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Zinc and Insulin Resistance: Biochemical and Molecular Aspects

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Abstract
Studies have shown the participation of minerals in mechanisms involved in the pathogenesis of insulin resistance. Zinc, in particular, seems to play an important role in the secretion and action of this hormone. Therefore, the aim of this review is to understand the role of zinc in increasing insulin sensitivity. We conducted a search of articles published in the PubMed and ScienceDirect database selected from March 2016 to February 2018, using the keywords "zinc," "insulin," "insulin resistance," "insulin sensitivity," and "supplementation." Following the eligibility criteria were selected 53 articles. The scientific evidences presented in this review show the importance of zinc and their carrier proteins in the synthesis and secretion of insulin, as well as in the signaling pathway of action of this hormone. Zinc deficiency is associated with glucose intolerance and insulin resistance; however, the effectiveness of the intervention with the zinc supplementation is still inconclusive.

Keywords Zinc · Insulin resistance · Insulin sensitivity · Insulin secretion · Supplementation

Introduction

Insulin resistance is characterized by reduced sensitivity of the peripheral tissues to the action of this hormone, particularly in the adipose tissue, muscle, and liver. This metabolic disturbance is associated with several diseases such as obesity, type 2 diabetes mellitus, metabolic syndrome, non-alcoholic fatty liver disease, cirrhosis, and polycystic ovary syndrome [1–4].

In this context, various factors are related with the development of insulin resistance, such as excess body fat (particularly the accumulation of intra-abdominal fat), chronic inflammation, oxidative stress, and endocrine disorders such as thyroid dysfunction and changes in cortisol homeostasis [3, 5–7].

In this regard, studies have shown the role of minerals in mechanisms involved in sensitivity to insulin. Zinc, in particular, has been a mineral of great interest for researchers, for its performance in inducing insulin secretion and insulin sensitivity. This micronutrient is required in the formation and crystallization of insulin, stimulation of phosphorylation of the β subunit of this hormone receptor, activation of the kinase 3 phosphatidylinositol enzyme, and induction of the translocation of glucose transporter 4 (GLUT4) [8–10].

Therefore, considering the complexity of insulin resistance and the high prevalence of this metabolic disorder in several diseases, as well as the likely participation of zinc in protection against resistance to this hormone, this review aims to understand the role of zinc in increasing insulin sensitivity.

Methods

This is a narrative review based on a bibliographical survey of articles in PubMed and ScienceDirect databases, without limit for the year of publication, selected from March 2016 to February 2018. The keywords used in the search were "zinc," "insulin," "insulin resistance," "insulin sensitivity," and "supplementation." The descriptors were used alone or combined using the boolean operators "AND" and "OR."

Studies that presented relevant aspects of the participation of zinc and its carrier proteins in mechanisms underlying the secretion and action of insulin were included. Only studies in English were included. Articles were selected for originality

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and relevance, considering the accuracy of the experimental design and adequacy of the sample size. Classic works and recent articles were preferentially used. Dissertations, theses, and articles in which only a summary was available, and those duplicated in different databases were excluded.

Then, we proceeded to the analysis of the included articles, starting with reading the titles, followed by summaries, and later the full text. The application of the exclusion criteria was performed at all stages, always by consensus of the reviewers. The literature included the following types of studies: experimental studies, clinical trials, cross-sectional studies, case control studies, and review articles. At the end, we selected 53 articles.

Zinc: Participation in the Secretion of Insulin

Several studies have shown the participation of zinc in protection against insulin resistance. Zinc deficiency appears to be associated with glucose intolerance caused by impairments in insulin secretion and action, whereas supplementation with zinc increases the concentration of this hormone in the β pancreatic cells and stimulates insulin secretion, as well as promotes improvement in insulin sensitivity [11–17].

Regarding the role of zinc in insulin secretion from pancreatic β cells, this trace element acts in the crucial steps of formation and crystallization of this hormone. It is worth mentioning that within the secretory granules present in pancreatic β cells, insulin undergoes a process of maturation and it is coupled with two zinc ions to form the hexameric complex $zinco_2$-$insulin_6$, necessary for secretion of this hormone [18, 19].

Cooper-Capetini et al. [15] investigated the effect of zinc supplementation on glucose homeostasis and pancreatic β cell function in an animal model of insulin resistance. These researchers verified that glucose tolerance, HOMA-IR index (homeostasis model assessment-insulin resistance), and glucose-stimulated insulin secretion were significantly improved by ZnCl2 supplementation in high fat-fed mice by a mechanism that enhances β cell function.

