

Zinc and Glycemic Control

INTRODUCTION

The oldest evidence for pure zinc (Zn) comes from Zawar in Rajasthan as early as the ninth century AD.^[1] Zn is an essential trace element for humans.^[2] Zn is required for the functions of over 300 enzymes and 1000 transcription factors^[3] and is stored and transferred in metallothioneins.^[4] It is the second most abundant trace metal in the humans after iron, and it is the only metal which appears in all enzyme classes. Roughly 2–4 g of Zn is distributed throughout the human body. Most Zn is in the brain, muscle, bones, kidney, and liver, with the highest concentrations in the prostate and parts of the eye.^[5] A variety of Zn compounds are commonly used in medicine such as Zn carbonate and Zn gluconate (as dietary supplements).

ZINC IN PANCREAS

Zn is greatly concentrated in endocrine pancreas.^[6] Dysregulation of Zn metabolism within the pancreas impairs a multitude of key processes, including glycemic control,^[7] pancreatic cancer,^[8] and chronic pancreatitis.^[9] Members of the SLC30A gene family (ZnT1–10) transport Zn from the cytoplasm, whereas members of the SLC39A gene family (Zip1–14) transport Zn into the cytoplasm.^[10] Localization of Zip1, Zip10, and Zip14 to pancreatic α -cells suggests that these transporters are responsible for importing Zn into the cell. Zn binds to and opens ATP-dependent K(+) channels, allowing the efflux of Zn from the α -cell and inactivation of voltage-dependent calcium channels, resulting in decreased glucagon secretion. Zn is transported into pancreatic β -cell cells via Zip4. Zn is transported into insulin granules by ZnT8.^[11] A Zn-containing hexameric unit is formed when two Zn ions associate with two insulin dimers and combine with an additional insulin dimer.^[10] Zn is transported into pancreatic acinar cells by Zip5. ZnT2 is responsible for the transport of Zn into zymogen granules by where it binds to and activates digestive enzymes.

ZINC AND GLYCEMIC CONTROL: MOLECULAR MECHANISMS

Antioxidant properties

Hypozincemia and hyperzincuria are known to be present in patients with both type-1 and type-2 diabetes. Zn supplementation is however controversial, and few studies have shown a beneficial effect. Oxidative stress measured by thiobarbituric acid reactive substances and selenium-dependent glutathione peroxidase, an antioxidant enzyme, significantly improved on supplementation of Zn 30 mg/day for 3–6 months.^[12]

Effects on carbohydrate and lipid metabolism

Zn stimulates glycolysis and inhibits gluconeogenesis. Zn is also known to be a concentration-dependent reversible inhibitor of α -glucosidase activity in the intestine.

In skeletal muscles, the phosphorylation of AMP-activated protein kinase is greatly stimulated by Zn- α 2-glycoprotein and increases cellular GLUT4 protein also been observed in adipose tissue with a resultant increase in glucose uptake.

Islet cell function

In vitro environments increasing the extracellular Zn concentration are known to increase the free insulin concentration in the immediate vicinity of β -cells, mediated by enhanced Zn-insulin dissociation. Human islet amyloid polypeptide amyloid fibrillogenesis is significantly inhibited by Zn, at concentrations similar to those found in *in vivo* extracellular environments. Reduced insulin content and decreased insulin secretion in response to hyperglycemic stimuli were seen in ZnT8 downregulated cells.^[11]

Insulin-mimetic compounds

Zn ions and its complexes have shown insulin-like action in both *in vitro* and *in vivo* experiments.^[13] *In vitro*, Zn complexes inhibit the release of free-fatty acids^[13] and activate the insulin signaling cascade. A significant reduction in blood glucose is induced by Zn oxide nanoparticles, and it also elevates serum insulin levels and glucokinase activity, while stimulating a higher expression of insulin, insulin receptor, GLUT-2, and glucokinase genes in STZ-induced (type-1) diabetic rats.^[14]

STUDIES ON ZINC AND GLYCEMIC CONTROL

Dietary intake of Zn was associated with a reduced risk of type-2 diabetes mellitus (T2DM).^[15] The effects of supplementation were investigated in randomized clinical trials that utilized Zn as the sole intervention (11 interventions, $n = 581$) or combined with other micronutrients (7 interventions, $n = 3397$). The dose of elemental Zn ranged from 3 to 240 mg/day (median: 30 mg/day). Zn supplementation produces a modest but significant reduction in glucose concentrations, with the effect being more pronounced in subjects who are classified as diabetic or obese.^[16] In a subset of trials, HbA1c tended to decrease following Zn supplementation, but insulin concentrations were not significantly affected. The response in healthy individuals is less clear. The SUVIMAX study is the one among the largest of trials, carried out in healthy men and women which showed no significant effect of Zn (20 mg) together with a mixture of micronutrients (Vitamins C and E, carotene, and Se) on the plasma glucose concentrations.^[17]

The study done by Naik *et al.* published in this issue assessed serum Zn levels and glycemic parameters in T2DM patients.

