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Original Article

Impact of Vitamin D on Glycemic and Metabolic Markers

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ABSTRACT

Background: Vitamin D is pivotal in calcium and phosphorus homeostasis and metabolic regulation, especially regarding glucose management and insulin sensitivity. We analyzed statistical trends to evaluate the relationship between vitamin D levels and metabolic parameters in prediabetic individuals over a 32-week period.

Methods: Prediabetic participants were monitored for 32 weeks, with serum vitamin D, glycated hemoglobin (HbA1c), fasting blood glucose (FBG), fasting insulin, insulin resistance (HOMA-IR), and beta-cell function (HOMA-B) measured at baseline, Week 0, Week 16, and Week 32' Statistical analyses were conducted to assess temporal trends and identify associations between vitamin D concentrations and glycemic parameters.

Results: Serum vitamin D levels significantly increased during the study, from 14.6 ± 10.7 ng/mL at baseline to 35.3 ± 16.7 ng/mL by Week 32 ($p < 0.0001$). HbA1c levels showed a progressive decline, indicating long-term glycemic control (Week 0: 5.84 ± 0.38%; Week 32: 5.33 ± 0.33%; $p < 0.0001$). A significant reduction in insulin resistance (HOMA-IR) was also observed ($p = 0.035$), along with an increase in beta-cell function (HOMA-B) ($p=.042$), and fasting insulin levels elevated significantly, rising from 17.3±4.9 ng/mL at baseline to 29.4±8.8 ng/mL by Week 32 ($p = 0.046$) which correlated with elevated vitamin D levels. However, no significant changes were seen in FBG ($p = 0.238$) and body mass index (BMI) ($p = 0.632$).

Conclusion: Enhanced vitamin D status was associated with improved glycemic control and reduced insulin resistance in individuals with prediabetes. Although BMI and fasting glucose did not change significantly during the follow-up study, the outcomes proposed that vitamin D supplementation may assist in reducing high HbA1c and insulin resistance. These findings imply the potential advantages of vitamin D in normalizing prediabetic cases, prompting the need for more research and long-term observation of many participants.

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Keywords: Vitamin D, Prediabetes, Glycemic control, HbA1c, Insulin resistance.

1 Introduction

One of the most important liposoluble vitamins is vitamin D, which balances phosphorus and calcium ions in the body, which are necessary for bone well-being. Originally, this vitamin is created under the skin by the action of UVB radiation from sunlight that converts 7-dehydrocholesterol by hydroxylation process first in the liver to 25 hydroxyvitamin (25OHD) and then mostly in the kidney to 1, 25 di-hydroxyvitamin D (1, 25(OH)2D). The reverse relationship of serum hydroxyvitamin D (25OHD) concentrations with BMI and with some other anthropometric or biochemical measurements has been reported by some studies[1].

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Throughout the previous few decades, scientific experiments have attended our noticed and ideas about the act of cholecalciferol regardless of its function in supporting and enforcing the skeletal system, proving its participation in several physiological functions, such as boosting the immune system, anti-inflammatory process, and regulating some metabolic health problems particularly glucose metabolism and insulin sensitivity[2,3]. Decreasing serum vitamin D concentrations increases the possibility of metabolic syndrome (MetS) continuously, as mentioned by researchers[4].

Due to vitamin D's great role, there has been increasing attention to its ability to prevent and/or normalize metabolic disorders such as obesity, insulin resistance, and type 2 diabetes, which are serious global health issues[5,6].

The influences of vitamin D are coordinated through its receptors (VDR), which are present in various tissues such as the liver, pancreas, muscles, and immune cells. Vitamin D may enhance

insulin secretion and insulin uptake in the pancreas and peripheral tissues by increasing insulin receptor expression, which ultimately results in glucose uptake. Thus, vitamin D deficiency diminishes calcium homeostasis and insulin secretion, eventually promoting the progression of insulin resistance[2,7]. Vitamin D reduces insulin resistance, particularly in obese individuals, which is a large risk factor for type 2 diabetes, by contributing to decreasing accumulation of adipocytes, inflammation, and oxidative stress, which act as a main factor for reducing insulin function in adipose and muscle tissues [8,9].

A major public health issue displayed the increasing rates of metabolic syndrome, including abdominal obesity, impaired insulin sensitivities, high blood sugar, hypertension, high triglycerides, and low serum high-density lipoprotein, which enhance the progression of type 2 diabetes and heart disease[10]. Linked to these conditions are several factors, including damaged glucose metabolism, insulin dysfunction, and raised cardiovascular risk. Insulin resistance is made worse by obesity, which triggers inflammation and impairs glucose metabolism. Pro-inflammatory cytokines are released by visceral fat, reduce insulin sensitivity, and cause hyperinsulinemia, which damages beta-cell function. Hypovitaminosis D is widespread in fat individuals, facilitating insulin resistance[11].