Studies have shown the expression of zinc carrier proteins in β pancreatic cells (Fig. 1), and that these transporters of zinc affect the secretion of insulin [20–22]. Cai et al. [22] examined all members (ZNT1-10) of the ZNT family in pancreatic islets and in β cell lines of humans and mice and there were no substantial differences in the expression of nine ZNT proteins in the human and mouse islets and β cells with exception of ZNT3, which was only detected in human β cells, but not in mouse β cells. Moreover, these researchers found that ZNT2 was localized on the cell surface of both human and mouse β cells, suggesting a role of ZNT2 in direct export of zinc out of the β cell.

Wijesakara et al. [23] evaluated the effect of zinc transporter protein ZNT-8 in pancreatic β cells and found that ZnT-8 gene knockout mice showed glucose intolerance, reduced concentration of intracellular zinc, atypical insulin granules, few secretory granules, increased levels of pro-insulin, and reduction in the first phase of insulin secretion. This indicates the importance of this protein in processing, crystallization, storage, and secretion of insulin and in glucose metabolism.

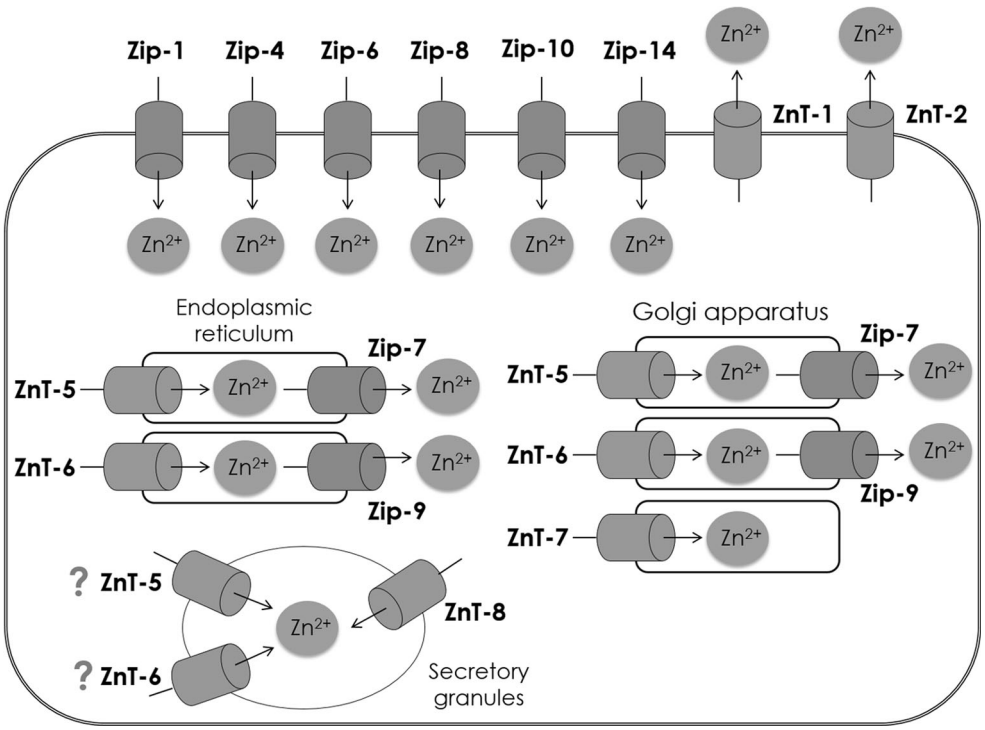

Fig. 1 Localization of zinc carrier proteins in pancreatic β cell. Legend: Zn^{2+}—zinc

ZNT-8 protein transports zinc from the cytoplasm of β pancreatic cells to insulin secretory granules, favoring the formation of zinc-insulin hexamer, which is essential for the secretion of this hormone. Studies show that single nucleotide polymorphisms in the SLC30A8 gene are associated with an increased risk of diabetes mellitus type 2. In conditions of zinc deficiency, whereby there is a reduction in the expression of the gene encoding ZnT-8 in human pancreatic islets and in glucose-stimulated insulin secretion, and an increase in expression of this protein restores the secretion of this hormone [24–26].

