www.bircu-journal.com/index.php/birci
Budapest International Research and Critics Institute-Journal (BIRCI-Journal)
Humanities and Social Sciences
ISSN 2615-3076 Online)
ISSN 2615-1715 (Print)
Budapest Institute

A Literature Review on the Relationship between Iron and Zinc Levels in Diabetes Mellitus and the Effects of Their Supplementation

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Abstract

This study aims to review the relationship between iron and zinc in diabetes mellitus and the effects of iron and zinc supplementation on changes in blood glucose levels. The results showed that diabetes mellitus was associated with low zinc levels and high levels of iron in body serum, as well as low iron levels in diabetes mellitus with iron deficiency anemia. Zinc supplementation in diabetes mellitus and iron in diabetes mellitus with iron deficiency anemia can reduce levels of fasting blood glucose and hemoglobin A1c. Nutritional therapy with zinc and iron supplements can decrease blood glucose levels with results that are influenced by dosage and period of supplementation. Screening for iron deficiency anemia needs to be done in diagnosing diabetes mellitus and implementing nutritional therapy with biomarkers of blood sugar levels in serum.

Keywords
blood glucose; diabetes mellitus; iron; nutritional therapy; zinc

I. Introduction

Diabetes mellitus (DM) is a chronic disease related to metabolic disorders. Diabetes mellitus type 2 (T2DM) is the most common type with biomarkers of hyperglycemia, insulin resistance, and low adiponectin levels (Abdella & Mojiminiyi, 2018; IDF, 2019b; Jiffri & Al-Dahr, 2017). The global prevalence of DM in 2019 was 463 million for ages 20 to 79 years where the prevalence increased by 151 million compared to 2018 (IDF, 2019a).

DM management can be done with nutritional diet therapy. Nutritional food therapy is critical in the management of diabetes patients, particularly those who are resistant to standard treatment. That is because nutritional therapy can help lower the likelihood of diabetic retinopathy, while also maintaining the retina's structure and function (Robles-Rivera et al., 2020). However, ineffective DM treatment therapy can lead to the development of DM can cause complications. Management solutions for T2DM related to nutritional diet therapy need to be developed to obtain the optimal T2DM management so that other disease complications do not occur (WHO, 2018).

Health Promotion is an effort to improve the abilityof the community through learning from, by, for and with the community, so that they can help themselves, and develop activities that are community-based, in accordance with local socio-cultural conditions and supported by public health-minded policies (Maswita, 2020). Diabetes mellitus is a chronic metabolic disorder due to insulin deficiency or due to peripheral tissue resistance to insulin action. The path physiology involved is (1) decreased sensitivity of skeletal and hepatic muscle to insulin and (2) inadequate insulin secretion. Pregnancy is a state of chronic low-grade inflammation. This is associated with increased levels of circulating C-reactive protein (CRP) and Interleukin-6 (IL-6). Both of these factors trigger

insulin resistance. The disorder lies in the secretion and action of insulin. The main effect is hyperglycemia (Yeni et al, 2020).

Several studies have found abnormal levels of micro-minerals such as iron and zinc in DM (Jiang et al., 2004; Xu et al., 2013). Iron and zinc supplementation in the treatment of DM has been carried out but has given controversial results concerning blood sugar levels. This study aims to review the effect of iron and zinc supplementation on blood sugar levels in the treatment of DM.

II. Research Methods

The purpose of this study was to determine the relationship between Iron and Zinc in Diabetes Mellitus, and their effect on the consumption of these two substances. This research uses qualitative research with descriptive analysis approach. The data used in this study are secondary data. The method of data collection in this research is to use the type of literature study. The results of the research are then discussed and analyzed from various points of view, to then draw a conclusion.

III. Results and Discussion

3.1 The Role of Iron in Health

Iron is a necessary nutrient but also a possible cytotoxin. Electron transfer reactions, gene regulation, oxygen binding and transport, differentiation, immune system enhancement, and cell growth regulation are all substantially influenced by a sufficient availability of iron in the body (Siddiqui et al., 2014).

