

Role of zinc in insulin regulation and diabetes

Resham Raj Poudel, Yuvaraj Bhusal¹, Biswaraj Tharu², Nisha Kusum Kafle³

Department of Internal Medicine, Western Reserve Health Education, Youngstown, OH, USA, ¹Department of Internal Medicine, BPK Institute of Health Science, Dharan, Nepal, ²Department of Internal Medicine and ³Public Health, Institute of Medicine, Kathmandu, Nepal

Abstract

Zinc (Zn) affects glucose metabolism through insulin regulation and has potential implication in diabetes. Zn deficiency has not been proven in diabetes; however, observations of hyperzincuria, hypozincemia, and Zn malabsorption in diabetes indicate additional requirements for Zn. Mutation in Zn transporter 8 – a key protein in insulin secretion – has been associated with Type 2 diabetes. Zn supplementation in prediabetics and diabetics has been supported to improve plasma glucose, hemoglobin A1c (HbA1c), and lipids and potentially improve insulin sensitivity, reduce oxidative stress, and protect from renal damage.

Keywords: Diabetes, hyperzincuria, hypozincemia, insulin, zinc

Address for correspondence: Dr. Resham Raj Poudel, Western Reserve Health Education, Youngstown, OH, USA.

E-mail: poudelresham@gmail.com

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INTRODUCTION

According to the World Health Organization statistics, 422 million people had diabetes in 2014. In 2012 alone, 1.5 million people died due to diabetes.^[1] The Centers for Disease Control and Prevention reports that more than 29 million Americans have diabetes and 86 million, i.e., >1/3rd of total American population, have prediabetes.^[2] Search for new approach for addressing glucose control is always on the run, be it drugs, diet, or activity influencing glucose metabolism. Here, we discuss the role of zinc (Zn) in insulin regulation and implication in diabetes.

ZINC PHYSIOLOGY

Zn is a vital mineral involved in numerous aspects of cellular metabolism. It is widely distributed in variety of food including oyster, red meat, poultry, beans, nuts, and whole grains.^[3] Zn is an essential component of more than 300 catalytic enzymes in our body.^[4,5] It plays a role

in DNA synthesis, protein synthesis, cell division, immune function, and wound healing.^[6,7] It supports normal growth and development^[8] and is also required for proper sense of taste and smell.^[9] The Zn content in pancreatic β -cells is among the highest of the body and it appears to be an important metal for insulin-secreting cells.^[10] A daily intake of Zn is required to maintain a steady state because the body has no specialized system to store it.^[11] The distribution of Zn throughout the body in various proteins and nucleic acids makes it difficult to accurately measure the levels using laboratory tests.^[12] Plasma or serum Zn levels, which are commonly used for evaluating Zn deficiency, do not accurately reflect cellular Zn status due to highly regulated homeostatic control mechanisms.^[13] Zn deficiency may be present in the absence of abnormal laboratory indices.^[8] Zn deficiency occurs due to inadequate Zn intake or absorption, increased loss of Zn from the body, or increased requirements for Zn.^[14] Zn deficiency has not been very well documented in diabetes; however, it is suggested that there may be additional requirements for

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Zn. Different studies have found decreased physiological measurements of Zn status in diabetics. Meanwhile, hyperzincuria and indications of Zn malabsorption have also been observed in both Type 1 and Type 2 diabetics.^[15]

THE ROLE OF ZINC IN INSULIN REGULATION

Zn plays a substantial role in insulin regulation and carbohydrate metabolism.^[16] Zn plays a key role in the storage and secretion of insulin by pancreas, which subsequently increases the uptake of glucose.^[17] Low plasma level of Zn adversely affects the ability of islet cells to produce and secrete insulin.^[17] Insulin is produced in the β -cells through preproinsulin and proinsulin precursors. In the Golgi apparatus of β -cells, proinsulin is stored along with Zn and calcium ions as hexamers, which is then converted into insulin hexamers after excision of c-peptide by proteolytic enzymes. These insulin hexamers have low solubility and are stored as crystals within the secretory vesicles. When these vesicles fuse with the plasma membrane, insulin crystals are expelled into the intercellular fluid. The insulin crystals then dissolve and dissociate into monomers and these monomers are transported to other tissues through the blood stream and they finally bind to the insulin receptors.^[18] Zn ions have very important role in formation of the crystalline nature of the insulin granule, condensing them and thus reducing contact with the surrounding membrane.^[19] Zn also promotes phosphorylation of Akt and GSK 3B, expression of hexokinase-2 and inhibits the negative regulators of Akt. These have significant roles in increasing expression of glucose transport type 4 and metabolism while decreasing cellular apoptosis, hyperglycemia, and excess glucose in kidney tissues.^[20]

