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Effect of Vitamin D supplementation on glycemic control in Type 2 diabetes subjects in Lagos, Nigeria

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Abstract

Introduction:

Improvement of glycemic control reduces the risk of diabetic complications. Reports suggest that Vitamin D supplementation improves glycemia. However, there are no data on the influence of Vitamin D on diabetes mellitus (DM) in Nigeria.

Objective:

To determine the effect of Vitamin D supplementation on glycemic control in Type 2 DM (T2DM) participants with Vitamin D deficiency.

Design:

This was a single-blind, prospective randomized placebo-controlled trial, involving T2DM participants attending the Diabetes Clinic of the Lagos University Teaching Hospital. Forty-two T2DM participants with poor glycemic control and Vitamin D deficiency were selected following a prior cross-sectional study on 114 T2DM participants for the determination of Vitamin D status and glycemia. These participants were randomized into two equal groups of treatment and placebo arms.

Intervention:

Three thousand IU of Vitamin D₃ were given to the participants in the treatment arm. Glycemic status was determined at baseline and after 12 weeks. Statistical analysis was performed using Statistical Package for Social Sciences version 20. $P < 0.05$ was considered statistically significant.

Results:

Vitamin D₃ supplementation resulted in a significant improvement in serum Vitamin D level and fasting plasma glucose in the treatment arm compared to placebo. There was a nonsignificant reduction in the mean HbA_{1c} level in the treatment group after 12 weeks of Vitamin D₃ supplementation ($Z = -1.139$; $P =$

0.127) compared to the placebo group, which had a further increase in the mean HbA1c level ($Z = -1.424$; $P = 0.08$). The proportion of participants with poor glycemic control (HbA1c > 6.5%) who converted to good control after Vitamin D supplementation was significantly higher in the treatment arm compared to placebo ($P < 0.05$).

Conclusion:

Vitamin D₃ supplementation in persons with T2DM and Vitamin D deficiency results in a significant improvement in glycemic control.

Keywords: Glycemic control, Type 2 diabetes mellitus, Vitamin D supplementation

INTRODUCTION

Type 2 diabetes has a major impact on the morbidity and mortality of the individual as well as on the quality of life. Controlling blood glucose minimizes the onset of micro- and macro-vascular complications and reduces the progression of existing ones.[1] Poor glycemic control has been associated with several factors including Vitamin D deficiency.[2,3]

Vitamin D deficiency is a global health care concern. A growing number of studies have reported widespread Vitamin D deficiency and insufficiency in both apparently healthy populations and patients with various pathologies including diabetes mellitus (DM).[4] It has been estimated that one billion people worldwide are affected by various degrees of Vitamin D deficiency.[5] Since the first report on the influence of Vitamin D on insulin secretion,[6] evidence has proposed a role for Vitamin D in both the occurrence[7] and treatment of Type 2 DM (T2DM).[8,9] There is now convincing evidence that Vitamin D has some role in both pancreatic insulin secretion and insulin sensitivity and thereby affects the pathogenesis of the disease.[8,9]

Several studies on the glycemic control of subjects with DM, done in various regions in Nigeria, have shown that poor glycemic control is common among Nigerian DM subjects.[3,10,11,12]

Reports suggest that Vitamin D supplementation improves glycemia.[13,14,15,16,17] However, there are no data on the Vitamin D status or relationship between Vitamin D and DM in Nigeria.

The objective of this study was to determine the effect of Vitamin D supplementation on glycemic control in T2DM participants with poor glycemic control and Vitamin D deficiency.

MATERIALS AND METHODS

This was a single-blind, prospective randomized placebo-controlled trial, involving T2DM participants attending the Diabetes clinic of the Lagos University Teaching Hospital. The study participants consisted of 42 T2DM participants with poor glycemic control and Vitamin D deficiency selected following a prior cross-sectional study on 114 T2DM participants for the determination of Vitamin D status and glycemia. These participants were randomized into two equal groups of treatment and placebo arms.

Levels of serum Vitamin D, fasting glucose, HbA1c, calcium, albumin, phosphate, creatinine, and alanine transaminase were determined. Serum Vitamin D level was assessed by the high-performance liquid chromatography method. Vitamin D₃ supplements (3000 IU daily) were given to the participants in the treatment arm and placebo (made of 50mg corn starch) given to the placebo arm.

