REVIEW ARTICLE

Unraveling the Complex Role of Zinc, Boron, Chromium, and Selenium in the Pathogenesis of Diabetes Mellitus: A Review

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ABSTRACT

Trace elements are micronutrient components that are only required in small amounts but are critical for the biological functions of many human body tissues. Studies in multiple settings found significant connections between diabetes mellitus (DM) and trace elements caused by disturbances of overlapping cellular metabolic systems. Zinc (Zn), boron (Br), chromium (Cr), and selenium (Se) at either extremely high or low levels could elicit some alteration in cellular metabolism. These lead to the development of DM. The changes include 1) the disturbance in the efficient release of insulin secretory granules, 2) the production of proinflammatory cytokines and oxidative stress state, 3) the failure of the insulin-signaling pathway, and 4) the reduction of glucose tissue uptake secondary to the downregulation of glucose-transporters. Both significantly high and low concentrations have been linked to the development of insulin resistance. Nevertheless, conflicting evidence makes their optimum nutritional levels difficult to establish. The purpose of this review is to emphasize the metabolic role of the 4 trace elements and their influence on the pathogenesis of DM when body levels are below optimal. Understanding the roles of these elements could pave the way for therapeutic possibilities and breakthroughs in personalized DM management.

Keywords
Trace element, Diabetes mellitus, Insulin resistance

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INTRODUCTION

Trace elements are inorganic compounds involved in numerous tissue-specific biological activities.[1] Trace elements have multifaceted functions in biochemistry and physiology. They serve as cofactors or components in biological macromolecules. Additionally, they may form integral parts of vitamins and hormones. These elements play a crucial role in regulating various essential functions in the body, such as growth, development, tissue repair, and metabolic processes.[2] They can be classified into nutritionally important, merely essential, and non-essential. Like vitamins and other micronutrients, our diet also consists of trace elements, which are only required in minute amounts.[3] The prevalence of diabetes mellitus (DM) and the development of its complications are on the rise despite the established screening methods and the advancement in pharmacological therapy.[4,5] The altered cellular metabolism of glucose and insulin dysfunction has been identified as the key component in the pathogenesis of DM.[5,6] Evidence in the literature found associations between DM and trace elements. For example, the action of insulin is potentiated by zinc (Zn), boron (Br), selenium (Se), iodine (I), and manganese (Mn).[1]

A reduction in the concentration of trace elements was implicated in the poorer glycaemic control. However, their sufficient plasma concentrations are yet to be established because their measurement methods for routine clinical testing are complex, laborious, and impractical.[7,8] In research, they are often measured by flame atomic absorption spectroscopy (FAAS), inductively coupled plasma atomic emission spectrometry (ICP-AES), colorimetric assays, inductively coupled plasma mass spectrometry (ICP-MS) and electrothermal atomic absorption spectroscopy (ETAAS).[8,9] Supplementation of trace elements in specific populations helps to improve glycaemic control and the development of its end-organ

complications, according to the current studies.[10–12] Nowadays, some of them are available in the form of over-the-counter tablets. However, due to the unavailability of an established optimum dose, consumption from dietary sources is still the practice.

Zn, Br, Cr, and Se are among the trace elements that deficiency has been proven to be associated with insulin resistance development worldwide.[1] Additionally, the therapeutic and diabetic preventive effects of these trace elements have been demonstrated in various studies.[2] A tightly regulated Zn homeostasis is crucial in the various cellular pathways involved in insulin signaling, storage, and secretion. The potential novelty of Zn-transporter as a therapeutic target in diabetes mellitus has gained countless interests.[6] Br containing compounds such as sodium pentaborate (NaB) and boric acid protect pancreatic β-cells from oxidative damage and improve the cells' viability.[13,14] As of now it is said to be a promising target for type 1 diabetes mellitus[13] Cr supplementation has been associated with great reduction in oxidative stress indices and elevation of antioxidant levels.[15] This has been substantiated in both animal and human studies, however, the exact mechanism and optimum dosage for supplementation through clinical trials are still lacking.[14, 15, 16] There is increasing evidence to suggest that Se in the form of selenoprotein could benefit in the management of diabetes mellitus.[17] However, obtaining an optimal dosage of Se supplementation is challenging as both its deficiency and excess could contribute to the development of diabetes mellitus.[17, 18]

In this review, we highlight the biological role of these 4 trace elements, namely, Zn, Br, Cr, and Se in the development of DM together with their therapeutic potentials.

