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VITAMIN D AND INSULIN RESPONSE IN STREPTOZOTOCIN-INDUCED DIABETIC RATS: AN IN VIVO INVESTIGATION

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ABSTRACT

Background: Type 2 diabetes mellitus (T2DM) is a widespread global health problem, defined by increasing insulin resistance and gradual deterioration of β-cell function. Vitamin D is posited to influence glucose metabolism, although the evidence about its impact on insulin dynamics is inconsistent. **Objective:** This study evaluated the effect of vitamin D supplementation on insulin levels in a streptozotocin (STZ)-induced diabetic rat model. **Methods:** Twenty-five Sprague Dawley rats were randomly assigned to five groups: A (healthy control), B (healthy + vitamin D 415 IU/day), C (T2DM control), D (T2DM + 415 IU/day), and E (T2DM + 1,100 IU/day). Diabetes was induced using a high-fat diet followed by STZ injection. Vitamin D supplementation was given orally for 30 days. Serum insulin and vitamin D were measured by ELISA, and group differences were analyzed using one-way ANOVA with Bonferroni post hoc testing. **Results:** Insulin concentrations differed significantly across groups ($p = 0.022$). Healthy rats receiving vitamin D (Group B) exhibited higher insulin levels compared with both diabetic controls ($p = 0.004$) and diabetic rats supplemented with the same dose ($p = 0.005$). Higher-dose supplementation in diabetic rats (Group E) showed only a nonsignificant trend toward increased insulin ($p = 0.224$). No significant correlation was observed between serum vitamin D and insulin levels ($r = 0.171$, $p = 0.415$). **Conclusion:** Vitamin D supplementation markedly enhanced insulin secretion in healthy rats but did not improve insulin output in diabetic rats. These findings suggest that vitamin D's stimulatory effects on insulin may be more pronounced in healthy or early metabolic conditions and less effective in established diabetes.

INTRODUCTION

Diabetes mellitus (DM) is a complex chronic metabolic condition that involves various organ systems and persists over time. It is primarily defined by prolonged hyperglycemia arising from insufficient insulin production, reduced insulin effectiveness, or a combination of these mechanisms[1,2]. Among its subtypes, type 2 diabetes mellitus (T2DM) is the most prevalent, accounting for about 95% of cases worldwide[1,3]. This form of diabetes is marked by progressive insulin resistance, declining insulin secretion, and, in some cases, relative insulin deficiency. The disease typically develops gradually and often presents without obvious early symptoms, making its diagnosis and management more challenging[2].

The worldwide prevalence of T2DM is on the increase. The NCD Risk Factor Collaboration (2022) estimates that 828 million individuals are currently diagnosed with DM, with projections indicating a significant increase by 2050[1,3]. It is essential to note that the occurrence of T2DM is no longer limited to older adults; it has also increased among younger individuals (under 40 years), with a two- to three-fold

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rise observed in recent decades[1]. The main mechanisms of pathophysiology associated with T2DM include dysfunction of β-cells, which results in inadequate insulin secretion, as well as insulin resistance observed in peripheral tissues like muscle, adipose tissue, and liver. These disturbances ultimately interfere with glucose homeostasis and lead to chronic hyperglycemia[1].

Beyond persistent hyperglycemia, T2DM is associated with severe complications, including cardiovascular disorders, renal failure, visual impairment, cognitive decline, and limb amputations, all of which substantially contribute to increased morbidity and mortality[3]. These complications underscore the critical need to investigate innovative preventive and therapeutic approaches for T2DM.

Growing evidence supports the idea that vitamin D influences glucose regulation. Traditionally valued for its role in calcium and bone physiology, it is now increasingly recognized for its possible anti-diabetic properties. These include enhancing insulin secretion and sensitivity, supporting pancreatic β-cell function, and exerting anti-inflammatory as well as immunomodulatory effects[4,5].

Epidemiological evidence indicates that inadequate vitamin D status increases the likelihood of developing T2DM, whereas optimal levels appear to support insulin responsiveness and β-cell activity. However, findings from intervention studies on vitamin D supplementation remain inconsistent. Several trials have reported that supplementation, even at varying doses, does not significantly reduce the risk of developing T2DM[4]. Nonetheless, additional studies evaluating indicators associated with T2DM, instead of the incidence itself, have yielded varying results. Mitri et al. (2011) showed that taking cholecalciferol at a dosage of 2,000 IU/day for 16 weeks led to enhancements in insulin secretion[6]. In a similar vein, Lemieux et al. (2019) discovered that a daily supplementation of 5,000 IU improved peripheral insulin sensitivity and the function of pancreatic β-cells[7]. Evidence from animal studies further supports this association, indicating that supplementation with vitamin D at varying doses contributes to reduced blood glucose levels in rats with induced T2DM[8].

