Impact of Zinc on Insulin Resistance and Hepatic Fat Accumulation

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Abstract: Insulin signaling plays a crucial role in cellular uptake of glucose and different metabolic pathways. Impairment in cellular insulin sensitivity due to various molecular pathways leads to Insulin resistance (IR) as well as fatty liver. In this review, mechanisms by which zinc involved in decreasing IR are described, focusing on oxidative stress, inflammation, immune system, gut flora and hepatic lipophagy. This study reviews the cause of IR and highlights the role of zinc in mechanisms diminishing IR and fatty liver.

Keywords: Insulin Resistance;Zinc supplementation; Oxidative stress; Inflammation; Gut microbiome; Hepatic lipophagy

Introduction

Following the reduction of cellular insulin sensitivity and glaucous tolerance, systemic IR creates in the cells, especially in in liver, adipose tissue and skeletal muscle (1). Long term IR starts and also develops many chronic diseases especially type 2 diabetes, liver cirrhosis, cardiovascular disease and kidney disease (2, 3). Understanding the molecular mechanisms involved in IR pave the way for therapeutic strategies to prevents or treatment. Given that many research are developing, there are other mechanisms remained undiscovered.

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Insulin as an anabolic hormone is secreted in response to eating and some other hormone from pancreatic β-cells. Insulin mediates blood glucose homeostasis through suppression the production of hepatic glucose and stimulation peripheral glucose uptake (4).

In the other hand, the liver is the main responsible organ for clearance of both endogenous and exogenous insulin (5). Reduction insulin clearance have been related to T2DM and inflammation as well as hepatic IR (6). So, hyperinsulinemia results of both cellular IR and reduction of insulin clearance.

Role of Free Fatty Acids on Insulin resistance

Despite the fact that dietary fat is factor for liver fat accumulation, FFA is a main responsible for liver TG accumulation. It has been demonstrated that high content of FFA and diacylglycerol in the intracellular in the liver results in IR through activation of protein kinase C (PKC) and consequence inhibition of phosphorylation of insulin receptor substrate-1 (IRS-1). In addition, increased FFA due to activation inflammatory toll-like receptors produces and then accumulates ceramide in the liver which in turn via inhibiting phosphorylation of Akt and induces IR in the liver. Additionally, excess of FFA through trigger Akt phosphatase protein phosphatase 2A (PP2A) and consequence inactivation of Akt results in IR in the liver. Moreover, excess of FFA in the liver either prompt storing lipid droplet and steatosis via synthesis of very-low-density lipoprotein and TG or oxidized in hepatic mitochondria by β-oxidation. Extra β-oxidation causes mitochondrial dysfunction and production reactive oxygen species (ROS) and oxidative stress.

Zinc and oxidative stress, Insulin Resistance

Zinc as an important element for cellular homeostatic. Small but vital amount of free zinc exist (unbounded) within organelles such as the reticulum endoplasmic (ER), Golgi and mitochondria

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as well as cytoplasmic (7, 8). In addition, more than 2800 protein including 300 enzymes bind to zinc (9). Reduction in antioxidant defense in the liver exposes mitochondria against oxidative stress, which, in turn, is a progressive factor in steatosis and insulin resistance. The effect of zinc supplementation on oxidative stress situation and IR have been demonstrated in many clinical trial studies (10). Zinc through several mechanisms suppresses oxidative stress.

1) Zinc as a cofactor of Cu, Zinc-superoxide dismutase 1,3 (SOD1 and SOD3) enzymes which catalyze O2- to H2O2 involve in first line of antioxidant system. Thus, contribution of zinc in antioxidant system accounts for essential role of zinc even in oxidative stress situation and modulation IR. Experimental studies have suggested elevating collagen synthesis and also inhibition its degradation in SOD1 in KO mice livers leads to liver fibrosis (11). SOD1 which function in the cytoplasm has shown ameliorating effects against oxidative stress and IR in hepatic cells and adipose tissues (12-14). Additionally, in extracellular Cu, Zn-SOD3 has been shown negatively relationship with T2DM, metabolic syndrome and IR (15, 16). Silencing SOD3 in human adipocytes cells resulted in elevating genes- related lipid metabolic pathways PPARγ and SREBP1c and caused the accumulation of triglycerides (16). Contrary, experimental studies has been suggested overexpression of the SOD gene modulates oxidative stress in islet cells in the pancreas after transplantation (17, 18).
2) Zin is distributed in intracellular space using metallothionine (1-4) by binding and releasing. Evidence has been demonstrated that overexpression of metallothionine has protective effects against oxidative stress and contrary its deficiency induces mitochondrial ROS generation, genes expression related to inflammation and apoptosis in hepatic stellate cell (19)
3) ER is a continuous membrane system within the cytoplasm where plays a pivotal role in in the synthesis, folding, modification, and transport of proteins. ER stress is one of the most

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important factors in pathogenesis of IR. In inflammation and oxidative stress situation, accumulation of unfolded proteins in the ER prompts ER stress and triggers unfolded protein response (UPR) signaling network. ER stress causes reduction in cell surface population of the insulin receptors by inhibition of delivery new insulin receptors to surface and results in IR. But Akt, as a main factor in insulin signaling pathway, is not affected by ER stress (20). Evidence have demonstrated zinc deficiency and its transporters is related to ER stress and its consequences such as T2DM and NAFLD (7, 21, 22).