Significant biomarkers such as glycosylated hemoglobin, fasting blood glucose (FBG), fasting insulin concentrations, and impaired insulin sensitivity assess metabolic health. Decreased vitamin D concentrations are linked to raised HbA1c, FBG, and fasting insulin, implying poor glucose uptake and poor insulin secretion and uptake. Hypovitaminosis D may contribute to high adiposity, worsening insulin resistance, and metabolic disorders[12].

Inadequate vitamin D is related to diminished insulin sensitivity. Meanwhile, vitamin D sufficiency may trigger insulin secretions. Taking vitamin D supplements in high doses regularly and continuously may enhance insulin sensitivity in various body tissue cells, lower fasting glucose, and decrease glycated hemoglobin in diabetic patients or those with metabolic syndrome, although the results vary. This is especially effective for those with hypovitaminosis D alongside the previously stated conditions [13,14]

There is no agreement on the most efficient way to treat vitamin D insufficiency. However, several treatments using every day or weekly dosages of cholecalciferol vitamin D3 have all produced satisfactory results. Carbonare et al. [15] discovered that eighty percent of people taking almost 2000 IU/day or 50,000 IU monthly over the course of six months increased hydroxyvitamin D concentrations above 30 ng/mL [15]. High or sufficient vitamin D concentrations are certainly critical to overall cardiovascular and metabolic disturbance regulation [16]. Many researchers have pointed out the desire for hydroxyvitamin D to be administered at different doses to maintain sufficient vitamin D concentrations, consequently lowering the risk of metabolic syndrome and corresponding disorders [17,18].

Several investigations have explained that an adequate vitamin D level has immunomodulatory impacts, and its inadequacy may be related to sub-inflammatory situations [17]. Metabolic syndrome and diabetes are severe medical and community health difficulties [18,19]. Based on International Diabetes Federation figures issued in 2021, 537 million individuals globally have diabetes. The total number is expected to elevate to 643 six hundred forty-three million by 2030 and reach 783 seven hundred eighty-three million by 2045, instead of the earlier estimate of 693 six hundred ninety-three million [20].

Low vitamin D status is common worldwide in all age groups, including in nations with year-round sun exposure, according to currently available data. It is significant to highlight that the issue is more widespread in the Middle East, especially regarding women and girls. Additionally, the data identify the areas where certain demographic groupings' data are absent. Data on newborns, kids, teenagers, and most South American and African nations are conspicuously lacking [19].

The equivalent of 1000 IU of vitamin D would be produced by exposure to UV radiation, equating to 25% of the minimal erythema dose (MED) over around 25% of the skin's surface (arms, hands, and face)[20]. During the summer, fifteen minutes of midday sun exposure over the entire body (about one MED) is equivalent to 10,000 IU (250 µg) of cholecalciferol [21]. Exposure to the sun for a third or a sixth of the MED on the arms, hands, and face is equivalent to 200–600 IU of cholecalciferol intake [22].

Numerous disease-related and experimental studies have revealed a link between vitamin D deficiency and the prevalence of type 1 and type 2 diabetes[21, 22]. Regarding this, numerous studies have documented the presence of various mechanisms that can clarify the capability effect of cholecalciferol in serum glucose regulation and the protection of pancreatic beta-cell function in prediabetic cases and T1DM [23, 6, 24].

2 Methodology

2.1 Study Design and Participants

This study is designed as a comparative follow-up study to improve and clarify the influence of vitamin D concentrations on glycemic control biomarkers, such as HbA1c, FBG, fasting insulin, insulin resistance, and anthropometric measurements. Participants were recruited from Sulaymaniyah province, specifically the Garmiyan region, through "Garmiyan Polytechnic University" and adhered to strict inclusion and exclusion criteria to ensure a representative sample. Ninety-two prediabetic and vitamin D-deficient individuals were selected. They consisted of 49 males and 43 females, whose ages ranged from 24 to 66 years. Study duration time (Duration of Trial) was determined in weeks and categorized into three distinct periods at baseline (starting point): Week 0, midterm Week 16, and final Week 32. They administered oral vitamin D supplements with a 50,000 IU/week dosage, VitaminD_3 as Cholecalciferol produced by 21st CENTURY CORPORATION, USA. The ethical code has received formal approval from the Human Research Committee

(HREC) of Salahaddin University-Erbil on December 20th 2023 according to reference number: 45/103.