The role of trace elements in association with diabetes mellitus

Zinc (Zn)

Zn is an essential dietary element obtained from various natural resources: meat, seafood, oilseeds, whole chicken eggs, cheese, cow's milk, yogurt, and grains like oats and rice. [8] Both dietary and pharmacological Zn therapy have been established as excellent antioxidant and anti-inflammatory agents that could improve and prevent the progression of certain conditions like hypogonadism and impede vulnerability towards viral infection.[19,20] Human duodenal and jejunal enterocytes mediate 33% of dietary Zn absorption. The majority of Zn is stored in the skeletal muscle (60%), bones (30%), liver, and skin (5%).[21] Only 0.1% is circulating in the blood.[21]

The homeostasis of Zn concentration is maintained through a tightly regulated influx and efflux system, i.e. the transmembrane Zn transporter (ZnT) proteins.[22] Ten homologous ZnT (Znt -1 to Znt -10) have been discovered.[22] ZnT-8 facilitates Zn efflux, while membrane-bound Zn-transporter proteins - ZIPs are responsible for the influx. [23] Along with Metallothioneins, an intracellular protein-binding metal, Zn homeostasis aids in the storage and secretion of insulin.[24] Metallothioneins release Zn to allow Zn incorporation with insulin secretory granules through the ZnT8. Together with the calcium ions, Zn is stored within proinsulin to form proinsulin hexamers. During hyperglycemia, proinsulin is cleaved into the active insulin form and is secreted into the circulation. This action will free up some Zn ions (Figure 1(A)). [25]

Zn delivery in this maturation and secretion of insulin process is mediated by the ZnT-8 located on the surface of the β-cell insulin granule B.[21] An overexpression of ZnT8 and Zn supplementation in animal models proved to increase the rate of glucose-stimulated insulin secretion.[25] On the other hand, the lack of ZnT8 expression and Zn deficiency impedes insulin formation secretion and stimulates pancreatic β-cell apoptosis. [26]

Furthermore, by assisting in insulin crystallization in the granules, Zn prevents insulin reactivity with its surrounding membrane. It also enhances insulin receptor phosphorylation and the expression of glucose-transporter type-4 (GLUT-4).[24] Zn has an antioxidant property that hinders cellular oxidative stress injury.[24, 25] This explained the pathogenesis of DM in patients with hyperzincuria or hypozincemia and auto-antibody (Znt-8 antibody) mediated DM. [21]

Targeted therapy towards ZnT-8 and ZIP has been of great interest in experimental and clinical research.[8,27] Wang et al. 2019 reported a decreased concentration of fasting, post-prandial glucose level, glycated hemoglobin, and Hs-C-reactive protein level with a mean dose of Zn of 35mg/d (from 4 to 240mg/d) following the duration of Zn administration of up to 12 months.[28] In gestational diabetes, Zn supplementation has also been proven to reduce fasting blood glucose and insulin levels.[17]

Zn supplementation for the treatment of diabetes has gained popularity due to the significant benefits of Zn in diabetes. Many animal studies have reported that the use of Zn medications for example in the form of zinc oxide (ZnO) nanoparticles significantly reduces the risk of diabetes as well as ameliorates diabetic complications in rats. [29] However, achieving an optimal therapeutic dose for dietary supplementation remains controversial as it interferes with the absorption of calcium (Ca), manganese (Mg), copper (Cu), Se, and iron (Fe). [8] For example, Zn antagonizes the uptake of copper, which is required to mediate the cellular uptake of Fe and hematopoietic cell differentiation. Therefore, cases of iron deficiency anemia, sideroblastic anemia, neutropenia, and even pancytopenia have been reported following overdosage of Zn. [30] The pharmacotherapeutic dosage of >40 mg/day of elemental Zn is proven to be safe but its therapeutic dosage is still a matter of debate and is influenced by multiple factors such as inhibition of its absorption following prolonged high amount of Zn intake.[8]

Boron (Br)