The Recommended Dietary Allowance (RDA) for iron at ages 19 to 50 years is 8 mg/day for men and 18 mg/day for women. At the age of more than 50 years, the recommended consumption of iron is 8 mg/day. The range of normal serum Fe levels in adults is 60-170 μg/dL (National Institute Health, 2021).

Iron has a key role in maintaining the pancreatic islet cells physiological function's. Iron is involved in the electron transport pathway in the mitochondria. Iron stimulates Adenosine Triphosphate (ATP) synthesis, which can directly stimulate the secretion of Glucose-Stimulated Insulin (GSIS). By boosting iron synthesis, Reactive Oxygen Species (ROS) play a critical role in the GSIS process. The synthesis of ROS and ATP due to the induction of iron plays a role in glucose-stimulated insulin secretion. Hydroxylation and iron-dependent degradation of hypoxia-induced factor-1α (HIF-1α) suppress insulin secretion and glucose-stimulated ATP synthesis. Insulin secretion can increase when HIF-1α reaches optimal levels, while non-optimal HIF-1α at values above or below the optimal will inhibit the process (Wang et al., 2015).

3.2 Iron and Diabetes Mellitus Relationship

Iron stores that are quite high above normal are associated with hemochromatosis, which is involved in the etiology of diabetes. Increased iron storage can result in diabetes via a number of processes, including reduced hepatic insulin extraction by the liver, impaired insulin's ability to regulate hepatic glucose synthesis, and oxidative damage to pancreatic cells (Siddiqui et al., 2014).

Iron is involved in the pathophysiology of diabetes mellitus, which is mediated via apoptosis and insulin resistance. The molecular processes by which these effects are mediated, including oxidative stress and adipokine regulation, as well as intracellular signal transduction pathways. Iron plays a function in the pathophysiology of diabetes

mellitus as evidenced by an increase in the incidence of T2DM in various risk factors for iron overload and a reduction in DM as measured by blood sugar levels. with iron chelation therapy resulting in a decreased iron load. The causative relationship with iron overload is shown by decreased iron stores, increased insulin secretion, and increased insulin sensitivity. The mechanism of DM related to iron levels can be explained in terms of liver dysfunction, insulin resistance and insulin deficiency. Insulin resistance is caused by an excess of iron either directly or indirectly through poor liver function. Insulin resistance is caused by an excess of iron either directly or indirectly through hepatic dysfunction (Swaminathan et al., 2007).

Iron overload reduces insulin secretory capacity through a mediating effect on pancreatic islet apoptosis. Pancreatic islets are susceptible to oxidative damage, because they rely on mitochondrial glucose metabolism for glucose-induced insulin release and have minimal antioxidant defense system expression. Additionally, high expression of divalent metal transporters predisposes cells to accumulate more iron than other cells, which may be hazardous due to iron-catalyzed oxidative stress (Swaminathan et al., 2007).

Increased iron intake and increased iron stores were stated as significant independent contributors to insulin resistance (Fernandez-Real et al., 2015). Iron metabolism in the development of DM insulin resistance can be explained by osteocalcin-stimulated adiponectin secretion from adipocytes. Increased serum ferritin levels can reduce adiponectin levels, accompanied by disturbances in fasting glucose and fasting insulin (Wang et al., 2015).

Excess iron stimulates inflammation of macrophages. It impairs insulin sensitivity and decreases adiponectin secretion. Iron that induces the suppression of osteocalcin secretion can affect adiponectin secretion from adipose tissue. Iron-induced activation of the hepatic kinase B1 (LKB1)/AMPK pathway mediated by ROS can directly inhibit insulin receptor phosphorylation in adipose tissue, muscle and liver. Iron deficiency leads to the pathogenesis of insulin resistance through its interaction with inflammation of macrophages, adiponectin secretion and hypoxia. (Wang et al., 2015).