2.2 Sample Collection and Preparation

After an 8–12 hour overnight fast, participants provided blood samples. Two blood samples were taken from participants, each consisting of 3 mL of blood, to obtain serum and plasma. The anticoagulated blood samples were centrifuged at 2000 rpm for 10 minutes for plasma. All samples were tested on the same day for greater accuracy and reliability.

2.3 Biochemical Analysis

The laboratory tests were carried out using a COBAS analyzer. Vitamin D levels were measured by COBAS E411 analyzer (Roche Diagnostics) using electrochemiluminescence immunoassay (ECLIA). All assays follow the manufacturer's guidelines, with calibration and quality control to ensure accuracy. Insulin samples were run in duplicate to enhance reliability. HbA1c and FBG were measured on the COBAS C111 analyzer (Roche Diagnostics). HbA1c was determined using a turbidimetric inhibition immunoassay, with results as percentages to reflect average blood glucose levels over 3–4 months. FBG was assessed using the hexokinase method. Standardized protocols and quality control procedures were applied throughout to guarantee reproducible results.

2.3.1 Insulin Resistance Calculation

IR was calculated using the Homeostasis Model Assessment for Insulin Resistance (HOMA-IR) formula:

$$\text{HOMA-IR} = \frac{\text{Fasting Insulin } (\mu\text{U/mL}) \times \text{ Fasting Glucose (mg/dL)}}{405}$$

2.3.2 Beta Cell Function Assessment

Homeostasis Model Assessment for Beta-Cell Function (HOMA-B) formula:

HOMA-B = (20 × fasting insulin (ng/mL) /fasting glucose (mmol/ml)) − 3.5

2.4 Statistical Analysis

Data were analyzed using the program Statistical Package for the Social Sciences (SPSS version 23). The results of continuous variables were displayed as mean ± standard deviation. One-way ANOVA was used to compare follow-up parameter results, with a p-value set at ($p < 0.05$) as a statistically significant difference among groups. Post hoc- Tukey's Honest Significant Difference (HSD) tests were performed as needed to identify significant group differences.

3 Results

The table highlights the impacts of cholecalciferol on various glycemic markers. Key findings are as follows:

1. Vitamin D Levels: Significantly increased in vitamin d levels were observed during follow-up dosing period, particularly in groups demonstrating better glycemic control ($p = 0.0001$).
2. Glycated Hemoglobin (HbA1c): Higher concentrations of vitamin D were strongly associated with reduced HbA1c, indicating improved long-term glycemic control throughout the study period ($p = 0.0001$).
3. HOMA-IR: Reduced insulin resistance correlated with higher vitamin D levels ($p = 0.035$).
4. Fasting insulin: increased significantly in conjunction with elevated vitamin D levels ($p=0.046$).
5. HOMA-B: Increased in HOMA-B values were also significantly correlated with rising levels of vitamin D ($p = 0.042$).
6. Other Markers: No statistically significant differences were observed in fasting blood glucose (FBG) and body mass index (BMI) over the study period.

The data suggest a beneficial relationship between vitamin D status and markers indicative of glucose metabolism. This association implies that increased vitamin D levels may contribute to better regulation of blood sugar levels, thereby potentially mitigating the risks associated with impaired glucose tolerance and other metabolic disorders. In summary, higher vitamin D levels are linked to improved glycemic control and reduced insulin resistance but appear to have no noticeable impact on FBG and BMI.

Table 1: presents a comprehensive analysis of the effects of vitamin D levels on various glycemic markers. The data indicate that elevated concentrations of vitamin D are correlated with enhancements in glycemic control.

Parameters	Mean± Std.			95% Confidence Interval for Mean	
	Week 0	Week 16	Week 32	P-Value	Sig.
Serum Vitamin D Levels ng/mL	14.6±10.7[a]	28.3±13.9[b]	35.3±16.7[c]	.0001	Highly Sig.
Fasting blood glucose (FBG) mg/dL	106.1±19.7[a]	104.5±19.8[a]	102.3±16.3[a]	.238	NS
Fasting Insulin ng/mL	17.3±4.9[a]	18.5±6.4[a]	29.4±8.8[b]	.046	Sig.

