growth, development and differentiation, RNA transcription, DNA synthesis, cell division and cell activation. Zinc deficiency is harmful to embryogenesis and early childhood development, deteriorating mainly the immune system (Pakasi et al. 2010). Besides, zinc affects sperm activity, which conditions reproduction (Barrier-Battut et al. 2002). Excess free zinc in tissues is toxic (Jae-Yong Koh 2010). In the periodic table of elements, zinc belongs to group IIb, which comprises two toxic metals: cadmium and mercury. Nevertheless, zinc is considered to be relatively non-toxic to humans (Plum et al. 2010).

Zinc is essential in members of all enzyme classes, including over 300 signaling molecules and transcription factors (Pakasi et al. 2010). An optimal nucleic acid and protein metabolism, as well as a proper cell growth, division and functioning require sufficient availability of zinc (Plum et al. 2010). Zinc is also an ionic signal. Zn^{2+} enters cells through gated channels, and moves among various organelles and storage depots within cells, where it modifies protein function by binding to and detaching from zinc-dependent proteins (Plum et al. 2010).

Free zinc in immune and tumor cells is regulated by 14 distinct zinc importers (ZIP) and transporters (ZNT1-8). Zinc deficiency induces cell death *via* apoptosis or necrosis, while sufficient zinc levels allow for the maintenance of autophagy. Cancer cells have disturbed zinc importers and frequently increased zinc levels, which help them to survive (Pakasi et al. 2010).

Zinc is taken up primarily in the proximal small intestine, and depends heavily on ZIP4. Once transported by enterocytes and into blood, zinc binds to albumin, transferrin, α-2 macroglobulin and immunoglobulin G. Then, the element is transported to the liver, where it is stored in hepatocytes until being released back into blood to bind to carrier molecules again and to travel to tissues, where its intake will be regulated by zinc import and transport proteins. Red meat is a primary source of zinc for people. Nuts, fruit, whole grain bread, dairy products and fortified breakfast cereals are other zinc supplies. Oysters have the highest zinc quantity per serving among any common foodstuff (John et al. 2010). Zinc is also known as an essential mineral for normal mobilization of vitamin A from the liver to plasma (Pakasi et al. 2010). Zinc supplementation protects against the hepatotoxic effects of alcohol (Maret, Krężel 2007).

Zinc deficiencies occur due to malabsorption syndromes and other gastrointestinal disorders, chronic liver and renal diseases, sickle cell disease, excessive alcohol intake, malignancy, cystic fibrosis, pancreatic insufficiency, rheumatoid arthritis and other chronic conditions – Figure 1 (John et al. 2010). Besides, severe zinc deficiency is characterized by skin lesions, growth retardation, impaired wound healing, anemia, mental retardation and impaired visual and immunological function, which were observed even in mild zinc deficiency (Haase, Rink 2009).

