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Effects of Vitamin D Supplementation on Blood Glucose Levels in Streptozotocin-Induced Diabetic Rats

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Abstract

Diabetes mellitus (DM) is a chronic metabolic disorder characterized by persistent hyperglycemia due to impaired insulin secretion, insulin resistance, or both. Poor glycemic control in DM leads to complications such as cardiovascular disease and nephropathy. Vitamin D has been suggested to influence glucose metabolism by improving insulin secretion and sensitivity thorugh mechanisms involving pancreatic β-cells and anti-inflammatory pathways. This study evaluates the effect of vitamin D supplementation on blood glucose levels in diabetic rats. An experimental study was conducted using 25 males Sprague Dawley rats, divided into five groups: Group A (negative control), Group B (non-DM + 415 IU/kgBW vitamin D), Group C (DM without vitamin D), Group D (DM + 415 IU/kgBW vitamin D), and Group E (DM + 1100 IU/kgBW vitamin D). Diabetes was induced using streptozotocin (50 mg/kg BW), and rats with random blood glucose levels >200 mg/dL were considered diabetic. Vitamin D supplementation was given via gavage for 30 days. Serum vitamin D and random blood glucose levels were measured 30 days after supplementation. Statistical analyses included ANOVA and Pearson correlation tests. Vitamin D supplementation significantly increased serum vitamin D levels in diabetic rats, especially in Group E (DM + 1100 IU/kgBW vitamin D; ($p < 0.05$). Random blood glucose levels decreased significantly in diabetic groups and Group E showed the largest glucose reduction ($p < 0.001$). A moderate negative correlation ($r = -0.47$, $p = 0.017$) between vitamin D levels and glucose changes was observed. Vitamin D supplementation reduces blood glucose levels in diabetic rats, with higher doses showing greater efficacy. These findings highlight vitamin D's potential as an adjunctive therapy for diabetes management. Further research is needed to explore underlying mechanisms.

Keywords *: blood glucose, diabetes mellitus, vitamin D*

I. INTRODUCTION

Diabetes mellitus (DM) is a chronic metabolic disorder characterized by persistent hyperglycemia due to impaired insulin secretion, insulin resistance, or both.[1] It is a significant global health concern, with type 2 diabetes mellitus (T2DM) comprising the majority of cases.The global prevalence of type 2 diabetes is expected to rise significantly, with projections estimating 7,079 individuals per 100,000 by 2030, while the number of affected individuals worldwide is anticipated to increase from 415 million currently to 642 million by 2040.[2,3] Data from the International Diabetes Federation (IDF) indicate that approximately 536.6 million individuals aged 20 to 79 years were living with type 2 diabetes mellitus (T2DM) in 2021. This number is projected to rise to approximately 783.2 million individuals by the year 2045.[4]

Poor glycemic control in diabetes is associated with a range of complications, including cardiovascular disease, neuropathy, nephropathy, and retinopathy. Hence, identifying factors that can mitigate hyperglycemia and improve glycemic control is critical for managing this condition effectively. [2,3]

Recent studies by Lei et al. (2023) demonstrated that vitamin D plays a significant role in regulating insulin resistance, with an inverse association between serum vitamin D levels and insulin resistance, highlighting its potential in glucose metabolism and diabetes management.[4] Vitamin D, a fat-soluble vitamin primarily obtained from sunlight exposure and dietary sources, exerts its effects through the vitamin D receptor (VDR), which is expressed in various tissues, including pancreatic β-cells, skeletal muscle, and adipose tissue. [5] These tissues are central to glucose homeostasis, suggesting a direct mechanistic link between vitamin D and glycemic control.

Vitamin D has been reported to influence insulin secretion and sensitivity through multiple pathways. It enhances insulin secretion by modulating calcium influx in pancreatic β-cells, which is essential for insulin release. Additionally, vitamin D reduces insulin resistance by regulating inflammatory pathways and improving the function of insulin receptor signaling. Vitamin D's anti-inflammatory and immunomodulatory properties may also play a role in mitigating diabetes-induced inflammation, which is a key contributor to insulin resistance. [6]

Despite growing epidemiological evidence supporting the association between vitamin D status and glucose metabolism, there remains a critical gap in preclinical research—particularly in experimental models that can help elucidate causality and underlying mechanisms. The streptozotocin (STZ)-induced diabetic rat model is widely recognized for mimicking several aspects of human type 2 diabetes mellitus, including β-cell dysfunction and insulin resistance. However, limited studies have explored the direct impact of vitamin D supplementation on glycemic regulation within this model, especially with regard to dose-specific effects, duration of treatment, and its influence on molecular targets involved in glucose homeostasis. Additionally, variability in study design, such as inconsistent supplementation protocols and outcome measures, has hindered the establishment of standardized guidelines. Therefore, investigating the role of vitamin D in STZ-induced diabetic rats is essential to bridge the gap between observational data and mechanistic understanding. Such preclinical studies are critical for validating the therapeutic potential of vitamin D and informing future clinical trials aimed at improving glycemic control in diabetes.