Glycated Hemoglobin (HbA1c)	5.84±.38[a]	5.59±.44[b]	5.33±.33[c]	.0001	Highly Sig.
HOMA-IR	4.7±3.8[a]	3.9±2.4[a]	2.3±1.9[b]	.035	Sig.
HOMA-B	60.3±0.4[a]	61.4±0.2[a]	73.5±0.7[b]	.042	Sig.
BMI	30.4± 0.3[a]	30.1± 0.6[a]	29.7± 0.7[a]	.632	NS
The same letters refer to non-significant differences. Different letters mean significant differences.					

In the case of serum vitamin D concentrations, the study demonstrated a significant increase in vitamin D levels, expressed in ng/mL, among prediabetic individuals throughout the study. Specifically, the analysis revealed that vitamin D levels increased significantly by the end of Week 16, with a p-value of < 0.0001 when comparing baseline measurements at Week 0 to those at Weeks 16 and 32. Additionally, a notable difference, with a p-value of < 0.001, was observed between Week 16 and Week 32. This upward trend persisted, with vitamin D levels at Week 32 reflecting further significant increases. These findings indicate that the participants experienced increased serum vitamin D levels, which appear to be attributable to administering vitamin D supplements throughout the study, as demonstrated in Table 1 and Figure 2A.

In prediabetic individuals, vitamin D levels steadily increased throughout the 32-week study, with a significant rise noted by Week 32 ($p < 0.05$). Meanwhile, HbA1c levels gradually declined over the same period, reflecting improved control. These findings indicate a possible connection between higher vitamin D levels and reduced HbA1c, as demonstrated in Table 1, Figure 1C, and Figure 5.

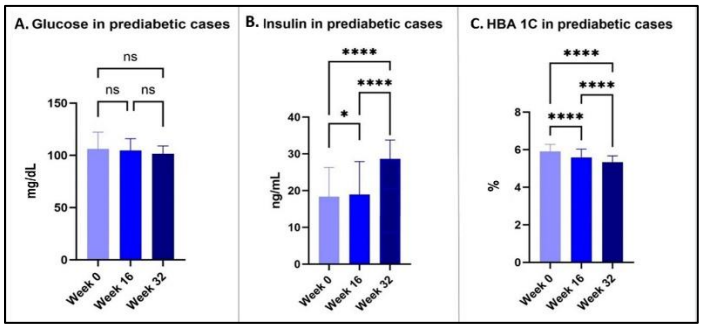

Figure 1: Presents the effects of vitamin D on fasting blood glucose levels (mg/dL), fasting serum insulin (ng/mL), and glycated hemoglobin (%) over the duration of the study, as indicated in sections A, B, and C, respectively.

Additionally, in the case of insulin resistance, the study exhibited a significant decline in insulin resistance (IR) in prediabetic subjects undergoing vitamin D supplements, as calculated by both the HOMA-IR and HOMA-B formulas. Particularly, the analysis revealed marked statistical significance, with a p-value of <0.032 and <0.042, respectively, when comparing from Week 0 to Week 32 and from Week 16 to Week 32. However, the differences between Week 0 and Week 16 did not reach statistical significance. This finding indicates a delayed yet substantial improvement in insulin sensitivity, underscoring the importance of time and consistent intervention in achieving significant metabolic health enhancements, as shown in Table 1 and Figure 2B.

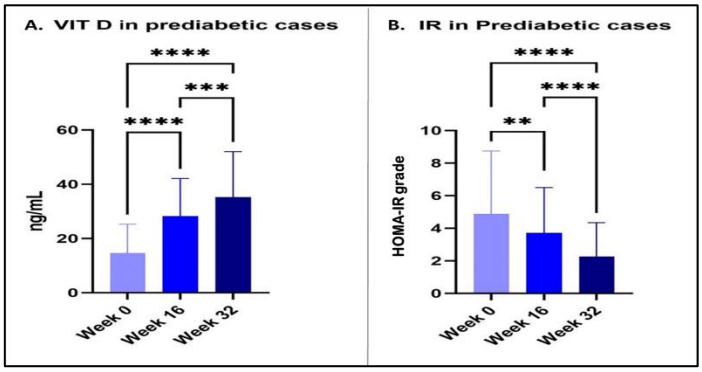

Figure 2: Progression of Vitamin D Levels (A) and Insulin Resistance (IR) (B) in Prediabetic Individuals over a 32-Week Period. Vitamin D levels (ng/mL) increased significantly over time. Insulin resistance (IR) gradually decreased, with a significant reduction.

Furthermore, fasting blood glucose levels exhibited a slight decrease during the study period, coinciding with an increase in vitamin D levels; however, this reduction did not reach statistical significance. These trends suggest potential benefits of vitamin D supplementation, despite the absence of significant effects on fasting glucose levels, as illustrated in Table 1 and Figure 3.