Zinc and Immune System and Inflammation and Insulin Resistance

Long term exposure of β-cells to inflammatory status induces apoptosis, and subsequently IR (23). Zinc involves in anti-inflammatory pathways through inhibition redox-sensitive proinflammatory transcription factors, resulting in decrease of production of proinflammatory cytokines, adhesion molecules and enzymes. Moreover, the enhancing expression of immune mediators such as IL-6, IL-1 and NF-kB, which deteriorate immune response and consequently β-cells disfunction have been demonstrated in T2DM patients with zinc deficiency (23).

Role of Zinc Transporters, Zinc Importer on Insulin Secretion and Insulin Resistance

Experimental studies have suggested zinc importer 14 , ZIP14, plays a crucial role in adaptation and suppression apoptosis in ER stress via enhancing intracellular zinc concentration (21). ZIP14 is upregulated in response to proinflammatory condition specially increased interleukin 6 (IL-6) and nitric oxide (NO). Upregulation of ZIP14 explains hepatic zinc accumulation and hypozincemia induced by inflammation and sepsis to help the liver regeneration and resistance to ER (24). In addition, ZIP14 involves in regulation endosomal insulin receptors activity and glucose homeostasis in hepatocytes and intestinal barrier function as well as biosynthesis and secretion of insulin by B cell pancreas (25).

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Moreover, other zinc importer and transporter including ZIP4, ZIP6, ZIP7, ZIP13 and ZnT8 have been shown to contribute to several mechanisms of insulin secretion or modulation IR through regulation zinc concentration in cytosol or ER (26-29).

Role of Zinc on Insulin Signal Transduction, Secretion and Receptor Activation

It is well acknowledged a pivotal role of zinc in insulin production, storage and action. Zinc deficiency and polymorphism variants in zinc transporters contributed to less sensitivity to insulin and impaired glucose tolerance as well as degranulate Langerhans islet and impaired insulin secretion (30).

Zinc contributes to stabilizing insulin hexamers and so insulin storage within the secretory granule in pancreatic cells through enhancing insulin binding to hepatocyte membranes (31). In addition, zinc involves on insulin signal transduction through activation Akt. Briefly, after binding insulin to its membrane receptor, activation the α-subunit of receptor induces conformational change to the receptor which, in turn, prompts autophosphorylations of the tyrosine residues in the β subunit of the receptor (32). Following this process, a set of intracellular tyrosine residues are phosphorylated which finally triggers the activation of various downstream target molecules, like protein kinase B (PKB or known as Akt) (33). In turn, zinc induces Akt phosphorylation and promotes cellular glucose uptake via translocation of GLUT4 from the cytosol to the plasma membrane (34). In the other hand, zinc involves in inhibition of glucagon secretion, a hormone which releases hepatic blood glucose, (35) attributed to K ATP-channel activation (36) and inhibition of a stimulatory α-cell receptor (37), or may stimulation cAMP like in β-cells (38).

All in all, zinc involves in blood glucose hemostasis and reduction IR through several mechanism including insulin secretion, signal transduction, storage as well as modulates

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oxidative stress and inflammation and immune system. However, there is still possible mechanisms by which zinc modulates insulin resistance. Lately new mechanisms by which either directly or indirectly zinc has positive influence on IR and steatosis have been noticed. some of these mechanisms including the effect of zinc on gut microbiome and the role of zinc on hepatic lipophagy.

