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Review article

The Potential Association of Iron and Zinc Levels with Insulin Resistance in Type 2 Diabetes, Obesity, and Apparently Healthy Adults

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Abstract
This narrative review explores the possible link between insulin resistance (IR) and alterations in iron and zinc status among individuals with type 2 diabetes mellitus (T2DM), obesity, and those considered healthy. Insulin resistance—characterized by a reduced cellular response to insulin—precedes the onset of T2DM and is influenced by metabolic, nutritional, and hormonal factors. Evidence suggests that iron and zinc, two essential trace elements with antioxidative and enzymatic functions, may play key roles in glucose homeostasis and insulin signaling. High iron levels have been associated with impaired insulin sensitivity, mitochondrial dysfunction, and adipose tissue inflammation, whereas iron deficiency may coexist with obesity due to inflammatory-mediated hepcidin activity. Zinc, crucial for insulin synthesis, storage, and secretion, is frequently reduced in metabolic disorders and may influence both insulin action and lipid metabolism. However, existing studies report mixed and sometimes conflicting findings. This review synthesizes data from research published between 2010 and 2025 and highlights that dysregulated iron and zinc levels may serve as surrogate markers of insulin resistance across various metabolic conditions. While these micronutrients show potential diagnostic and therapeutic relevance, further large-scale, well-designed studies are needed to confirm their roles and guide clinical applications.
Keywords. Insulin Resistance, Type 2 Diabetes Mellitus, Obesity, Iron Metabolism, Zinc Metabolism, Micronutrients.

Introduction

A decreased glucose response to a specific dosage of insulin is known as insulin resistance (IR) [1]. Insulin levels rise as the body tries to overcompensate for insufficient insulin action by pumping out more insulin from the pancreas; this development of insulin resistance leads to compensatory hyperinsulinemia, which characterizes the shift from insulin resistance to type 2 diabetes [2, 3]. Diabetes mellitus (DM) is a chronic illness associated with metabolic abnormalities. The most prevalent kind of diabetes mellitus is type 2 (T2DM), which is characterized by low levels of adiponectin, insulin resistance, and hyperglycemia [4, 5, 6]. In 2019, there were 463 million people worldwide between the ages of 20 and 79 who had diabetes, an increase of 151 million from 2018 [5].

Numerous studies [7] have examined the impact of several micronutrients on type 2 diabetes, one of the most prevalent non-communicable diseases (6.28% of the global population [8]). To control type 2 diabetes, a variety of nutritional approaches have been suggested, such as losing weight, distributing macronutrients properly, selecting foods with a low glycemic index, ingesting more than 40 grams of fiber daily, and consuming free sugars in moderation [9]. Diet and nutrition are crucial in the development of metabolic disorders because of the complex interplay of genetic, metabolic, and environmental variables [10]. Dietary micronutrients like iron (Fe), copper (Cu), and zinc (Zn) are well known for their antioxidative properties and interaction with a variety of enzymes. These micronutrients are therefore thought to play a role in metabolic syndrome (MetS) and diabetes mellitus [11-13]. In order to shed light on the relationships between blood concentrations of Zn or Fe and DM, a few observational studies were conducted; however, the findings were mixed [14-16]. Serum levels of Cu and Fe appear to be favorably correlated with the risk of diabetes mellitus (DM) in recent meta-analyses; however, the relationship between serum levels of Zn and DM was unclear [17-19]. Furthermore, it was discovered that iron and zinc were crucial components in the development of obesity, gestational diabetes mellitus, and type 2 diabetes [20–23].

However, insulin resistance comes before non-physiologic increased plasma glucose levels, which are the main clinical sign of type 2 diabetes. Insulin levels rise in prediabetic individuals to satisfy normal insulin requirements, which can result in persistent hyperinsulinemia, hyperglycemia-induced β-cell failure, and ultimately type 2 diabetes [24]. Although the mechanism of insulin resistance has not been fully established, several theories are generally considered reasonable. This review summarizes the possible role of the most important elements in the body (iron and Zinc) in the stimulation of insulin resistance under different abnormal conditions. In light of the aforementioned, we made an effort in this narrative review to compile the results of a number of earlier studies that had recently addressed this subject and to compare them in order to arrive at several recommendations.

