THE IMPACT OF DIFFERENT REGIMENS OF VITAMIN D3 ON GLUCOSE HOMEOSTASIS IN TYPE 2 DIABETIC PATIENTS

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ABSTRACT

Objective: Vitamin D has a role in the regulation of pancreatic β-cell function and insulin sensitivity. Accordingly, Vitamin D deficiency is considered to be a risk factor for the development of type 2 diabetes mellitus (T2DM) and its complications. Therefore, the aim of the study was to assess and compare the effect of different regimens of Vitamin D3 on glucose homeostasis in patients with T2DM.

Methods: The study included 80 patients with T2DM taking oral antidiabetic drugs. The patients were randomized to receive antidiabetic drugs alone or with different regimens of Vitamin D3 for 3 months. Vitamin D3-treated patients were supplemented by either daily oral 4000 IU Vitamin D3, weekly oral 50,000 IU Vitamin D3, or a single parenteral dose of 300,000 IU Vitamin D3. In addition to the assessment of patient characteristics, laboratory measurements of serum creatinine, blood urea, total and ionized calcium, serum phosphorus, fasting blood glucose, fasting serum insulin, homeostasis model assessment of insulin resistance, hemoglobin A1c, and 25(OH) Vitamin D levels were measured at the beginning and after 3 months.

Results: After 3 months, the increased Vitamin D levels resulting from the daily and weekly oral doses of Vitamin D3 caused a significant decrease in metabolic parameters, whereas the parenteral dose demonstrated a non-significant decrease.

Conclusion: Oral daily and weekly doses of Vitamin D3 could improve glucose homeostasis equally in patients with T2DM and better than a single parenteral dose of Vitamin D3.

Keywords: Diabetes, Glucose, Insulin resistance, Vitamin D.

INTRODUCTION

Although the management of type 2 diabetes mellitus (T2DM) has been improved over the past few decades, it remains a worldwide healthcare problem [1-3]. Therefore, further efforts in developing measures for the management and prevention of T2DM and its complications are thus required.

Recently, particular attention has been focused on the relationship between Vitamin D deficiency and a wide array of diseases, including T2DM [4-8]. In addition to the Vitamin D effects on calcium (Ca) homeostasis and bone health, Vitamin D also mediates non-calcemic actions in different tissues through Vitamin D receptors (VDRs) [9,10].

Vitamin D regulates pancreatic β-cell function and insulin sensitivity through several potential mechanisms. Similar to various cells, the pancreatic β-cells contain VDR and 1α-hydroxylase enzyme, which allow direct stimulation of insulin secretion [11]. Vitamin D also can regulate the Ca pool of β cells, decrease reactive oxygen species formation, and modulate chronic inflammation to further control insulin secretion and decrease insulin resistance [10,12-14].

Vitamin D supplementation is currently the best approach to combat Vitamin D deficiency. Unfortunately, the results of Vitamin D supplementation on glucose homeostasis yielded inconclusive results, and no previous studies compared the effect of different regimens of Vitamin D3 [15-18].

In the current study, we aimed to assess and compare the effect of administration of three different regimens of Vitamin D3 (continuous daily oral, intermittent weekly oral regimen, and a loading dose of intramuscular [IM] injection) on glucose homeostasis in patients with T2DM.

METHODS

Subject selection

The participants were recruited from the diabetes clinic of the Alexandria Main University Hospital. The study was approved by the Ethical Committee of the Alexandria Faculty of Medicine, Egypt (IRB No: 00007555), and informed consent was obtained from all participants before their enrollment. The study was also conducted in accordance with the Declaration of Helsinki.

The exclusion criteria included the following: Patients with type 1 diabetes mellitus or insulin-dependent diabetes, patients who changed the type or the dose of antidiabetic agents in the past 3 months, pregnancy, lactation, use of Ca, multivitamins, Vitamin D supplements, use of drugs that affect Vitamin D status, dietary Ca intake exceeding 1500 mg/d [estimated from diet history], hypo- or hyperthyroidism, smoking, and use of antiepileptic drugs. Known sarcoidosis, tuberculosis, potentially terminal illness, inflammatory bowel disease, liver or kidney disease, and malignancy were also excluded from the study.