Due to the variability in existing results, more investigation is warranted to determine the role of vitamin D supplementation in insulin regulation. In this study, we examine whether vitamin D administration alters insulin levels in rats with T2DM.

METHODS

Experimental Animals

All experimental procedures were conducted in accordance with the ARRIVE (Animal Research: Reporting In Vivo Experiments) guidelines. The study followed the established protocol from our prior investigation[9], with modifications limited to the measured variables. A total of twenty-five male Sprague-Dawley rats (*Rattus norvegicus*), aged 8–12 weeks and weighing 150–200 g, were housed under controlled temperature, light, and humidity, with ad libitum access to water and diets specific to assigned groups.

Study Design

The study included five experimental groups, each consisting of five rats. Group A served as the non-diabetic negative control and received no vitamin D supplementation. Group B consisted of non-diabetic rats supplemented with 415 IU/kg/day vitamin D, equivalent to approximately 62–83 IU/day per rat. Group C comprised diabetic rats without vitamin D treatment. Diabetic rats receiving the low-dose and high-dose vitamin D regimens were assigned to Groups D and E, respectively, with Group D receiving 415 IU/kg/day (~62–83 IU/day per rat) and Group E receiving 1,100 IU/kg/day (~165–220 IU/day per rat). All doses were calculated based on individual body weights of 150–200 g and selected for translational relevance using the Animal Equivalent Dose (AED) formula according to body surface area scaling (Table.1).

Table 1. Rational Vitamin D Dosing

Parameter	Group B & D	Group E
Dose in IU/kg/day	415	1,100
Dose in µg/kg/day (1 IU = 0.025 µg)	10.4 µg/kg	27.5 µg/kg
Approx. per-rat IU/day (150–200 g)	62–83 IU/day	165–220 IU/day
AED (mg/kgBW)[10]	Human dose (mg/kgBW) x Km ratio (rat Km = 6.2)	
Approx. human-equivalent dose	4,000 IU/day	10,000 IU/day

Vitamin D supplementation doses were selected based on preclinical and clinical evidence. In rodents, supplementation at 12.5–25 µg/kg BW for 14 days

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increased GLUT4 expression compared to controls[11], suggesting a potential mechanism for improving glucose uptake in diabetes. In humans, Billington et al. (2020) reported that daily doses of 4,000 and 10,000 IU vitamin D3 were generally safe and well-tolerated,[12] supporting the translation of these doses to the rat model via allometric scaling.

Experimental Protocol

Type 2 diabetes mellitus (T2DM) was induced in Groups C, D, and E by feeding rats a high-fat diet for three weeks, followed by a single intraperitoneal injection of streptozotocin (STZ; Sigma-Aldrich, Cat. No. S0130, ≥75% α-anomer, ≥98% HPLC, powder) at 50 mg/kg B, freshly dissolved in ice-cold 0.1 M citrate buffer (pH 4.5), protected from light, and administered intraperitoneally within 10–15 min of preparation. Rats were fasted for 12 h before STZ and given 10% glucose for 24 h to prevent hypoglycemia. Diabetes was confirmed at 72 hours and re-verified on day 7 after a 12-hour fast using a calibrated glucometer (<brand/model> and animals with fasting blood glucose ≥200 mg/dL, with rats exhibiting fasting blood glucose ≥200 mg/dL classified as diabetic[13].

Groups A and B remained non-diabetic and received standard feed with their respective vitamin D treatments. Vitamin D supplementation (Cholecalciferol; Cat. No. 020734; SUPRA FERBINDO FARMA®, Jakarta, Indonesia) was administered daily by oral gavage for 30 days, with cholecalciferol dissolved in aquabides[14] and given once each morning at 1 mL/100 g BW.

Sample Collection and Biochemical Analysis

At study completion, rats were euthanized under deep anesthesia (ketamine 90 mg/kg + xylazine 10 mg/kg, IP). Depth of anesthesia was confirmed by loss of pedal withdrawal and corneal reflexes. Terminal blood collection was performed via cardiac puncture, followed by a secondary physical method (bilateral thoracotomy) to ensure death, in accordance with institutional and AVMA guidelines[15]. Animals were monitored daily and twice daily for 72 hours post-STZ and during interventions. Pre-specified humane endpoints included: ≥20% body-weight loss; persistent anorexia or dehydration (≥24–48 h); severe unrelieved distress (e.g., inability to reach food or water); respiratory compromise; or refractory hypothermia. Animals meeting any endpoint were euthanized under the same anesthesia and terminal procedure.