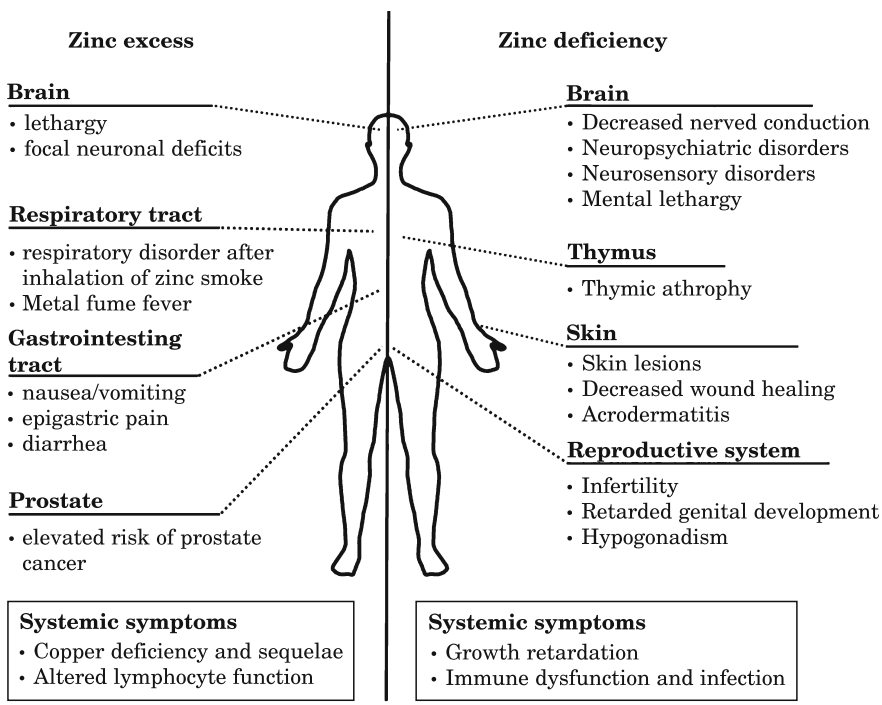

Fig. 1. Comparison of the effects of zinc intoxication *versus* deficiency (Plum et al. 2010)

ZINC DEFICIENCES

Zinc supplementation in pregnant women

3.5 million deaths each year are caused by maternal and child malnutrition. There was a micronutrient supplementation trial conducted on 4998 pregnant women in rural Nepal from 1999 to 2001. The effect of zinc supplementation on child growth and body composition at 6–8 years of age was examined. The results showed that child growth may benefit from antenatal zinc supplementation, especially in areas where zinc deficiency is common (Steward et al. 2009).

Anemia

There were some studies in Mexico, where children less than 2 years old with several micronutrient deficiencies were examined. The most widely used indicators were plasma or serum zinc concentration. The results showed that zinc deficiency may stop children from attaining the full growth and development potential. One out five children had anemia. Low serum zinc concentrations were found in one out of three children living in urban areas and in one out of ten living in rural areas (Duque et al. 2007).

Acute diarrhoea in children

In 2003, diarrhoea was estimated to account for 18% of the reported 10.6 million deaths of children aged less than five years (Winch et al. 2008). In developing countries, each year, almost 2.5 million child deaths are caused by diarrhoea, 35% of which are due to acute diarrhoea. The importance of zinc in the pathophysiology of acute diarrhoea is prominent in higher daily fecal losses of these elements during acute diarrhoeal episodes. Fortunately, zinc supplementation improves the transport of water and electrolytes across the intestinal mucosa, preventing villous atrophy and improving immunity (Patel et al. 2009). Besides, zinc can contribute to a reduced application of antimicrobials, inappropriate for children, in the treatment of childhood diarrhoea through a replacement effect (Winch et al. 2008).

The impact of zinc supplementation for acute diarrhoea has a beneficial effect by shortening the duration of diarrhoea (Patel et al. 2009)

Rickets in children

Zinc plays a significant role in bone maturation, especially in the early stages of mineralization. The vitamin D receptor contains 2 zinc-finger domains. Zinc increases the promoter response to 1,25-dihydroxyvitamin D in osteoblasts. It has been suggested that zinc deficiency might predispose children to rickets, due to calcium deficiency which limits bone mineralization, especially in children with very low calcium intakes (Thacher et al. 2009).

Innate and adaptive immunity

Zinc deficiency affects multiple aspects of innate and adaptive immunity. As a result, people suffer from thymic atrophy, altered thymic hormones and lymphopenia (JOHN et al. 2010). Thymic artrophy and high susceptibility to bacterial, fungal and viral infection are observed in patients suffering from *Acrodermatitis enteropathica*, which is a rare autosomal recessive inheritable disease. The zinc-specific malabsorption syndrome is induced by a mutation of the gene responsible for the intestinal zinc transport protein hZip4. Fortunately, all symptoms can be reversed by nutritional supplementation of zinc (HAASE, RINK 2009). Zinc deficiency is associated with the rapid progression of HIV. Zinc acetate has been shown to be effective in the long-term treatment of Wilson disease because of its ability to compete with copper for binding sites (SAPER , RASH 2009). Zinc deficiency also plays a role in the immunosenescence of the elderly (HAASE, RINK 2009). Zinc-deficient patients had severe immune dysfunction, mainly affecting T helper cells (PARASAD, 2008). During zinc deficiency, changes in the gene expression for cytokines, DNA repair enzymes, zinc transporters and signaling molecules are observed. Besides, oral zinc supplementation improves immunity and anti-inflammatory responses, which suggests that zinc is critical for normal immune cellular functions. Zinc deficiency disturbs proliferation of lymphocytes. Thymulin, a hormone secreted by thymic epithelial cells, requires zinc as a cofactor. It exists in plasma in the zinc-bound, active form and the zinc-free, inactive form. For this reason, zinc is essential for the differentiation and functioning of T cells. Furthermore, a decrease in the number of T cells is caused by zinc deficiency, which depressed production of Th1 cell cytokines, IFN-g, IL-2 and tumor necrosis factor (TNF)-α, which play a major role in tumor suppression. Zinc deficiency reduces the lytic activity of natural killer cells, impairs NKT cell cytotoxicity and immune signaling, impacts the neuro-endocrine-immune pathway and alters production of cytokines in mast cells. Zinc supplementation improves NK cell functions. Zinc homeostasis is mediated by metallothioneins (MTs), small cysteine-rich proteins that bind zinc. Tumor cells are mainly affected by zinc through its regulatory role in gene expression and cell survival (JOHN et al. 2010).