In individuals classified as prediabetic, serum vitamin D levels steadily increased throughout the 32-week study period, culminating in a statistically significant elevation by Week 32 ($p < 0.05$). Additionally, insulin concentrations exhibited a progressive rise, with a pronounced increase observed by the study's conclusion. These findings suggest a potential positive correlation between insulin secretion and vitamin D levels, as displayed in Table 1, Figure 1B, and 4.

Discussion

Hypovitaminosis D has been connected to the development of metabolic irregularities, such as impaired glucose uptake and

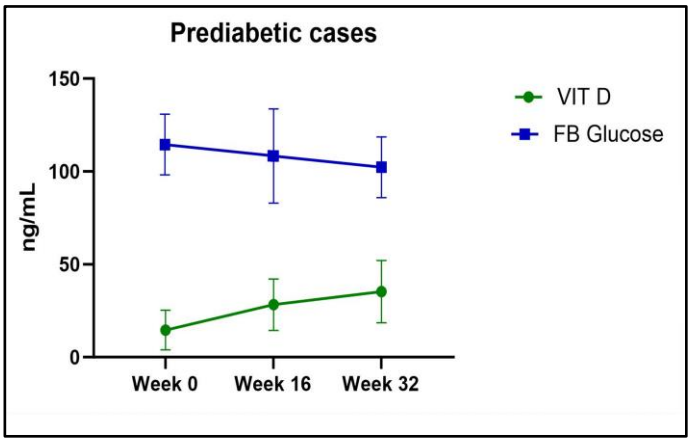

Figure 3: Illustrates the trends in serum vitamin D levels (ng/mL) and fasting blood glucose levels (FB Glucose, ng/mL) in prediabetic individuals over a 32-week period. The data demonstrate a steady increase in vitamin D levels, while fasting glucose levels exhibited a slight, albeit not statistically significant, decrease, remaining relatively stable throughout the study. Measurements were obtained at Week 0, Week 16, and Week 32.

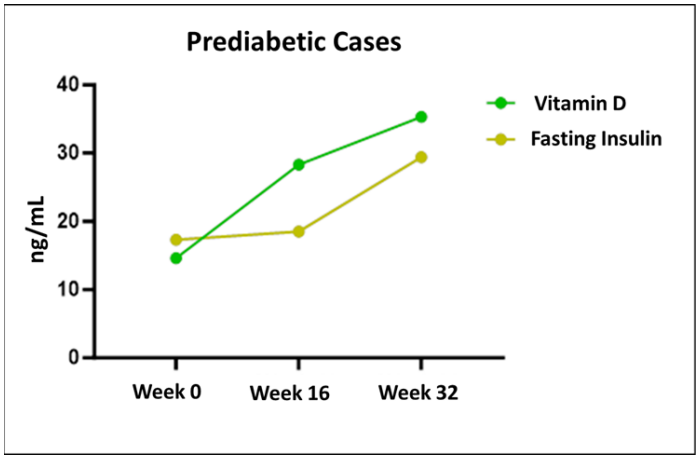

Figure 5: This illustration depicts the increase in serum vitamin D (ng/mL) and insulin levels (ng/mL) in prediabetic cases over a 32-week administration period. Data were measured at Weeks 0, 16, and 32.

impaired insulin sensitivity, which are the main characteristics of diabetes. Some advanced clinical studies proposed that vitamin D acts as a key factor in the homeostasis of blood sugar by promoting pancreatic beta-cell function, reducing pro-inflammatory biomarkers, and improving insulin sensitivity [6,17]. This study aims to analyze the influence of vitamin D administration on glycemic control, such as glycated hemoglobin, insulin secretion, insulin resistance, and other metabolic disorder markers, especially at a high dose of 5oooo IU/week and over 32 weeks in prediabetic individuals.

The 32-week regimen led to significant improvements in metabolic markers, advising that vitamin D may serve as an effective approach for managing prediabetes and potentially averting the initiation of diabetes[11,18].

This study's findings show significant improvements in increasing serum 25-hydroxyvitamin D levels. The increase in vitamin D concentrations (ng/mL), as shown in Table 1 and Figure 2A, was statistically significant. Differences were observed among all time points (****p < 0.0001: Table 1), in addition to decreasing several glycemic parameters, such as HbA1c and insulin resistance, as shown in Table 1, Figure 1C, 2B, and Figure 5. These improvements are signs of effective interventions or natural physiological adjustments of vitamin D contributing to better glycemic control and insulin sensitivity.