Randomization and blinding were implemented to minimize bias. Group allocation was performed using simple computer-generated randomization with a cage-balance rule. Dosing personnel were separate from outcome assessors, and treatments were coded with neutral alphanumeric labels, with the allocation key held independently until data lock. For ELISA assays, all samples were re-coded and arranged on randomized plate maps to ensure blinding of operators and analysts. Each sample was measured in duplicate using per-plate standard curves.

Plasma samples were centrifuged at 5000 rpm for 10 minutes to separate the serum. The supernatant was transferred to a new tube and stored at -20°C. To separate the serum. The supernatant was transferred to a new tube and stored at -20°C. Vitamin D and insulin concentrations were quantified using ELISA kits (Vitamin D: Cat. No. E-EL-0014; Insulin: Cat. No. E-EL-3034; Elabscience®, USA) following the manufacturer's instructions.

Statistical Analysis

Data analysis was performed using SPSS version 26.0 (IBM Corp., Armonk, NY, USA). Normality was evaluated using the Shapiro–Wilk test and homogeneity of variance using Levene's test. Variables meeting both assumptions were analyzed with one-way ANOVA followed by Bonferroni post hoc testing. All statistical results were independently verified in Python v3.12.11 using pandas, NumPy, SciPy, and statsmodels, while matplotlib and seaborn were used for data visualization.

RESULTS

Characteristics of insulin levels across the five experimental groups

To provide a clear overview of the dataset before inferential testing, serum insulin concentrations (μIU/mL) were summarized for all five experimental groups. Mean ± SD values were 267.51 ± 87.32 in Group A, 337.66 ± 89.76 in Group B, 179.27 ± 48.42 in Group C, 182.28 ± 69.83 in Group D, and 240.33 ± 82.06 in Group E. All groups satisfied normality based on the Shapiro–Wilk test (p=0.144–0.884), and homogeneity of variance was confirmed by Levene's test (p=0.924). These descriptive distributions indicate

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numerical differences among groups, warranting subsequent analytical comparisons.

Effect of Vitamin D Supplementation on Insulin Levels

To determine whether vitamin D supplementation produced statistically meaningful differences in insulin response, inferential analyses were conducted across the experimental groups. One-way ANOVA demonstrated a significant overall difference in insulin concentrations across groups ($F(4,20)=3.649$, $p=0.022$, $\eta^2=0.422$). Bonferroni-adjusted post-hoc tests showed that healthy rats receiving 415 IU/day vitamin D (Group B) had significantly higher insulin levels compared with diabetic rats without supplementation (Group C, $p^{adj} = 0.029$) and diabetic rats receiving the same dose (Group D, $p^{adj} = 0.0331$). No other pairwise comparisons reached statistical significance ($p^{adj} \geq 0.302$). Although Group E (1,100 IU/day vitamin D) exhibited numerically higher insulin levels than diabetic controls, the increase was insufficient to achieve statistical significance, indicating that vitamin D supplementation enhanced insulin secretion in healthy animals but did not effectively restore β-cell function in diabetic conditions (Figure 1).

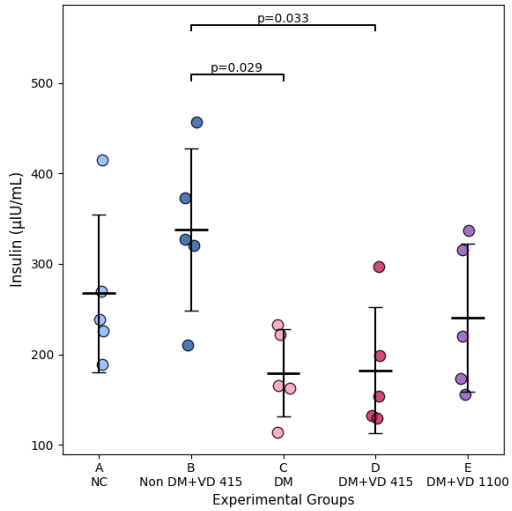

Figure 1. Effect of vitamin D supplementation on insulin levels.
Scatter points represent individual animals (n=5 per group), with horizontal bars and error bars indicating the mean ± SD. Groups on the x-axis are coded as A–E: A, negative control; B, non-diabetic rats receiving 415 IU/day vitamin D; C, diabetic rats without vitamin D; D, diabetic rats supplemented with 415 IU/day vitamin D; and E, diabetic rats supplemented with 1,100 IU/day vitamin D. Horizontal brackets with p-values denote statistically significant pairwise differences.