This study aims to evaluate the relationship between blood glucose levels and vitamin D supplementation in diabetic rats. By

investigating this connection, we hope to elucidate the potential role of vitamin D as an adjunctive therapeutic strategy in the management of diabetes.

II. MATERIALS AND METHOD

This study employed an in vivo experimental design using 25 male Sprague Dawley rats (Rattus norvegicus) weighing 150–200 grams, aged 8–12 weeks, and conducted at the Animal House Laboratory, Faculty of Medicine, Universitas Baiturrahmah, Padang, West Sumatera, Indonesia. All animals were acclimated in the animal house facilities for 1 week prior to the experiment. The rats were housed under controlled laboratory conditions. They were provided with food and water *ad libitum*. The study protocol was reviewed and approved by the Ethics Committee of the Faculty of Medicine, Universitas Baiturrahmah (No: 041/ETIIK-FKUNBRAH/03/07/2024).

Rats were divided into five experimental groups, each consisting of five animals, and kept in separate cages. Group A =negative control, Group B =Non DM + 415 IU/kgBW Vitamin D supplementation, Group C= DM without Vitamin D supplementation, Group D =DM + 415 IU/kgBW Vitamin D supplementation, Group E =DM + 1100 IU/kgBW Vitamin D supplementation.

We based our dosing on a study conducted by Dewi et al., in which type 2 diabetes mellitus (T2DM)-induced rats were supplemented with vitamin D at doses of 12.5–25 μg/kg for 14 days. The study demonstrated differences in GLUT4 expression in adipocytes between the control and treatment groups. However, a study by Elly involving diabetic rats supplemented with vitamin D at doses of 25–100 ng did not show any differences in GLUT4 expression in skeletal muscle between the treatment and control groups. Therefore, we aim to investigate effect of supplementation high-dose vitamin D (10–27 μg/kg or 415–1100 IU/kg) in diabetic rats.[7,8]

Rats in group A were fed with a standard diet and group B - E were fed with a high-fat diet.
After being fed with a high-fat diet (30 grams/day) for 3 weeks, rats in group C, D, and E were induced with diabetes using intraperitoneal streptozotocin (STZ) at 50 mg/kg body weight. Ten days post-injection, all rat's random blood glucose was measured, and if a random blood glucose level >200 mg/dL was obtained, the rats were considered successfully induced. Post diabetes, the rats were fed and given Vitamin D using a gavage tube according to their respective groups for 30 days. The leftover food was weighed daily to calculate the average daily intake. On day 30th, the rats were terminated and the blood samples were collected through the heart.

The samples were centrifuged at 3000 rpm for 10 minutes to separate blood serum for measuring random blood glucose and vitamin D levels. Random blood glucose was assessed using a glucometer by applying a drop of whole blood to a test strip, while serum vitamin D concentrations were quantified using an ELISA kit (Cat. No. E-EL-0014, Elabscience®, USA) following the manufacturer's instructions. The ELISA method is based on the principle of a specific antigen–antibody reaction, wherein vitamin D in the sample binds to antibodies coated on the microplate, followed by detection using an enzyme-labeled secondary antibody and a colorimetric substrate reaction.

The data from this study will be analyzed using the Statistical Product and Service Solution (SPSS) version 26.0. The normality of the data for each parameter will first be tested using the Shapiro-Wilk test, and homogeneity will be assessed using the Levene's test. Statistical analysis will be performed using ANOVA with Bonferroni post hoc test if the data are normally distributed, or the Kruskal-Wallis test with

Mann-Whitney post hoc if the data are not normally distributed. Correlations between variables will be analyzed using the Pearson correlation test. Data will be presented as mean ± standard deviation.