ZNT-6 protein transports cytoplasmic zinc to the Golgi apparatus and other vesicular compartments and appears to be involved in pro-insulin metabolism and insulin secretion; however, the underlying mechanism is still unclear [18, 21]. Fukunaka et al. [27] demonstrated, in experiment with cell cultures, that ZNT-6 forms a heterodimer with ZNT-5 and transports zinc to secretory granules. Thus, ZNT-6 and ZNT-5 appears to be important in secretory processes, like for example, the secretion of insulin.

Another protein important is ZNT-7, responsible for the transport of the mineral from the cytoplasm to the Golgi complex of β pancreatic cells, influencing the insulin formation process. Huang et al. [28] demonstrated that overexpression of ZnT-7 in the islet of Langerhans in the mouse pancreas promotes an increase in insulin mRNA expression by modulating the activity of the metal responsive transcription factor-1 (MTF-1), and overexpression of ZnT-7 stimulates the synthesis and secretion of this hormone.

Zinc transporter ZNT-3 is also expressed in β pancreatic cells, and under conditions of hyperglycemia and deficiency of this mineral, an increase in its expression occurs. Deletion of the ZnT-3 gene ($ZnT\text{-}3^{-/-}$) reduces expression of the gene coding for insulin, affects the secretion of this hormone and increases fasting glucose in mice during streptozotocin-induced β cell stress. However, the mechanisms involved in the action of ZNT-3 carrier remain unknown [29].

Concerning the role of ZIP proteins in the metabolism of insulin, it is worth mentioning that the protein ZIP-10 carrier is expressed in the plasma membrane of α and β pancreatic cells. In a zinc deficiency situation, ZIP-10 is translocated to the membrane of intracellular vesicles, and ZIP-10 promotes an efflux of zinc of these vesicles into the cytoplasm of these cells [30–32].

Carrier proteins ZIP-6, 7, and 8 are expressed in various organelles, and ZIP-6 and 8 are located in the plasma membrane and ZIP-7 in the endoplasmic reticulum and Golgi complex [33]. Bellomo et al. [34] have shown that an increase in blood glucose in mice changes zinc homeostasis, inducing the expression of genes Zip-6, 7, and 8 and favoring increased mineral content in pancreatic β cells. Thus, the ZIP-6 and 8 carriers may operate by recycling zinc released during the insulin secretory process.

Liu et al. [35] showed that downregulation of ZIP-6 and 7 carriers in human and mouse islets β pancreatic cells reduces cytosolic zinc content, impairing insulin secretion stimulated by glucose. Moreover, the authors showed that ZIP-6 protein interacts with the peptide glucagon receptor 1, protecting pancreatic β cells from apoptosis.

Thus, the carriers ZIP-6 and 8 located in the plasma membrane of β pancreatic cells, contribute to the uptake of plasma zinc. Moreover, these proteins act by recycling the mineral secreted with insulin to be reused in the synthesis of the hormone in these cells. ZIP-7, in turn, functions in releasing zinc from the endoplasmic reticulum and Golgi apparatus to the cell cytoplasm, while maintaining the homeostasis of the mineral during maturation and secretion of insulin [33].

Zinc: Participation in the Action of Insulin

Regarding the role of zinc in signaling pathways involved in insulin action, this mineral acts via different molecular mechanisms (Fig. 2). This mineral stimulates phosphorylation of the β subunit of the insulin receptor and promotes the activation of phosphatidylinositol 3 kinase and protein kinase B or Akt, thereby enhancing glucose transport into the cells [9, 10, 36, 37].

Accordingly, Bellomo et al. [38] demonstrated the presence of binding sites for zinc in protein tyrosine phosphatase (PTPase) 1B, an enzyme that regulates insulin action by catalyzing the dephosphorylation of the β subunit of its receptor. Thus, the nutrient deactivates this enzyme, thereby increasing the phosphorylation of insulin receptor.

Zinc also inhibits the action of phosphatase and tensin homolog (PTEN), an enzyme that promotes the dephosphorylation of phosphatidylinositol 3,4,5-triphosphate (PIP3), and it inhibits activation of the protein Akt signaling pathway of insulin. Moreover, this mineral induces directly the action of enzymes phosphatidylinositol 3 kinase and protein Akt. Thus, zinc promotes translocation of GLUT4 and the subsequent glucose uptake by cells (Fig. 2) [10].

Associated with this, zinc acts on the structural components involved in glucose transport and ensure their responsiveness to insulin-regulated aminopeptidase (IRAP) molecule, which is necessary to maintain the concentration of GLUT4 in appropriate amounts in the adipose and muscle cells (Fig. 2) [39].