3.3 Effect of Iron Supplementation on Mellitus Diabetes

High levels of iron can be obtained through large amounts of vegetables, fruit, magnesium, whole grains, cereal fiber, and multivitamin supplements. A high heme iron intake is connected with increased consumption of total and saturated fat, carbs, protein, and red meat, as well as a lower glycemic load. The iron diet was found to be inversely associated to the likelihood of developing type 2 diabetes. (Rajpathak et al., 2006). In the previous explanation, it was explained that high iron levels are a risk of DM, but lack of iron intake is also a risk factor for T2DM. This can be shown by meeting DM patients with iron deficiency anemia.

Lack of iron stores is associated with increased glycation of hemoglobin A1C (HbA1c). In DM with iron deficiency anemia (IDA), HbA1c levels are higher than in non-IDA. (Ahmed et al., 2019; Katwal et al., 2020). The mechanism of elevated HbA1c levels in patients with IDA is unclear. Shanthi et al. (2013) propose that IDA makes the quaternary structure of the Hb molecule convertible and facilitates the glycation of the β-globin chain. El-Agouza, Abu Shahla and Sirdah (2002) suggested that decreased Hb concentration could increase glycated fraction at a constant glucose level. This is because hemoglobin A1c (HbA1c) is measured as a percentage of the total HbA. HbA1c levels shifted to be higher in the pre DM and normoglycemic ranges, but not in the DM range in individuals with IDA. Thus, HbA1c should be considered if it is to be used for the pre-

DM screening test for individuals with IDA (Hong et al., 2015). The relationship between iron and HbA1c levels is inversely related. Several studies developed iron supplementation therapy to lower blood sugar levels (Table 1).

Table 1. Effects of iron supplementation on DM

No.	Study	Formulation, dosage, period	Note
1	Randomized, placebo-controlled, single-blind clinical trial on T2DM patients (Nasli-Esfahani et al., 2017)	200 mg/day iron supplement, 3 months	Iron supplementation therapy can reduce HbA1c in patients with iron deficiency anemia and T2DM.
2	Clinical trial on 125 male Saudi adult normal, IDA, and T2DM (Ahmed et al., 2019)	N/A	HbA1c and fasting blood glucose (FBG) decreased significantly after iron supplementation on T2DM with IDA
3	Clinical study anemia defisiensi besi dengan DM dan prediabetes (Madhu et al., 2017)	100 mg iron supplement, 3 months	Iron supplementation reduces HbA1c levels in prediabetes and DM with IDA

Source: data proceed

Iron supplementation studies had been done in DM patients, especially DM patients with iron deficiency anemia. Iron supplementation with a dose of 200 mg/day or 100 mg/day in DM patients with IDA for 3 months has been able to reduce HbA1c. HbA1c is generally used to assess long-term blood glucose control in DM patients so that it can be used as a predictor of the risk of developing many chronic complications of DM (Nasli-Esfahani et al., 2017). Ahmed et al. (2019) reported similar results but lowered not only HbA1c but also FBG although they did not report the period and dose of iron supplementation. Low iron levels increase HbA1c and FBG levels. IDA is a risk factor for TDM. Iron supplementation in DM with IDA reduces the risk of DM complications.

Soliman et al. (2017) studied iron supplementation therapy in DM and non-DM. The results indicated that iron supplementation decreased HbA1c in diabetic and non-diabetic individuals. Thus, iron levels should be considered when measuring the HbA1c concentration in diabetic or non-diabetic patients. DM complications can be prevented by increasing glycemic control through early diagnosis and treatment of ID in DM patients. Nasli-Esfahani et al. (2017) also reported that there was an association between iron and HbA1c therapy in T2DM patients. In addition to blood glucose levels, HbA1c levels are also influenced by various other factors including iron deficiency status. Changes in HbA1c levels due to IDA are associated with decreased ferritin levels and increased red blood cell lifespan. The ferritin concentration was independently associated with the development of T2DM (Jiang et al., 2004). Other studies have shown that the increase in ferritin levels in T2DM occurs by the main mechanism being inflammation other than iron overload (Hernandez et al., 2005).

IDA can increase the levels of HbA1c and FBG in DM patients compared to non-IDA. HbA1c and FBG measurements become less accurate for the diagnosis and monitoring of DM in individuals with IDA. Therefore, measurement of HbA1c and FBG levels can be used for the diagnosis and monitoring of DM by screening for iron deficiency anemia.

