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SERICIN MAY CONQUERS THE PATHOGENESIS OF TYPE 2 DM BY ELEVATING THE INTESTINAL ABSORPTION OF ZINC, AND MAGNESIUM IN RATS

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ABSTRACT
The pathophysiology of type 2 diabetes mellitus (DM) is not yet clearly understood. Impaired insulin secretion and insulin resistance are the major factor contributing to the pathogenesis of type 2 DM. Various mechanisms are involved in the secretion of insulin and its resistance. However, some ions such as zinc and magnesium are necessary for adequate insulin secretion and insulin resistance. The natural macromolecule Sericin may augmented the intestinal absorption of Zn and Mg. This may be the achievable target for the treatment of type 2 DM.

KEYWORDS: Type 2 DM, Sericin, Zinc, Magnesium.

INTRODUCTION

Diabetes mellitus, particularly type 2 diabetes mellitus (T2DM), is a very distressing disease worldwide. Amid thorough study, the precise mode of T2DM pathogenesis remains uncertain. Therefore, the investigators are actively attempting to explore the pathogenesis of T2DM, particularly development of T2DM through alleviate levels of Zn and Mg.

Pancreatic β cells are considered to possess very large amounts of zinc relative to certain other cells.[1] In fact, insulin secretory granules have been found to have the lowest zinc content in the β cells.[2,3] Three protein families have been shown to regulate cellular zinc homeostasis, namely metallothioneins (MTs), zinc importers (ZIP, SLC39A) and zinc exporters (ZnT, SLC30A). ZnT8 plays a vital function in the aggregation of zinc in insulin hidden granules.[4] Zinc is also important for the proper synthesis of insulin, its storage and structural stability.[5]

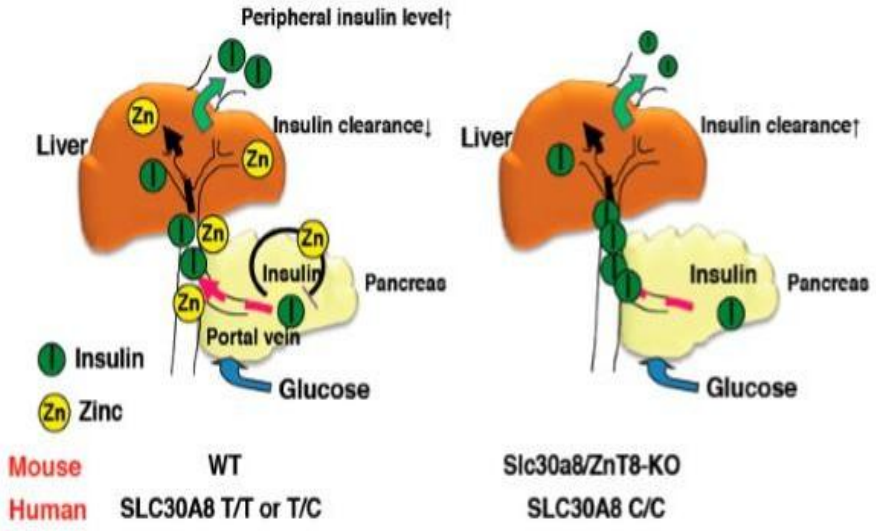

Figure 1: Schematic representation of insulin clearance in WT and ZnT8-KO mice. Zinc co-secreted with insulin suppresses insulin secretion from pancreatic β cells and inhibits hepatic insulin clearance in WT mice (left). In contrast, reduced zinc secretion results in enhanced insulin secretion from β cells in ZnT8-KO mice and hepatic insulin clearance is not suppressed (right). Thus, peripheral insulin levels in ZnT8-KO mice are maintained at lower levels than in WT mice.