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The iron regulatory role in insulin

Iron is both an essential nutrient and a potential cytotoxin. A proper amount of iron in the body has a significant impact on electron transfer processes, gene control, oxygen binding and transport, differentiation, immune system augmentation, and cell growth regulation [25]. It is also a component of many essential enzymes in the development of cells, growth of the appropriate cells of the brain, muscle, and immune system [26].

Iron and insulin signaling interact intricately, regulating cellular responses to insulin through sophisticated molecular regulatory processes. Iron is an important micronutrient that affects several aspects of glucose homeostasis by modulating insulin sensitivity. An important part of this complexity is iron's regulatory function in insulin receptor activity. It controls the phosphorylation of insulin receptors, a critical process that starts signaling cascades downstream [27].

Moreover, high iron levels have been linked to decreased insulin sensitivity and interference with insulin-mediated glucose absorption. The link between increased iron levels and insulin resistance is supported by data from population studies, clinical research, and animal models. Understanding how iron dysregulation contributes to metabolic dysfunction is further complicated by the impact of iron on adipose tissue macrophages and mitochondrial function. In order to create targeted treatment interventions to address metabolic diseases and improve overall health outcomes, it is essential to unravel the molecular pathways that link iron metabolism to insulin resistance [28–31].

In this regard, various studies have found iron deficiency in obesity; this has primarily been linked to the inflammatory state of excess adipose tissue, which involves an increase in proinflammatory cytokines like hepcidin, which decreases iron absorption [32, 33]. On the other hand, other reports indicate that patients with type 2 diabetes (T2DM) and cardiovascular diseases have moderate to high levels of body iron [34], and that patients with type 1 diabetes and T2DM have low HDL cholesterol and high ferritin and triglycerides [35]. The idea that iron dysregulation could contribute to insulin resistance is hotly debated. High body iron may be linked to the risk of diabetes and cardiovascular disease, according to population studies that have found correlations between ferritin and cardiovascular markers [36, 37]. As a result, Vaquero et al.'s investigation found a connection between reduced iron transport efficiency and insulin resistance and iron storage [38].

However, because both insulin resistance and insufficiency play a role, the pathophysiological process underlying iron overload (IO)-induced diabetes is complex [39, 40]. The exact processes by which iron might cause insulin resistance are unclear, and it is thought that IO in skeletal muscle is underestimated [41, 42]. Conversely, skeletal muscle insulin sensitivity was considerably reduced by IO, according to a study by Jahng et al. (Figure 1) [43]. They discovered that using an iron chelator to prevent excess free iron levels in L6 cells could prevent IO-induced insulin resistance and metabolic dysfunction. This is consistent with the fact that clinical interventions to lower free iron can improve insulin sensitivity and postpone the onset of type 2 diabetes [41, 43].

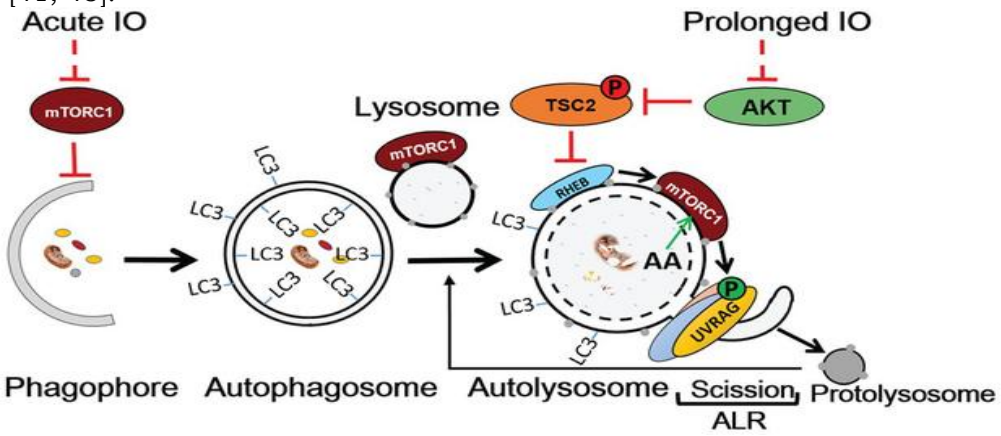

Figure 1. Iron overload-mediated autophagy regulation schematic diagram. The mechanism by which IO regulates autophagy. Acute IO causes mTORC1 to be inhibited, which triggers autophagy

