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The Role of Zinc in Treating Diabetes Mellitus: A Review

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ABSTRACT

Chronic hyperglycemia status noticed in diabetes mellitus favors the manifestation of oxidative stress by increasing the production of reactive oxygen species and/or by reducing the antioxidant defense system activity, some minerals are essential parts of some of the enzymes for their biological activities. Diabetes mellitus is a disease of metabolic abnormality, minerals as such or as a component of enzymes may play a significant role in developing and controlling diabetes mellitus. Amongst minerals, zinc is involved in the development and control of diabetes mellitus. Zinc has been shown to have an antioxidant potential through the nonenzymatic stabilization of biomembrane and biostructures. A recent finding indicated that there is a direct relationship between low zinc levels, greater body fat content, and insulin resistance.

Keywords: diabetes mellitus, Zinc, hyperglycemia.

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1. Introduction

Diabetes mellitus is a leading cause of morbidity and mortality worldwide, with an estimated 387 million adults being affected in the year 2014, a figure which is expected to increase by nearly 40 % by the year 2035 [1]. Ninety to ninety-five percent of those with the disease have type-2 diabetes. Pathophysiologically, type- 2 diabetes is a multi-organ, multi-factorial condition characterized primarily by insulin resistance, hyperinsulinemia, and β-cell dysfunction, which ultimately leads to β-cell failure [2]. Type-1 diabetes has historically been most prevalent in populations of European origin, and the latest edition of the Diabetes Atlas estimates that 490,100 children below the age of 15 years are living with type-1 diabetes [1]. Diabetes is also associated with a host of potentially disabling macro- and microvascular complications. Hence, there is also a much larger burden in the form of lost productivity as a result of restricted daily activity. The rapidly increasing prevalence of diabetes is attributable to population growth, aging, urbanization, unhealthy dietary habits, increasing prevalence of obesity, and physical inactivity [3]. Minerals are essential components of diets and hence of life. They perform important functions in the various biochemical processes of the body. Some minerals, particularly trace minerals, are active participants in metabolism. Some of the minerals are the essential part of some of the enzymes for their biological activities. As diabetes mellitus is a disease of metabolic abnormality, minerals as such or as a component of enzymes may play a significant role in developing and controlling diabetes mellitus. Zinc is a multi-functional nutrient involved in glucose and lipid metabolism, hormone function, and wound

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healing. Zinc is an essential trace mineral that is necessary for health and growth and for the function and activity of enzymes [4].

1.2. Diabetes Mellitus

Diabetes is a long-term, persistent disease that occurs due to the body's inability to process and regulate blood glucose due to the over-secretion of insulin from the pancreas or the inability of the insulin to regulate the blood glucose levels [5]. Insulin is a polypeptide hormone secreted by the beta cells of the islets of Langerhans of the pancreas, and its functions are the regulation of glucose levels in the blood, the assimilation, and the utilization of glucose [6]. In a diabetic patient, a phenomenon called "insulin resistance" is present. It occurs when the body's cells resist the hormone "insulin", causing a lack of insulin response. Insulin resistance is summed up as a decline in sensitivity to the biochemical actions of insulin as well as insulin-mediated glucose disposal. This leads to a buildup of glucose in the bloodstream, eventually leading to type 2 diabetes [7]. There are a range of reasons diabetes can occur, and how it is managed depends on the type.

1.3. Types of Diabetes Mellitus

There are various types of diabetes but three main types: type 1 diabetes, type 2 diabetes, and gestational diabetes (pregnancy-induced diabetes)

1.3.1. Type 1 diabetes

Type 1 diabetes is a persistent autoimmune disease marked by insulin insufficiency and consequent hyperglycemia [8]. It is caused by autoimmune beta-cell destruction in the pancreas, which leads to total insulin deficiency [9]. Type 1 diabetes affects several people globally and needs cautious supervision to avoid grave complications, which include cardiovascular and renal disease, loss of vision, and stroke. The overall treatment for type 1 diabetes is insulin therapy, which stems from "exogenic insulin substitution therapy." Unfortunately, this method is unable to achieve optimal blood glucose control in many individuals [10].

1.3.2. Type 2 diabetes

It is a common metabolic disorder caused by a combination of two main features: deficient insulin secretion by the β-cells of the pancreas and the inability of tissues to respond properly to insulin [11]. The risk factors for this disorder are high blood glucose levels, obesity, hypertriglyceridemia, unhealthy eating habits, lack of exercise, aging, family history, stress, anxiety, and depression [12]. Insulin therapy in conjunction with metformin and other glucose-lowering agents is required for the treatment and management of type 2 diabetes [13].

1.3.3. Gestational diabetes (pregnancy-induced diabetes)

It is a condition in which a pregnant woman has high or elevated blood sugar. It occurs only during gestation in some women and can affect both mother and child. It is triggered by a range of factors, such as obesity, family history of diabetes, and maternal age. It is associated with type 2 diabetes and ischemic heart disease [14]. Gestational diabetes is usually diagnosed in the second or third trimester of pregnancy in patients with no history of diabetes preceding the period of gestation. It is the most common complication of pregnancy [15]. This disorder can be managed using two strategies: insulin therapy and lifestyle modification, including nutritional therapy [16].