Association Between Vitamin D Levels and Insulin Levels

The analysis showed no significant correlation between vitamin D and insulin levels (p=0.415), although a weak positive relationship was observed (r=0.171) (Figure 2). Consequently, while there appeared to be a trend indicating that elevated vitamin D levels correlated with higher insulin levels, the association was not robust enough to achieve statistical significance according to our analysis.

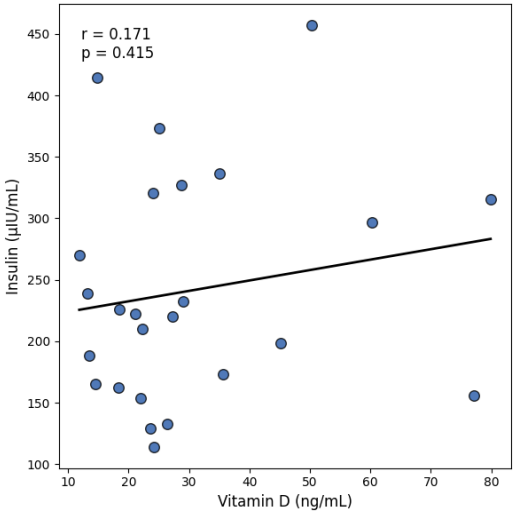

Figure 2. Association between serum vitamin D and insulin concentrations.
Scatter plot showing individual data points for serum vitamin D and insulin levels across all animals (n = 25). The solid line represents the linear regression fit. The Pearson correlation coefficient (r) and corresponding p-value are shown in the plot to indicate the strength and significance of the association.

DISCUSSION

Vitamin D has long been proposed to modulate β-cell function and glucose homeostasis, yet experimental and clinical studies have yielded inconsistent evidence regarding its influence on insulin secretion[16]. Understanding the physiological conditions under which vitamin D enhances insulin output is therefore essential, particularly given its potential relevance for diabetes prevention and metabolic regulation. In this study, healthy rats (Group B) receiving vitamin D supplementation exhibited significantly higher insulin concentrations than all diabetic groups, aligning with established mechanisms indicating that 1,25-dihydroxyvitamin D_3 enhances glucose-stimulated insulin secretion (GSIS). This occurs through activation of the vitamin D receptor

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(VDR) in β-cells, which modulates voltage-gated calcium channels[17,18], including R-type VGCCs essential for calcium influx and insulin granule exocytosis[17]. The presence of 1α-hydroxylase (CYP2B1) in pancreatic β-cells further enables local conversion of circulating 25(OH)D to its active form, enabling local conversion of circulating 25-hydroxyvitamin D into its active form, amplifying autocrine and paracrine vitamin D signaling[18–20]. These mechanisms provide a coherent explanation for the enhanced insulin secretion observed in vitamin D–supplemented non-diabetic rats in our study.

Vitamin D supplementation produced only a non-significant numerical increase in insulin levels in diabetic rats. This attenuated response is biologically plausible, as type 2 diabetes is characterized by progressive β-cell dysfunction driven by chronic inflammation, oxidative and endoplasmic-reticulum stress, and impaired insulin signaling. Prior studies in prediabetic models demonstrate that vitamin D_3 improves glycemic control (FBG, OGTT, HOMA-IR), preserves islet architecture, and restores key insulin-related pathways, reducing IRS1 (Ser307) phosphorylation, enhancing PPARγ expression, suppressing NF-κB activity, improving glucose tolerance, and preserving islet structure[21,22]. However, these benefits diminish substantially once structural β-cell impairment is established, limiting the potential of vitamin D to restore insulin secretion in overt diabetic states[23]. Our findings therefore support the concept that vitamin D may exert greater benefit as a preventive or early-stage intervention rather than as a monotherapy for advanced diabetes.

In addition to direct effects on β-cells, vitamin D contributes to glucose homeostasis through broader molecular mechanisms, including regulation of intracellular calcium handling and modulation of PKA- and PLC-dependent pathways involved in insulin exocytosis[6,24]. In advanced T2DM, however, peripheral insulin resistance, chronic oxidative stress, and β-cell apoptosis collectively restrict the responsiveness of β-cells to hormonal or nutrient-mediated stimuli. Although vitamin D possesses anti-inflammatory, antioxidant, and cytoprotective properties that may attenuate β-cell injury, such as enhanced autophagy and reduced apoptosis[25]. These mechanisms may be insufficient to fully restore insulin secretory capacity once irreversible β-cell loss has occurred. The current findings are therefore consistent with the complexity of vitamin D's role in diabetes, suggesting that its functional impact becomes increasingly constrained as β-cell pathology progresses.