Zinc stimulates the phosphorylation of glycogen synthase kinase 3 (GSK-3) and transcription factor forkhead box protein O1 (FoxO1), similar to the action of insulin (Fig. 2). The phosphorylation of GSK-3 serine residues inhibits its action, favoring the dephosphorylation and activation of glycogen synthase, involved in glycogen synthesis. Phosphorylation of FoxO1 induces translocation from the nucleus to the cytoplasm and inhibits its action to stimulate the expression of gluconeogenic genes. Thus, zinc induces the storage of glucose as glycogen and inhibits the production of this monosaccharide, thereby contributing to glucose homeostasis [10, 40].

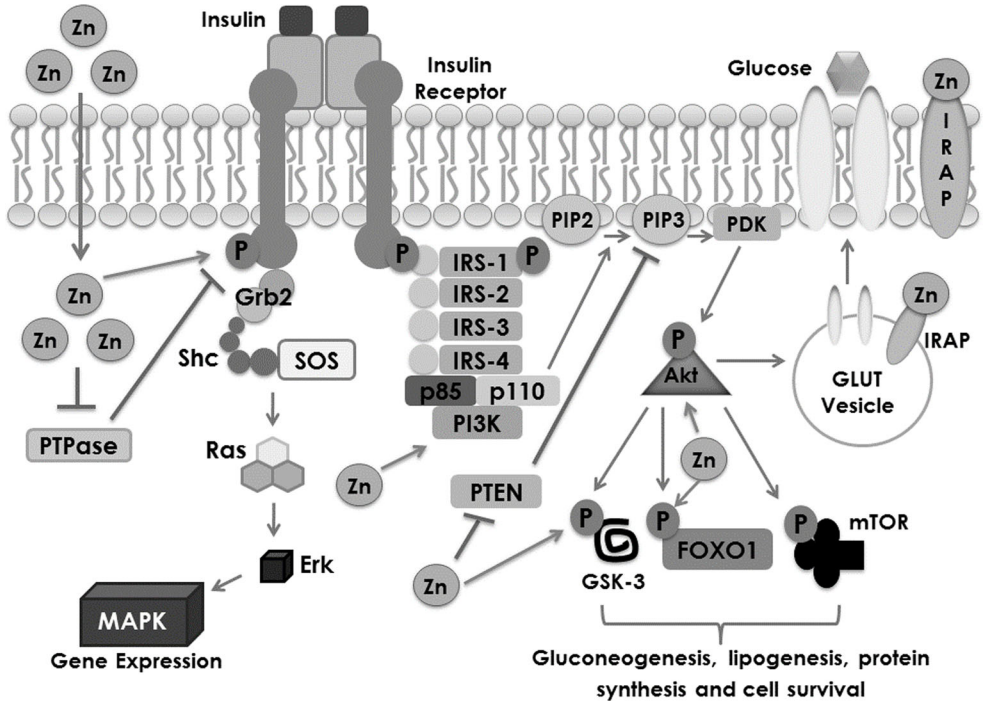

Fig. 2 Molecular mechanisms involved in the participation of zinc in the insulin signaling pathway. Legend: Zn—zinc; PTPase—protein tyrosine phosphatase; Grb2—growth factor receptor-bound protein 2; SOS—son of sevenless protein; Erk—extracellular signal regulated kinases; MAPK—mitogen-activated protein kinases; IRS—insulin receptor substrate; PI3K—phosphoinositide 3-kinase; PIP2—phosphatidylinositol 4,5-bisphosphate; PIP3—phosphatidylinositol 3,4,5-trisphosphate; PDK—phosphoinositide dependent kinase; PTEN—phosphatase and tensin homolog; Akt—protein kinase B; GSK-3—glycogen synthase kinase 3; FOXO1—*forkhead box protein O1*; mTOR—mechanistic target of rapamycin; GLUT—glucose transporter; IRAP—insulin-regulated aminopeptidase

Accordingly, Wu et al. [41] demonstrated that zinc can increase glucose uptake by myocytes by modulating the action of insulin signaling pathway proteins. These researchers found that the mineral favored activation of Akt enzyme and GLUT4 translocation and stimulated the phosphorylation of GSK-3β protein, promoting glucose uptake and glycogen synthesis, respectively.