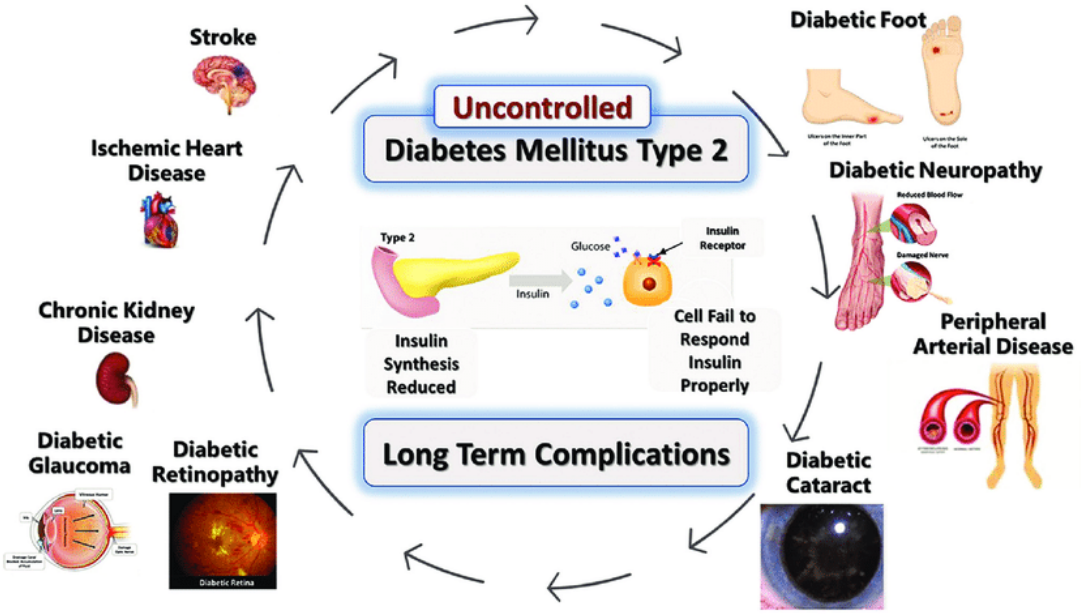

Fig. 1. Pathogenesis of diabetes mellitus and its chronic complications (17).

1.4. Diagnosis of Mellitus Mellitus

Diabetes can be diagnosed using a range of tests listed and discussed below. They are:

1.4.1. Hemoglobin A1C:

The HbA1C test is a diagnostic test used to check a patient's glycemic level (Table 1). The value shown is a two to three-month average of a patient's glycemic level. It is useful and effective in evaluating patients with diabetes or at risk of diabetes complications [18].

1.4.2. Fasting Plasma Glucose:

The fasting plasma glucose (FPG) test calculates blood glucose levels simultaneously. For accuracy, the test is administered in the morning after a fasting period of about 8 hours. A value larger than 126 mg/dL infers diabetes [19].

1.4.3. Random Plasma Glucose:

The blood sample is taken and analyzed after food has been ingested. Diabetes is suspected when the value is greater than 200 mg/dL [18].

1.4.4. Oral Glucose Tolerance Test:

It is a medical test conducted when glucose is administered, and the blood sample is analyzed to measure how fast glucose has been cleared out. It is used to screen for type 2 diabetes mellitus [20].

1.4.5. C-Peptide:

The beta cell function of the pancreas is measured. The measurement and analysis of urine and serum samples are carried out and the value helps diagnose and treat diabetes [18].

1.4.6. Autoantibody:

The presence of autoantibodies, such as insulin autoantibody and islet autoantibody anti-glutamic acid decarboxylase (GAD) autoantibodies suggests auto-immune response also noticed in type 1 diabetes. The presence of autoantibodies for diabetes in the blood confirms type 1 diabetes [18].

1.5. Treatments of Diabetes

Although lifestyle modifications can help enhance glycemic control, medications will be required in the long run to effectively manage the disease.

1.5.1. Treatment of type 1 diabetes mellitus

The basis of the treatment for type 1 diabetes is insulin therapy [22].

1.5.2. Treatment of type 2 diabetes mellitus

The various drugs administered to treat type 2 diabetes mellitus patients have different mechanisms to reverse the effects of hyperglycemia by reducing blood sugar levels [21].

1.5.2.1. Sulfonylureas

Sulfonylureas are insulin secretagogues that have been used extensively in the treatment of patients with diabetes. They are mostly metabolized in the liver and sometimes excreted by the kidneys [21]. Irrespective of blood glucose levels, sulfonylureas trigger insulin secretion from the pancreas [23]. Also, sulfonylureas inhibit glucagon secretion, enhance insulin sensitivity in peripheral tissues, and reduce hepatic insulin clearance [21].

1.5.2.2. Meglitinides

Meglitinides are drugs that increase insulin secretion from the pancreas, and they are dependent on glucose levels, which reduces the risk of hypoglycemia. It has a short duration of action and can be administered to match the postprandial increase in glucose [21].

1.5.2.3. Metformin (Glucophage)

Glucophage improves hepatic insulin sensitivity and reduces hepatic glucose production. It also reduces insulin resistance in the peripheral tissues by reducing free fatty acids, triglycerides, and high blood glucose levels [21]. It carries out its antihyperglycemic action without influencing insulin secretion [24]. Also, it elevates gut glucose utilization and triggers GLP-1 secretion. Metformin is commonly administered as the first pharmacological agent in the treatment of diabetes because of its affordable price, efficiency, and few side effects [21].

1.5.2.4. Sodium-glucose transport protein 2 (SGLT2) inhibitors

They are a class of oral antidiabetic agents administered to lower blood glucose levels in adult patients with type 2 diabetes mellitus. Its action is not affected by insulin resistance or the insulin levels in the body [21].

