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ZINC CONTRIBUTION TO THE REGULATION OF GLUCOSE DISPOSAL, LIPID METABOLISM AND STRIATED MUSCLE CONTRACTIONS

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Abstract:

Zinc is the second, after iron, most abundant trace metal in the human body. In living systems zinc performs three categories of functions- catalytic, structural and regulatory. Zinc homeostasis is tightly regulated by zinc bioavailability and expression of specific zinc transporters in cell membranes and cellular organelles of alimentary tract, brain, muscle, pancreas and other tissues. In the literature there are numerous studies concerning zinc contribution to metabolic processes such as cell signaling, insulin sensitivity, antioxidant protection and lipid/ lipoprotein turnover. Zinc deficiency, common in developing countries, is detrimental for health causing growth retardation, decreased immunocompetence, anorexia, skin lesions, bleeding tendency, reproductive abnormalities and skeletal defects. In Western countries latent zinc deficiency is observed in about 12% of the population, however, its diagnosis is difficult due to the lack of reliable and simple methods evaluating human zinc status. Depressed zinc status is noted in type 2 diabetes and atherosclerosis, but data concerning beneficial effects of zinc supplementation in humans are equivocal. On the other hand, animal studies indicate that zinc enhances the phosphorylation of insulin-receptor substrates to activate a series of signal transductions that increase glucose uptake in insulin-sensitive cells and inhibits lipolysis in adipose tissue. Furthermore, zinc probably directly affects lipid metabolism since its deficiency down-regulates fatty acid utilization in mitochondria and peroxisomes and up regulates lipid synthesis affecting the expression of genes encoding enzymes contributing to liver lipid homeostasis. It is well documented that zinc plays a substantial role in muscle morphology and contraction in vitro, but it also affects performance in vivo. In physically active subjects dietary zinc deficiency was found in triathletes of both sexes and in female athletes engaged in sport focused on leanness. Thus, there is no need for zinc supplementation in all athletes. On the other hand, zinc supplementation if needed has to be carefully monitored due to detrimental effects of zinc excess on iron and copper absorption, and possibly energy metabolism.

Key words: *zinc homeostasis, zinc deficiency, insulin sensitivity, lipids, striated muscle*

After iron, zinc is the second most abundant trace metal in the human body. An average 70 kg adult human contains approximately 2.3 g of zinc localized mostly in intracellular compartment (1). Most of body zinc is bound to proteins. Approximately 50% of all body zinc is found in striated muscle, about 25-30% in bone and about 20% in other tissues, with slightly higher content in the liver that in other tissues (2).

In living systems zinc performs three categories of functions- catalytic, structural and regulatory (3). The first zinc metalloenzyme, carbonic anhydrase II, was discovered in 1940 and since then more than 300 zinc enzymes covering all classes of enzymes in different species have been identified (4,5) In addition, zinc stabilizes tertiary structure of many proteins vital for body functions such as zinc fingers and nuclear receptors. Recently zinc has been recognized as a neurotransmitter and a second messenger in intracellular signaling (6-10). Moreover, zinc contributes to the regulation of intracellular redox state as a constituent of superoxide dismutase (SOD), but also by protecting sulphydryl groups and inducing metallothionein gene expression (11-13) (Table 1).

Table 1. *Selected zinc-dependent enzymes and proteins in mammals*

Catalytic function of zinc
Lyases (e.g.carbonic anhydrase I and II)
Hydrolases (e.g. alkaline phosphatase)
Oxidoreductases (e.g. lactate dehydrogenase)
Metalloproteinases (e.g. collagenases)
Structural function of zinc
Superoxide dismutase
Zinc fingers
Nuclear hormone receptors (e.g. glucocorticoids, mineralcorticoids, sex hormones)

The role of zinc in human body functions was thoroughly studied due to detrimental effects of its deficiency on health which include growth retardation, decreased immunocompetence, anorexia, skin lesions, bleeding tendency, reproductive abnormalities and skeletal defects (14-16). Further studies have indicated that zinc deficiency disturbs hematopoiesis, synaptic signaling and induces apoptosis in a variety of tissues (17-19). Moreover, zinc deficiency was recognized to increase the risk of DNA damage and cancer (20). It is worth noting that depleted body zinc has been found in many chronic disease such as obesity, asthma, diabetes and Alzheimer disease (21-23).

However, disturbed body functions resulting from zinc deficiency are also possibly due to its close interaction with vitamin A, because both in humans and animals it has been demonstrated that zinc status affects vitamin A absorption, transport and utilization (24). Additionally, zinc nutriture seems to be related to the vitamin E status since in the rat a low zinc diet has been found to deplete tissue α-tocopherol concentration (25).