III. Results and Discussion

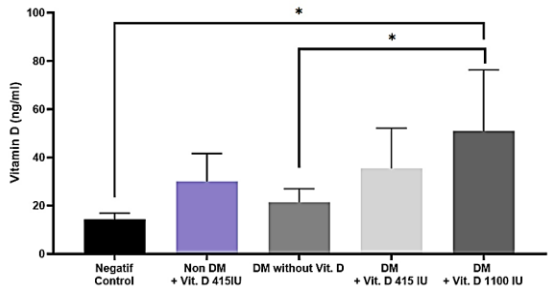
Serum Vitamin D Levels

The results of this study showed a significant difference in serum vitamin D levels among the treatment groups after vitamin D supplementation (p = 0.009). Based on the post-hoc test results, the diabetic rat group supplemented with 1100 IU/kgBW of vitamin D had significantly higher serum vitamin D levels compared to the negative control group (p = 0.009) and the diabetic group without vitamin D supplementation (p = 0.049) (Fig. 1). The serum vitamin D levels in the diabetic group supplemented with 1100 IU/kgBW were also higher than those in the non-diabetic group supplemented with 415 IU/kgBW and the diabetic group supplemented with 415 IU/kgBW, although the differences between these groups were not statistically significant (p>0,05).

Table 1. Serum Vitamin D level (pg/mL)

	Control	Non DM + Vit D 415 IU	DM without Vit D	DM + Vit D 415 IU	DM + Vit D 1100 IU	p*
Vit D level (ng/mL)	14,37±1,13	30,09±5,15	21,45±2,5	51±11,34	51±11,34	0,009

*p<0,05, one-way ANOVA



*= Serum vitamin D levels are significantly different from the diabetic group supplemented with 1100 IU/kgBW vitamin D (p < 0.05).

Figure 1. Serum Vitamin D Levels after Supplementation

In this study, we found a significant difference in serum vitamin D levels, particularly in the diabetic rat group supplemented with 1100 IU/kgBW of vitamin D compared to the negative control group and the diabetic rat group without vitamin D supplementation. This findings indicate that vitamin D supplementation at a dosage of 1100 IU/kg body weight (BW) significantly elevates serum vitamin D levels in diabetic rats compared to both negative controls (healthy rats) and diabetic rats without supplementation. This suggests that higher doses of vitamin D may be necessary to achieve optimal serum levels in diabetic conditions.

The results of this study are consistent with the findings of Nadimi et al. (2019), which demonstrated that vitamin D supplementation significantly increased serum vitamin D concentrations compared to the negative control (healthy rats) and diabetic rats without vitamin D supplementation.[9] Similarly, a study by Krisnamurti et al. (2023) reported an increase in serum vitamin D concentrations in prediabetic rats supplemented with 1000 IU/kgBW of vitamin D.[10]

Administering higher doses of vitamin D supplementation can lead to increased serum vitamin D levels in diabetic rats due to several factors. First, higher doses of vitamin D supplementation can enhance vitamin D bioavailability. Higher doses of vitamin D elevate the concentration of the vitamin in the bloodstream, increasing its availability for metabolic processes. This is particularly important in diabetic conditions, where vitamin D metabolism may be impaired.[11] Beside that, increased vitamin D intake enhances the substrate availability for

hepatic conversion into 25-hydroxyvitamin D, the main circulating form of vitamin D. This process is crucial for maintaining adequate serum levels, especially in diabetic states where conversion efficiency might be compromised.[12]

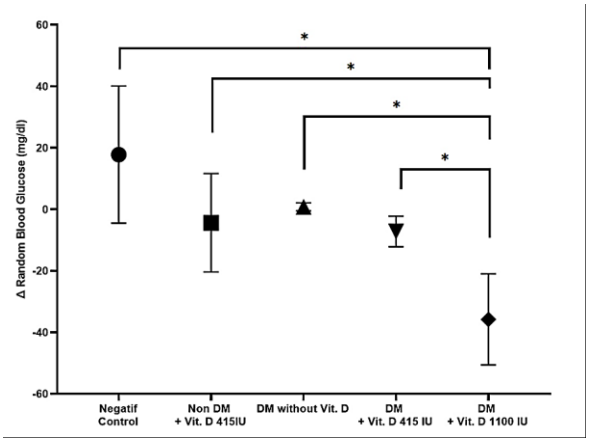
Diabetes can also induce alterations in vitamin D receptor expression and function, leading to reduced responsiveness to normal vitamin D levels.[13] Higher doses may be necessary to overcome this resistance, ensuring sufficient receptor activation and subsequent biological effects. Research by Sîrbe et al in 2022 indicates that high-dose vitamin D supplementation can modulate receptor expression, thereby enhancing its efficacy in diabetic models.[14] Elevated vitamin D levels can suppress pro-inflammatory cytokines, which are often increased in diabetes and can interfere with vitamin D metabolism. By reducing inflammation, higher vitamin D doses may restore normal metabolic pathways, facilitating increased serum vitamin D levels. Studies have shown that vitamin D supplementation decreases inflammatory markers in diabetic conditions, supporting this mechanism.[14]