1.5.2.5. Glucagon-like peptide-1 (GLP-1)

GLP-1 is produced and stored in the L cells of the ileum and colon. Neural and hormonal mechanisms coupled with the presence of food in the gastrointestinal tract trigger its release. GLP-1 enhances insulin secretion by the beta cells and inhibits glucagon secretion by the alpha cells when blood glucose levels are elevated above normal [21].

1.5.2.6. Pramlintide (symlin)

Pramlintide is a synthetic derivative of amylin. It is soluble in nature and administered orally. In response to nutrient stimuli, the pancreas secures Amylin with insulin. It reduces postprandial stimulated glucagon secretion, slows down gastric emptying, and suppresses appetite [21].

1.5.2.7. Bromocriptine-QR

Bromocriptine reduces insulin sensitivity and resistance, leading to a decrease in hepatic glucose production and an increase in glucose disposal. It does not elevate insulin levels, making it effective in patients who produce insulin but are insulin-resistant. Bromocriptine-QR improves glycemic levels in patients with type 2 diabetes mellitus when administered as a monotherapy drug or combined with other antihyperglycemic agents [21].

1.5.2.8. Thiazolidinediones (TZDS)

TZDS reduce insulin resistance while simultaneously activating the insulin response. TZDs improve glycemic control and act to reverse certain disease complications like polycystic ovarian syndrome, atherosclerosis, and other cardiovascular diseases in patients with type 2 diabetes mellitus. However, side effects like weight gain and osteoporosis can be very serious, causing its use to be limited [21].

Fig. 2. The current therapeutic options of diabetes mellitus (25).

1.6. Diabetes Mellitus and Oxidative Stress

Oxidative stress is a condition caused by the overproduction of reactive species, known as pro-oxidants, and the incapability of the antioxidant defense system to scavenge these species (26). Highly reactive species are normally generated as a by-product of aerobic metabolism in the body (27). These reactive species at a certain amount are often necessary to maintain normal metabolic processes (28). However, the excess radical species produced is likely to bring deleterious effects to the human body (29); thus they need to be sufficiently removed by the body's antioxidant defense system to maintain the homeostasis of the body system (30). In diabetes, chronic hyperglycemia induces excessive formation of these reactive species that might diminish antioxidant activity, leading to the domination of oxidative stress (26,31). Oxidative stress then further propagates the production of more reactive species, subsequently causing the development of pathological conditions in DM and its secondary complications (32).

1.7. Antioxidant defense system and antioxidants

Antioxidant defense system plays a pivotal role in scavenging excess radical species and neutralize the toxicity arising from the elevated amount of reactive species. The system is generally divided into endogenous and exogenous antioxidants (33). Enzymatic endogenous antioxidants include superoxide dismutase, catalase, and glutathione (oxidized/reduced) while exogenous antioxidants can be acquired from diet and supplements.

1.8. Sources of Zinc

Zinc is the second most abundant micronutrient found in nature after iron [34-37]. The dietary sources of zinc include both animal- and plant-based foods. Meat, seafood, whole grains, and oil seeds are the primary dietary sources of zinc [38]. The recommended dietary allowance (RDA) for zinc is 11 mg/day for adult males and 8 mg/day for adult females [39]. These amounts are considered adequate to support the activity of zinc-dependent metalloenzymes and maintain overall health. However, meeting the daily dietary need for zinc solely through food sources would require the consumption of excessive amounts of protein,

dietary fiber, and fat, leading to a surplus of caloric intake and increased bowel movements due to the high fiber and fat content [38]. The pharmacological dosage of zinc is considered to be more than 40 mg/day for individuals 19 years of age and older [39]. The chelated zinc doses used in various studies typically fall between 220 mg/day and 660 mg/day [40,41]. The forms of zinc commonly used for oral administration include zinc sulfate, zinc gluconate, zinc picolinate, and zinc citrate, as these forms are generally better absorbed than zinc oxide [42].

1.9. Zinc and Glucose Metabolism

Zinc plays a crucial role in the crystallization and signaling of insulin. Specifically, zinc promotes the activation of the PI3K/Akt pathway, which is essential for glucose metabolism [43]. As a cofactor, zinc has a critical function in the action of antioxidants and the metabolism of carbohydrates [44,45]. This micronutrient also aids in the phosphorylation of the β-subunit of the insulin receptor and the translocation of glucose transporter 4 (GLUT4) [46,47]. Importantly, insulin forms a hexameric structure by coupling with two zinc ions, a process necessary for the maturation of insulin within the secretory granules of pancreatic β-cells and the subsequent release of insulin [48, 49]

Pancreatic β-cells express specific zinc carrier proteins that play crucial roles in insulin secretion **[50-52]**. One such key protein is ZnT8, which is essential for the crystallization, processing, storage, and secretion of insulin, as well as the overall metabolism of glucose **[53]**. The ZnT8 transporter is responsible for shuttling zinc into the secretory granules of pancreatic β-cells, thereby facilitating the formation of the zinc-insulin hexamer, a critical step in insulin maturation and release **[53-56]**. Zinc deficiency leads to a reduction in the expression of ZnT8, ultimately impairing insulin secretion. In addition to ZnT8, other zinc transporter proteins, such as ZnT6 and ZnT5, are involved in the transport of zinc into the vesicles of pancreatic β-cells, where micronutrients participate in the metabolism of proinsulin and the subsequent secretion of mature insulin **[48,53,57]**. Furthermore, the zinc transporter protein ZnT7 is responsible for transporting zinc to the Golgi apparatus of pancreatic β-cells, an essential process for the proper formation of insulin **[57,58]**. In addition to its role in glucose transport, zinc enhances glucose storage. Zinc stimulates the phosphorylation of glycogen synthase kinase 3 (GSK3) and the transcription factor forkhead box protein O1 (FoxO1). Phosphorylation of GSK3 promotes the activation of glycogen synthase, whereas phosphorylation of FoxO1 prevents it from stimulating the expression of gluconeogenic genes. Collectively, these actions of zinc help promote glycogen storage and inhibit glucose production **[47,59]**.