Br is an essential micronutrient obtained through drinking water and myriads of plant-based resources such as legumes, nuts, vegetables, and fruits. [31] In the form of borax pentahydrate and boric acid, their role in maintaining calcium-vitamin D homeostasis and bone health, stimulating sex hormone production, providing antioxidative benefits, accelerating wound healing, and alleviating inflammation have been largely proven.[32] Although it does not accumulate in the human body, Br measurement of bone, nails, and hair revealed a higher concentration, while a low concentration was observed in fat tissues.[33]

In DM, Br has been proven to show some medicinal benefits. It inhibits the action of interleukin-1beta (IL-1β), a proinflammatory cytokine that induces the apoptosis of pancreatic β-cell (Figure 1(B).[13] The excessive generation of free radicals in DM defeats the expression of potent antioxidants, namely Superoxide dismutase (SOD), glutathione peroxidase (GPx) and catalase in pancreatic β-cells.[34] It is documented that Br portrays some SOD activity that prevents the development of various metabolic diseases, such as atherosclerosis and hypertension.[14] The administration of sodium pentaborate pentahydrate and boric acid was proven to cause a rapid rise in the level of SOD and GPx, hence are beneficial to reduce oxidative stress. [13]

Boric acid also augments calcium influx and the activity of voltage-gated calcium channels in the β-cells, stimulating insulin release.[1,13] Br-rich diet has also been demonstrated to improve lipid profile and reduce body mass index after one month of consumption; hence, the potential to prevent the development of metabolic syndrome.[7,31] It improved bone health in non-obese diabetic mice.[10] Br treatment has also been observed to decrease free radicals in a dose-dependent manner and maintain pancreatic β-cell function in diabetic rats. [35] A negative correlation between a low Br level with glucose and HbA1c has been observed in patients with diabetes, and a markedly higher Br level in control groups compared to the diabetic groups proves that low Br level has the potential to be a biomarker for metabolic diseases. [36]

Chromium (Cr)

Cr forms vary according to their oxidation state. [37] While hexavalent Cr (Cr(VI)) is a toxic form that is carcinogenic to humans, trivalent Cr (Cr(III)) constitutes the most stable form and can be found in food like broccoli, spinach, cheese, liver, meat, Brewer's yeast, and seafood. [37, 38] In the human body, Cr(III) is vital for glucose and fat metabolism. [37] Its role is not limited to preventing and improving glycaemia in DM, but it also treats hyperlipidaemia. [16] By augmenting the insulin signaling pathway in various tissues, Cr(III) is an effective glucose tolerance factor that potentiates insulin action. [39]

The absorption of Cr(III) in the gut is via passive diffusion.[40] However, only 1% of Cr(III) is absorbed through this mechanism.[40] This is because many elements such as Ca, Mg, Zn, titanium (ti), Fe, and phosphate may compete for their effective absorption. On the other hand, ascorbic acid, aspirin, oxalic acid, simple sugar, nicotinic acid, and some amino acids improve Cr absorption. [37]

The structural similarity of Cr(III) to the ferric ion allows transferrin-Cr(III) complex formation that aids in the Cr (III) transport.[40] The binding of chromodulin to four Cr (III) ions allows its conversion into holochromodulin, the active Cr(III) form. Upon binding to the insulin receptor of the β-subunit, the tyrosine kinase receptor is activated, thus stimulating GLUT-4 expression and accelerating glucose uptake into the tissue.[41]

Low serum Cr level is significantly lower in diabetes with and without complications than non-diabetic individuals.[36] In the form of niacin-bound Cr (NBC), a cellular study showed NBC supplementation potentiated AMP protein kinase (AMPK) stimulation, protein kinase Akt phosphorylation, and the GLUT4 membrane translocation (Figure 1(C).[16] In type 2 DM patients, three months of Cr dinicocysteinate (400μg/day) supplementation revealed a significant reduction in tumor necrosis factor (TNF) level.[12] Along with other pharmaconutrients, a systematic review involving 119 RCTs on Cr; coenzyme Q10; omega-3 fatty acids; vitamins C, D, and E; alpha-lipoic acid; Se; and Zn marked improvement in glycaemic control of diabetic patients were observed.[42] Its co-effect on lipid profile proves that Cr supplementation is vital in managing metabolic syndrome.[37]

Selenium (Se)