Study protocol

A total of 231 patients with T2DM 30 years of age or greater were assessed for eligibility. Only 85 were enrolled and then allocated into four groups by the block randomization method. The first group (Group I) received only their oral antidiabetic agents. The second group...
Ali et al. was treated with three different regimens of Vitamin D3 (cholecalciferol, Medical Union Pharmaceuticals, Egypt) as follows: Group IIA received continuous oral Vitamin D3 in a dose of 4000 IU daily for 3 months. Group IIb was treated with an intermittent regimen of Vitamin D3 in a dose of 50,000 IU weekly for 3 months. Group IIC received a single IM injection of 300,000 IU of Vitamin D3 at the start of the study. Group II continued their oral antidiabetic agents as usual in addition to Vitamin D supplement. All patients were followed up and interviewed regularly during the 3 months of the study to confirm that there was no change in their medications or lifestyle and to check their compliance.

All the participants were subjected to history taking with a focus on age, duration of diabetes, and antidiabetic treatment. Patient weight, height, and body mass index were also measured initially.

Laboratory analysis
Sample collection
All laboratory investigations were done at the beginning and after 3 months of treatment. After overnight fasting, venous blood samples were drawn from an antecubital vein and collected into plain vacutainer tubes for the measurement of serum creatinine, blood urea nitrogen, total and ionized Ca, serum phosphorus, fasting serum glucose, fasting serum insulin, and 25(OH)D3 levels. All these parameters were assessed on the same day of sampling. Ethylenediaminetetraacetic acid tubes were also used to assess hemoglobin A1c (HbA1c).

Analysis of samples
The patient’s serum creatinine, blood urea nitrogen, total and ionized Ca, and serum phosphorus were assessed by Roche/Hitachi Cobas c systems (Roche Diagnostics, GmbH, Mannheim, Germany). The fasting serum glucose levels were measured by enzymatic colorimetric kit (BioSystems, Barcelona, Spain). An enzyme-linked immunosorbent assay kit was used to measure fasting serum insulin (eBioscience, Vienna, Austria). Serum 25(OH)D3 was measured by electrochemiluminescence immunoassay using Cobas e-411 analyzer and related kits (Roche Diagnostics GmbH, Mannheim, Germany). HbA1c levels were calculated by the enzymatic method using the Hitachi 911 chemistry analyzer (Roche Diagnostics, GmbH, Mannheim, Germany) according to the manufacturer’s instructions. A homeostasis model assessment (HOMA) calculator was used to estimate the HOMA of insulin resistance (HOMA-IR%).

Statistical analysis
The data were analyzed using the Statistical Package for the Social Sciences (IBM SPSS, version 20). The Shapiro-Wilk test was used for determining the normality of the parameters. Quantitative data were shown as mean±standard deviation, whereas qualitative data were presented as numbers and percentages. Tests of significance were applied as indicated. The Chi-square test was applied for qualitative data; the paired t-test and analysis of variance test were applied for normally distributed quantitative data, and the Wilcoxon signed-rank test and the Kruskal–Wallis test were used for abnormally distributed quantitative data. The effect of treatment was evaluated by calculating the change of values from baseline, and pairwise comparison between each of the two groups was done using post hoc test (Dunn Test for Multiple Comparisons). p<0.05 was considered to be statistically significant.

RESULTS
Five of 85 patients withdrew from the study; 20 patients (5 men and 15 women) in the control group and 60 patients in the Vitamin D3-treated groups completed the study (21 men and 39 women) (Fig 1).

Table 1 shows the demographic data of the groups. There were insignificant differences between the four groups with regard to the baseline characteristics.

At the start of the study, the mean baseline serum 25(OH)D3 level was <20 ng/mL in all studied groups, with no statistically significant difference among them. However, serum 25(OH)D3 level was significantly increased after treatment with the different regimens of Vitamin D when compared with their baseline levels (Table 2). Regarding the change from baseline values, 25(OH)D3 levels increased significantly less in patients treated with a single parenteral dose of Vitamin D3 compared with patients treated with daily or weekly oral doses. Moreover, there was a non-significant difference between the oral daily and oral weekly groups regarding the change in 25(OH)D3 levels from baseline values (Table 3).

