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EFFECT OF ZN SUPLEMENTATION ON BLOOD GLUCOSE LEVELS AND INSULIN RESISTANCE IN DIABETES MELLITUS

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ABSTRACT

Diabetes mellitus (DM) is a metabolic disorder characterized by high levels of glucose in the blood. Micromineral levels are related to the mechanism of glucose homeostasis. The abnormal zinc levels can be risk factors for DM. Improvement of micro-mineral levels can improve blood sugar levels. This study aimed to review the effects of zinc supplementation on blood glucose levels and insulin resistance. This study showed that DM was associated with low zinc levels in body serum. Zinc supplementation reduced fasting blood glucose, hemoglobin A1c levels, and insulin resistance in rat model DM and human researchs. It occurs in many types of Zn supplements. Differences in results may be due to differences in the characteristics of the subjects, doses, and periods of administration. Zn can be used for nutritional therapy in DM by considering the dose and period of supplementation, and patient characteristics to get optimal results.

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; Federation, 2019; Jiffri & Al-Dahr, n.d.). The global prevalence of DM in 2019 was 463 million for ages 20 to 79 years where the DM management can be done with nutritional diet therapy. Nutritional diet therapy plays a very important role in the treatment of DM patients, especially in DM patients who are resistant to conventional treatment. That's because nutritional therapy can reduce the risk of diabetic retinopathy, structure of the retina, and maintaining normal 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 (Organization, 2018).

Several studies found that the abnormal zinc levels can be risk factors for DM (Jiang et al., 2004; Xu et al., 2013). 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 zinc supplementation on blood sugar levels and insulin resistance in the treatment of DM.

Research Method

This study uses the literature review method. The article search strategy was carried out using national international journal articles that were searched through Google Scholar. Articles were searched with the keywords “Zn supplementation”, “insulin resistance”, “blood glucose”, and “diabetes

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mellitus". The search obtained as many as 1,640 articles.

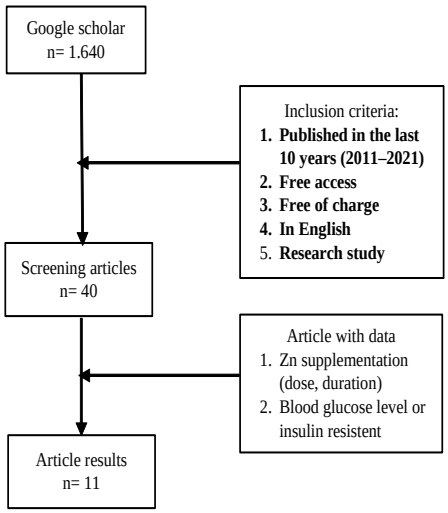

Figure 1
Search Scheme Of Articles

Articles were screened with inclusion criteria, namely articles published in the last 10 years (2011–2021), free access, free of charge, using English, and types of research. Screening results obtained 40 articles. There were 11 articles that matched the research topic containing the results of Zn supplementation on insulin resistance and blood glucose levels.

Discussion

Zinc aids in the use of glucose and fat and is required as a cofactor for the function of intracellular enzymes involved in the metabolism of protein, lipids, and glucose (Siddiqui et al., 2014). The Recommended Dietary Allowance (RDA) for zinc for ages 19 and over is 11 mg/day for men and 8 mg/day for women. Zinc can be obtained from food or supplements. Foods that contain zinc include red meat, poultry, nuts, certain types of seafood (such as oysters, crab, and lobster), 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 (Khan, 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).

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 (Sharifah et al., 2018; 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 (Sharifah et al., 2018).

Zinc stimulates the oligomerization of higher molecular weight forms of adiponectin by modulating the formation of disulfide bonds. There is a positive correlation between serum Zn and adiponectin levels. 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 cause of decreased serum Zn levels in DM is an increase in urine output. Hyperglycemia impairs active transport back to tubular cells. Other causes can interfere

with the metabolism of zinc metalloenzymes and abnormal binding of Zn to tissue proteins, leading to hyperzincuria. Zinc has been found to increase the effectiveness of insulin in-vitro and hence, Zn deficiency can worsen insulin resistance in T2DM. Antioxidant enzymes such as oxide dismutase, catalase, and peroxidase require Zn. Insulin, stored as a hexamer containing two Zn ions in pancreatic β cells and released into the portal venous system during β cell de-granulation (Afkhami-Ardekani et al., 2015).

Zn supplementation has many beneficial effects on DM in animal and human (Table 1). 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). Study review showed that the effect of zinc supplementation in diabetic patients indicated that supplementation Zinc has a beneficial effect on glycemic control (Jayawardena et al., 2012). Zinc plays an important role in β cell function, glucose homeostasis, insulin action, and the pathogenesis of diabetes and its complications (Ranasinghe et al., 2015).

Zn supplementation caused significant reductions in FBG and HbA1c in humans and rat with DM. In rats, DM model rat were prepared by induced streptozotocin (STZ), 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 (Ranasinghe et al., 2015; Ryadinency et al., 2018). Similar results were reported with supplementation with 10 mg/kg zinc sulphate (Ryadinency et al., 2018), 10 mg/kg ZnONP (Afify et al., 2019), and 150 mg/kg curcumin–Zn complex in the on-Rats DM model.