Zinc promotes the uptake of glucose by cells, induces the expression of glucose transporter genes (GLUT1 and GLUT4), and regulates gluconeogenic enzymes such as glucose-6-phosphatase (G6Pase) and phosphoenolpyruvate carboxykinase (PEPCK), thereby improving glucose metabolism **[60]**. Consequently, zinc deficiency can lead to disturbances in glucose metabolism, potentially contributing to the development of diabetes mellitus.

1.10. Antioxidant role of zinc

It is appropriate to draw attention to the antioxidant role of zinc. This mineral acts as a cofactor for the superoxide dismutase enzyme, regulates the glutathione metabolism and the metallothionein expression, competes with iron and copper in the cell membrane, and also inhibits the nicotinamide adenine dinucleotide phosphate-oxidase (NADPH-oxidase) enzyme [62,63].

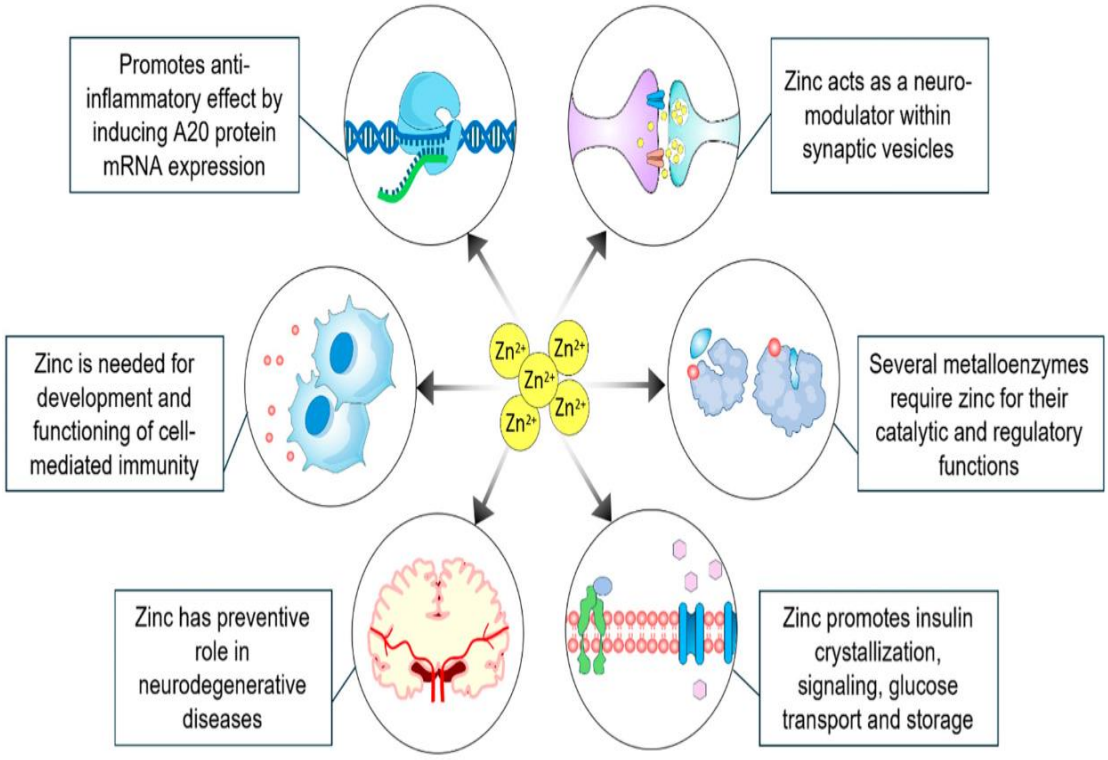

Fig. 3. Zinc is an essential micronutrient that plays a critical role in human health by exerting positive effects on immune system function, maintaining cellular homeostasis, and delaying neurodegenerative and infectious diseases to maintain overall health and well-being (61).

Another important point is the action of a group of antioxidants enzymes called superoxide dismutase, which regulates the detoxification of reactive oxygen species and catalyzes the dismutation of superoxide anion into hydrogen peroxide and oxygen [64,65]. Mammals have three isoforms of this enzyme, but only isoforms 1 (CuZnSOD) and 3 (SOD extracellular) need zinc as a cofactor for its enzymatic activity and to act predominantly and respectively in the intracellular space and extracellular fluids [62, 66, 67].

A study by Zhu *et al* [64] with diabetic mice shows that the zinc supplementation increased the activity of superoxide dismutase and reduced malondialdehyde concentrations in both serum and pancreas. According to the authors, low levels of zinc in the organism impair the action of the antioxidant defense system. Corroborating previous findings, Li *et al* [69] verified that zinc supplementation increased the activity of superoxide dismutase and decreased lipid peroxidation in the liver of diabetic rats, emphasizing that zinc can protect the liver from oxidative damage.

Action of zinc on glutathione metabolism is significant and as such must be mentioned. Zinc indeed influences the expression of glutamate-cysteine ligase enzyme involved in the synthesis of glutathione, which directly acts on the neutralization of free radicals and indirectly as a cofactor of glutathione peroxidase [62,68].