After 3 months, T2DM patients treated with either oral or weekly Vitamin D3 showed a significant decrease in the mean levels of serum creatinine and blood urea compared with their initial values. However, patients treated with a single dose of parenteral Vitamin D3 showed an insignificant decrease in the mean levels of serum creatinine and blood urea (Table 2).
Table 2: Effect of Vitamin D supplementation on different laboratory parameters, before and after 3 months of treatment in patients with type 2 diabetes mellitus

| Parameter                                | Control group (%) | Daily oral Vitamin D3 group (%) | Weekly oral Vitamin D3 group (%) | Parenteral Vitamin D3 group (%) | p       |
|-------------------------------------------|-------------------|---------------------------------|---------------------------------|---------------------------------|---------|
| Creatinine (mg/dL)                        |                   |                                 |                                 |                                 |         |
| Baseline                                  | 0.71±0.09         | 0.156                           | <0.001*                         | 0.83±0.19                       | <0.001* |         |
| After 3 months                            | 0.74±0.14         | 0.66±0.06                       | 0.016                           | 0.61±0.16                       |         |
| Blood Urea (mg/dL)                        |                   |                                 |                                 |                                 |         |
| Baseline                                  | 29.10±5.97        | 0.157                           | <0.001*                         | 27.70±5.33                      | <0.001* | 28.50±8.85 |
| After 3 months                            | 29.65±6.90        | 0.156                           | 0.016                           | 19.80±3.75                      | 25.90±7.64 |
| Total calcium (mg/dL)                      |                   |                                 |                                 |                                 |         |
| Baseline                                  | 9.83±0.46         | 0.428                           | 0.064                           | 9.67±0.33                       | 0.104   | 9.59±0.56 |
| After 3 months                            | 9.84±0.45         | 0.56±0.33                       | 0.016                           | 9.82±0.32                       | 9.72±0.23 |
| Ionized calcium (mg/dL)                    |                   |                                 |                                 |                                 |         |
| Baseline                                  | 4.75±0.20         | 1.000                           | 0.464                           | 4.69±0.16                       | 0.345   | 4.72±0.12 |
| After 3 months                            | 4.75±0.23         | 0.70±0.11                       | 0.464                           | 4.73±0.12                       | 4.79±0.18 |
| Phosphorus (mg/dL)                        |                   |                                 |                                 |                                 |         |
| Baseline                                  | 3.47±0.19         | 0.110                           | 0.883                           | 3.37±0.30                       | 0.498   | 3.08±0.59 |
| After 3 months                            | 3.50±0.24         | 0.46±0.49                       | 0.340                           | 3.40±0.28                       | 3.16±0.50 |
| Fasting blood glucose (mg/dL)              |                   |                                 |                                 |                                 |         |
| Baseline                                  | 175.7±49.19       | 0.352                           | <0.001*                         | 166.5±56.18                     | <0.001* | 181.8±71.20 |
| After 3 months                            | 176.7±50.29       | 1.26±48.71                      | 0.016                           | 143.5±56.92                     | 0.092   | 178.3±67.63 |
| Fasting serum insulin (µL/mL)              |                   |                                 |                                 |                                 |         |
| Baseline                                  | 14.85±4.01        | 0.005                           | 19.66±11.66                     | 0.005                           |         | 19.49±9.46 |
| After 3 months                            | 15.57±3.47        | 1.52±8.65                       | 15.22±8.65                      | 12.55±4.61                      | 0.232   | 17.94±7.94 |
| Homeostasis model assessment of insulin resistance (%) |                   |                                 |                                 |                                 |         |
| Baseline                                  | 2.23±0.54         | 0.003                           | 2.75±1.60                       | 0.002                           | <0.001* | 3.04±1.42 |
| After 3 months                            | 2.33±0.45         | 2.01±1.12                       | 2.63±0.97                       | 0.002                           | 2.73±1.15 |
| Hemoglobin A1c (%)                        |                   |                                 |                                 |                                 |         |
| Baseline                                  | 9.40±1.29         | 0.014                           | 8.40±2.09                       | 0.002                           | <0.001* | 8.47±2.14 |
| After 3 months                            | 9.45±1.28         | 7.59±1.66                       | 8.77±1.75                       | 0.001                           | 8.13±1.81 |
| Serum 25(OH) Vitamin D3 (ng/mL)           |                   |                                 |                                 |                                 |         |
| Baseline                                  | 12.98±3.69        | 0.003                           | 11.78±3.64                      | <0.001*                         | <0.001* | 14.16±7.30 |
| After 3 months                            | 12.60±3.73        | 38.92±11.56                     | 46.03±5.49                      | <0.001*                         | <0.001* | 25.30±6.55 |