Lower dietary zinc intake and lower serum zinc concentrations may be associated with higher risk of cardiovascular disease, diabetes and glucose intolerance. Many studies have recorded that higher intakes of zinc have protective effects against metabolic syndrome.[2,6] A broad population-based retrospective analysis showed that higher zinc consumption could be correlated with lower incidence of form 2 DM in women.[3] In other groups, lower plasma zinc levels have been found in patients with DM.[7] Others, however, also indicated that serum zinc concentrations do not vary according to glucose tolerance.[8,9] Evidence of the casual role of zinc in the production of diabetes is still uncertain, but there is compelling proof of enhanced insulin secretion.[4]

The production of insulin hexamer is achieved by the dissociation of C-peptide, regulated by the dissociation of prohormone convertase (PC) through the Golgi apparatus.[10] Limited environments of insulin-secretory-granules under which elevated amounts of acidic pH in both insulin and zinc are preserved.[11,12] These crystallized insulins can be seen by electron microscopy as dense main granules, and by insulin crystal when they are secreted from pancreatic ß cells.[13,14]

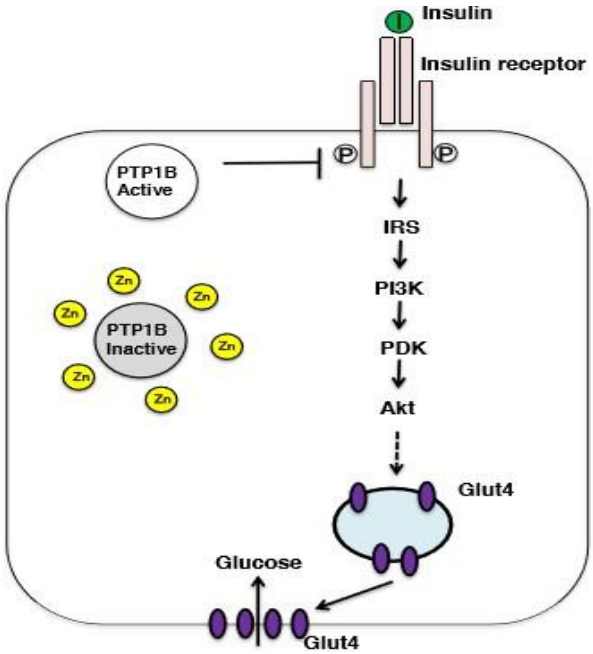

Figure 2: Insulin signaling pathway and insulin mimicking function of zinc ions. Insulin binds to the insulin receptor located in the plasma membrane in the peripheral tissues, such as liver and muscle. The insulin-signaling pathway is activated and the glucose transporter GLUT4 is translocated to the plasma membrane. Zinc might inhibit the activity of PTP1B, which activates the insulin-signaling pathway. PI3K, phosphatidylinositol-3-kinase; IRS, insulin receptor substrate; PKD, protein kinase D.

Zinc can be referred to as insulin mimetic since zinc activates lipogenesis and glucose uptake in isolated adipocytes, and zinc act as an insulin mimetic by providing an indirect impact on the insulin signaling pathway.[15] Zinc ion inactivates PTP1B by non-covalent binding to its cysteine residues, which is essential to enzymatic function, and the reactive oxygen species is often established to inactivate the enzyme in a similar way.[16,17] In general, oxidative stress is more controlled in most patients with diabetes and diabetic animals, more mechanistic research is required to explore the risks and benefits of zinc supplementation as a means of alleviating obesity and type 2 diabetes.

Magnesium (Mg) is an essential element employed as a cofactor in all of the body's biochemical reactions. Higher consumption of Mg and higher plasma amounts of Mg are correlated with metabolic syndrome, insulin tolerance and type 2 diabetes.[18]

Mg^{2+} was widely accepted as essential for the auto phosphorylation of b-subunits of the insulin receptor. Two Mg^{2+} ions can bind to the tyrosine kinase domain, as can be seen in the crystal structure of the tyrosine kinase domain.[19] In vitro work utilizing isolated insulin receptors demonstrated the role of this Mg^{2+} binding. Mg^{2+} enhances the function of tyrosine kinase by increasing the ATP receptor finiteness.[20,21] In comparison, increased insulin receptor phosphorylation has been seen in the liver tissue of rats fed Mg^{2+} deficient diets for 11 weeks.[22] Nonetheless, the validity of this analysis may be criticized since insulin phosphorylation was common in rats with the same serum Mg^{2+} at 6 weeks or in muscle tissue. Overall, Mg^{2+} seems to be an essential element in auto phosphorylation of the insulin receptor. Defective insulin receptor phosphorylation is thus known to be the key process by which hypomagnesaemia leads to insulin resistance in T2DM patients.