Thus, directly or indirectly zinc has the potential to affect metabolic processes which are fundamental for health. Consequently, to maintain zinc pool in the organism its homeostasis has to be tightly regulated.

Mechanism of zinc homeostasis

The control of intracellular zinc levels is achieved through a balance of zinc uptake, storage and efflux. Each of these processes is mediated by a distinct family of proteins. Until now, in mammals several zinc transporters have been identified. According to Liuzzi and Cousins (25) nine ZnT transporters reduce intracellular zinc availability by promoting zinc efflux from cells or into intracellular vesicles. In contrast, fifteen ZiP transporters increase intracellular zinc availability promoting extracellular zinc uptake and possibly, vesicular zinc release into the cytoplasm. Due to their function ZnT transporters are localized intracellularly, ZiP transporters – in plasma membranes (27). Animal studies have indicated that both ZnT and ZiP transporters are expressed in variety of tissues including small intestine, pancreas, liver, kidney, brain, ovary and testis, however, their precise function is far from being elucidated (28).

Most of the transporters are sensitive to zinc availability. For example, ZnT 1 expression in the rat intestine increases when dietary zinc is low and decreases with high zinc content in the diet providing body protection against both zinc deficiency and excess (29). In the mouse intestine ZiP 4 expression is induced during zinc deficit, but ZiP 5 expression is not sensitive to the fluctuations in the dietary zinc (30). However, during zinc deficiency ZiP 5 is removed from the cell surface and internalized, but ZiP 4 is recruited to the cell surface. The above data may suggest that at least in the mouse intestine ZiP4 function is antagonistic to that of ZiP 5 in the control of zinc homeostasis.

Zinc transporter response to dietary zinc has been demonstrated in the human intestine with reduced ZnT1 and ZnT 5 expression in subjects taking zinc supplements (25 mg/day) (31). The importance of zinc transporters in humans is clearly seen in acrodermatitis enteropatica –an inherited zinc deficiency probably due to a mutation in the ZiP 4 transporter in the intestine (32). It is also postulated that zinc accumulation in the brain observed in Alzheimer disease is due to increased expression of the ZnT 1 transporter (33).

It should be stressed that in mammals other proteins contributing to zinc homeostasis have been identified (e.g. DMT1 and DMT2, metallothionein), however, the interplay between different mechanisms of zinc transport is not fully elucidated (26). Until now it has been established that metallothionein gene expression in rat intestine, liver, bone, bone marrow, muscles, skin, and kidneys and in serum is induced by dietary zinc (34). Furthermore, in metallothionein-null mice no zinc was accumulated in the hepatocytes (35). On the contrary, overexpression of metallothionein I and II has been found to protect mice against zinc deficiency (36). More recent studies have found that there is no relationship between metallothionein and zinc transporter levels in the intestine and suggested that metallothionein possibly reduces the absorption of zinc excess but does not contribute to zinc transport into enterocytes (37).

It is worth noting that the response of intestine zinc transporters to zinc deficiency is rather slow, thus in the face of low zinc intake the decline in urine and fecal zinc excretion play a crucial role in the regulation of its homeostasis. In addition, in the case of decreased extracellular pool zinc is released into the blood from the tissues, mostly striated muscles containing the greatest amount of body zinc (38).

Notwithstanding all the doubts concerning molecular mechanisms of cellular zinc influx and efflux the above data indicate that zinc content in the diet is crucial in the regulation of its homeostasis. On the other hand, it should be pointed out that similar zinc content in the diet does not necessarily mean similar absorption, since its bioavailability from food is affected by other dietary compounds. It is well documented that an excess of iron and copper which share the same transport proteins in alimentary tract, inhibits zinc absorption (39). Similarly, phytate and fiber which produce insoluble zinc complexes and also unabsorbed fat depress zinc absorption from the gut (40-42). On the contrary, animal proteins, especially rich in histidine and cysteine, polyunsaturated arachidonic acid as well as low molecular weight organic acids have a

beneficial effect on zinc absorption in the alimentary tract (43,44).

Therefore, the amount of zinc which is absorbed by enterocytes results from the interplay between its content in the food and bioavailability.

Dietary zinc deficiency

It should be stressed that the inherited zinc deficiency mentioned earlier , acrodermatitis enteropathica, is rare (in 1 per 500,000 children), but dietary zinc deficiency is a common problem in developing countries (45-47).

In industrialized countries inadequate zinc daily intakes are observed in low-income people, but also in vegetarians (48,49). Additionally, there are data indicating that in Western countries asymptomatic marginal zinc deficiency is observed in about 12% of the population (16). Our data concerning zinc daily intake in Polish students have shown that 12.2 % of males and 25.7% of females are at risk of zinc deficiency (50).