3.4 The Role of Zinc on Health

Zinc promotes glucose and fat utilization and is necessary as a cofactor for the operation of intracellular enzymes involved in protein, lipid, and glucose metabolism (Siddiqui et al., 2014). Zinc's Recommended Daily Allowance (RDA) for men and women over the age of 19 is 11 mg per day for men and 8 mg per day for women. Zinc is a mineral that can be gained from food or supplementation. Zinc-rich foods include red meat, chicken, nuts, some types of seafood (such as oysters, crab, and lobster), as well as whole grains, cereals, and dairy products. Supplements that contain zinc include zinc sulfate, zinc acetate, and zinc gluconate with different zinc content for each supplement (National Institue of Health, 2021).

The normal range of Zn in serum/plasma is 84-159 μg / dL. One of the levels of Zn in the breath that is not within normal limits is related to disease, one of which is DM. The antigenic nature of Zn affects insulin binding to the hepatocyte membrane and deficiency can increase insulin resistance and hyperglycemia (Siddiqui et al., 2014).

3.5 Zinc and Diabetes Mellitus Relationship

Serum levels of Zn in T2DM patients are lower than in non-diabetic individuals because impaired endogenous intestinal reabsorption and increased excretion of zinc into the intestine during digestion can lead to low serum Zn levels (Praveeena et al., 2013; Siddiqui et al., 2014). Zn is very complex, with no clear causal relationship. Zinc has a role in the storage, secretion and synthesis of insulin, as well as the integrity of the hexameric conformation of insulin. This role may regulate the occurrence of intracellular insulin receptors that affect the ability to support normal pancreatic reactions and glucose tolerance to glucose load. It affects the protection of β cell damage and has an antiviral effect (Praveeena et al., 2013).

Zinc promotes the oligomerization of adiponectin with a higher molecular weight through influencing the production of disulfide bonds. Serum zinc and adiponectin levels are positively correlated. Zinc-α 2-glycoprotein (ZAG) functions in adipose tissue. Downward or upward ZAG expression is governed by negative or positive stimuli. In adipose tissue, ZAG inhibits the activity of FAS and Acetyl-CoA carboxylase 1 (ACC1), thereby causing a decrease in fatty acid synthesis. Lower levels of free fatty acids together with increased expression of Zinc-a2-glycoprotein (ZAG)-induced adiponectin can significantly reduce insulin resistance (Olechnowicz et al., 2018).

The drop in serum Zn levels in diabetes mellitus is due to an increase in urine production. Hyperglycemia inhibits active transport from tubular cells to the nucleus. Other factors can impair the metabolism of zinc metalloenzymes and result in aberrant zinc binding to tissue proteins, resulting in hyperzincuria. Zinc has been shown to boost insulin efficacy in vitro, and so zinc deficiency can exacerbate insulin resistance in T2DM. Zn is required for the activity of antioxidant enzymes such as superoxide dismutase, catalase, and peroxidase. Insulin is stored in pancreatic cells as a hexamer containing two zinc ions and is released into the portal venous system during cell β cell de-granulation (Afkhami-Ardekani et al., 2015).

Table 2. Effects of Zn supplementation on DM

No.	Study	Diet Period	Formulation and dosage	Note
1	A cohort study on T2DM rats (Ryadinency et al., 2018)	30 days	5 mg/kg zinc sulfate	10 mg / kg zinc supplementation decreased FBG levels
2	Male Wistar rat (Moustafa, 2004)	72 hours	5 mg/kg ZnCl2 and alloxan 100 mg/kg	Blood glucose and plasma insulin levels decreased after 24 supplementation
3	Randomized clinical trial on 70 diabetic patients (Afkhami-Ardekani et al., 2015)	8 weeks	100 mg/day zinc sulfate	Zinc supplementation caused a significant reduction in HbA1c
4	Randomized clinical trial on T2DM patient (Seet et al., 2011)	3 months	240 mg/day Zn gluconate	No beneficial effects on FBG and Insulin.