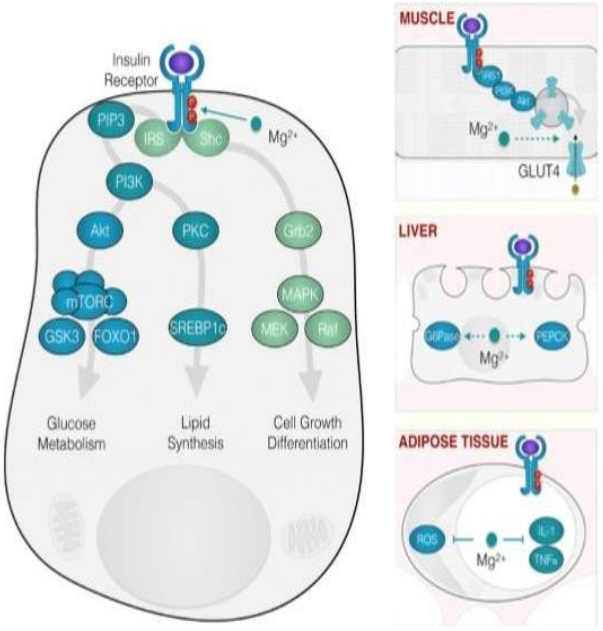

Figure 3: Mg^{2+} affects insulin sensitivity. Mg^{2+} regulates the insulin signaling pathway by increasing the affinity of the insulin receptor tyrosine kinase for

ATP. Consequently, hypomagnesemia is associated with a reduced activity of all downstream pathways. In the muscle, Mg^{2+} therefore regulates the membrane trafficking of GLUT4. In the liver, Mg^{2+} is an important regulator of enzymes in gluconeogenesis, including G6Pase and PEPCK. In adipose tissue, Mg^{2+} acts as an anti-inflammatory factor reducing IL-1 and TNF-a secretion.

FOXO1, forkhead box class O1; Grb2, growth factor receptor-bound protein 2; GSK3, glycogen synthase kinase 3; MEK/MAPK, mitogen-activated protein kinase kinase; P, phosphorylation; PIP3, phosphatidylinositol 3,4,5trisphosphate; PI3K, phosphatidylinositol 3-kinase; PKC, protein kinaseC; ROS, reactive oxygen species; Shc, Src homology 2 domain containing transforming protein.

Clinical knowledge of the function of Mg^{2+} in insulin secretion is restricted and less well studied than the impact of Mg^{2+} on insulin sensitivity, although some recent clinical trials indicate that T2DM patients with hypomagnesemia have decreased insulin secretion. In persons without diabetes, reduced serum Mg^{2+} concentrations are correlated with increased insulin secretion.[23]