Role of Zinc on Gut Microbiome, Insulin Resistance and Hepatic Fat Accumulation

Recently, finding the new extraintestinal mechanisms related to gut flora and zinc have attracted researchers. In previous studies, the interaction between micronutrients and the diversity of gut microflora has been indicated (39). It has been demonstrated that gut microflora with zinc deficiency compensate their own deficiency by obtaining zinc from the host cells. So, zinc deficiency has a disruptive influence on both intestinal microflora and host cells, culminating in inflammation of the intestinal wall (40). In one observational study alteration of gut microbiome were reported in school-aged children with zinc deficiency (41).

leaky intestinal epithelial cells which increase permeability of the gut mucosal are made transferring lipopolysaccharide (LPS) into systemic circulation resulting IR and hyperinsulinemia following activation of the Toll-like receptor (TLR) 4 and 2 and LPS receptor CD14 as well as immune system (42). Moreover, the portal vein is the main functional link for gut-liver axis which beside nutrients, translocates gut-derived antigens into the liver and leads to impressive inflammatory response in the liver (43). So, gut microflora disruption can be transferred into the liver and blood circulation and different organs can be affected. Thus, keeping balance gut microflora is one of the crucial approaches in fighting against hepatocytes inflammation. Although the human studies about interaction zinc and gut microbiome is rare, it appears zinc supplementation besides other dietary and non-dietary factors, at least in zinc

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deficiency status, can be effective strategy in IR and steatosis. Experimental studies have been shown zinc supplementation can effectively fight against bacterial pathogenesis or xenobiotic and has beneficial influence on protecting commensal gut microflora and their biodiversity (44). Elevating small chain fatty acids (SCFAs) especially butyrate have been illustrated in response to chitosan-chelated zinc supplementation in animal study challenged with E. Coli (45). Although some evidence have been illustrated zinc biofortified food improves gut microbiome, whether zinc supplementation can be effective in zinc sufficient state or not need more investigation (46). However, several animal studies have shown excessive zinc exposure not only does not modulate pathogenic bacteria but also shifts to growth them through disruption in immunity mechanisms (47, 48). Exposure the pathogenic bacteria to elevated free zinc levels result of exceeding the binding capacity is believed to shifts the balance to E. coli or other bacterial pathogens (47). Considering the expression, it seems that the sufficient amount of zinc and probiotic co-supplementation will be intensified the effects of each other. In this line, it has been illustrated zinc and probiotic co-supplementation have beneficial effects on zinc bioavailability and growth gut microflora (49, 50). However, for determining effective doses, it needs to more clinical trial studies.

Role of Zinc on Hepatic Lipophagy

Lipophagy is one kind of autophagy in which physiological lipid turn over manner breaks down intracellular lipid droplets (51). Disturbing of Lipophagy leads to increasing three-acylglycerol (TAG) deposit in them resulting in steatosis. Several proteins or genes involved in each four steps of hepatic lipophagy including phagophore initiation and nucleation, phagophore

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elongation and autophagosome formation, lysosome docking and fusion to form the autolysosome, and autolysosome breakdown have been discovered.

Studies to understand the pathways in which zinc involved in hepatic lipophagy are rising. The results of one study indicated that zinc- mediated autophagy and lipid depletion through activation calcium/calmodulin-dependent protein kinase-b (Ca2+/CaMKKb) /AMPK signaling and element-binding transcription factor (Zn2+/MTF-1) /PPARa pathways (52). In addition, water contamination of zinc and copper heavy metal of yellow catfish highlights the antagonist effect of these metals on hepatic lipid deposition and revealed that the Zn-induced deacetylation of Beclin1 resulting lipophagy is a crucial pathway to modulate Cu-induced lipid accumulation (53). So, apart from zinc concentration, the levels of copper or preparation of zinc to copper has a pivotal role in hepatic lipophagy.

In a high-fat diet animal model study, Dogra et al. (2019) showed a positive effect of the administration of zinc oxide nanoparticles on hepatic steatosis. This study indicated inhibition of palmitate-induced hepatic lipid accumulation by zinc oxide nanoparticles via the SIRT1/LKB1/AMPK pathway. In fact, zinc oxide nanoparticles through diminishing intracellular ATP and following that AMPK activation leads to ameliorating hepatic steatosis and peripheral insulin resistance (54). Although different sort of mechanisms involved in lipophagy and diminishing IR and steatosis, clinical trial studies are rare and inconsistent. Our last clinical trial study exhibited daily intake of 30 mg elemental zinc improved IR but no significant effect on liver steatosis. (55). Therefore, it is need more cellular and clinical studies to clarify the effects of zinc supplementation on lipophagy and steatosis.

Conclusion

Taken together, considering zinc deficiency is one of the most common nutrient deficiencies among patients with NAFLD and also pivotal role of zinc on IR and hepatic lipophagy, understanding the underling mechanisms is necessary. Especially, identifying the effective daily dose of zinc to overcome IR and induce lipophagy in patients with NAFLD is warrant. Moreover, ascertaining the exact role of zinc status on diversity and colonization of gut microbiota as well as the effects of zinc and probiotic co-supplementation on both intestinal and extraintestinal state paves the way to find novel mechanisms for controlling IR and its consequences.

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Author Contributions

All process including creating the concept of study, investigation and writing was done by M.F.

Conflict of Interest

The author declares no potential conflict of interest.

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