Se exists in soil, water, and air, but the human body obtains Se from various dietary sources like wheat, maize, meat, dairy products, fish, and seafood.[18] Se has been proven beneficial in subjects with insulin resistance.[18] It poses an insulin-like activity and antioxidant property that could help neutralize reactive oxygen species.[4] Selenoprotein, in the form of Glutathione peroxidase-1 (GPx-1), is known for its capability to combat oxidative stress (Figure 1(A). Se supplementation enhanced GPxs activity, raised superoxide dismutase level, suppressed anti-inflammatory cytokines, and reduced serum malonaldehyde, a biomarker of oxidative damage.[43,44] Se supplementation in human beings can also potentially be relevant in managing metabolic syndrome and cardiovascular diseases.[4, 45]

It is well known that chronic inflammation of the visceral white adipose tissue, liver, and pancreatic islet inflammation are thought to be key contributors to β-cell malfunction and insulin resistance that underlies the pathogenesis of DM and its complications such as obesity and cardiovascular disease (CVD). In this condition, M1-like macrophages, being the predominant immune cells in these tissues serve as the main source of cytokines that promote inflammation.[46] Due to this fact, many researchers have focused on the beneficial effect of Se in DM, obesity, and CVD. Se exhibits distinctive regulatory characteristics on macrophages which are the key cells in the immune response and inflammation. The activation of macrophages can result in their subsequent differentiation into the classical M1 and the alternative M2 phenotypes.[47] Se plays a role in controlling macrophage polarization, steering them away from the pro-inflammatory M1 phenotype and towards the anti-inflammatory M2 phenotype. Additionally, Se can decrease the release levels of pro-inflammatory cytokines, including inducible nitric oxide synthase (iNOS), Interleukin -1beta (IL-1β), Interleukin -10 (IL-10), prostaglandin E (PTGE), and nuclear factor kappa B (NF-Kb). Animal studies have shown that both mice with Se deficiency and those enriched with Se displayed a faster resolution of inflammation in the Se-enriched group.[47, 48] However, Se is also known for its biphasic dose response property, where it is proven favorable at an optimized dose but harmful at too low or high doses.[18] Animal studies showed a potential β-cells, insulin signaling destructive effect with excessive glutathione peroxidase-1 (GPx-1). Compared to GPx-1 null mice, overexpressed GPx-1 mice have significantly poor glycaemic control.[4] Moreover, a high dose of Se level disturbs the cellular redox state, increasing cellular ROS level (Figure 1(B)). [4] The increase in Se up to 140 to 160 μg/L has been associated with increased glucose and glycated

hemoglobin concentration, hence the overall prevalence of DM. [49] On the contrary, a significantly low level would also accelerate the diabetic state. Mice fed a low Se ≤0.10 mg/kg diet developed impaired glucose tolerance and insulin resistance due to impaired muscle AK strain transforming (AKT) phosphorylation on S473, crucial for insulin-mediated glucose uptake signaling. [50]

Furthermore, there was an unclear association between the risk of developing type-2-DM (T2DM) with a Se-deficient and Se-rich diet among different observational studies and randomized clinical trials (RCTs).[4] Zhao 2022 suggests that Se exposure and the risk of type 2 DM is dose-dependent, where only a moderate to high concentration is associated with increased type 2 DM risk.[17] This shows that Se has a narrow therapeutic index, and levels must be optimized for balanced glucose and lipid homeostasis.[45] Nonetheless, the heterogeneity in evidence supports the need for further research on optimal supplementation in DM prevention and management.

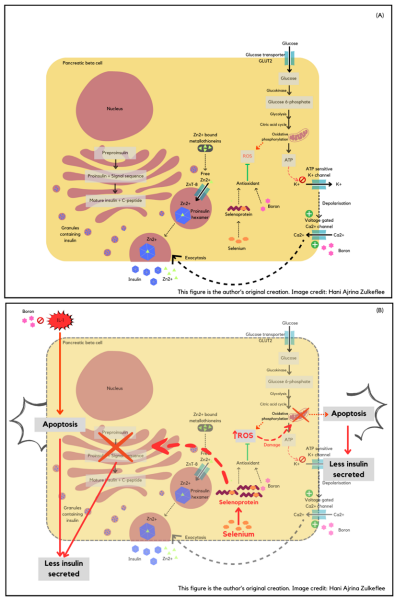

Figure 1: The complex cellular interplay of Zinc (Zn), Boron (Br), Chromium (Cr), and Selenium (Se). Cellular disruption caused by abnormal levels of these trace elements could lead to the pathogenesis of diabetes mellitus.