Another mechanism that explains the antioxidant role of zinc in type 2 diabetes mellitus, refers to its ability to compete with iron and copper for binding sites on the cell membrane. The iron and copper ions can catalyze the production of lipid peroxides, and the replacement of these metals for zinc in the plasma membrane could prevent lipid peroxidation in diabetic patients [68].

1.11. Zinc and Inflammation

Zinc is a crucial micronutrient that plays a vital role in the proper function of the immune system and the maintenance of overall health. It is essential for the proliferation and differentiation of immune cells [70] and potentially reduces viral infections [71,72]. Zinc has been found to bind nearly three thousand different proteins in the human body [73]. Many metalloenzymes require zinc for their regulatory and catalytic functions [73,74]. Zinc also serves as an important signaling molecule within the immune system and acts as a neuromodulator in synaptic vesicles. Several studies have indicated that zinc deficiency may contribute to the development of chronic and metabolic diseases, such as diabetes, neurodegenerative disorders, cancer, and intestinal diseases [86,75–80]. Adequate levels of zinc are essential for maintaining oral health [81] and for various hormonal functions [82]. Furthermore, zinc plays a role in lipid metabolism during obesity, often associated with type 2 diabetes. Studies have shown that zinc status can influence lipid profiles, the functionality of adipose tissue, adipokine production, and insulin sensitivity [83,84]. Earlier studies reported that zinc can exert insulin-like effects on adipocytes, influencing adipogenesis and glucose metabolism, and that zinc may play a role in enhancing insulin sensitivity in adipose tissues [85].

1.12. Conclusion

Human and animal studies demonstrated the effective role of zinc in the management of diabetes mellitus. Zinc plays a vital role in the proper functioning of β-cells in the pancreas, the insulin action, and the homeostasis of glucose. Conversely, zinc deficiency can dysregulate glucose metabolism through improper β-cell function, as well as the induction of oxidative stress and inflammation. Previous studies have shown the positive impact of zinc administration on glycemic control in patients with diabetes mellitus. Efforts should be made to raise awareness among healthcare professionals regarding the benefits of a diet rich in micronutrients and adequate macronutrient intake. Promoting the consumption of a high-quality, micronutrient-dense diet may help reduce the development of inflammatory complications among individuals with diabetes.

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REFERENCES

1) IDF Diabetes Atlas - The Economic Impacts of Diabetes. [http:// www.diabetesatlas.com/content/economic-impacts-diabetes]
2) Stumvoll M, Goldstein BJ, van Haeften TW. Type 2 diabetes: principles of pathogenesis and therapy. Lancet. 2005;365(9467):1333–46.
3) Stuckler D. Population Causes and Consequences of Leading Chronic Diseases: A Comparative Analysis of Prevailing Explanations. The Milbank Quarterly. 2008;86(2):273–326.
4) Khan A, and Safdar M. Role of Diet, Nutrients, Spices and Natural Products in Diabetes Mellitus; Pakistan Journal of Nutrition 2003, 2 (1): 1-12
5) Centers for Disease Control and Prevention. National Diabetes Statistics Report. November 11, 2022. https://www.cdc.gov/diabetes/pdfs/data/statistics/nat ional diabetes-statistics-report.pdf.
6) Yameny, A. Diabetes Mellitus Overview 2024. *Journal of Bioscience and Applied Research*, 2024; 10(3): 641-645. doi: 10.21608/jbaar.2024.382794
7) Hill MA, Yang Y, Zhang L, Sun Z, Jia G, Parrish AR, et al. Insulin resistance, cardiovascular

stiffening and cardiovascular disease. Metabolism 2021;119(0026-0495):154766. https://doi.org/10.1016/j.metabol.2021.154766.