*Statistically significant at \( p \leq 0.05 \), data are expressed as mean±standard deviation, numbers of patients in each group; control group (n=20), daily oral group (n=20), weekly oral group (n=20), parenteral group (n=20).
Table 3: Comparison between different groups according to change from baseline values after 3 months of treatment in patients with type 2 diabetes mellitus

| Parameter                  | Control group | Daily oral Vitamin D3 group | Weekly oral Vitamin D3 group | Parenteral Vitamin D3 group | p       |
|----------------------------|---------------|----------------------------|-----------------------------|-----------------------------|---------|
| Creatinine (mg/dL)         | 7.03±0.08     | 10.20±0.11                 | 10.23±0.10                  | 10.07±0.16                 | <0.001* |
| Blood urea (mg/dL)         | 10.55±1.67    | 17.20±2.86                 | 17.90±3.23                  | 12.60±9.52                 | <0.001* |
| Fasting blood glucose (mg/dL) | 11.0±5.56    | 12.90±11.08               | 12.30±7.92                  | 1.50±5.90                  | <0.001* |
| Fasting serum insulin (µIU/mL) | 10.72±1.01   | 14.44±5.18                | 15.88±6.46                  | 1.55±9.38                  | <0.001* |
| Homeostasis model assessment of insulin resistance (%) | 10.10±0.14 | 10.71±0.75                | 10.87±0.60                  | 10.30±1.26                | <0.001* |
| Hemoglobin A1c (%)         | 10.05±0.08    | 10.8±0.77                  | 10.82±0.87                  | 10.34±1.47                | <0.001* |
| Serum 25(OH)D3 (ng/mL)     | 10.30±0.50    | 12.74±8.51                | 13.18±5.02                  | 11.14±4.24                | <0.001* |

*Statistically significant at p≤0.05, data are expressed as mean±standard deviation, numbers of patients in each group; control group (n=20), daily oral group (n=20), weekly oral group (n=20), parenteral group (n=20). "Significant between control and each other group, "Significant between daily oral Vitamin D3 group and each other group, "Significant between weekly oral Vitamin D3 group and parenteral Vitamin D3 group.

(FBG), and the lowering effects of the two groups were insignificantly different after removing the baseline effect. Otherwise, the parenteral group demonstrated a non-significant decrease in FBG at the end of the study, and after removing initial values, the change in FBG was statistically insignificantly different from that of the control group (Tables 2 and 3).

The administration of daily and weekly Vitamin D3 for 3 months resulted in a significant decrease in both serum insulin levels, and insulin resistance with insignificant differences between the effects of both doses, whereas the single parenteral dose of Vitamin D3 demonstrated insignificant changes in serum insulin levels, and insulin resistance, when compared with their baseline values. However, after removing the effect of baseline values, the change in serum insulin and HOMA-IR became statistically significant when compared with the control group and were insignificantly different from the daily and weekly groups (Tables 2 and 3).

The intake of oral daily and weekly doses of Vitamin D3 was effective in decreasing HbA1C at the end of the study, whereas the changes from basal levels by the two doses were statistically non-significantly different between the two oral groups. However, a group of patients treated with a single parenteral Vitamin D3 dose showed an insignificant decrease in the mean HbA1C after 3 months compared with the mean pre-treatment value, and the change from initial value was insignificantly different from the control group (Tables 2 and 3).

DISCUSSION

More than 97.5% of patients with T2DM in the current study had Vitamin D deficiency at the start of the study. This result is in agreement with a meta-analysis by Song et al. [19], who reported an inverse association between the risk of T2DM and vitamin D status in diverse populations. Moreover, Parker et al. [20], in a meta-analysis, stated that elevated levels of Vitamin D were related to a decrease in cardiovascular disease, T2DM, and metabolic syndrome in middle age and elderly populations.