Figure 1 illustrates a schematic representation elucidating the complex interplay among Zn, Br, Cr, and Se in the pathogenesis of diabetes mellitus.

As depicted in Figure 1(A), during hyperglycemia, glucose enters pancreatic beta cells via glucose-transporter (GLUT2), initiating catabolic processes that yield ATP within mitochondria and generate reactive oxygen species (ROS). Br and Se (selenoprotein) eliminate ROS. Elevated intracellular ATP levels prompt the closure of ATP-sensitive potassium channels, eliciting β-cell depolarization and subsequent calcium influx. Br further enhances calcium channel activity, amplifying calcium influx. Simultaneously, Zn liberation from metallothioneins enables its entry into insulin granules through the ZnT-8 channel. Zn integration forms proinsulin hexamers. Elevated intracellular calcium levels prompt insulin secretion into the bloodstream, leading to the cleavage of proinsulin hexamers into active insulin. The final step allows the release of free Zn into circulation.

Figure 1(B) shows the effect of excessive ROS on mitochondria which results in pancreatic beta cell apoptosis and diminished insulin secretion. Excessive Se disturbs insulin signaling. Meanwhile, Br mitigates the action of interleukin-1βeta, a proinflammatory cytokine that inhibits pancreatic beta cell apoptosis.

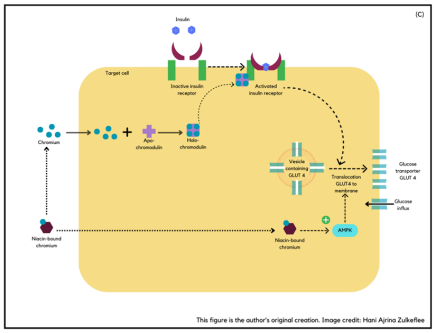

Figure 1(C) illustrates insulin action at target cells, such as skeletal muscle. Insulin binding to its receptor initiates receptor activation, prompting vesicular translocation of glucose-transporter (GLUT4) and consequent augmentation of glucose uptake. Cr binding to apo-chromodulin yields holo-chromodulin, which binds to the beta subunit of the insulin receptor, facilitating receptor activation. In its niacin-bound form, Cr stimulates AMP protein kinase, promoting GLUT4 membrane translocation.

Future Perspectives

The summary of trace elements' effects in the pathogenesis of diabetes mellitus has been detailed in Table 1. Currently, aims of the future research are to dive into the impact of trace elements on the targeted nutritional interventions that could help reduce the prevalence of diabetes mellitus by providing good glycaemic control and minimizing vascular complications. The interventions could involve dietary changes, supplements, or personalized diets based on an individual's trace element profile. Studies looking into

optimum trace elements cut off in the human body could be the potential niche contributing to personalized medicine realization.

Table 1: The summary of the effect of trace elements in relation to diabetes mellitus

Trace elements	Mechanisms contributing to the pathogenesis of DM		Therapeutic potentials
	Excess	Deficiency	
Zinc (Zn)	Not applicable (NA)	Low Zn level causes a lack of ZnT8 expression and Zn deficiency hinders insulin formation and secretion, thus stimulating pancreatic β-cell apoptosis.	Dysfunction of the Zn transporter and Zn deficiency are both related to diabetes mellitus development. Compounds that regulate Zn transporter as a form of therapeutic target have gained numerous interests.
Boron (Br)	NA	Br inhibits pro-inflammatory cytokine; interleukin-1βeta (IL-1β) and poses superoxide dismutase (SOD) activity (a potent antioxidant). Therefore, low Br level predisposes cells to oxidative damage of pancreatic β-cells. Br also augments calcium influx and the activity of voltage-gated calcium channels in the β-cells, thus stimulating insulin release.	Br-containing compounds like sodium pentaborate (NaB) and boric acid protect and improve pancreatic β-cells viability. It is said to be a promising target for type 1 diabetes mellitus.
Chromium (Cr)	NA	In the form of holochromodulin, Cr binding to the insulin receptor of the β-subunit allows activation of the tyrosine kinase receptor, thus stimulating GLUT-4 expression and accelerating glucose uptake into the tissue. Cr also augments the insulin-signalling pathway. Therefore, a low Cr level suppresses insulin release.	Cr supplementation has been associated with a great reduction in oxidative stress indices and elevation of antioxidant levels. This has been proven in both animal and human studies, however, the exact mechanism and optimum dosage for supplementation through clinical trials are lacking.
Selenium (Se)	In the form of selenoprotein or Glutathione peroxidase-1 (GPx-1), Se combats oxidative stress. However, a high Se level causes an excessive GPx-1 activity that potentiates β-cells and insulin signaling destructive effect.	Low Se causes an impaired muscle AKT phosphorylation on S473 which is crucial for insulin-mediated glucose tissue uptake. This predisposes to insulin resistance.	There is increasing evidence to suggest that Se in the form of selenoprotein could benefit the management of diabetes mellitus. However, obtaining an optimal dosage of Se supplementation is challenging as both its deficiency and excess could contribute to the development of diabetes mellitus.