Another important action of zinc with respect to modulation of transcription of the insulin receptor gene is via zinc finger proteins, which contain three zinc fingers needed for binding. The binding of these proteins is required to enable the expression of the gene coding for the insulin receptor. The zinc finger protein 407 regulates glucose uptake by insulin by increasing levels of messenger RNA of Glut4 and stimulating its transcription, favoring increased concentration of GLUT4 in adipocytes of mice [42].

ZNT-7 also acts in peripheral tissues, stimulating the signaling pathway of insulin action. This zinc transporter is expressed in muscle cells of mice, while deletion of the ZnT-7 gene (ZnT-7$^{-/-}$) favors reduction of the expression of mRNA of the insulin receptor, the insulin receptor substrate 2 (IRS-2), and Akt protein. Moreover, overexpression of ZnT-7 increases the expression of IRS-2 mRNA, phosphorylation of this substrate, and Akt protein and stimulates glucose uptake in muscle cells [43]. In this context, Tepaamorndech et al. [44] demonstrated that ZNT-7 deficiency contributes to the manifestation of insulin resistance, as it reduces the insulin-stimulated phosphorylation of Akt protein in the subcutaneous adipose tissues of mice, affecting the glucose uptake in this tissue. Zinc transporter ZIP-7 is also involved in glycemic control in the muscle cells of mice, because the inhibition of its expression compromises the phosphorylation of Akt protein and glycogen synthesis in these cells [45].

ZIP-14 protein is located in the plasma membrane of adipocytes, hepatocytes, and pancreatic β cells, and it transports plasma zinc into the cytoplasm of these cells. The expression of this protein is increased during inflammation, thus favoring the "sequestration" of zinc in the liver and adipose tissue. Furthermore, the carrier affects glucose homeostasis, as the deletion of the Zip-14 gene (Zip-14$^{-/-}$) favors an increase in phosphorylation of the insulin receptor, phosphatidylinositol 3-kinase, and Akt as well as improves the transport of glucose, reduces fasting glucose, activates lipogenesis, inhibits lipolysis, and increases the concentration of serum insulin and hepatic glucose [28, 46, 47].

Aydemir et al. [48] demonstrated that zinc is distributed to multiple sites in hepatocytes of mice through translocation of ZIP14 from plasma membrane to endosomes, and verified that endosomes from Zip14 knockout mice were zinc-deficient. Thus, ZIP-14 is important to zinc cellular distribution. This

study also verified that ZIP14-mediated zinc transport contributes to regulation of endosomal insulin receptor activity and glucose homeostasis in hepatocytes.

A systematic review and meta-analysis of the effects of zinc supplementation in patients with diabetes demonstrated that zinc supplementation has beneficial effects on glycaemic control and promotes healthy lipid parameters [17]. Other meta-analysis of randomized placebo-controlled supplementation trials in humans verified reduction in glucose concentrations and tendency for a decrease in glycated hemoglobin (HbA1c) following zinc supplementation, suggesting that zinc may contribute to the management of hyperglycemia in individuals with chronic metabolic disease [36].

Considering the important functions performed by zinc in the secretion and action of insulin, several studies have been conducted with an aim to investigate the effect of supplementation with this mineral in people with resistance to insulin. Ranasinghe et al. [49] and Islam et al. [50], for example, evaluated the effect of zinc supplementation in elderly and adult diabetic individuals. Ranasinghe et al. [49] verified that the intervention with 20 mg of elemental zinc for 12 months reduced fasting plasma glucose concentrations, oral glucose tolerance test and HOMA-IR index, with significant improvement in β cell function. Islam et al. [50] verified that supplementation with 30 mg of zinc sulfate for 24 weeks improves fasting plasma glucose concentrations, function of β cells and insulin sensitivity.

Some studies also have evaluated the effect of zinc supplementation in obese individuals [8, 51–53]. Payahoo et al. [51] supplemented 60 adult obese individuals with 30 mg of zinc gluconate or placebo for 4 weeks, and zinc supplementation reduced concentrations of serum insulin, and HOMA-IR index. However, some researchers did not verify benefic effect of zinc supplementation on glycemic control parameters [53].

Conclusions

The scientific evidences presented in this review show that zinc and its carrier proteins are involved in insulin synthesis and secretion as well as in the molecular signaling pathways underlying the action of this hormone. This nutrient acts to modulate transcription of the gene coding for the insulin receptor via zinc finger proteins. Thus, zinc deficiency is associated with glucose intolerance and insulin resistance; however, the effectiveness of the intervention with the zinc supplementation is still inconclusive.

Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interest.

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