Pulmonary tuberculosis patients

A clinical trial conducted in Indonesia showed that patients suffering from severe tuberculosis, when given zinc supplementation, had their sputum conversion time significantly reduced and experienced other significant health benefits (PAKASI et al. 2010).

Positive effect on skin

Nanostructures which include inorganic physical UV filters such as titanium dioxide (TiO_2) and zinc oxide (ZnO) are widely used in cosmetic dermatology. They can be found in sunscreens, in which they appear in particles

sized between 60 to 200 nm in order to obtain transparent emulsion. Miniaturization of these minerals increases both their transparency and filtering capacity because of a higher reflective index (Morganti 2010).

It has been reported that some alopecia areata patients have zinc deficiency. Zinc supplementation has a positive effect on such patients and could serve as an adjuvant therapy (Hoon et al. 2009). Delayed wound healing is associated with zinc deficiency. It has been noticed that zinc supplementation activates the nuclear factor-kappa B (NF□B), expression of pro-inflammatory cytokines (interleukin-1b and tumor necrosis factor-a) and neutrophil infiltration, which play a significant role in wound healing (Basavaraj et al. 2010).

ZINC IN ACUTE BRAIN INJURY

Zinc accumulation as a cause of neuronal death

Accelerated accumulation of zinc is a potent killer of neurons and glial cells. In 1986, some scientists demonstrated that a brief (15 min) exposure to 300-600 μM zinc resulted in extensive neuronal death in cortical cell culture. The fact that zinc was cytotoxic suggested that it might play a major role in neuronal injury (Jae-Yong Koh 2010).

ZINC IN NEURODEGENRATIVE DISEASES

Alzheimer disease

Alzheimer disease (AD) is characterized by the loss of cortical neurons and progressive deterioration of cognitive function, memory and self-care (Jae-Yong Koh 2010). In a healthy person, a normal amount of interstitial zinc is needed for the degradation of Aβ by zinc-dependent proteinases, which prevents its accumulation in the interstitium. Metalloproteinases are present in cerebrospinal fluid (CSF) for example neprilysin, insulin degrading enzyme (IDE) and matrix metalloproteinases (MMP2 and 3) (Strozyk et al. 2009). During Alzheimer disease, the accumulation of amyloid-β (Aβ) protein, which is linked to Zn^{2+}, neurofibrillary tangles (NFTs) and neurophil threads in the neocortex is observed (Jae-Yong Koh 2010). A high concentration of zinc (1 mM) has been found within amyloid plaques (Strozyk et al. 2009). Free Zn^{2+} in the extracellular fluid induces amyloid deposition. Transient hypoperfusion, head trauma or local paroxysmal neuronal firing lead to an increase in extracellular zinc levels, which might induce the binding of zinc to Aβ (Jae-Yong Koh 2010).

Parkinson disease (PD)

Zinc concentration was significantly lower in severe PD compared to controls. The data revealed an imbalance of inter-element relations and suggested some disturbance in the homeostasis of elements during the progression of PD (Muralidhar, Ponnuswamy 2004)

Amyotrophic Lateral Sclerosis (ALS)

Some abnormalities of zinc-metalloproteins have implicated zinc in the pathophysiology of ALS (Lou Gehrig disease). The familial form of ALS in man is accompanied by mutations in metalloenzyme Cu-Zn-superoxide dismutase (SOD). (Jae-Yong Koh 2010).