THE EFFECT OF VITAMIN D SUPPLEMENTATION ON RANDOM BLOOD GLUCOSE

In this study, we found a significant difference in the change in blood glucose levels after vitamin D supplementation ($p < 0.001$). Post-hoc test results showed that the significant reduction in random blood glucose levels was observed in the diabetic group supplemented with 1100 IU/kgBW of vitamin D compared to the negative control group ($p < 0.001$), the non-diabetic group supplemented with 415 IU/kgBW of vitamin D ($p = 0.022$), the diabetic group without vitamin D supplementation ($p = 0.006$), and the diabetic group supplemented with 415 IU/kgBW of vitamin D ($p = 0.045$) (Fig. 2). These findings suggest that supplementation with 1100 IU/kgBW of vitamin D can reduces random blood glucose levels in STZ-induced diabetic rat.

TABLE 2. RANDOM BLOOD GLUCOSE PRE AND POST SUPPLEMENTATION

	Baseline of Random Blood Glucose (mg/dL)	Random Blood Glucose after supplementatio (mg/dL)	p
Negative control	104±5,52	121,8±21,3	0,149
Non DM + Vitamin D 415 IU	118±18,5	113,6±21,77	0,572
DM without Vit D	435±80,15	435,8±79,9	0,242
DM + Vit D 415 IU	317±190,92	309±191,9	0,032
DM + Vit D 1100 IU	474,2±108,1	438,4±94,69	0,006



*= Indicates a significant difference in blood glucose levels compared to the diabetic group supplemented with 1100 IU/kgBW of vitamin D ($p < 0.05$).

FIGURE 2. EFFECT OF VITAMIN D SUPPLEMENTATION ON RANDOM BLOOD GLUCOSE LEVELS

The results of the study showed a significant reduction in random blood glucose levels in the group of rats supplemented with 1100 IU/kgBW of vitamin D compared to the other groups. The study's findings indicate that vitamin D supplementation at a dosage of 1100 IU/kg body weight (BW)

significantly reduces random blood glucose levels in streptozotocin (STZ)-induced diabetic rats. This effect was notably more pronounced compared to the negative control group, non-diabetic rats supplemented with 415 IU/kgBW of vitamin D, diabetic rats without vitamin D supplementation, and diabetic rats supplemented with 415 IU/kgBW of vitamin D.

Research conducted by Moharir et al. (2020) also demonstrated a reduction in blood glucose levels in diabetic rats supplemented with 4000 IU/kgBW of vitamin D compared to the control group and diabetic rats not receiving vitamin D supplementation.[15] Similarly, a meta-analysis conducted by Musazadeh (2023) revealed that vitamin D supplementation effectively reduces blood glucose levels in diabetic conditions.[16]

The potential mechanisms through which vitamin D affects glucose metabolism include rapid non-genomic effects or slower genomic effects, such as stimulating insulin secretion by upregulating vitamin D receptor (VDR) expression. Additionally, vitamin D may reduce the release of pro-inflammatory cytokines, which are thought to play a role in insulin resistance. This hypothesis is supported by evidence linking low serum 25(OH)D levels to increased C-reactive protein concentrations. Furthermore, vitamin D might indirectly regulate extracellular and intracellular calcium levels, a critical factor in facilitating glucose transport within target tissues.[5,15]

Vitamin D plays a critical role in modulating insulin sensitivity in peripheral tissues, such as muscle and adipose tissue, through its effects on insulin receptors and glucose transporters. It enhances the expression of insulin receptors on the surface of cells, increasing their ability to bind insulin and initiate glucose uptake.[13] Furthermore, Vitamin D upregulates the production and activity of GLUT4 (Glucose Transporter Type 4), a key protein responsible for transporting glucose from the bloodstream into cells.[17] When insulin binds to its receptor, GLUT4 translocates to the cell membrane, where it facilitates efficient glucose uptake. This enhanced glucose clearance from the bloodstream contributes to the reduction of blood glucose levels, especially in insulin-sensitive tissues.[18]