Through AKT-TSC-Rheb-mTORC1-UVRAG signaling abnormalities, prolonged IO inhibits ALR-mediated creation of new lysosomes. In skeletal muscle, autophagy suppression and insulin resistance are caused by a deficiency of free lysosomes [43]. Additionally, insulin resistance also contributes to gestational diabetes in women. In order to prevent and identify gestational diabetes mellitus (GDM) in pregnant women, it may be essential to identify the factors that can cause insulin resistance in these individuals. On the other hand, high levels of iron and ferritin have been linked to the development of type 2 diabetes in several previous articles, but their effects on insulin resistance in pregnant women have received less attention. According to a number of earlier studies, fetal hyperinsulinemia is linked to macrosomia [45], and modest iron intake in non-anemic pregnant women can affect blood glucose and cause hyperinsulinemia and oxidative damage in their children [46].

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Serum transferrin and waist circumference (WC) were shown to be significantly correlated with the Homeostasis model assessment of insulin resistance (HOMA-IR), according to cross-sectional data from the 2019 China Health and Nutrition Survey, which examined 689 children and adolescents. Furthermore, there were notable correlations between HbA1c and BMI, transferrin, and soluble transferrin receptor (sTfR). In contrast, serum ferritin (SF) levels were considerably greater than those of healthy controls in a Chinese study involving people who had just received a T2DM diagnosis [47]. Notably, diabetic patients had higher levels of serum iron (SI) and transferrin saturation (TSAT), and male diabetic patients had a lower percentage of transferrin (Trf) levels below normal than their female counterparts. Trf was found to be an independent protective factor for beta-cell function in male patients, whereas SF was found to be an independent risk factor in female patients, according to further stratification analysis [47, 48].
Elevated fasting hyperglycemia and triglycerides were found to positively correlate with blood iron levels by other researchers. Furthermore, a number of metabolic variables, such as age, sex, current smoking, current drinking, exercise habits, BMI, and HOMA-IR, were associated with higher serum iron concentrations. The findings verified a favorable correlation between the likelihood of developing metabolic syndrome (MetS) and serum iron levels [47, 49].

Role of zinc in insulin regulation

The synthesis, storage, release, and elimination of insulin are all dependent on zinc, the second most important trace element. Zinc is therefore essential for controlling and preserving a healthy glycemic balance [50, 51]. In terms of human health, zinc has two functions. Although zinc is an important mineral for maintaining appropriate insulin signaling, it is still unclear how dysregulated zinc levels, especially high amounts, affect insulin resistance [52-54]. Due to growing knowledge of the insulin-like characteristics of trace elements like zinc, researchers are currently interested in learning more about the role of zinc in IR and diabetes [55]. The results of the Ghafouri-Taleghani et al. and Bjørklund et al. studies underscore the significance of additional research and highlighted the intricate involvement of zinc status in the pathophysiology of IR as well as glucose and lipid metabolism [56, 57]. Physiologically, pancreatic β-cells have one of the highest zinc contents in the body, and it seems to be a crucial metal for cells that secrete insulin [58]. Because the body lacks a specific system to store zinc, a daily dose is necessary to maintain a stable level [59]. It is challenging to precisely determine the amounts using laboratory testing since zinc is distributed throughout the body in different proteins and nucleic acids (Figure 2) [60, 61].