8) DiMeglio LA, Evans-Molina C, Oram RA. Type 1 diabetes. Lancet 2018;391(10138):2449–62.
9) American Diabetes Association. Standards of medical care in diabetes—2022 abridged for primary care providers. Clin Diabetes 2021;40(1). https://doi.org/10.2337/cd22-as01.
10) Akil AAS, Yassin E, Al-Maraghi A, Aliyev E, Al-Malki K, Fakhro KA. Diagnosis and treatment of type 1 diabetes at the dawn of the personalized medicine era. J. Transl. Med. 2021;19:137. https://doi.org/10.1186/s12967-021-02778-6.
11) Galicia-Garcia U, Benito-Vicente A, Jebari S, Larrea-Sebal A, Siddiqi H, Uribe KB, et al. Pathophysiology of type 2 diabetes mellitus. Int. J. Mol. Sci. 2020;21(17):6275. https://doi.org/10.3390/ijms21176275.
12) Kyrou I, Tsigos C, Mavrogianni C, Cardon G, Van Stappen V, Latomme J, et al. Sociodemographic and lifestyle-related risk factors for identifying vulnerable groups for type 2 diabetes: a narrative review with emphasis on data from Europe. BMC Endocr. Disord. 2020;20(S1):134. https://doi.org/10.1186/s12902-019- 0463-3.
13) Bailey CJ, Day C. Treatment of type 2 diabetes: future approaches. Br. Med. Bull. 2019;126(1):123–37. https://doi.org/10.1093/brimed/ldy013.
14) Li G, Wei T, Ni W, Zhang A, Zhang J, Xing Y, et al. Incidence and risk factors of gestational diabetes mellitus: a prospective cohort study in Qingdao, China. Front. Endocrinol. 2020;11:636. https://doi.org/10.3389/fendo.2020.00636.
15) Simjak P, Cinkajzlova A, Anderlov a K, Parízek A, Mr az M, Krsek M, et al. The role of obesity and adipose tissue dysfunction in gestational diabetes mellitus. J. Endocrinol. 2018;238(2):R63–77. https://doi.org/10.1530/JOE-18-0032.
16) Oskovi-Kaplan ZA, Ozgu-Erdinc AS. Management of gestational diabetes mellitus. Adv. Exp. Med. Biol. 2021;1307:257–72. https://doi.org/10.1007/5584_2020_552.
17) Akter, F., & Haque, M. (2021). Smash of diabetes mellitus on smile. Advances in Human Biology, 11(3), 273-280.
18) Nakrani MN, Wineland RH, Anjum F. Physiology, glucose metabolism. In: StatPearls [Internet]. Treasure Island (FL). StatPearls Publishing; 2023. https://www.ncbi .nlm.nih.gov/books/NBK560599/.
19) NIDDK. Diabetes Tests & Diagnosis. National institute of diabetes and digestive and kidney diseases; 2019. https://www.niddk.nih.gov/health information/diabetes/overview/tests-diagnosis.
20) Ojo, O. A., Ibrahim, H. S., Rotimi, D. E., Ogunlakin, A. D., & Ojo, A. B. (2023). Diabetes mellitus: From molecular mechanism to pathophysiology and pharmacology. Medicine in Novel Technology and Devices, 19, 100247.
21) Feingold KR. Oral and injectable (non-insulin) pharmacological agents for the treatment of type 2 diabetes. In: Feingold KR, Anawalt B, Blackman MR, Boyce A, Chrousos G, Corpas E, et al., editors. Endotext [Internet]. South Dartmouth (MA): MDText.com, Inc; 2022.
22) Otto-Buczkowska E, Jainta N. Pharmacological treatment in diabetes mellitus type 1-insulin and what else? Int. J. Endocrinol. Metabol. 2017;16(1):e13008. https:// doi.org/10.5812/ijem.13008. 2017.
23) Costello RA, Nicolas S, Shivkumar A. Sulfonylureas. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2023. https://www.ncbi.nlm.nih .gov/books/NBK513225/.
24) Kalra S, Bahendeka S, Sahay R, Ghosh S Md F, Orabi A, Ramaiya K, et al. Consensus recommendations on sulfonylurea and

sulfonylurea combinations in the management of type 2 diabetes mellitus – international task force. Indian J. Endocrinol. Metab. 2018;22(1):132–57. https://doi.org/10.4103/ijem.IJEM_556_ 17.

25) Ruan, S., Guo, X., Ren, Y., Cao, G., Xing, H., & Zhang, X. (2023). Nanomedicines based on trace elements for intervention of diabetes mellitus. Biomedicine & Pharmacotherapy, 168, 115684.
26) Halliwell B, Gutteridge J. Free radicals in biology and medicine. Biosciences, Oxford, 2007.
27) Miwa S, Brand M. Mitochondrial matrix reactive oxygen species production is very sensitive to mild uncoupling. Portland Press Limited, 2003.
28) Gomes EC, Silva AN, Oliveira MRD. Oxidants, antioxidants, and the beneficial roles of exercise-induced production of reactive species. Oxid Med Cell Longev 2012; 756132.
29) Zwart dLL, Meerman JH, Commandeur JN, Vermeulen NP. Biomarkers of free radical damage: applications in experimental animals and in humans. Free Radic Biol Med 1999; 26(Suppl 1-2):202-26.
30) Valko M, Leibfritz D, Moncol J, Cronin MT, Mazur M, Telser J. Free radicals and antioxidants in normal physiological functions and human disease. Int J Biochem Cell Biol 2007; 39(1):44-84.
31) Pandey KB, Mishra N, Rizvi SI. Protein oxidation biomarkers in plasma of type 2 diabetic patients. Clin Biochem 2010; 43(4):508-11.
32) Moussa S. Oxidative stress in diabetes mellitus. Rom J Biophy 2008; 18(3):225-36.
33) Pham-Huy LA, He H, Pham-Huy C. Free radicals, antioxidants in disease and health. Int J Biomed Sci 2008; 4(2):89-96.
34) Maret, W. Zinc in pancreatic islet biology, insulin sensitivity, and diabetes. Prev. Nutr. Food Sci. 2017, 22, 1–8.
35) Blakemore, L.J.; Trombley, P.Q. Zinc as a neuromodulator in the central nervous system with a focus on the olfactory bulb. Front. Cell. Neurosci. 2017, 11, 297.
36) Lim, K.H.C.; Riddell, L.J.; Nowson, C.A.; Booth, A.O.; Szymlek-Gay, E.A. Iron and zinc nutrition in the economically-developed world: A review. Nutrients 2013, 5, 3184–3211.
37) Saper, R.B.; Rash, R. Zinc: An essential micronutrient. Am. Fam. Physician 2009, 79, 768–772.
38) Santos, H.O.; Teixeira, F.J.; Schoenfeld, B.J. Dietary vs. pharmacological doses of zinc: A clinical review. Clin. Nutr. 2020, 39, 1345–1353.
39) DRI Dietary Reference Intakes. Applications in Dietary Assessment: Washington, DC, USA, 2000.
40) Wang, L.J.; Wang, M.Q.; Hu, R.; Yang, Y.; Huang, Y.S.; Xian, S.X.; Lu, L. Effect of zinc supplementation on maintenance Hemodialysis Patients: A systematic review and meta-analysis of 15 randomized controlled trials. BioMed Res. Int. 2017,2017, 1024769.
41) Ranasinghe, P.; Wathurapatha, W.; Ishara, M.; Jayawardana, R.; Galappatthy, P.; Katulanda, P.; Constantine, G. Effects of Zinc supplementation on serum lipids: A systematic review and meta-analysis. Nutr. Metab. 2015, 12, 1–16.
42) Wegmüller, R.; Tay, F.; Zeder, C.; Brni´c, M.; Hurrell, R.F. Zinc absorption by young adults from supplemental zinc citrate is comparable with that from zinc gluconate and higher than from zinc oxide. J. Nutr. 2014, 144, 132–136.
43) Ferdowsi, P.V.; Ahuja, K.D.K.; Beckett, J.M.; Myers, S. Capsaicin and Zinc signalling pathways as promising targets for managing insulin resistance and type 2 diabetes. Molecules 2023, 28, 2861.
44) Olechnowicz, J.; Tinkov, A.; Skalny, A.; Suliburska, J. Zinc status is associated with inflammation, oxidative stress, lipid, and