They have, for the first time, studied Zn levels in patients on treatment with oral antidiabetic agents. They have documented low levels in both the groups of patients on metformin alone and those taking metformin and SU. Diabetics having low Zn levels is a well-documented fact; however, Zn levels in diabetics on OAD have not been studied. Their study has not shown a significant difference between the groups of treatment or with different parameters of glycemic control. Eshak *et al.* have also shown that persons with good glycemic control had normal Zn levels. The uncontrolled diabetic seemed to have a greater reduction in Zn levels.

A word of caution should also be exercised as high doses of Zn may induce copper deficiency, decrease high-density lipoprotein, and decrease biomarkers of iron status. Hence, further studies are required to substantiate the need for Zn supplementation and define the adequacy.

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REFERENCES

- Kharakwal JS, Gurjar LK. Zinc and brass in archaeological perspective. *Ancient Asia* 2006;1:139.
- Maret W. Zinc and human disease. In: Sigel A, Sigel H, Sigel RK, editors. *Interrelations between Essential Metal Ions and Human Diseases*. Dordrecht: Springer Netherlands; 2013. p. 389-414. Available from: http://link.springer.com/10.1007/978-94-007-7500-8_12. [Last accessed on 2019 Apr 26].
- Cherasse Y, Urade Y. Dietary zinc acts as a sleep modulator. *Int J Mol Sci* 2017;18. pii: E2334.
- Cotton FA, editor. *Advanced Inorganic Chemistry*. 6th ed. New York: Wiley; 1999. p. 1355.
- Wapnir RA. *Protein Nutrition and Mineral Absorption*. Boca Raton, Fla: CRC Press; 1990. p. 334.
- Kelleher SL, McCormick NH, Velasquez V, Lopez V. Zinc in specialized secretory tissues: Roles in the pancreas, prostate, and mammary gland. *Adv Nutr* 2011;2:101-11.
- Hall AG, Kelleher SL, Lönnerdal B, Philipps AF. A graded model of dietary zinc deficiency: Effects on growth, insulin-like growth factor-I, and the glucose/insulin axis in weanling rats. *J Pediatr Gastroenterol Nutr* 2005;41:72-80.
- Jayaraman AK, Jayaraman S. Increased level of exogenous zinc induces cytotoxicity and up-regulates the expression of the znT-1 zinc transporter gene in pancreatic cancer cells. *J Nutr Biochem* 2011;22:79-88.
- Girish BN, Rajesh G, Vaidyanathan K, Balakrishnan V. Zinc status in chronic pancreatitis and its relationship with exocrine and endocrine insufficiency. *JOP* 2009;10:651-6.
- Jenkins A, Lengyel I, Rutter GA, Lowe N, Shai I, Tirosh A, *et al.* Obesity, diabetes and zinc: A workshop promoting knowledge and collaboration between the UK and Israel, November 28-30, 2016 – Israel. *J Trace Elem Med Biol* 2018;49:79-85.
- Fukunaka A, Fujitani Y. Role of zinc homeostasis in the pathogenesis of diabetes and obesity. *Int J Mol Sci* 2018;19. pii: E476.
- Faure P, Benhamou PY, Perard A, Halimi S, Roussel AM. Lipid peroxidation in insulin-dependent diabetic patients with early retina degenerative lesions: Effects of an oral zinc supplementation. *Eur J Clin Nutr* 1995;49:282-8.
- Yoshikawa Y, Ueda E, Miyake H, Sakurai H, Kojima Y. Insulinomimetic bis(maltolato)zinc(II) complex: Blood glucose normalizing effect in KK-A(y) mice with type 2 diabetes mellitus. *Biochem Biophys Res Commun* 2001;281:1190-3.
- Alkaladi A, Abdelazim AM, Afifi M. Antidiabetic activity of zinc oxide and silver nanoparticles on streptozotocin-induced diabetic rats. *Int J Mol Sci* 2014;15:2015-23.
- Eshak ES, Iso H, Maruyama K, Muraki I, Tamakoshi A. Associations between dietary intakes of iron, copper and zinc with risk of type 2 diabetes mellitus: A large population-based prospective cohort study. *Clin Nutr* 2018;37:667-74.
- Capdor J, Foster M, Petocz P, Samman S. Zinc and glycemic control: A meta-analysis of randomised placebo controlled supplementation trials in humans. *J Trace Elem Med Biol* 2013;27:137-42.
- Czernichow S, Couthouis A, Bertrais S, Vergnaud AC, Dauchet L, Galan P, *et al.* Antioxidant supplementation does not affect fasting plasma glucose in the supplementation with antioxidant vitamins and minerals (SU.VI.MAX) study in France: Association with dietary intake and plasma concentrations. *Am J Clin Nutr* 2006;84:395-9.

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