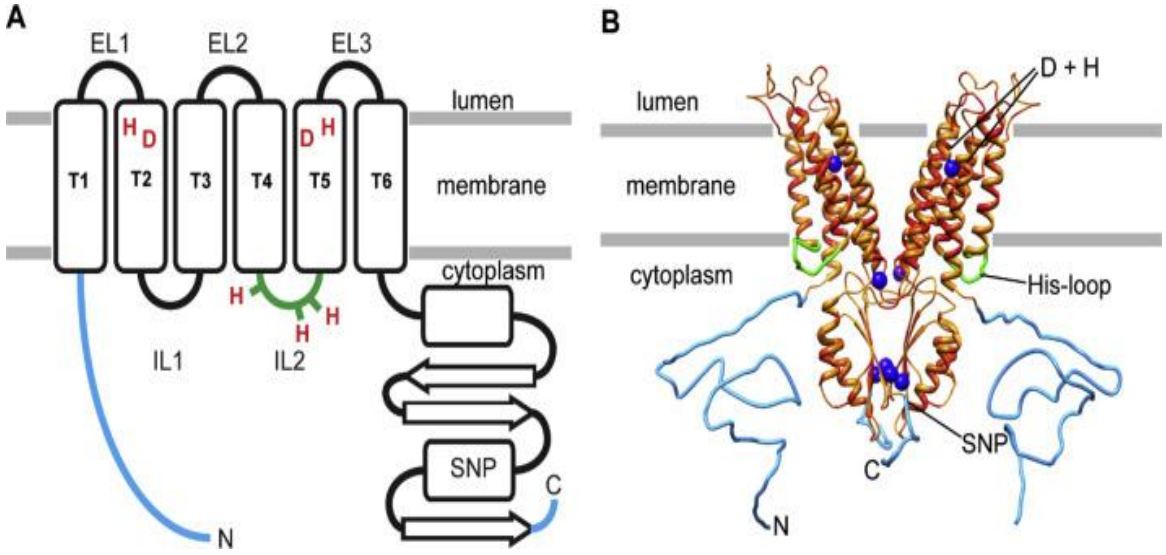

Figure 2. Schematic illustration of ZnT8 proteins and transcripts.

Models of ZnT8 topology and structure based on the bacterial homolog YiiP has been ullustrated in figure 2. (A) ZnT8 topology model showing the locations of the zinc-sensing His-rich loop (IL2), the pair of His (H) and Asp (D) residues in TM 2 and 5 that are conserved in human ZnT proteins, and the R325W SNP. The 49 amino-terminal and about 12 carboxy-terminal residues that are absent from YiiP are also displayed. (B) ZnT8 homology model with identical residues in YiiP (red), conserved substitutions (dark orange), expanded ZnT8 N- and C-termini (light blue), and zinc atoms seen in YiiP (dark blue spheres) [61].
Conversely, there is little few and conflicting research on Zn and MetS. The National Health and Nutrition Examination Survey (NHANES) in Korea and the IMMIDIET study in Europe both failed to show a correlation between serum Zn levels and MetS [62, 63]. Similarly, during a three-year follow-up, the blood concentration of Zn was not linked to an elevated risk of MetS in a Chinese nested case-control study [64]. The only study that found a positive correlation between men's serum zinc and triglycerides was the NHANES in Korea [65]. Moreover, studies on the effects of zinc supplementation on insulin resistance and FBS have been conducted

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in a variety of groups, indicating that zinc supplementation may be useful in managing the condition [66, 67]. Only a few studies have looked at the relationship between insulin resistance and insulin sensitivity markers (HOMA-IR, HOMA-B, QUICKI index), some glycemic markers (insulin and glucose), and serum zinc levels in GDM. As previously mentioned, there are no statistically significant correlations between zinc and parameters. Interestingly, confounding effects are not taken into account while calculating correlations [68, 69]. Furthermore, even after adjusting for age and race in healthy early-adolescent girls, there is no correlation between plasma zinc and insulin or HOMA-IR [70]. In this regard, it is important to note that a study by Karajibani et al. [71] discovered a significant correlation between serum zinc levels and indices like height, IR ($p<0.001$), gestational age ($p<0.03$), and diastolic blood pressure ($p<0.001$), which was consistent with the results of another study by Feng et al., [72].

