Zinc Supplements – Any Benefit in Diabetes?

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Abstract

Zinc is a divalent cation mainly present intracellularly and exerts several indispensable effect therefore maintaining zinc homeostasis is essential. Zinc has a pivotal role in the insulin production, storage and pathways and in carbohydrate metabolism. Plays also an important function in the development of diabetes mellitus and diabetic complications as well. Based on preclinical and clinical studies here we present the most important contributions of zinc to diabetic state and briefly demonstrate why zinc supplementation is beneficial for diabetic patients.

Keywords: Zinc, Supplementation, Diabetes mellitus

Introduction

Zinc (Zn) is the third abundant bivalent cation in the human body, after calcium. Zn is found 99.8% intracellularly. It is part of several hundreds of enzymes and of ca. two thousand cofactors. Stored mainly in skeletal muscle and brain neurones. Zn plays very important role in cognitive functions and learning, in cell proliferation, in immune system, the physical development of infants and children, the skin, the metabolic processes, etc. Unfortunately, plasma zinc is insensitive to early zinc deficit and detection of hypozincemia is not a routin process. Zinc deficiency produce a myriad of symptoms but none of them is typical for the Zn deficit. However, as an ubiquitous trace element, zinc has a role in the carbohydrate metabolism and its regulation as well. Diabetes mellitus (DM) is a disease based on absolute or relative insulin deficiency with subsequent disturbances in carbohydrate metabolism. DM exists in two basic forms like type I and type II diabetes (T1DM and T2DM, respectively). Although the two types of diabetes are totally different from ethiology point of view there are numerous well defined and similar Zn effects in both T1DM and T2DM. Hypozincemia and hyperzincuria is part of the typical clinical symptoms of both DM forms therefore control of Zn deficiency in diabetic patients is necessary [1].

In the present compilation we briefly demonstrate some facts and rational considerations about use of zinc supplementation in diabetes patients.

1. Preclinical Experiences

Pancrease Beta-Cell Stimulation

Zinc exert a dual effect in beta-cells: via direct effect Zn is increasing of free insulin concentration near to beta cells besides it has an inhibitory effect on glucose stimulated insulin secretion. Transient elevation of se-glucose concentration increase free cytosolic Zn levels facilitating insulin storage, but chronic high intracellular zinc concentration resulting in beta cell dysfunction, in the extreme also cell death. Metabolic stress and hypoxia downregulate zinc-importer ZnT8 protein with subsequent decrease in the intracellular/intragranular Zn concentration. Research group of Liu demonstrated that also ZnT6 and ZnT7 transporters are needed to defend insulin secretion in beta-cells and the insulin storage [2].

Zn in Insulin

Pancreatic beta cells have exceptionally high zinc content. Zinc is a prerequisite for the hexamerization (ie. three dimer structure of insulin), which is the storage form of insulin (Fig 1.) in the beta-cell granules [3]. But Zn is also necessary to the transformation from proinsulin to insulin. Therefore to maintain normal function of the production and storage of insulin zinc is indispensable [4].

Figure 1. Insulin hexamer with stabilizer Zn²⁺ in the middle.
Insulin Mimetic Function

Among others also trace elements (eg, vanadium) may have insulin-like properties. In vitro (cell culture) zinc administration is able to activate insulin signaling pathway [5]. Several mechanisms of action were assumed, eg, rat experiments supported that insulin-mimetic actions of zinc are mediated via inhibition of glycogen synthase kinase 3beta. In vivo ZnO nanoparticles – in mice and rat model – improve glucose tolerance, decrease blood glucose levels, increase expression of DM related genes, eg. that of insulin and insulin receptors, GLUT2 and glucokinase, furthermore elevate blood insulin concentration [6]. Zn also augment insulin-binding on insulin-receptors.

Modification of Carbohydrate Metabolism

Zinc hinders carbohydrate absorption by inhibiting alpha-glucosidase activit (direct binding resulting in conformation-change) in the small intestine. The low zinc intake increases glucose utilization in rats [7]. It increases phosphofructokinase and pyruvate kinase enzymes thus support glycolysis and the subsequent lactate production. Zinc overcome the inactivation of pyruvate kinase by glucagon, too. This ion also enhances glucose transport in adipocytes and blocks glycogen synthesis by indirect enzyme inhibition [8]. Noteworthy, Zn improve lipogenesis and support expression of PPARgamma, one of the regulators of fatty acid storage and glucose metabolism, furthermore insulin sensitizer.

"ZnT8 transmembrane protein is essential component of plasma membrane of insulin secretory granules of pancreatic beta-cells. Its imbalance basically influence beta cell function and may contribute to development of glucose intolerance.

Antioxidant Effect

In diabetes mitochondria produce more reactive free oxigen radicals which have direct (modification of insulin signaling) and indirect (diabetes-induced complications) effects [9,10]. This is one of the hypotheses why use of antioxidants in diabetes is recommended. Zinc exert antioxidant effect in various targets and normalize the in diabetes low levels of glutathion peroxidase, restore catalase and superoxide dismutase activity and activates antioxidant metallothionein synthesis [11].

Interactions among the Trace Elements

Copper administration in rats impairs body gain, diminishes the se-zinc and tissue zinc levels and worsened clinical chemical blood parameters like alkaline phophatase, lactic dehydrogenase and amylase in diabetes as well as in non-diabetes animals. Addition of high dose of zinc to food ameliorated the referred parameters [12]. High doses of zinc hinders absorption of copper. Presence of moderate amounts of iron and iron-fortificated food does not influence significantly the Zn-absorption. In contrast, zinc supplementation improve iron uptake in the diabetic intestine [13]. Zn inhibit N-methyl-D-aspartate (NMDA) receptors therefore Zn deficit results in increased intracellular Ca-levels [14]. These and other examples demonstrate that the abovementioned bivalent cations are normally in balance and supplementation of the trace elements should be administered simultaneously.