Glycemic status was determined at baseline and after 12 weeks of Vitamin D₃ supplementation in the treatment arm. Doses of their oral antidiabetics were kept constant during this period. The sample size was calculated using the formula below:[18]

$$n = \frac{2 \times C_p \cdot \text{power}}{d^2}$$

Where:

n = number of subjects required in each arm

d = standardized mean difference (an index of the intrinsic variability of the studied endpoint)

$$= \frac{\text{Target difference}}{\text{Standard deviation}}$$

Target difference = The minimal effect size considered as clinically relevant expected to be found in this study

Cp.power = a constant defined by chosen *P* value and Power.

Cp.power = 7.9 (statistical significance of 0.05 and power of 80%).[18]

Target difference of Vitamin D levels = 28 nmol/l,[9]

Standard deviation (SD) = 31.0.

Standardized difference, $d = 28/31 = 0.9$.

The number of participants required in each arm of the trial, *n*:

$$n = \frac{2 \times 7.9}{0.9^2}$$
$$= \frac{15.8}{0.81} = 19.5$$

N = 20 (nearest even number)

To allow for 10% attrition, a total of 44 subjects (22 subjects in each intervention-arm) were estimated to be used in the second phase interventional study.

Inclusion and exclusion criteria for the study participants

Inclusion criteria

The following groups of persons were eligible for recruitment into the study:

- Participants aged 35–65 years with T2DM and on oral antidiabetics
- Participants who gave informed consent
- T2DM participants with Vitamin D deficiency and poor glycemic control as evidenced by HbA1c > 6.5%.

Exclusion criteria

Those who were excluded from the study were:

- Participants below 35 years or above 65 years
- Participants with T1DM
- T2DM participants on insulin (due to influence of insulin antibodies on serum insulin assay)
- Pregnant women (serum Vitamin D levels are generally low in pregnancy)
- Participants with chronic diseases including renal insufficiency (glomerular filtration rate <30 ml/min), history of chronic liver disease or alanine transferase >5 times upper reference limit, tuberculosis, diarrheal, or malabsorption state.

Statistical analysis was done using the Statistical Package for Social Sciences, version 20 (IBM, Armonk, NY, United States of America). Results were expressed as mean (SD) and percentages. Comparisons between treatment groups were made using Wilcoxon, Chi-square, and Z-tests. *P* <0.05 was considered statistically significant.

RESULTS

A total 45 (39.5%) T2DM participants had both low Vitamin D₃ levels and poor glycemic control, three of them could not be reached, and hence, 42 participants were randomized into two equal arms of 21 participants each. The study response rate (study completers) at the end of 12 weeks, follow-up was 17 (80.9%) in the treatment arm, and 16 (76.2%) in the placebo arm. Participants' flow chart is shown on [Figure 1](#).

The mean age of the participants was 52.5 ± 2.2 in the treatment group and 51.1 ± 1.9 in the placebo group ($P > 0.05$). There were 10 (58.8%) females and 7 (41.2%) males in the treatment group, and 9 (56.3%) females and 7 (43.7%) males in the placebo group ($\chi^2 = 0.02$, $P = 0.88$).

Patients adherence assessed by tablet counts at each visit showed an overall adherence of 62.2% and 59.9% in the treatment and placebo groups, respectively. Tables [1](#) and [2](#) show the effect of Vitamin D₃ supplementation on biochemical variables in the treatment arm and the changes in the placebo arm.

There was a significant reduction in the fasting plasma glucose in the treatment group compared to control group. Vitamin D₃ supplementation significantly lowered the plasma fasting glucose levels in the treatment group on week 4 and week 8 (Friedman's test, $\chi^2 = 8.46$, $P = 0.03$). *Post hoc* analysis with Wilcoxon signed rank test was conducted with Bonferroni correction applied resulting in a significance level set at $P < 0.013$. A significant FPG reduction was noted at weeks 4 and 8 ($Z = -2.39$, $P = 0.008$ and $Z = -2.43$, $P = 0.007$, respectively). The FPG in the placebo group showed an insignificant drop on week 4 and then increased through weeks 8–12. ($\chi^2 = 2.64$, $P = 0.45$). The mean differences in serum Vitamin D₃ and glycemia after 12 weeks of treatment are shown in [Table 3](#).

There was a nonsignificant drop in the mean HbA1c level in the treatment group after 12 weeks of Vitamin D₃ supplementation ($Z = -1.139$; $P = 0.127$) compared to the placebo group, which had further increase in the mean HbA1c level ($Z = -1.424$; $P = 0.08$) as shown in [Figure 2](#).

The proportion of participants with poor glycemic control (HbA1c $> 6.5\%$) who converted to good control after Vitamin D supplementation was significantly higher in the treatment arm compared to placebo ($P < 0.05$) as shown in [Figure 3](#).