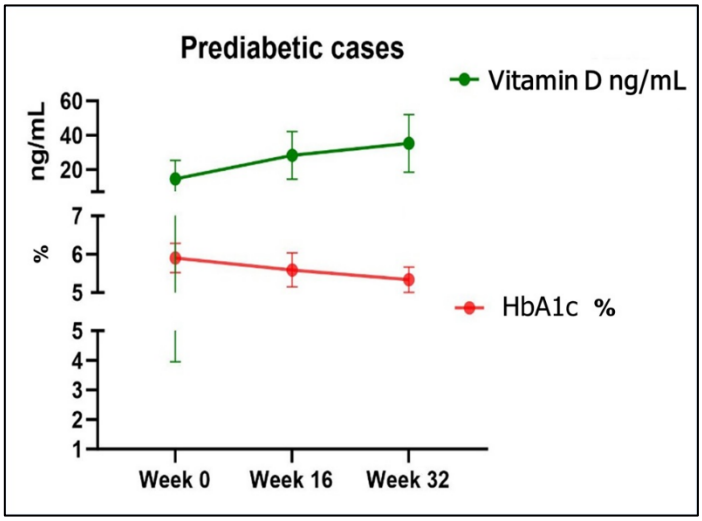

Figure 4: Trends in serum vitamin D (ng/mL) and HbA1c (%) levels in prediabetic cases over 32 weeks. Vitamin D levels showed a consistent increase, while HbA1c levels were declining. Data were measured at Week 0, Week 16, and Week 32.

At the beginning of our study, regarding blood glucose and insulin concentrations at baseline (Week 0), the fasting blood glucose levels observed in individuals classified as prediabetic were moderately elevated, while fasting insulin concentrations were found to be low. This mild elevation in fasting blood glucose, coupled with a reduction in fasting serum insulin levels among the prediabetic participants, indicates increased insulin resistance and elevated body mass index (BMI) (Table 1). This phenomenon may be attributed to excessive adipose tissue accumulation in the abdominal region, which adversely affects insulin secretion by pancreatic beta cells and the effective uptake of insulin by hepatocytes and other peripheral cells. Furthermore, our study demonstrated that gradual increases in vitamin D levels over the course of the follow-up period were associated with a reduction in serum fasting glucose concentrations, as illustrated in Table 1 and Figure 3. This gradual decline in glucose levels suggests the role of vitamin D3, which may slow the conversion of prediabetes to type II diabetes. Although this decline was not statistically significant, it may be due to keeping the subjects on the same dietary and lifestyle regimens. In this context, Al-Zahrani et al. (2014) present findings contradicting our results. They reported no significant differences in fasting blood glucose levels among 183 participants who received vitamin D supplements at a dosage of 45,000 IU per week. Whereas, Nikooyah and his collaborators [70], as well as Bhatt and Misra [72], support our study.

On the other hand, throughout the study, fasting insulin concentration (ng/mL) increased slightly from week 0 to week 16 and rose significantly from week 16 to week 32, as illustrated in Table 1, Figure 1B, and Figure 4. This indicates that the elevation of insulin levels was significantly different from the second half of the study (P=0.046: Table 1). These minor fluctuations in fasting insulin concentration correspond to reduced serum blood glucose in the first half of the study. Increasing insulin secretion along with rising vitamin D levels in the blood results from the regulation of insulin production in pancreatic beta-cells by the action of vitamin D indirectly, such as the regulation of calcium ion concentrations inside the beta-cells because calcium ions prompt insulin secretion by the activation of insulin vesicles mobilization and excretion, as well as, studies explained that vitamin D3 depolarizes the plasma membrane of pancreatic beta cells, increasing calcium ions by opening its channels[5,12,25–31]. An alternative molecular mechanism of this process is that vitamin D3 triggers protein kinase A and improves channel function by L-type voltage-dependent calcium ion channel-related protein phosphorylation[30]. Also, vitamin D3 stimulates vitamin D receptors to manage the voltage-gated calcium channels, which promote insulin secretion [32].

In pancreatic beta-cells, vitamin D3 is induced by the genomic pathway, resulting in the expression of both vitamin D receptors and CYP27B1, which promotes insulin synthesis and secretion because the vitamin D response element (VTDE) is located in the promoter region of the insulin gene[33,34]. Importantly, studies conducted on mice lacking functional VDR have shown that insulin synthesis and secretion are impaired following a glucose load[35].