Significantly reduced zinc levels in diabetic patients compared to healthy individuals have also been found in other studies [73–75]. According to Ahmad et al. [76], the reduced zinc levels seen in type 2 diabetic patients have been linked to an increase in urine zinc excretion and a decrease in zinc absorption from the gastrointestinal tract. HbA1c and blood zinc levels are significantly correlated negatively in people with diabetes, according to several studies. Crucially, insulin couples with two zinc ions to form a hexameric structure, which is required for insulin to mature inside the secretory granules of pancreatic β-cells and then be released (Figure 3) [77, 78]. It forms crystalline insulin-zinc hexamers by entering insulin granules via ZnT8. Additionally, zinc binds to metal-responsive transcription factor-1 (MTF-1), which moves to the nucleus to increase MT gene expression. Reactive oxygen species (ROS) and oxidized MT (MT-Ox) [77, 78].

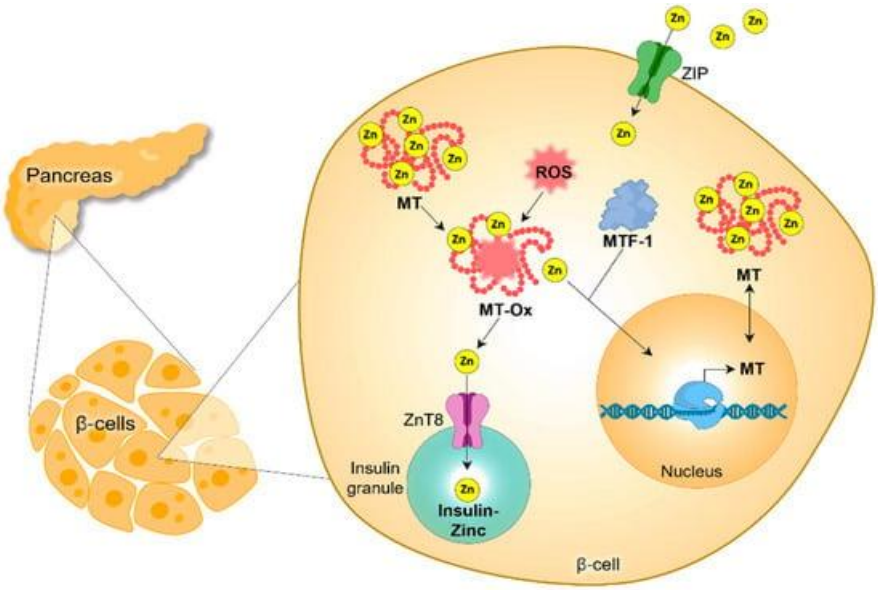

Figure 3. Zinc homeostasis and pancreatic β-cell: During cellular stress, intracellular free cytosolic zinc can be liberated from metallothionein (MT) or imported via ZIP transporters.

Conclusion

Iron and zinc microminerals are involved in the pathophysiology of diabetes mellitus. The pathophysiology of diabetes mellitus involves low zinc and iron levels below normal limits. Blood sugar levels can be lowered by modifying the iron supplementation, particularly in diabetes mellitus who are iron-deficient. Because FBG and HbA1c levels are linked to iron deficiency anemia, screening the body for iron levels is essential for both diagnosing and treating diabetes mellitus. Inadequate intake, malabsorption, excessive excretion, and increased usage can all lead to zinc and iron deficiencies, which are more common in developing nations where the prevalence of diabetes, primarily type 2 diabetes, is also on the rise. This analysis reveals a new possible role of zinc and iron status and its strong connections with indices of insulin sensitivity and insulin resistance, albeit these findings need to be confirmed by additional, larger, and expanded studies. The review's findings demonstrate that these novel surrogate biomarkers can be employed as computational laboratory indices for the detection of insulin resistance in patients with diabetes mellitus, obesity, pregnant women, and certain other physiological situations. Moreover, reducing diabetes risk could be possible by medically modifying the levels of these elements, a possibility that warrants further investigation in future studies.

Conflicts of Interest

The authors declare no conflicts of interest.

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