DISCUSSION

The proportion of females in this study was higher than the male counterpart, with female to male ratio of 1.4:1 in the treatment arm and 1.3:1 in the placebo arm. This is in contrast to some previously documented reports on an overall higher prevalence of diabetes in males than females. A possible explanation for this might be due to the higher life expectancy in females.[\[19\]](#) In part, this finding may be a reflection of the female to male sex distribution of the diabetes subjects attending the diabetes clinic of the Lagos University Teaching Hospital where this study was carried out, which was put at 1.8. Greater use of hospital facility by women or lack of time to visit hospital by employed males may also be a reason.

Vitamin D₃ supplementation in the treatment arm resulted in a significant increase in the serum Vitamin D₃ concentration after 12 weeks of treatment compared to the placebo group, although the serum Vitamin D was still below normal. This may be due to the short duration of supplementation. Assessing the adequacy of Vitamin D replacement can prove difficult. This is partly due to methodology issues for measuring Vitamin D.[\[20\]](#) There is often a lag time in response of measured Vitamin D levels to oral Vitamin D replacement. This is due to the highly fat soluble nature of Vitamin D and its distribution within the large body fat compartment, before distribution within the smaller extracellular fluid compartment. It takes several months to correct Vitamin D deficiency.[\[20\]](#) For monitoring of response to Vitamin D replacement, it is best to measure serum Vitamin D, 3–4 months after commencing therapy.[\[20\]](#)

This study found a significant reduction in mean FPG from baseline values, a drop in HbA1c levels in T2DM subjects after Vitamin D supplementation; whereas the FPG and HbA1c increased further in the placebo arm. In addition, the proportion of T2DM subjects with poor glycemic control who converted to good control after Vitamin D₃ supplementation was significantly higher in the treatment group compared to control.

These findings are in agreement with the results of previous studies.[13,14,15,16,17] Amal reported a significant reduction of the mean fasting blood glucose and HbA1C from baseline after 6 months of Vitamin D₃ supplementation.[16] Pittas *et al.*[13] in a double-blind, randomized, controlled trial reported that in healthy adults with impaired fasting blood glucose, supplementation with calcium and Vitamin D may attenuate increases in glycemia and insulin resistance that occur over time. In addition, a retrospective study conducted by Sabherwal *et al.*[14] indicated that Vitamin D and calcium replacement therapy in South Asian patients with T2DM produced a significant decrease in both HbA1c and weight, which might be attributed to the increase in Vitamin D levels posttreatment. Consistent with finding of this study, Nikooyeh *et al.*[17] showed that daily intake of a Vitamin D fortified yogurt drink, either with or without added calcium, improved glycemic status in T2DM patients.

Study limitations

- Study participants were assumed to have kept doses of other antidiabetics constant during the intervention period
- The study participants were also assumed not to be taking Vitamin D containing complimentary medicines alongside their medications during the intervention period
- It takes several months to correct Vitamin D deficiency. Measurement of response to Vitamin D therapy takes several months (at least 3–4 months).[20]

The minimal changes in serum Vitamin D levels noted after supplementation in this study may be due to the reasons above. Longer periods of follow-up during supplementation would have been more ideal. However, this was not feasible due to time constraints and cost.

CONCLUSION

Vitamin D₃ supplementation in persons with T2DM with Vitamin D deficiency and poor glycemic control results in a significant improvement in glycemic control. The findings of improvement in glycemic control may help us understand the role of Vitamin D on glycemia in persons with T2DM. An implication of this is the possibility of making decisions on the recommendation of Vitamin D treatment in persons with T2DM with Vitamin D deficiency and poor glycemic control in Nigeria.

Further research in this field would be of great help to confirm these findings, possibly with different Vitamin D₃ doses, larger sample size, and a longer period of follow-up.

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Conflicts of interest

There are no conflicts of interest.

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Figures and Tables

Figure 1

[Open in a separate window](#)

Participants Flow Chart.

Table 1

Effect of Vitamin D₃ supplementation on biochemical variables in treatment arm

[Open in a separate window](#)

Table 2

Changes in biochemical variables in the placebo arm

[Open in a separate window](#)

Table 3

Mean changes in serum Vitamin D₃ and glycemia after 12 weeks of treatment

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Figure 2

[Open in a separate window](#)

Effect of Vitamin D₃ on long-term glycemic control

Figure 3

[Open in a separate window](#)

Proportions of Type 2 diabetes mellitus subjects with normal HbA_{1c} status after treatment