In addition to its direct effects on insulin receptors and GLUT4, Vitamin D also supports insulin signaling by modulating pathways like the PI3K-Akt pathway, which plays a central role in glucose transport.[19] Its anti-inflammatory properties further aid insulin sensitivity by reducing pro-inflammatory cytokines such as TNF-α and IL-6, which can impair insulin receptor function.[20] Moreover, Vitamin D regulates intracellular calcium levels, which are essential for insulin receptor activation and GLUT4 translocation. Together, these mechanisms ensure better glucose utilization, reducing blood glucose levels and alleviating insulin resistance, particularly in conditions such as diabete.[21]

In contrast, the lack of significant changes in random blood glucose levels in the other groups may be attributed to insufficient dosing or the absence of supplementation. This underscores the importance of determining optimal vitamin D dosages to achieve therapeutic effects in diabetic conditions.

THE CORRELATION BETWEEN VITAMIN D AND RANDOM BLOOD GLUCOSE

The Pearson correlation test revealed a statistically significant correlation between vitamin D levels and changes in random blood glucose levels ($p = 0.017$). The results indicated a moderate negative correlation ($r = -0.47$), suggesting that as vitamin D levels increase, random blood glucose levels tend to decrease (Fig. 3).

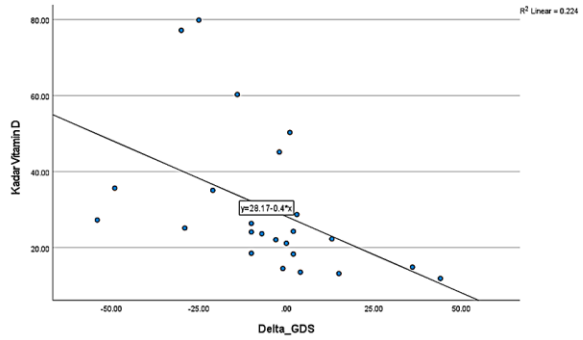


FIGURE 3. CORRELATION BETWEEN VITAMIN D LEVELS AND CHANGES IN RANDOM BLOOD GLUCOSE LEVELS

The Pearson correlation analysis in this study revealed a statistically significant moderate negative correlation ($r = -0.47$, $p = 0.017$) between serum vitamin D levels and changes in random blood glucose levels. This finding suggests that as vitamin D levels increase, there is a corresponding decrease in blood glucose levels. A systematic review and meta-analysis conducted by Lei et al. (2023) also demonstrated a negative correlation between increased vitamin D concentrations and blood glucose levels.[4]

The mechanisms underlying this correlation may involve vitamin D's influence on insulin secretion and sensitivity. Vitamin D receptors are present in pancreatic β-cells, and their activation can enhance insulin secretion. Additionally, vitamin D may improve insulin sensitivity in peripheral tissues by modulating the expression of insulin receptors and glucose transporters. Furthermore, vitamin D's anti-inflammatory properties can reduce systemic inflammation, a known contributor to insulin resistance, thereby facilitating better glucose utilization and lower blood glucose levels.[22]

One limitation of this study is the absence of comparison groups receiving either antidiabetic medication alone or in combination with vitamin D supplementation. The inclusion of such groups would have enabled a more comprehensive assessment of the therapeutic potential and possible synergistic effects of vitamin D when used alongside standard antidiabetic treatments.

IV. CONCLUSION

This study demonstrated that vitamin D supplementation significantly improves blood glucose in streptozotocin (STZ)-induced diabetic rats. Higher doses of vitamin D (1100 IU/kgBW) resulted in greater reductions in random blood glucose levels compared to lower doses (415 IU/kgBW) or no supplementation. Additionally, a significant moderate negative correlation between serum vitamin D levels and blood glucose changes suggests a dose-dependent relationship between vitamin D and glycemic regulation. These findings highlight the potential role of vitamin D as an adjunctive therapeutic approach for managing hyperglycemia in diabetes. Future studies should explore the molecular mechanisms involved, determine optimal dosing strategies, and include clinical trials to assess translational relevance. It is also recommended to include groups treated with antidiabetic drugs alone and in combination with vitamin D to evaluate potential synergistic effects.

LIMITATION

Future studies are recommended to include these comparison arms to better elucidate the role of vitamin D as an adjunct therapy. Additionally, further investigations should explore different dosages, durations of supplementation, and molecular mechanisms underlying the effects of vitamin D on glucose metabolism. Longitudinal studies assessing long-term outcomes and tissue-specific responses will also be valuable for translating preclinical findings into clinical applications.

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