glucose metabolism. J. Physiol. Sci. 2018, 68, 19–31.

45) Ranasinghe, P.; Pigera, S.; Galappatthy, P.; Katulanda, P.; Constantine, G.R. Zinc and diabetes mellitus: Understanding molecular mechanisms and clinical implications. DARU J. Pharm. Sci. 2015, 23, 1–13.

46) Kelishadi, R.; Hashemipour, M.; Adeli, K.; Tavakoli, N.; Movahedian-Attar, A.; Shapouri, J.; Poursafa, P.; Rouzbahani, A. Effect of zinc supplementation on markers of insulin resistance, oxidative stress, and inflammation among prepubescent children with metabolic syndrome. Metab. Syndr. Relat. Disord. 2010, 8, 505–510.

47) Vardatsikos, G.; Pandey, N.R.; Srivastava, A.K. Insulino-mimetic and anti-diabetic effects of zinc. J. Inorg. Biochem. 2013, 120, 8–17.

48) Chimienti, F. Zinc, pancreatic islet cell function and diabetes: New insights into an old story. Nutr. Res. Rev. 2013, 26, 1–11.

49) Li, Y.V. Zinc and insulin in pancreatic beta-cells. Endocrine 2013, 45, 178–189.

50) Myers, S.A. Zinc transporters and zinc signaling: New insights into their role in type 2 diabetes. Int. J. Endocrinol. 2015, 1–7.

51) Kambe, T.; Hashimoto, A.; Fujimoto, S. Current understanding of ZIP and ZnT zinc transporters in human health and diseases. Cell. Mol. Life Sci. 2014, 71, 3281–3295.

52) Cai, Y.; Kirschke, C.P.; Huang, L. SLC30A family expression in the pancreatic islets of humans and mice: Cellular localization in the beta-cells. J. Mol. Histol. 2018, 49, 133–145.

53) Wijesekara, N.; Dai, F.F.; Hardy, A.B.; Giglou, P.R.; Bhattacharjee, A.; Koshkin, V.; Chimienti, F.; Gaisano, H.Y.; Rutter, G.A.; Wheeler, M.B. Beta cell-specific Znt8 deletion in mice causes marked defects in insulin processing, crystallisation and secretion. Diabetologia 2010, 53, 1656–1668.

54) Davidson, H.W.; Wenzlau, J.M.; O'Brien, R.M. Zinc transporter 8 (ZnT8) and beta cell function. Trends Endocrinol Metab. 2014, 25, 415–424.

55) Foster, M.; Chu, A.; Petocz, P.; Samman, S. Zinc transporter gene expression and glycemic control in post-menopausal women with type 2 diabetes mellitus. J. Trace Elements Med. Biol. 2014, 28, 448–452.

56) Lefebvre, B.; Vandewalle, B.; Balavoine, A.-S.; Queniat, G.; Moerman, E.; Vantyghem, M.-C.; Le Bacquer, O.; Gmyr, V.; Pawlowski, V.; Kerr-Conte, J.; et al. Regulation and functional effects of ZNT8 in human pancreatic islets. J. Endocrinol. 2012, 214, 225–232.

57) Cruz, K.J.C.; de Oliveira, A.R.S.; Morais, J.B.S.; Severo, J.S.; Mendes, P.M.V.; Melo, S.R.d.S.; de Sousa, G.S.; Marreiro, D.D.N. Zinc and insulin resistance: Biochemical and molecular aspects. Biol. Trace Elem. Res. 2018, 186, 407–412.

58) Huang, L.; Yan, M.; Kirschke, C.P. Over-expression of ZnT7 increases insulin synthesis and secretion in pancreatic beta-cells by promoting insulin gene transcription. Exp. Cell Res. 2010, 316, 2630–2643.

59) Walter, P.L.; Kampkötter, A.; Eckers, A.; Barthel, A.; Schmoll, D.; Sies, H.; Klotz, L.-O. Modulation of FoxO signaling in human hepatoma cells by exposure to copper or zinc ions. Arch. Biochem. Biophys. 2006, 454, 107–113.

60) Tamura, Y. The role of zinc homeostasis in the prevention of diabetes mellitus and cardiovascular diseases. J. Atheroscler. Thromb. 2021, 28, 1109–1122.