The present study is the first to compare the impact of three different supplemented doses of Vitamin D3 in patients with T2DM. We found that a daily oral dose of 4000 IU and a weekly oral dose of 50,000 IU (~8000 IU/d) of Vitamin D3 for 3 months were effective to increase 25-hydroxy Vitamin D3 levels from <20 ng/mL to >30 ng/mL. Whereas, a single parenteral dose of 300,000 IU (~4000 IU/d) of Vitamin D3 increased 25-hydroxy Vitamin D3 levels from <20 ng/mL to >20 ng/mL, but still lower than 30 ng/mL.

It is worth noting that the 25(OH)D3 levels after 3 months did not vary between the oral daily and oral weekly groups. In the parenteral group, Vitamin D3 levels did not reach normal levels, although the parenteral dose was approximately equal to the daily dose.

We could explain the insignificant difference between the two oral doses regarding the increase in 25(OH)D3 levels as the conversion of Vitamin D3 by hepatic 25-hydroxylase into 25(OH)D3, which was first-order kinetics at the start of Vitamin D intake. However, later on, metabolism transformed the response to zero-order kinetics as the hepatic 25-hydroxylase became saturated by the large doses of Vitamin D3 administered to the patients. The change in the kinetics of Vitamin D3 was explained by a dose-response curve conducted by Heaney et al. [21], who found that the conversion of Vitamin D3 by hepatic 25-hydroxylase into 25(OH)D3 transforms to zero-order kinetics when the 25(OH)D3 level is approximately 35.2 ng/mL.

Actually, there are numerous factors that can affect the response to Vitamin D supplementation. These factors include the supplemented dose of Vitamin D3, duration of administration, the compliance of the patient, and the absorption of the administered doses of Vitamin D3 from the gastrointestinal tract. Bhagwate et al. [22] found that the doubling of the Vitamin D3 dose was effective to reach normal levels more rapidly and earlier than the lower dose, although both had the same cumulative levels at the end of the study and both were effective to correct suboptimal 25(OH)D3 levels.

The duration of the current study was 3 months, which might clarify the discrepancy in response between the daily oral and the single parenteral doses. It had been previously reported that the oral dose produced a rapid increase in 25(OH)D3 levels, whereas a parenteral dose showed delayed response and needed a longer duration to show maximum response. As in the study conducted by Whyte et al. [23], 25(OH)D3 level started to increase within hours after a single large oral dose of Vitamin D3 equal to 100 µg/kg = 4000 IU/kg, and its maximum serum level was reached after 1 week whereas a single parenteral dose equal to 200 µg/kg = 8000 IU/kg began to increase Vitamin D levels after 1 week, and the level continued to increase until 7 weeks later. In addition, Hashemipour et al. [24] stated that 2 weeks after administration of 300,000 IU and 60,000 IU of Vitamin D3 parenterally, the 25(OH)D3 levels were insignificantly different from baseline levels. However, the levels of 25(OH)D3 became significantly higher and were still increasing 4 months later. Diamond et al. [25] further demonstrated that a single parenteral 60,000 IU dose of Vitamin D3 was effective to continue increasing the serum Vitamin D level up to 1 year after the stop of supplementation of Vitamin D3.

Previous observational studies showed that 25(OH)D3 levels were lower in patients with T2DM than in non-diabetic patients, and there was an inverse association between 25(OH)D3 levels and glycemic control parameters and inflammatory mediator [4-7,26]. However, the findings of interventional studies regarding the effect of Vitamin D3 administration on the control of T2DM are controversial [17].

Tabesh et al. [27], in their randomized controlled study, found that combined administration of Vitamin D3 with Ca produced a significant decrease in metabolic parameters compared with Vitamin D3 alone. Whereas in the SUNNY trial in patients with T2DM taking oral antidiabetic treatment, monthly administration of 50,000 IU of Vitamin
D3 for 6 months did not improve glycemic control parameters [28]. Moreover, the studies conducted by Witham et al. [29] and Sugden et al. [30] reported that a single high dose of Vitamin D3 did not show improvement in glucose homeostasis. In addition, a meta-analysis by George et al. [31] concluded that Vitamin D3 supplementation to diabetics and nondiabetics did not have a beneficial effect on glycemic control.