Source: data proceed

Zn supplementation has many beneficial effects on DM in animal and human (Table 2). A study giving a single injection of alloxan and ZnCl2 in mice resulted in a significantly reduced alloxan-induced increase in blood glucose concentrations at 24, 48, and 72 hours post-treatment with ZnCl2 (Ranasinghe et al., 2015). A study of the literature revealed that zinc supplementation has a favorable effect on glycemic control in diabetes individuals (Jayawardena et al., 2012). Zinc is required for normal cell function, glucose homeostasis, insulin action, and the pathophysiology of diabetes and its consequences (Ranasinghe et al., 2015).

Zn supplementation caused significant reductions in FBG and HbA1c in humans and mice with DM. In rats, a decrease in sugar levels occurred with 5 mg/kg zinc sulfate supplementation for 30 days and even a decrease in glucose levels was seen 24 hours after 5 mg/kg ZnCl2 and 100 mg/kg alloxan supplementation (Moustafa, 2004; Ryadinency et al., 2018). In humans, a decrease in HbA1c levels occurred after supplementation of 100 mg/day zinc sulfate for 8 weeks (Afkhami-Ardekani et al., 2015). Different results were reported in the study Seet et al. (2011) that supplementation with 240 mg/day Zn gluconate in T2DM does not affect FBG and insulin.

Zn supplementation affects the regulation of blood glucose levels which can be explained by various molecular mechanisms. The mimetic and hypoglycemic properties of insulin via the Zn (II) complex have been studied in in-vivo and in-vitro research. Protein tyrosine phosphatase 1B (PTP 1B), the primary regulator of insulin receptor phosphorylation status, is a zinc ion target. Zinc may contribute to increased peripheral insulin sensitivity by enhancing insulin-stimulated glucose transport. Zinc has a critical part in cell physiology. Zinc supplementation also reduces the HbA1c value (Jayawardena et al., 2012).

Soheilykhah et al. (2012) studied that Zn significantly increased adiponectin levels, but decreased insulin levels and insulin resistance. Zinc significantly increases adiponectin levels in diabetic patients. Insulin levels and the homeostasis model assessment (HOMA) index after Zn supplementation decreased but this decrease was not significant. Zinc supplementation increases adiponectin levels.

Increased circulating insulin and adipose tissue expression of the zinc-alpha2-glycoprotein (ZAG) gene. ZAG mRNA was adversely related with insulin resistance indicators such as plasma insulin and the homeostasis model of insulin resistance (Chen et al. 1998). However, ZAG and adiponectin mRNA were found to be positively correlated, and ZAG boosted adiponectin production via human gluconeogenesis and glucose adipocytes. Chen et al. (1998) investigated the effect of zinc supplementation on insulin and glucose levels in obese and lean control mice. Zinc supplementation resulted in a 51% reduction in fasting plasma glucose in obese mice and a 25% reduction in lean animals.

Thus, Zn supplementation can benefit DM patients by performing glycemic control which also increases adiponectin levels. However, not all studies provide relevant results because studies were conducted with subjects with different characteristics and with different doses, types of supplements, and periods and the various mechanisms involved cannot be fully explained with certainty that could affect the results on blood glucose levels. Thus, dosage, type of supplement, and zinc supplementation period need to be considered in providing optimal therapy in DM patients.

IV. Conclusion

Zinc and iron microminerals play a role in the pathogenesis of DM. Low zinc levels and high iron levels below normal limits are the pathogenesis of DM. Low iron levels are also a risk factor for DM. Iron supplementation can reduce blood sugar levels and so can iron supplementation, but especially in DM with iron deficiency. The link between FBG and HbA1c levels with iron deficiency anemia makes it necessary to screen iron levels in the body at the diagnosis of DM and in treating DM. This is done to provide proper nutritional therapy to DM patients when using blood sugar levels as a biomarker for the development of DM. Human studies are still few and there are not many studies on the factors that influence therapeutic effectiveness as well as the proper dosage and period of nutritional therapy, so further research is needed.

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