METALLOTHIONEINS, ZINC TRANSPORTERS, AND INHIBITORS: ROLE IN INSULIN METABOLISM

There are three classes of protein which control the concentration of Zn in the cytoplasm. Metallothioneins, Zn transporters (ZnTs) encoded by solute linked carrier 30 (SLC30) and Zrt, Irt-like proteins (ZIPs) encoded by SLC39 genes.^[21] Metallothioneins control Zn availability in β -cells. When Zn is needed for formation of Zn proteins, the metallothioneins release Zn. If there is excess Zn, it forms metallothionein.^[22] ZnTs function to reduce cytoplasmic Zn concentration by transporting them to intracellular vesicles or extracellular spaces.^[23,24] There are nine forms of ZnTs named from ZnT1-8 and ZnT10.^[25] ZnT8, encoded by SLC30A8 belongs to cation diffusion facilitator family.^[10] It delivers Zn into the granules for insulin maturation and secretion^[24] as shown in Figure 1.^[26] Studies have shown that ZnT8 overexpression leads to increased glucose-stimulated insulin secretion,

especially for high glucose challenge and protection from Zn depletion-induced cell death.^[23] Similarly, ZnT8 knockdown is associated with increased intracellular insulin with reduced insulin secretion and increased apoptosis of β -cells, as well as increased hepatic insulin clearance and low peripheral blood insulin. Zn decreases hepatic insulin clearance by inhibiting clathrin-dependent insulin endocytosis.^[27,28] It is well established that ZnT8 is a key protein for the regulation of insulin secretion from the pancreatic β -cells, and its mutation has been associated with Type 2 diabetes mellitus (T2DM).^[29] Roles of other ZnTs have been identified such as ZnT3 knockdown has been also associated with decreased insulin secretion as well as apoptosis of β -cells.^[23,27] Similarly, ZnT7 overexpression results in increased insulin synthesis while ZnT7 knockdown results in low glucose uptake and increased lipogenesis in adipocytes.^[30] Zn chelation inhibits ZnT8 and insulin expression, leading to diabetes as well as apoptosis of β -cells.^[31] ZIPs increase cytoplasmic Zn concentrations, especially during low glucose exposure.^[22,23] ZIP6 also facilitates the protective effect of glucagon-like peptide 1 on β -cell survival.^[32]

Human Islet Amyloid Polypeptide and zinc

Human Islet Amyloid Polypeptide, an amyloidogenic protein, is cosecreted with insulin in response to glucose. It is found in pancreatic islets especially of diabetic patients and is linked to loss of β -cells.^[33] Zn promotes the formation of oligomers while it inhibits the formation of amyloid fibers.^[34]

NORMAL SERUM ZINC, URINE ZINC EXCRETION CHANGES IN DIABETES

Normal serum Zn level in healthy individuals varies from 0.66 to 1.10 mcg/mL.^[34] Fecal excretion of Zn is the

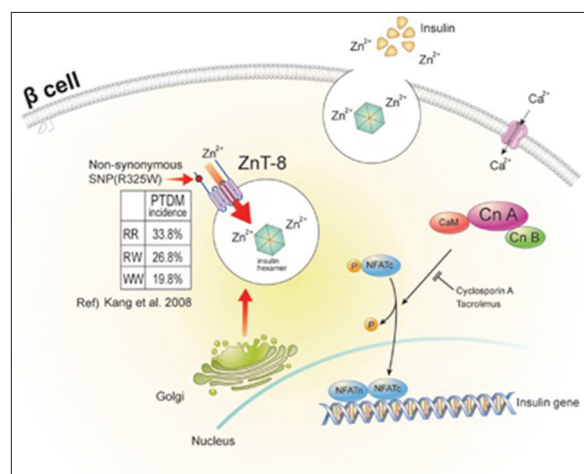


Figure 1: Schematic representation of vesicular Zinc transporter-8 expression and R325W polymorphism in pancreatic islet β -cells^[26]

dominant route of elimination. Renal excretion is a minor secondary elimination pathway. Normal daily excretion of Zn in the urine ranges from 20 to 967 mcg/24 h.^[35] The pathophysiology of diabetes has been associated with hyperzincuria and hypozincemia.^[36,37] Zn deficiency is more common in developing countries, where diabetes is also showing an exponential rise.^[38,39] Type 2 diabetic patients have suboptimal Zn level in blood due to increased urinary depletion (hyperzincuria) resulting hypozincemia.^[40] A comparative study showed serum Zn levels as $64.2 \pm 12.6 \mu\text{g/dl}$ for T1DM versus $68.9 \pm 11.9 \mu\text{g/dl}$ for T2DM versus $83.4 \pm 12.5 \mu\text{g/dl}$ for healthy controls.^[41] However, in other studies, diabetic patients despite having excess urinary excretion of Zn had normal serum Zn levels, possibly from compensatory hyperabsorption or increased Zn content in the diabetic diet.^[42] Zincuria has been associated with hyperglycemia, polyuria, glycosuria, and proteinuria.^[43-45] Urinary Zn excretion has been shown to be higher in diabetics than in controls ($P < 0.0001$) and was significantly correlated with urine glucose ($P < 0.004$) and volume ($P < 0.0007$).^[43] In comparison to controls, T1DM women lost 4 times more protein in urine, and the urinary protein loss correlated with the urinary Zn loss ($P < 0.007$).^[44] Zincuria was higher in patients with excessive microalbuminuria ($>15 \text{ mg/L}$) ($P < 0.001$), although zincuria and microalbuminuria did not correlate significantly.^[45]