Consistent with the modest group differences observed, the relationship between serum vitamin D and insulin concentrations was weak and not statistically meaningful. This pattern aligns with findings from Haidari et al. (2016), who also reported no significant association between circulating vitamin D and insulin levels, suggesting that vitamin D's effects on insulin dynamics are often subtle and may be detectable only under specific physiological or metabolic conditions. The weak correlation observed in our study, therefore, likely reflects the multi-factorial nature of insulin regulation, in which vitamin D represents only one of many contributing influences[26].

Beyond these direct β-cell effects, vitamin D contributes to insulin secretion through several additional molecular pathways involving intracellular calcium regulation. The active form, 1,25-dihydroxyvitamin D, can activate protein kinase A (PKA) and phospholipase C (PLC), promoting calcium release from the endoplasmic reticulum and enhancing calcium influx primarily through L-type voltage-dependent calcium channels. The resulting rise in cytosolic Ca^{2+} triggers the fusion of insulin granules with the plasma membrane, thereby facilitating insulin exocytosis[21,24]. Despite this mechanistic framework, empirical evidence from clinical and epidemiological studies remains inconsistent. Meta-analytic findings report weak negative correlations between vitamin D and insulin or HOMA-IR ($r \approx -0.08$ to -0.06)[27], while some reports in patients with type 2 diabetes describe positive associations with β-cell function (HOMA-B) and reduced insulin resistance[28]. Other studies, however, highlight minimal or uncertain effects of vitamin D supplementation on glycemic control across human populations[27,29]. These mixed outcomes underscore the context-dependent nature of vitamin D's metabolic actions.

Consistent with this complexity, the current study identified only a weak and non-significant association between serum vitamin D and insulin levels ($r = 0.171$, $p = 0.415$). This likely reflects the combined effects of metabolic heterogeneity, physiological variability, and

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the relatively narrow vitamin D range across experimental groups. While vitamin D clearly enhanced insulin secretion in healthy rats, its broader impact across mixed metabolic states appears modest when evaluated using correlation analyses. Taken together, our findings suggest that vitamin D can support insulin secretion under intact β-cell conditions, but its measurable effects become increasingly constrained in the presence of established metabolic dysfunction.

Although this study provides mechanistic and metabolic insight, several physiological and safety parameters were not evaluated. Body-weight trajectories, feed intake, and observable signs of toxicity such as lethargy or vitamin D-related hypercalcemia were not systematically monitored, and serum calcium and phosphate levels were also not measured. Because vitamin D plays a central role in mineral metabolism, the absence of these assessments limits the ability to determine whether the metabolic changes observed in this study occurred independently of alterations in calcium–phosphate homeostasis. Incorporating these physiological and biochemical measures in future work would allow for a more complete evaluation of both the safety profile and the mechanistic consequences of vitamin D supplementation in metabolic disease models.

CONCLUSION

The findings of this study demonstrate that vitamin D supplementation enhanced insulin secretion in healthy rats, indicating that its metabolic effects are most evident when endogenous insulin production remains intact. In diabetic rats, however, supplementation with either 415 IU/day or 1,100 IU/day did not produce a meaningful increase in insulin levels compared with diabetic controls, suggesting that vitamin D offers limited benefit once insulin secretory capacity is substantially disrupted. The lack of a significant overall association between serum vitamin D and insulin concentrations supports the interpretation that vitamin D is not a primary determinant of insulin output across heterogeneous metabolic states. Collectively, these results indicate that vitamin D may influence insulin secretion more readily in early or less severe stages of metabolic disturbance. Future studies incorporating measures such as pancreatic insulin content, islet morphology, or indicators of β-cell mass will be important for clarifying the stage-specific role of vitamin D in pancreatic endocrine regulation.

ETHICAL APPROVAL

The study protocol received approval after thorough review by the Ethics Committee at the Faculty of Medicine, Universitas Baiturrahmah (No: 031/ETIK-FKUNBRAH/03/06/2025).

CONFLICTS OF INTEREST

The authors affirm that there are no conflicts of interest to disclose.

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AUTHOR CONTRIBUTIONS

Conceptualization, RBH, RH, KMH, and WS; methodology, KMH and WS; software, WS, GK, SPP; validation, RBH and RH; formal analysis, KMH and WS; investigation, RBH, RH, KMH, and WS; resources, RBH; data curation, RH; writing-original draft preparation, KMH and WS; writing-review and editing, RBH, GK, SPP and RH; visualization, WS, GK; supervision, RBH and RH; project administration, RBH; funding acquisition, RBH.

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