Nevertheless, it is worth noting that asymptomatic zinc deficiency may be even more common than that reported on the basis of dietary records. This assumption is supported by Hambridge (51), who reported that in North America zinc supplementation improved growth and development in otherwise healthy infants, toddlers and preschool children. However, the diagnosis of marginal zinc deficiency is difficult, because until now, despite many studies, there is no simple and reliable method providing information concerning body zinc status (52).

Zinc, carbohydrate and lipid metabolism

Numerous data indicating depressed zinc status in type 2 diabetes and/or atherosclerosis suggest a role for zinc in insulin action, glucose disposal and lipid metabolism (53,54).

Zinc, insulin action and glucose disposal

Besides its role in the stabilization of tertiary structure of insulin zinc plays an important role in the regulation of insulin action. In zinc-depleted rats peripheral insulin resistance has been noted together with impaired hepatic glucose production (55). In turn, in diabetic rats supranormal zinc levels have been found to normalize whole body glucose uptake and muscle glycogen synthesis (56,57). Similarly, in genetically obese *(ob/ob)* mice zinc supplementation alleviates hyperglycemia (58,59). Moreover, in diabetes-prone BB Wistar rats dietary zinc supplementation decreases the incidence of diabetes (by 60%) in comparison with animals fed a low zinc diet (60). In addition, zinc supplemention improved insulin sensitivity in fructose-fed insulin resistant rats (61).

Studies in humans have shown that high doses of zinc (220 mg of zinc sulphate x 3/day for 7-8 weeks) improve glucose intolerance in patients with type 2 diabetes (62). Positive effect of zinc supplementation on insulin sensitivity has also been demonstrated in healthy volunteers (63).

Zinc, insulin and lipid metabolism

There are also data indicating insulino-mimetic action of zinc on lipid metabolism. In isolated rat adipocytes zinc has been found to counteract adrenaline-induced lipolysis and to stimulate lipogenesis (64,65). Furthermore, zinc-deficient rats fed coconut or linseed oil were characterized by elevated activities of lipogenic enzymes (acetyl-CoA carboxylase and fatty acid synthase) and developed a fatty liver (66). Recent human studies have indicated ZnT and ZiP transporter expression in both visceral and subcutaneous fat, with different expression in lean and obese subjects (67). Thus, it seems feasible that either zinc affects lipid accumulation or obesity affects the expression of the zinc-transporting system.

Zinc contribution to adipose and liver lipid metabolism markedly affects lipoprotein turnover. In zinc-deficient rats lowered plasma HDL-cholesterol and some apoproteins (A1, A2, C and E) but also elevated total cholesterol concentrations have been observed (68,69). On the other hand, zinc supplementation has been shown to inhibit the development of atherosclerosis in rabbits fed a high cholesterol diet (70). Moreover, in LDL-receptor null mice with disturbed lipoprotein homeostasis zinc supplementation decreased plasma triacylglycerol and free cholesterol levels (71).

The results of human *in vivo* studies concerning the relationship between zinc status and lipoprotein profile are equivocal. Hiller et al. (72) have revealed that in healthy subjects higher serum zinc levels were associated with unfavorable lipoprotein profile (higher total and LDL-cholesterol and triacylglycerol levels). On the other hand, it has been noted that plasma zinc levels are not different in patients with established atherosclerosis versus controls (73). Moreover, after 5 years of zinc supplementation (80 mg zinc oxide daily), despite significant elevation in plasma zinc levels, no changes in plasma lipoproteins were found (74). No effect of zinc supplementation (30 mg/day) on plasma lipoproteins has been confirmed in a double-blinded, randomized study (75).

In contrast, in type 2 diabetic subjects after 12-week of zinc treatment (100 mg of zinc sulphate/day) significant decrease in plasma total cholesterol and triacylglycerol have been noted together with elevated plasma HDL-cholesterol concentration (76).

The reason for these discrepancies is unclear. However, it should be stressed that the interpretation of *in vivo* data concerning zinc effects on lipid metabolism as well as on insulin action is complicated because zinc

deficiency commonly exists with other micronutrient shortages and it is difficult to separate their effects on metabolic processes (77). Additionally, according to Beletate et al. (78) only one study concerning metabolic effects of zinc in humans was randomized and provided reliable conclusions on its action.