61) Ahmad, R.; Shaju, R.; Atfi, A.; Razzaque, M.S. Zinc and Diabetes: A Connection between Micronutrient and Metabolism. Cells 2024, 13, 1359. https://doi.org/10.3390/cells13161359

62) Foster M, Samman S. Zinc and redox signaling: perturbations associated with cardiovascular disease and diabetes mellitus. Antioxid Redox

Signal 2010; 13: 1549-1573 [PMID: 20568953 DOI: 10.1089/ars.2010.3111]

63) Ruz M, Carrasco F, Rojas P, Codoceo J, Inostroza J, Basfi-fer K, Valencia A, Vásquez K, Galgani J, Pérez A, López G, Arredondo M, Perez-Bravo F. Zinc as a potential coadjuvant in therapy for type 2 diabetes. Food Nutr Bull 2013; 34: 215-221 [PMID: 23964394]

64) Zhu K, Nie S, Li C, Huang J, Hu X, Li W, Gong D, Xie M. Antidiabetic and pancreas-protective effects of zinc threoninate chelate in diabetic rats may be associated with its antioxidative stress ability. Biol Trace Elem Res 2013; 153: 291-298 [PMID: 23625696]

65) Arif M, Islam MR, Waise TM, Hassan F, Mondal SI, Kabir Y. DNA damage and plasma antioxidant indices in Bangladeshi type 2 diabetic patients. Diabetes Metab 2010; 36: 51-57 [PMID: 20036596 DOI: 10.1016/j.diabet.2009.05.007]

66) Di Naso FC, Simões Dias A, Porawski M, Marroni NA. Exogenous superoxide dismutase: action on liver oxidative stress in animals with streptozotocin-induced diabetes. Exp Diabetes Res 2011; 2011: 754132 [PMID: 21437212 DOI: 10.1155/2011/754132]

67) Kurinenko BM, Kashkin AP, Kalacheva NV, Meringova LV, Nekhoroshkova ZM. [Structural and antigenic differences of pancreatic RNAse preparations modified by dextran ethers in an azo-combination reaction]. Biokhimiia 1985; 50: 581-588 [PMID:2408680 DOI:10.5999/aps.2013.40.5.517]

68) Oteiza PI. Zinc and the modulation of redox homeostasis. Free Radic Biol Med 2012; 53: 1748-1759 [PMID: 22960578 DOI: 10.1016/j.freeradbiomed.2012.08.568]

69) Li Y, Jaddoe VW, Qi L, He Y, Wang D, Lai J, Zhang J, Fu P, Yang X, Hu FB. Exposure to the chinese famine in early life and the risk of metabolic syndrome in adulthood. Diabetes Care 2011; 34: 1014-1018 [PMID: 21310886 DOI: 10.2337/dc10-2039]

70) Maret, W. Zinc in cellular regulation: The nature and significance of “zinc signals”. Int. J. Mol. Sci. 2017, 18, 2285.

71) Razzaque, M.S. COVID-19 pandemic: Can zinc supplementation provide an additional shield against the infection? Comput. Struct. Biotechnol. J. 2021, 19, 1371–1378.

72) Razzaque, M.S. COVID-19 Pandemic: Can maintaining optimal zinc balance enhance host resistance? Tohoku J. Exp. Med. 2020, 251, 175–181.

73) Andreini, C.; Banci, L.; Bertini, I.; Rosato, A. counting the zinc-proteins encoded in the human genome. J. Proteome Res. 2006, 5, 196–201.

74) King, J.C. Zinc: An essential but elusive nutrient. Am. J. Clin. Nutr. 2011, 94, 679S–684S.

75) Jones, S.; Farr, G.; Nimmanon, T.; Ziliotto, S.; Gee, J.M.W.; Taylor, K.M. The importance of targeting signalling mechanisms of the SLC39A family of zinc transporters to inhibit endocrine resistant breast cancer. Explor. Target. Antitumor 2022, 3, 224–239.

76) Maywald, M.; Rink, L. Zinc in human health and infectious diseases. Biomolecules 2022, 12, 1748.

77) Bitirim, C.V. The role of zinc transporter proteins as predictive and prognostic biomarkers of hepatocellular cancer. PeerJ 2021, 9, e12314.

78) Fong, L.Y.; Farber, J.L.; Croce, C.M. Zinc intake, microRNA dysregulation, and esophageal cancer. Aging 2016, 8, 1161–1162.

79) MacKenzie, S.; Bergdahl, A. Zinc homeostasis in diabetes mellitus and vascular complications. Biomedicines 2022, 10, 139.

80) Wessels, I.; Maywald, M.; Rink, L. Zinc as a gatekeeper of immune function. Nutrients 2017, 9, 1286.

81) Uwitonze, A.M.; Ojeh, N.; Murererehe, J.; Atfi, A.; Razzaque, M.S. Zinc adequacy is essential for the maintenance of optimal oral health. Nutrients 2020, 12, 949.

82) Amos, A.; Razzaque, M.S. Zinc and its role in vitamin D function. Curr. Res. Physiol. 2022, 5, 203–207.
83) Olechnowicz, J.; Tinkov, A.; Skalny, A.; Suliburska, J. Zinc status is associated with inflammation, oxidative stress, lipid, and glucose metabolism. J. Physiol. Sci. 2018, 68, 19–31.
84) Fukunaka, A.; Fujitani, Y. Role of Zinc homeostasis in the pathogenesis of diabetes and obesity. Int. J. Mol. Sci. 2018, 19, 476.
85) Coulston, L.; Dandona, P. Insulin-like effect of zinc on adipocytes. Diabetes 1998, 29, 665–667.
86) Maret, W. Zinc in pancreatic islet biology, insulin sensitivity, and diabetes. Prev. Nutr. Food Sci. 2017, 22, 1–8.