Table 1 shows the effects of abnormal trace element concentration that leads to the development of diabetes mellitus. Insufficiency of all 4 trace elements; Zn, Br, Cr, and Se is proven to be associated with the development of diabetes mellitus. However, when Se concentration is high, the favorable outcome of GPx-1 in suppressing oxidative stress is countered by the unfavorable β-cells and insulin signaling destructive effect, hence the difficulty in establishing the optimum therapeutic dose.

CONCLUSION

Several trace elements are required for optimal glucose homeostasis. However, both a lack of it and an excess of it have been associated with the development of diabetes mellitus and poorer glycemic control. For most elements, deciding on the optimal nutritional or supplemental levels is still controversial, especially with elements that portray narrow therapeutic indexes such as Se. Despite suggestions to include these micronutrients in diabetic management, further research is still required to determine their potential therapeutic roles and optimum doses.

LIST OF ABBREVIATIONS

DM: Diabetes Mellitus**, T2DM:** Type-2-DM**, Zn:** zinc**, Cr:** chromium**, Se:** selenium**, ZnT:** Zn transporter**, ZIPs:** zinc transporter proteins**, GLUT:** glucose-transport type**, IL-1β:** interleukin-1beta**, SOD:** Superoxide dismutase, **GPx:** glutathione peroxidase**, NBC:** niacin-bound chromium**, TNF:** tumour necrosis factor, **RCT:** randomized clinical trials, **ROS:** Reactive oxygen species**, HOMA-IR:** homeostasis model assessment of insulin resistance, **FPG:** fasting plasma glucose, **MnSOD:** Manganese superoxide dismutase

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CONFLICT OF INTEREST

The authors declare no conflict of interest concerning this manuscript.