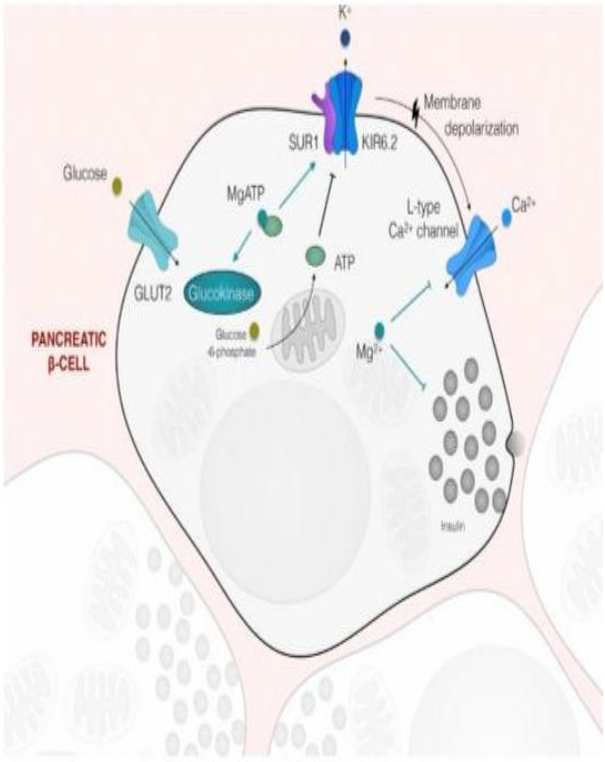

Figure 4: Mg^{2+} regulates insulin secretion in pancreatic b-cells. In pancreatic b-cells, Mg^{2+} directly influences the rate of glucokinase activity by acting as a cofactor for adenine nucleotides. The product of this enzymatic reaction, G6P, is further processed in glycolysis producing ATP. Closure of the KATP channel is dependent on ATP by its binding to the Kir6.2subunits. Conversely, MgATP initiates channel opening by binding to the SUR1 subunits of the channel. Importantly, the physiological consequence of channel closure is the depolarization of the membrane, which triggers the influx of Ca^{2+} via the L-type Ca^{2+} channels. This final step initiates insulin vesicle release, which is negatively controlled by Mg^{2+} acting on both Ca^{2+} influx and the L-type Ca^{2+} channels.

Protein, sericin, is the major constituent of silk (20-30 per cent of the overall weight of cocoon) enveloping the sticky fibroin layers.[24,25] As coconuts are used for silk textiles, they are often extracted from the coconut and disposed of without any application. Sericin has been shown to have antioxidant activity and inhibitory function of tyrosinase.[26] Such signature results of sericin render this protein an essential natural product for the food industry. Owing to its large content of aspartic acid (-19%) as well as serine[27], sericin can have a good attraction to certain elements by chelating the hydroxyl and carboxyl groups to the elements. In recent experiment, they have noticed that sericin is resistant to many. In view of these characteristics, we have presumed that sericin consumption may increase the intestinal absorption of a number of minerals by improving their solubilization in the intestinal tract by undigested sericin. This research was therefore undertaken to investigate the impact of dietary introduction of sericin on the obvious absorption of Zn and Mg in rats.

From their experimental data[28], Sericin intake improved the evident absorption of Zn and Mg in rats, suggesting greater intestinal absorption of the elements in rats through sericin intake. In fact, dietary sericin did not affect the urinary excretion of these components. Such findings indicate that sericin consumption improves the bioavailability of all these components. Casein phosphopeptides (CPPs) have been documented to improve intestinal absorption of Ca, Fe and Zn in rats.[29-31] The results were known to be at least partly regulated by improving the solubilization of the components in the intestinal tract. However, no other proteins (or peptides) have been recorded to have a similar impact. Sericin is, to our understanding, the second protein found to facilitate the absorption of minerals.

Their research showed an improvement in the evident absorption of Zn, Fe, Mg and Ca by sericin intake. While the findings of this experiment presented partial proof indicating an increase in the intestinal absorption of the elements by sericin, a precise trial utilizing radioisotope is required in order to draw a conclusion. Sericin produces large amounts of serine (hydroxyl group) and aspartic acid (carboxyl group) and is resistant to many proteases. As a consequence, undigested sericin can enhance the solubilization of the elements in the intestinal tract through the chelation of their hydroxyl and carboxyl groups, leading to increased availability of the elements.

From this above review, I may say that sericin increases the intestinal absorption of Zn and Mg. Due to this consequences, sericin may increases the insulin secretion and overcomes insulin resistance. So, this may shows that sericin is the evidencable target to treat type 2 DM.

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