Cerebral ischemia

In cerebral ischemia, zinc is able to function both as a signaling mediator and neurotoxin. Both neurotoxic and neuroprotective capabilities were noticed. The earliest research provided indirect evidence for the toxic translocation of zinc from presynaptic neurons into selective postsynaptic neurons. On the other hand, during a brief period of global ischemia, intracellular zinc accumulation in vulnerable CA1 pyramidal hippocampal neurons preceded degeneration, which could be prevented by intracerebroventricular administration of zinc-chelator, ethylenediaminetetraacetic acid (EDTA) saturated with calcium (Ca-EDTA). The administration of extracellular zinc chelator prevents intracellular zinc accumulation, which precedes neuronal degeneration. Increased intracellular zinc levels during ischemia serve as a critical mediator of neuronal death. Equal doses of zinc chloride (ZnCl2), PP (protoporphyrin) and ZnPP (zinc protoporphyrin) were found to reduce the size of lesions, but only ZnPP and PP were detected to improve the health of a patient with ischemic brain edema. That suggests that in comparison to protoporphyrin, zinc ions provide neuroprotection *via* mechanisms other than reducing brain edema. Zinc supplementation could provide neuroprotection to the CA1 hippocampal subfield during global ischemia in the gerbil. (Galasso, Dyck, 2007)

Implications for Diseases with Particular Emphasis on Diabetes

Zinc is involved in many aspects of insulin metabolism and signaling. In type 2 diabetes, oxidative stress disturbs both zinc metabolism and MT levels, in which the proper control of zinc availability is essential for normal functions. This type of diabetes is associated with the polymorphism of the pancreatic β-cell-specific zinc transporter ZnT-8 (SLC30A8). ZnT-8 provides zinc for insulin maturation or storage in these cells. Zinc supplementation in

animals and humans improves antidiabetogenic and insulinomimetic properties.

As a result, zinc-containing drugs are being synthesized and tested. Because cardiovascular diseases are a major cause of mortality in type 2 diabetes, major studies focus on the diabetic heart. There were some investigations in which the level of free zinc increases from 520 pM in normal to 870 pM in diabetic rat cardiomyocytes. However, activities of metallothionein and reduced glutathione and other enzymes of the antioxidant defense decreased (Maret, Krężel 2007).

Breast cancer

Increased amounts of zinc transporter LIV-1 (SLC39A6) are present in estrogen receptor–positive breast cancer and in tumors that spread to lymph nodes. The LIV-1 subfamily of ZIP zinc transporters consists of nine human sequences. It is a highly conserved group of eight transmembrane domain proteins, which are situated on the plasma membrane and which are responsible for zinc transport into cells. LIV-1 has been used as a reliable marker of luminal A type clinical breast cancer (Taylor et al. 2007).

Prostate cancer

Zinc accumulated in the epithelial cells of a prostate is essential to production and secretion of citrate. The production of citrate and its secretion into prostatic fluid is important for reproduction. In human prostate cancer, zinc downregulates HIF-1a protein levels. The lost ability of the malignant cells to accumulate zinc and citrate is an important factor in the development and progression of the malignancy of prostate cancer (Pasternak et al. 2011). This process is the result of decreased expression of specific zinc uptake transporters and glioblastoma cells under hypoxia. Research into the molecular mechanisms involved showed that zinc induced HIF-1a proteasomal degradation, which was prevented by treatment with proteasomal inhibitor MG132. Besides, zinc could be useful as an inhibitor of HIF-1a in human tumors to repress important pathways involved in tumor progression. Furthermore, it could be used in anticancer therapies (Nardinocchi et al. 2010). Zinc may modulate the IGF-1 metabolism in relation to carcinogenesis. It was observed that an optimal prostate zinc concentration plays a protective role against cancer (Prasad et al. 2010).

CONCLUSIONS

This paper discusses both excess and deficiency of zinc. Zinc is toxic to neurons and glial cells if its accumulated becomes accelerated. On the other hand, an optimal level of zinc in humans is necessary for the proper func-

tioning of our bodies. Zinc supplementation has a positive effect on the skin and immune system. It also helps to prevent or treat many diseases such as anemia, rickets, diarrhoea, prostate cancer and pulmonary tuberculosis. Besides, the level of zinc transporter LIV1 could be a reliable marker of breast cancer. Moreover, zinc-containing drugs are tested on diabetic patients because of their anti-diabetogenic and insulinomimetic properties.

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