The inability of Vitamin D3 to change metabolic parameters could be clarified by such differences in intervention features as the study populations, duration of the study, dose, and dosage forms of supplemented Vitamin D3 and different sample sizes. Apart from these factors, several participant’s features such as genetic factors and, most importantly, the baseline value of 25(OH)D3 also play important roles in modifying the efficacy of supplementation [17,18].

In our study, we found that supplementation with Vitamin D3 to patients with T2DM for 3 months caused a significant decrease in metabolic parameters, and the lowering effect of oral doses was superior to that of the parenteral dose.

A recent meta-analysis supports our finding that Vitamin D3 supplementation improved glycemic control in patients with T2DM [32]. They recommend a minimum dose of 4000 IU daily of Vitamin D3 to exert a significant decrease in FBG, HbA1c, and HOMA-IR in patients with T2DM. Likewise a meta-analysis conducted by Li et al. [15] suggested that the increase in serum 25(OH)D3 after Vitamin D3 supplementation could decrease metabolic parameters, especially when Vitamin D3 was administrated in large doses >2000 IU/day for a short period of time (≤ 3 months), and to non-obese patients of Middle Eastern descent who were Vitamin D deficient.

Meanwhile, Talaei et al. [33] showed a significant decrease in serum FPG, insulin, and HOMA-IR in patients with T2DM who received weekly oral 50,000 IU of Vitamin D3 for 2 months. In addition, Upreti et al. [34] stated that Vitamin D3 for 6 months at a dose of 60,000 IU every week for the first 6 weeks and then once every 4 weeks until completion of the study had a beneficial effect on FBG and HbA1c levels.

Furthermore, Shaeed et al. [17] reported improvement in HbA1C after 3 months of treatment in patients with T2DM by a single high dose of Vitamin D3 300,000 IU intramuscularly. This result is in line with the effect of the single parenteral dose in the present study. Furthermore, Jehle et al. [35] found that the treatment of patients with T2DM with 300,000 IU of Vitamin D3 IM could improve insulin resistance and positively affect the course of HbA1C.

The beneficial effect of Vitamin D on glycemic control parameters could be explained by several mechanisms that control insulin resistance and pancreatic β-cell dysfunction. On the one hand, Vitamin D enhances insulin synthesis directly through stimulating the insulin gene and promoting β-cell survival by downregulating Fas-related pathways [36,37]. On the other hand, Vitamin D improves insulin secretion indirectly through regulating calbindin, a cytosolic Ca-binding protein in β cells, which modulates depolarization-mediated insulin release by regulating intracellular Ca. Furthermore, Vitamin D increases insulin secretion by suppressing parathyroid hormone (PTH), as increased PTH inhibits insulin synthesis and secretion in β cells and induces insulin resistance in target cells by causing Ca paradox. Ca paradox is a paradoxical increase in intracellular Ca with impairment in the Ca signal that is needed for glucose-stimulated insulin secretion [38].

Moreover, Vitamin D enhances insulin sensitivity through inducing expression of insulin receptors and stimulating peroxisome proliferator-activated receptor δ, which increases fatty acid metabolism in skeletal muscles and adipose tissue [39]. Furthermore, Vitamin D can decrease insulin resistance directly through inactivation of nuclear factor-κB, blockade of dendritic cell differentiation, inhibition of lymphocyte proliferation, enhanced regulation of T lymphocytes, downregulation of cytokine expression, as well as suppression of the pancreatic RAAS, which impairs glucose uptake in vascular and skeletal muscle tissue [36,37,39,40].

CONCLUSION

From the present study, we conclude that the effect of oral daily and weekly doses of Vitamin D3 on glucose homeostasis is more favorable than a single parenteral dose. Thus, Vitamin D3 supplementation, especially oral daily and weekly doses, should be included in the treatment of patients with T2DM who are 25(OH)D3-deficient.

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AUTHORS’ CONTRIBUTIONS

The author declares that all the named authors have contributed equally to this article.

CONFLICTS OF INTEREST

The authors have no conflicts of interest to disclose.

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