Our results align with Lemieux et al. [36] 2019, who found that administering 5000 IU vitamin D3 daily for approximately six months in prediabetic cases significantly improves beta-cell function and escalates peripheral insulin sensitivity. Additionally, our findings align with Babarawi et al. [37] from 2020 regarding prediabetic cases. They demonstrated that administering moderate to high doses of vitamin D at least 1000 IU/day for at least one year markedly decreased the risk of non-insulin-dependent diabetes mellitus (T2DM) compared to the placebo group. Conversely, our findings do not align with those of Talari et al. [38] in 2019, as they reported that co-supplementation of 50,000 IU vitamin D every 14 days along with 2000 mg/day of n-3 fatty acids from flaxseed oil for at least six months, resulted in a significant decrease in fasting blood glucose, serum insulin levels, impaired insulin sensitivities, as well as a significant increase in HDL and insulin uptake compared to the placebo group.

Furthermore, our results contrast with those of Wallace et al.[39] in 2019, who emphasized that administering 3000 IU (75 µg) of cholecalciferol daily for 26 weeks does not change any values of glycemic control in prediabetic cases. Additionally, regarding glycated hemoglobin, the significant reduction in HbA1c levels throughout the study is evidence of vitamin D enhancement in regulating glycemic parameters, as observed in our trial study (****$p < 0.0001$: Table 1 and Figure 5). This finding is aligned with Nikooyeh and his collaborators in 2014, who found that participants who received vitamin D showed a significant decrease in HbA1c levels compared to those given a placebo [70]. Furthermore, this reduction in glycated hemoglobin does not align with Chen and his collaborators' outcomes [40], while supported by Mirhosseini and his friends [12] and Ozougwu et al. [41]Conversely, a study conducted by Azadbakht and his collaborators does not support our findings. It involved 118 participants and mandated that they receive either vitamin D alone, vitamin D combined with calcium, or a placebo. Notable HbA1c reductions were found in the group receiving vitamin D and calcium altogether, while no significant changes were detected in the group taking only vitamin D [71].

Insulin signaling pathway disturbance is the main factor leading to a decline in insulin sensitivity and impaired insulin uptake, which causes type 2 diabetes mellitus[42]. Emerging evidence emphasizes the vital role of calcitriol in managing insulin resistance, a situation where the body's response to insulin declines [2.12].

Additionally, [24,43,44] explained that low serum 25(OH)D concentration causes the progression of impaired insulin sensitivities and type 2 diabetes mellitus. Even though the physiological mechanisms are incomprehensible, the presented mechanisms in which vitamin D adjusts glycemic control include insulin excretion by pancreatic beta cells, enhancing peripheral glucose uptake by hepatic cells in both direct and indirect mechanisms, and mitigating inflammation [5,12,24–30].

Hence, the role of 25(OH)D is critical in regulating blood sugar and insulin sensitivity, and its insufficiency and/or deficiency may participate in the elevation of HbA1c and insulin resistance. Calcium ions are well-known second messengers that play a crucial role in the intracellular processes triggered by insulin in muscle and adipose tissue [23]. Therefore, changes in intracellular calcium ions significantly affect the diverse actions of insulin. Several investigations showed that low intracellular calcium ions in insulin-sensitive tissues are linked to decreased glucose transporter activity, which can lead to the development of peripheral insulin resistance [24].

The concentration of intracellular calcium ions in insulin-responsive tissues, such as adipose tissue and skeletal muscle, is regulated through various mechanisms [2, 44]. One key mechanism involves the action of the parathyroid hormone, which increases intracellular calcium ions in these tissues while also decreasing the insulin-mediated transport of glucose [2, 44]. Accordingly, the rise in intracellular calcium concentration, combined with a reduced presence of GLUT-1 and GLUT-4 transporters on cell membranes due to PTH activity, contributes to the insulin resistance characterized by diminished glucose utilization [2,45].

Moreover, a strong correlation of hypovitaminosis D with impaired glucose uptake and insulin resistance is concluded by several studies, with the relevance of continuously sustaining sufficient amounts of vitamin D in prediabetic individuals [24]. Our study concluded that there was a significant reduction of insulin resistance statistically throughout our follow-up vitamin D administration time (Table 1 and Figure 2B). This result refers

to the impact of a high dose of 25(OH)D on IR and an improvement in insulin sensitivity. However, the subjects remained in the risk zone, but the reduction rate was significant statistically (p=0.035: Table 1). This is consistently aligned with [44, 46], and [47], but it contradicts [48]. Furthermore, our study aligns with those of Wright et al. [49], which demonstrated that cholecalciferol decreased insulin resistance in adipose and skeletal tissues by increasing intracellular calcium ions, which support GLUT-4 translocation to the muscle cell membrane and glucose uptake.