2. Zinc Supplementation

The most natural way of zinc intake is food consumption. In general, fruits and vegetables are poor in zinc except potatoes and in less extent green beans and kale. Concentrated dairy products like cheese contains more Zn and one serving of nuts (cashew, almonds, pine nut) or seeds (especially hemp, flax or pumpkin-seed) is also containing the estimated average requirement of this cation. Best sources from this aspect are red meat (beef, in lower degree lamb, pork) and shellfish (oysters are paticularly high in Zn but, crab, shrimps, mussels are also very rich in zinc). Zinc content of some groups of food is presented in Table 1. Recommended Daily Allowance (US Institute of Medicine) for zinc is between 8 – 11 mg/day. It seems in case of zinc deficiency restoration of body zinc content by food intake is difficult.

Table 1. Zinc content of selected foods.

<table>
<thead>
<tr>
<th>Food</th>
<th>Cereals (ready-to-eat)</th>
<th>Shellfish, mussels</th>
<th>Beef, meat</th>
<th>pumpkin seed</th>
<th>Lamb, chicken</th>
<th>Cheese</th>
<th>Fruits, fruit cocktail</th>
<th>Milk, dairy</th>
<th>Mushrooms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mg Zn/100g food</td>
<td>10-30</td>
<td>50-70</td>
<td>6-12</td>
<td>10</td>
<td>2-4</td>
<td>3-6</td>
<td>0,5-7</td>
<td>0,3-0,5</td>
<td>0,6-1,2</td>
</tr>
</tbody>
</table>

Various attempts have been made to improve Zn-content of staple foods. It seems high Zn-content of soil or Zn-spaying of plants during the growth (biofortification of food) may help in zinc-deficiency on population level.

Zinc absorption takes place mainly in the proximal jejunum and distal duodenum. Absorption from food ranges from 11 to 22% but absorbed proportion depends on the body Zn-content and the form of zinc as well as on the constituents of the specific food (enhancers and inhibitors) [15]. The high protein-content may rise the Zn-absorption and high Cu+ hampers its absorption. These conditions may explain why zinc absorption from the US diet is estimated around 30% [16]. In contrast, high phytyte content of food (phytate: zinc molar ratio >ca.14) can inhibit zinc intake [17]. The list of high phytyte-containing foods are presented in Table 2. The aggregation of zinc deficiency in low-income developing countries supposedly due to regular consumption of high phytyte-containing plant-based food [18]. Various pure chemical supplements, like zinc oxide, zinc sulfate, zinc citrate, zinc gluconate, demonstrated an absorption of 49.9 – 61.3% in human [19]. Constant cytosolic Zn concentration is maintained by SLC 30 and SLC39 gene families controlled zinc transporters, named ZnT-s with 10 members and ZIP-s with 14 members, respectively [20]. Zinc transporter gene SLC 30A1 plays a direct role in inorganic zinc (eg. ZnCl, ZnSO4) absorption. The absorption from Zn-gluconate is very rich in zinc). Zinc content of some groups of food is presented in Table 1. Recommended Daily Allowance (US Institute of Medicine) for zinc is between 8 – 11 mg/day. It seems in case of zinc deficiency restoration of body zinc content by food intake is difficult.

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was better by 8.1% [21]. The uptake of organic Zn-compounds (e.g., Zn-glycine and Zn-methionine) is less dependent on this transporter system [22].

<table>
<thead>
<tr>
<th>Food</th>
<th>Phytate content (mg/100g)</th>
</tr>
</thead>
<tbody>
<tr>
<td>kidney beans</td>
<td>610–2.380</td>
</tr>
<tr>
<td>peas</td>
<td>510–1.770</td>
</tr>
<tr>
<td>lentils</td>
<td>270–1.510</td>
</tr>
<tr>
<td>maiss</td>
<td>720–2.200</td>
</tr>
<tr>
<td>wheat (whole)</td>
<td>390–1.350</td>
</tr>
<tr>
<td>rice</td>
<td>60–1.080</td>
</tr>
<tr>
<td>peanuts</td>
<td>170–4.470</td>
</tr>
<tr>
<td>almonds</td>
<td>650–9.420</td>
</tr>
<tr>
<td>walnuts</td>
<td>200–6.690</td>
</tr>
</tbody>
</table>

Discussion

Scientific literature of zinc is rich enough however there are few evidences from clinical point of view, ie. randomized controlled studies supporting confident knowledge about the use of zinc supplementation in diabetes mellitus are scarce. Physiological zinc levels in somatic cells are very low but extremely constant. Therefore the presence of stored Zn and the concerted regulation seems to be essential. If zinc levels in blood were low, symptoms appear slowly and signs usually are aspecific, in this situation supplementation is recommended. In diabetes plasma zinc concentration should be kept within the normal range otherwise insulin-resistance as well as diabetes complications worsen. In case of hypozincemia zinc supplementation improves glycemic control. In prediabetes, when zinc levels are still normal or near normal, supplemental administration of zinc has no beneficial effect. Collectively: if diabetic patient had low zinc concentration, permanent zinc supplementation is needed and should be administered in supraphysiological doses. Contemporary formulations, especially nano-formulations are effective in normalization of zinc homeostasis and dysregulations of diabetes originate in hypozincemia can be corrected by Zn supplementation.

References


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