EFFECTS OF ZINC SUPPLEMENTATION IN DIABETES

Zn supplementation has been supported to improve Zn level, glucose metabolism, lipid profile, and proteinuria. In a meta-analysis, there was a significant increment in serum Zn levels ($2.42 \pm 0.25 \mu\text{mol/L}$, $P < 0.001$) in patients with T2DM after Zn supplementation.^[46] Some studies have shown that Zn supplementation increased high-density lipoprotein (HDL) cholesterol levels while significantly reduced fasting and postprandial blood glucose, HbA1c, plasma total cholesterol, low-density lipoproteins cholesterol, and triglycerides levels.^[41,47,48] In a study, Zn + multivitamin/mineral (MVM) group had a significant mean change of fasting plasma glucose (FPG) -0.33 mmol/L (standard error of the mean 0.21 mmol/L) ($P = 0.05$) when compared with the other two groups (mean change in the MVM group $+0.19 (0.31) \text{ mmol/L}$ and $+0.43 (0.23) \text{ mmol/L}$ in the control group, respectively).^[47] In 12 different studies comparing the effects of Zn supplementation in FPG in T2DM, the pooled mean difference in FPG between Zn supplemented and placebo groups was 18.13 mg/dl . 2 h postprandial blood sugar also showed a

similar distinct reduction (34.87 mg/dl) in the Zn-treated group. The reduction in HbA1c was 0.54% in the Zn-treated group.^[49] A study showed decreased HDL cholesterol ($-0.10 \pm 0.02 \text{ mmol/L}$, $P < 0.001$) after Zn supplementation, equivalent to a 7% decrease from baseline in healthy individuals.^[46] However, on comparing 8 studies in T2DM, the pooled mean difference for total cholesterol between Zn supplemented and placebo groups was 32.37 mg/dl ($P < 0.05$). Low-density lipoprotein also showed a distinct reduction in the Zn-treated group; the pooled mean difference from random effects analysis was 11.19 mg/dl ($P < 0.05$).^[49] A double-blind randomized controlled trial with Zn supplementation for 3 months showed a significant reduction in albumin excretion, from 90 ± 60 to $85 \pm 57 \text{ mg/g creatinine}$ ($P = 0.003$). This outcome might be due to the antioxidant effect of Zn.^[48] Zn supplementation improves insulin resistance in obese individuals of both sexes.^[50] Prediabetic adults who took daily oral Zn supplementation also improved their FPG ($5.37 \pm 0.20 \text{ mmol/L}$ vs. 5.69 ± 0.26 , $P < 0.001$), β -cell function, and insulin sensitivity over 6 months compared to placebo group.^[51]

Zn supplementation decreases oxidative stress

Hyperglycemia increases oxidative stress in DM.^[52] Zn may protect the cells from oxidative injury decreasing blood glucose levels. Zn administration alone or combined with chromium decreased plasma thiobarbituric acid reactive substances' (TBARS) levels – an oxidant which is increased in diabetics. An inverse correlation was found between Zn plasma levels and plasma TBARS.^[53] After 6 months of Zn supplementation, there was a 15% decrease of plasma TBARS with no significant changes in the placebo group.^[53] In animal study involving diabetic rats with Zn administration, glutathione levels increased; whereas, lipid peroxidation, nonenzymatic glycosylation, urea, and creatinine levels decreased in their kidneys.^[54]

Zn supplementation protects from kidney damage

Zn supplementation in T1DM rats showed fewer pathological changes in kidney compared to a placebo as evidenced by lower levels of glomerular basement membrane thickness, mesangial index and tubulointerstitial damage.^[55,56]

CONCLUSION

Zn deficiency can occur from insufficient intake, malabsorption, excess excretion, and increased utilization, and this deficiency exists, particularly in developing countries where the prevalence of diabetes (mostly T2DM) is also rising. The physiology of Zn in insulin regulation has been well established for long. Zn plays a role in formation, release, and transport of insulin molecules. Different ZnTs

including ZnT8, ZnT3, and ZIP6 have specific roles in insulin pathway. There is no evidence associating Zn deficiency with incidence of diabetes; however, the fact that hyperzincuria and hypozincemia has been observed in people with diabetes and cellular Zn deficiency can occur even with normal blood Zn levels points toward some role of Zn in diabetes and potential of Zn supplementation and or optimization. Zn supplementation has been observed in several studies to positively affect glucose, A1c, and lipid levels in diabetics, with potential for decreasing oxidative stress and protecting from renal damage. At this time, we have no guidelines for Zn measurement or supplementation in diabetes; however, ensuring Zn as a part of regular dietary requirement through healthy food or oral supplementation would positively affect diabetes health.

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Conflicts of interest

There are no conflicts of interest.

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