Additionally, regarding beta-cell function, the HOMA-B formula showed a significant increase, particularly from week 16 to week 32 during our follow-up study on vitamin D consumption, and this increase coincided with a rise in fasting insulin concentration during the same period. These results are supported by outcomes from [50], which observed the positive impact of vitamin D on insulin secretion and beta-cell function. Likewise, another study performed by Norman et al. [51] on in vitro pancreatic beta-cells of rats explained that a deficiency of calciferol restricts the secretion of insulin. Furthermore, some studies align with ours, noting that human pancreatic beta-cells express both 1-alpha-hydroxylase [51] and vitamin D receptors [38]. Additionally, vitamin D receptor elements have been observed in the insulin gene promoter [39].

Furthermore, regarding body mass index, our results showed no statistically significant changes in BMI with increased vitamin D concentrations throughout a follow-up study (Table 1). This outcome is supported by [52] findings that there is no relationship between body mass index and hypovitaminosis D, as reported by Gallagher et al. [53], they found no changes in BMI observed after 400 to 4800 IU of cholecalciferol every day for about 12 months. Alternatively,[6] showed that vitamin D administration had no significant effect on BMI compared to a placebo. Moreover, [7] concluded that daily administration of vitamin D in doses of 600, 1000, and 2000 IU for six months did not affect BMI. This outcome is supported by Subih et al.[54] in 2020, who concluded that with a vitamin D3 supplement alone at a dose of 50000 IU/week for about three months, no significant changes occurred relevant to decreased BMI or enhancement of obesity biomarkers. Additionally, [43] confirmed that administering cholecalciferol at a dose of 25000 to 600000 IU per month for a period of one month to one year did not affect weight. Similarly, Golzarand et al. [55] found no statistically significant changes occurred in body fat with the administration of cholecalciferol at doses of 400 to 7000 IU/day for about 3 to 12 months.

As well as, Duan et al. [56] also found that administration of cholecalciferol at doses ranging from 100 to 8571 IU daily for about 1.5 months to 3 years causes no change in body mass index.

In contrast to our findings, Lotfi-Dizaji et al. [57] concluded in 2019 that the administration of vitamin D at a dose of 50,000 IU/week significantly reduced body fat and weight. Our findings do not align with this result because they used a weight-reduction diet along with a bolus of vitamin D for their obese participants regularly over about 12 weeks.

Our study displayed that there is a greater chance of obesity in individuals with hypovitaminosis D, although the mechanisms that clarify the correlation between vitamin D and body mass index are not perfectly illustrated. Several investigation findings have implied that insufficiency of 25(OH)D can lead to a higher accumulation of adipocytes, which in turn increases fat production [58]. Alternatively, [59] explained that vitamin D is one of the main elements in the production of leptin, which is critical in promoting the progression of obesity. Hence, a reduction in vitamin D can enhance appetite and result in obesity.

Another important factor that has also been documented previously by [60–68] return the causes of increased levels of PTH and di-hydroxyvitamin D in obese individuals to negative feedback control during the creation of 25-(OH)D in the liver, which causes diminish in the secretion of insulin and impaired insulin uptake, obesity, hypertension, enhancing insulin resistance, and T2DM, and hypovitaminosis D. Additionally[68] believed that the accumulation and distribution of body fat may be correlated to vitamin D status, and this is reliant on some metabolic factors. Furthermore, [48] proposed that inhibition of 25-hydroxyvitamin D synthesis and increased PTH concentrations result in the progression of weight gain and trigger the collection of fat cells in the body. Moreover, another study [69] proposed that increasing serum vitamin D by supplementation may avert the overweight process but not weight loss in obese individuals. This prediction is also aligned with our results.

Conclusion

Obvious elevation in serum cholecalciferol among prediabetic individuals emphasizes the efficiency of the vitamin D supplements throughout our follow-up study. Our findings illustrate the importance of vitamin D supplements in improving metabolic dysregulation, specifically in prediabetic cases concerning glycemic imbalance. The substantial reduction in HbA1c and insulin resistance, along with increased vitamin D levels, indicates the vital influence of vitamin D administration, especially at high doses, in delaying and/or preventing the progression and/or conversion of prediabetes to type 2 diabetes mellitus. These findings suggest that vitamin D supplementation may help reduce glycated hemoglobin and insulin resistance, emphasizing the need for further research and long-term studies.

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