Mechanisms of metabolic zinc effects

At present there is no doubt that zinc plays a substantial role in the regulation of insulin action and lipid metabolism and zinc deficiency is detrimental for health (79). However, the molecular mechanism of zinc action is still under debate. It is well documented that zinc is an important mediator of insulin storage and secretion from the pancreas (80). In addition, pancreatic β-cells utilize a very efficient transporter ZnT 8 to accumulate zinc inside the cells (81). Thus, zinc deficiency or alterations in ZnT 8 expression have a potential to depress insulin secretion. Moreover, it is well documented that zinc enhances the phosphorylation of insulin-receptor substrates to activate a series of signal transduction that increase glucose uptake in insulin-sensitive cells and inhibit lipolysis in adipose tissue (82, 83).

In consequence, zinc deficiency either affecting insulin secretion or signal transduction possibly brings about hyperglycemia and elevates free fatty acid release into the circulation and its availability to the liver and excessive lipoprotein synthesis.

Besides zinc contribution to insulin secretion and action zinc directly affects lipid metabolism. Recently it has been shown that in the rat liver zinc deficiency down regulates fatty acid utilization in mitochondria and peroxisomes and up regulates lipid synthesis affecting the expression of genes encoding enzymes contributing to liver lipid homeostasis (84).

Most of the above cited data originate from animal studies and have to be confirmed in humans especially in the context of discrepancies concerning the effects of zinc supplementation in type 2 diabetes and atherosclerosis.

Zinc, striated muscle and physical performance

Besides the above mentioned zinc functions there are studies indicating its substantial importance in skeletal muscles. Early studies of Isaacson and Sandow and Richardson and Drake (85,86) have shown that elevated zinc concentration in incubating medium increases muscle strength and delays fatigue. In addition, *in vitro* zinc deficiency in the medium has a detrimental effect on rat myoblast differentiation by direct inhibition of myogenin mRNA expression (87). Additionally, in post-weaning rats 4-weeks zinc deficiency changed the proportion of fast and slow-twitch fibers in the soleus and the lateral portion of the diaphragm increasing the percentage of fast twitch fibers (88). On the other hand, in frail, dystrophin-deficient (mdx) mice zinc-carnosine supplementation increased the magnitude of twitch force in the soleus muscle (89).

However, recent data of Grider et al. (90) have revealed that both zinc deficiency (5 ppm for 42 days) and zinc supplementation (200 ppm for 42 days) negatively affect skeletal muscle function depressing myosin light polypeptide and carbonic anhydrase synthesis in the rat soleus. The above data suggest that both zinc deficit and overload are harmful for the muscle.

In humans supraphysiological zinc supplementation (135 mg/day, 14 days) has been found to increase time to exhaustion and muscle strength (91). On the contrary, low zinc daily intake (0.3 mg/day vs. recommended 12 mg/day) has been shown to depress performance during isometric upper and lower-body exercise (92). In addition, low dietary zinc (3.8 mg/day) has been found to reduce erythrocyte carbonic anhydrase I and II activities, duration of maximal exercise and total work as well as submaximal performance (93).

On the other hand, physical exercise affects body zinc distribution and stores. Short-term exercise brings about the elevation in plasma zinc concentration due to water shift into the intracellular compartment (94). On the contrary, prolonged exercise and regular training reduce plasma zinc levels and its body stores due to zinc losses with sweat and urine (95). Moreover, according to Lukaski (96) in many athletes, but especially in long distance runners of both sexes and in female athletes engaged in sports focused on leanness zinc provision with diet is not adequate because of restricted energy intake. Additionally, the carbohydrate-rich diet recommended for sportsmen is low in zinc and has reduced zinc absorption due to high phytate content (97).

These findings and beneficial effect of zinc on performance mentioned earlier suggest the need for zinc supplementation in high performance athletes.

However, there are also data indicating that plasma zinc concentrations in athletes and sedentary controls are similar despite marked zinc sweat losses in the athletes (98). In addition, a comparison of zinc daily intakes in athletes of both sexes and sedentary subjects has indicated that most male athletes consume an adequate amount of zinc, but low zinc intakes are common in female runners and in triathletes of both sexes (99).

Thus, it does not seem feasible that there is a common need for zinc supplementation in athletes. On the other hand, it should be stresses that zinc excess irreversibly damages major enzymes of energy production and antioxidant defense *in vitro* (100). In addition, because the range between safe and unsafe intakes of zinc is relatively narrow, supplementation

with high doses of zinc is hazardous for health since zinc excess inhibits copper and iron absorption and induces their deficiency which in turn brings about hematological and lipoprotein disturbances, depressed antioxidant protection and neurological symptoms. In consequence, zinc supplements have to be used with copper to prevent harmful effects of zinc excess (101).

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A – Study Design
B – Data Collection
C – Statistical Analysis
D – Data Interpretation
E – Manuscript Preparation
F – Literature Search
G – Funds Collection