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REFERENCES

1. Dubey P, Thakur V, Chattopadhyay M. Role of minerals and trace elements in diabetes and insulin resistance. Nutrients. 2020; 12:1864.
2. Islam MR, Akash S, Jony MH, et al. Exploring the potential function of trace elements in human health: a therapeutic perspective. Mol Cell Biochem. 2023; 13:1-31.
3. Silva CS, Moutinho C, Ferreira da Vinha A, Matos C. Trace minerals in human health: Iron, zinc, copper, manganese and fluorine. Int J Sci Res Methodol. 2019; 13:57-80.
4. Kohler LN, Florea A, Kelley CP, et al. Higher plasma selenium concentrations are associated with increased odds of prevalent type 2 diabetes. J Nutr. 2018; 148:1333-40.
5. Galicia-Garcia U, Benito-Vicente A, Jebari S, et al. Pathophysiology of type 2 diabetes mellitus. Int J Mol Sci. 2020; 21:6275.
6. Hara T, Yoshigai E, Ohashi T, Fukada T. Zinc transporters as potential therapeutic targets: An updated review. J Pharmacol Sci. 2022; 148:221-8.
7. Kuru R, Yilmaz S, Balan G, et al. Boron-rich diet may regulate blood lipid profile and prevent obesity: A non -drug and self-controlled clinical trial. J Trace Elem Med Biol. 2019; 54:191-8.
8. Santos HO, Teixeira FJ, Schoenfeld BJ. Dietary vs. pharmacological doses of zinc: A clinical review. Clin Nutr. 2020; 39:1345-53.
9. de Sousa Melo SR, Dos Santos LR, da Cunha Soares T, et al. Participation of magnesium in the secretion and signaling pathways of insulin: an updated review. Biol Trace Elem Res. 2022; 200:3545-53.
10. Dessordi R, Spirlandeli AL, Zamarioli A, Volpon JB, Navarro AM. Boron supplementation improves bone health of non-obese diabetic mice. J Trace Elem Med Biol. 2017; 39:169-75.
11. Liu M, Jeong EM, Liu H, et al. Magnesium supplementation improves diabetic mitochondrial and cardiac diastolic function. JCI Insight. 2019; 4:e123182.
12. Saiyed ZM, Lugo JP. Impact of chromium dinicocysteinate supplementation on inflammation, oxidative stress, and insulin resistance in type 2 diabetic subjects: an exploratory analysis of a randomized, double-blind, placebo-controlled study. Food Nutr Res. 2016; 60:31762.
13. Aydın S, Demirci S, Doğan A, et al. Boron containing compounds promote the survival and the maintenance of pancreatic β-cells. Mol Biol Rep. 2019; 46:5465-78.
14. Ri CC, Mf CR, IR S, MA SU. Boron-Containing Compounds for Prevention, Diagnosis, and Treatment of Human Metabolic Disorders. Biol Trace Elem Res. 2023; 201:2222-39.
15. Kooshki F, Tutunchi H, Vajdi M, et al. A Comprehensive insight into the effect of chromium supplementation on oxidative stress indices in diabetes mellitus: A systematic review. Clin Exp Pharmacol Physiol. 2021; 48:291-309.
16. Zhou Q, Guo W, Jia Y, Xu J. Comparison of Chromium and Iron Distribution in Serum and Urine among Healthy People and Prediabetes and Diabetes Patients. Biomed Res Int. 2019; 2019:3801639.
17. Zhao J, Zou H, Huo Y, Wei X, Li Y. Emerging roles of selenium on metabolism and type 2 diabetes. Front Nutr. 2022; 9:1027629.
18. Ouyang J, Cai Y, Song Y, et al. Potential Benefits of Selenium Supplementation in Reducing Insulin Resistance in Patients with Cardiometabolic Diseases: A Systematic Review and Meta-Analysis. Nutrients. 2022; 14:4933.
19. Santos HO, Teixeira FJ. Use of medicinal doses of zinc as a safe and efficient coadjutant in the treatment of male hypogonadism. Aging Male. 2020; 23:669-78.
20. Nedjimi B. Can trace element supplementations (Cu, Se, and Zn) enhance human immunity against COVID -19 and its new variants?. Beni Suef Univ J Basic Appl Sci. 2021; 10:1-5.
21. Barman S, Srinivasan K. Diabetes and zinc dyshomeostasis: Can zinc supplementation mitigate diabetic complications?. Crit Rev Food Sci Nutr. 2022; 62:1046-61.
22. Kambe T. An overview of a wide range of functions of ZnT and Zip zinc transporters in the secretory pathway. Biosci Biotechnol Biochem. 2011; 75:1036-43.
23. Chabosseau P, Rutter GA. Zinc and diabetes. Arch Biochem Biophys. 2016; 611:79-85.