Table 1
Effects of Zn supplementation on DM

No.	Study	Diet Period	Formulation and dosage	Result
1	Rats DM model with STZ induction (Ryadinency et al., 2018)	30 days	5 dan 10 mg/kg body weight/rat/day berat tikus zinc sulfate	Zinc supplementation at 5 mg/kg significantly reduced FBG levels, but not at 10 mg/kg
2	Male Wistar rat (Ranasinghe et al., 2015)	72 hours	5 mg/kg ZnCl2 and alloxan 100 mg/kg	Blood glucose and plasma insulin levels decreased after 24 supplementation
3	Rats DM model with STZ induction (Afify et al., 2019)	21 days	10 mg/kg body weight/rat/day ZnONPs	ZnONP decreasing blood glucose and increasing serum insulin
4	Rats DM model with STZ induction (Al-Ali et al., 2016)	45 days	150 mg/kg body weight/rat/d for curcumin–Zn complex	Curcumin–Zn complex significantly reduced blood glucose and HbA1c.
5	Randomized clinical trial on diabetic patients (Afkhami-	8 weeks	100 mg/day zinc sulphate	Zinc supplementation caused a significant reduction in HbA1c

	Ardekani et al., 2015)			
6	Randomized clinical trial on T2DM patient (Seet et al., 2011)	3 months	240 mg/day Zn gluconate	No beneficial effects on FBG and Insulin.
7	Randomized clinical trial DM patient (Soheilykhah et al., 2012)	12 weeks	50 mg/day zinc gluconate	HOMA IR and insulin decrease but not significant
8	Randomized, double-blind, placebo-controlled Phase II on DM patient (Ranasinghe et al., 2015)	12 months	20 mg/day Zinc gluconate	OGTT, FBG, HOMA-IR significantly reduced
9	Randomized controlled clinical Trial on DM patient (Witwit et al., 2021)	6 weeks	50 mg/day Zinc sulphate	Insulin resistance and HbA1c were significantly decreased
10	Clinical trial on gestational diabetes (Roshanravan et al., 2015)	8 weeks	30 mg/day zinc gluconate	Serum levels of insulin, fasting blood sugar and HOMA-IR were significantly decreased
11	Double-blind randomized placebo-controlled trial patients with non-proliferative diabetic retinopathy (Naghizadeh et al., 2018)	3 months	30 mg/day zinc gluconate	Fasting insulin, FBG, HOMA-IR significantly decreased, but not in HbA1c.

In human researches (Table 1), a decrease in HbA1c levels occurred after supplementation of 100 mg/day zinc sulfate for 8 (Afkhami-Ardekani et al., 2015), and 50 mg/day zinc sulphate for 8 weeks (Jayawardena et al., 2012). Significant reduction in FBG levels occurred after supplementation with 20 mg/day Zinc gluconate for 12 months (Ranasinghe et al., 2015) nd 30 mg/day zinc gluconate for 3 months (Naghizadeh et al., 2018). (Naghizadeh et al., 2018) reported that HbA1c was not significantly decreased with supplementation of 30 mg/day zinc gluconate for 3 months in patients with non-proliferative diabetic retinopathy. (Seet et al., 2011) reported 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 main regulator of the phosphorylation state of insulin receptors, targets Zn ions. Zinc can play a role in increasing peripheral insulin sensitivity because it can increase glucose transport stimulated by insulin. Zinc has an important functional role in β cell physiology. Zinc supplementation also reduces the HbA1c value (Jayawardena et al., 2012).

Zn supplementation not only affects blood sugar levels but also insulin resistance. Several studies reported a significant reduction in insulin resistance based on the homeostasis model assessment (HOMA) index after Zn supplementation in DM patients (Ranasinge, Roshanravan, Naghizadeh). Different result reported by (Soheilykhah et al., 2012) that Zn significantly increased adiponectin levels, but not significantly decreased insulin levels and insulin resistance.

Increased circulating insulin and adiposity decrease the expression of zinc-alpha2-glycoprotein (ZAG) gene in adipose tissue. ZAG mRNA and insulin resistance parameters such as plasma insulin and the homeostasis model of insulin resistance were negatively associated (Chen et al., 1998). However, ZAG and adiponectin mRNA were positively related, and ZAG increased adiponectin production by human gluconeogenesis and increased glucose adipocytes. (Chen et al., 1998) evaluated the effect of Zn supplementation on insulin and plasma glucose levels in obese and lean control mice. As a result, zinc supplementation reduced fasting plasma glucose in obese mice by 51% and in lean mice by 25%.

Conclusion

Zinc deficiency played role in the pathogenesis of DM. Zinc supplementation reduced blood sugar levels and insulin resistance in DM. These results were even obtained from various types of Zn supplements. The implication of these results is that zinc supplements can be useful as an alternative nutritional therapy for DM patients who are able to reduce blood sugar levels and insulin resistance.

However, some irrelevant results are possible due to differences in characteristics subject, doses, and periods of zinc supplementation. The various mechanisms involved have not been fully elucidated with certainty that may affect the outcome on blood glucose levels and insulin resistance. Research related to variations in dosage and duration of zinc supplementation as well as patient characteristics need to be studied in further research to find out the effectiveness of supplementation. 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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