24. Poudel RR, Bhusal Y, Tharu B, Kafle NK. Role of zinc in insulin regulation and diabetes. Journal of Social Health and Diabetes. 2017; 5:83-7.
25. MacKenzie S, Bergdahl A. Zinc homeostasis in diabetes mellitus and vascular complications. Biomedicines. 2022; 10:139.
26. Tamaki M, Fujitani Y, Hara A, et al. The diabetes-susceptible gene SLC30A8/ZnT8 regulates hepatic insulin clearance. J Clin Invest. 2013; 123:4513-24.
27. Norouzi S, Adulcikas J, Sohal SS, Myers S. Zinc transporters and insulin resistance: therapeutic implications for type 2 diabetes and metabolic disease. J Biomed Sci. 2017; 24:87.
28. Wang LJ, Wang MQ, Hu R, Yang Y, et al. Zinc supplementation improves glycemic control for diabetes prevention and management: a systematic review and meta-analysis of randomized controlled trials. Am J Clin Nutr. 2019; 110:76-90.
29. Ruan S, Guo X, Ren Y, et al. Nanomedicines based on trace elements for intervention of diabetes mellitus. Biomed Pharmacother. 2023; 168:115684
30. Wahab A, Mushtaq K, Borak SG, Bellam N. Zinc-induced copper deficiency, sideroblastic anemia, and neutropenia: A perplexing facet of zinc excess. Clin Case Rep. 2020; 8:1666-71.
31. Kuru R, Yilmaz S, Tasli PN, Yarat A, Sahin F. Boron content of some foods consumed in Istanbul, Turkey. Biol Trace Elem Res. 2019; 187:1-8.
32. Farrin N, Rezazadeh L, Pourmoradian S, et al. Boron compound administration; A novel agent in weight management: A systematic review and meta-analysis of animal studies. J Trace Elem Medicine Biol. 2022; 72:126969.
33. Uluisik I, Karakaya HC, Koc A. The importance of boron in biological systems. J Trace Elem Medicine Biol. 2018; 45:156-62.
34. Lei XG, Vatamaniuk MZ. Two tales of antioxidant enzymes on β cells and diabetes. Antiox Redox Signal. 2011; 14:489-503.
35. Coban FK, Liman R, Cigerci IH, et al. The antioxidant effect of boron on oxidative stress and DNA damage in diabetic rats. Fresenius Environ Bull. 2015; 24:4059-66.
36. Demirdogen RE. Relationship among blood boron level, diabetes mellitus, lipid metabolism, bone metabolism and obesity: Can boron be an efficient indicator for metabolic diseases. Health Sci J. 2020; 14:1-1.
37. Genchi G, Lauria G, Catalano A, Carocci A, Sinicropi MS. The double face of metals: The intriguing case of chromium. Applied Sciences. 2021; 11:638.
38. Khodavirdipour A, Haddadi F, Keshavarzi S. Chromium supplementation; negotiation with diabetes mellitus, hyperlipidemia and depression. J Diabetes Metab Disord. 2020; 19:585-95.
39. Pantelić M, Jovanović LJ, Prodanović R, et al. The impact of the chromium supplementation on insulin signalling pathway in different tissues and milk yield in dairy cows. J Anim Physiol Anim Nutr. 2018; 102:41-55.
40. Edwards KC, Kim H, Vincent JB. Release of trivalent chromium from serum transferrin is sufficiently rapid to be physiologically relevant. J Inorg Biochem. 2020; 202:110901.
41. Chen G, Liu P, Pattar GR, et al. Chromium activates glucose transporter 4 trafficking and enhances insulin -stimulated glucose transport in 3T3-L1 adipocytes via a cholesterol-dependent mechanism. Mol Endocrinol. 2006; 20:857-70.
42. Kim Y, Oh YK, Lee J, Kim E. Could nutrient supplements provide additional glycemic control in diabetes management? A systematic review and meta -analysis of randomized controlled trials of as an add -on nutritional supplementation therapy. Arch Pharm Res. 2022; 45:185-204.
43. Galan-Chilet I, Grau-Perez M, De Marco G, et al. A gene-environment interaction analysis of plasma selenium with prevalent and incident diabetes: The Hortega study. Redox Biol. 2017; 12:798-805.
44. Wu H, Zhao G, Liu S, et al. Supplementation with selenium attenuates autism-like behaviors and improves oxidative stress, inflammation, and related gene expression in an autism disease model. J Nutr Biochem. 2022; 107:109034.
45. Yin T, Zhu X, Xu D, et al. The association between dietary antioxidant micronutrients and cardiovascular disease in adults in the United States: a cross-sectional study. Front Nutr. 2022; 8:799095.
46. Steinbrenner H, Duntas LH, Rayman MP. The role

of selenium in type-2 diabetes mellitus and its metabolic comorbidities. Redox Biology. 2022; 50:102236.
47. Zhang F, Li X, Wei Y. Selenium and Selenoproteins in Health. Biomolecules. 2023; 13:799.
48. Shimada BK, Alfulaij N, Seale LA. The impact of selenium deficiency on cardiovascular function. Int J Mol Sci. 2021; 22:10713.
49. Vinceti M, Filippini T, Wise LA, Rothman KJ. A systematic review and dose-response meta-analysis of exposure to environmental selenium and the risk of type 2 diabetes in nonexperimental studies. Environ Res. 2021; 197:111210.
50. Huang YC, Wu TL, Zeng H, Cheng WH. Dietary selenium requirement for the prevention of glucose intolerance and insulin resistance in middle-aged mice. J Nutr. 2021; 151:1894-900.