ORIGINAL RESEARCH ARTICLE

Impact of Vitamin D Supplementation on Glycaemic Control in Type 2 Diabetes Patients: A Double Blind Randomized Controlled Trial

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ABSTRACT

Introduction: Vitamin D deficiency is a global health concern affecting diverse populations and it has been linked to various ailments. This study aimed to investigate vitamin D levels among T2DM patients and evaluate the impact of supplementation on those deficient, alongside its effect on quality of life and comorbidities.

Methodology: A double-blinded randomized controlled trial was conducted among T2DM patients aged 18-75 years with HbA1c ≥ 7% and vitamin D deficiency (<12 ng/mL). Participants were divided into intervention (vitamin D supplementation) and control (placebo) groups. Data on demographics, diabetic status, and comorbidities were collected. Blood samples were analyzed for HbA1c and Vitamin D levels.

Results: Of the 66 participants initially recruited, 60 completed the study. No adverse effects were observed. There was no significant difference in glycemic control between the intervention and control groups at 3 and 6 months. Quality of life showed no significant improvement with supplementation.

Conclusion: This study did not find evidence supporting the efficacy of vitamin D supplementation in improving glycemic control or quality of life among T2DM patients with vitamin D deficiency. Further research is warranted to explore alternative interventions or factors influencing glycemic control and quality of life in T2DM patients.

Keywords: Vitamin D, Type 2 Diabetes Mellitus, glycemic control, quality of life, supplementation

ARTICLE INFO

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INTRODUCTION

Vitamin D or calciferols are lipid-soluble vitamins that refer to both Vitamin D2 (ergocalciferol) and vitamin D3 (cholecalciferol). Vitamin D is synthetized under the skin to the exposure of sun which accounts for 90% of the required amount.[1] Vitamin D deficiency is a pandemic that affects across borders irrespective of genetics, geography, sex, and age. Prevalence of Vitamin D varies from 17% to 100% It mainly affects the musculoskeletal system (i.e. Rickets, osteomalacia, osteoporosis, etc.,) and it is widely reported to increase the risk of autoimmune diseases, cancers, cardiovascular diseases, tuberculosis, etc. Studies have shown an inverse association between Vitamin D and insulin resistance as well as beta cell function.[2-9]

Type 2 Diabetes Mellitus Patients are found to lack vitamin D this may be a coincidence or vitamin d deficiency may be a predisposing cause for Type 2 Diabetes mellites. Various observational studies have shown an association between vitamin D deficiency and Diabetes mellites.[10-11] Various studies have suggested that vitamin D deficiency plays a vital role in the pathogenesis and complications of Type 2 Diabetes mellitus like peripheral insulin resistance, pancreatic insulin secretion, downregulation of the insulin receptor gene, inflammation, and immune activation.[12]

A systematic review which included 20 trials from all over the world concluded that Vitamin D supplementation has enhanced vitamin D levels and reduced insulin resistance compared to the placebo group.[13] However various other trials have examined the role of Vitamin D on fasting, post-prandial glucose, and glycated Hemoglobin (HbA1c) in varied settings and the results between the Vitamin D group vs. placebo group have been ambiguous.[14-16]

Considering the importance of vitamin D, and the paucity of data in our state, the study was planned with the primary objective to find the levels of Vitamin D among Type 2 diabetics and consequently analyze the effect of Vitamin D supplementation among those who are deficient. The study's secondary objective was intended to analyze the effect of Vitamin D supplementation on the quality of life along with other co-morbidities among the study population.

METHODOLOGY

Trial Design and Participants: The study design was a double-blinded randomized controlled trial that was conducted among patients attending a Diabetic clinic in a tertiary care hospital in Kelambakkam, Chengalpattu district. The study was conducted between October 2022 to October 2023 and was prospectively registered in the clinical trial registry of India (CTRI) CTRI/2022/10/046193. There was no deviation in the methodology after the commencement of the trial. Ethical approval was obtained from the institutional human ethical committee of Chettinad Academy of Research and Education (IHEC-II/0163/22). Subjects were eligible for the trial if they met the following Inclusion and exclusion criteria.

The study's inclusion criteria encompassed adults aged 18 to 75 years diagnosed with Type 2 Diabetes mellitus and possessing an HbA1c level of ≥ 7%. Additionally, participants were required to have a vitamin D deficiency with levels below 12 ng/mL (<50 nmol/L). Conversely, individuals were excluded if they had uncontrolled Type 2 diabetes mellitus treated with insulin therapy, uncontrolled hypertension, renal complications, or were seriously ill with other diseases or disorders. Furthermore, patients who were unwilling to participate were also excluded from the study.

First visit: A pilot-tested and semi-structured questionnaire was used to collect data after obtaining informed consent from the participants. Details were collected regarding the socio-demographic details, diabetic status, quality of life, and other co-morbidities. Complications and co-morbidities associated with diabetes were assessed during the initial visit using standardized clinical criteria and medical records. Participants were categorized as having complications if they had documented evidence or clinical symptoms consistent with diabetic complications. Then blood samples were collected for assessing HbA1c (high-performance liquid chromatographic (HPLC) method.) & Vitamin D (quantitative chemiluminescent immunoassay (CLIA) method).

Interventions: The study group was started on Vitamin D supplementation (dosage-weekly 60,000IU for a month followed by monthly once for five months) and the control group on placebo (Vitamin B complex 10 mcg at same intervals) both drugs were given orally.

Outcomes: The primary outcome variable was to find the effect of Vitamin D supplementation on glycemic control in the study population. Secondary outcomes included changes in quality of life along with other co-morbidities among the study population. Quality of life was assessed using THE WHOQOL-BREF [17] which consists of four domains namely Domain 1 (Physical health), Domain 2 (Psychological), Domain 3 (Social relationships), and Domain 4 (Environment). Each domain consists of several items that respondents rate on a scale from 1 to 5, with 1 indicating low or negative perception and 5 indicating high or positive perception. To calculate scores for each domain, the raw scores of the items within each domain are summed, and then transformed linearly to a scale from 0 to 100. This transformation ensures that scores from different domains are comparable. Therefore, higher scores indicate a better quality of life in that particular domain.

Sample size: To determine the change in outcome with an alpha error of 5%, Two-sided significance level(1-alpha) of 95%, Power (1-beta) of 80%, and 10% dropout rate the effective sample size was calculated to be 66 participants, with ratio of sample size to be 1:1 there were 33 each in intervention and control group. The sample size was calculated using Open Epi software. As aimed, we recruited 66 eligible participants among which a total of 6 participants were lost to follow-up (Figure 1). Required data and information were obtained from 60 participants, 30 each in the Intervention and control groups as 10% of dropouts were expected the study was completed with an adequate sample size in each group.

Randomization and blinding: Randomization was done with a computer-generated block randomization technique by the Statistician using Microsoft Excel with an equal allocation ratio. A sample size of 66 was randomized into two blocks of equal size each carrying 33 participants. Allocation was concealed using brown opaque sealed labeled envelopes. These concealed envelopes were handed over to a medical officer in the diabetic clinic who was not involved in any other part of this study. As informed consent was obtained during their first visit for all the 200 participants the medical officer allotted the participants to their respective groups, namely Group A (intervention group) and Group B (control group), and handed them the tablets in an identical sequential labeled brown opaque bag with same prescription of one tablet weekly for a month followed by monthly once for five months. Double blinding was maintained in this study as both the participants and the investigators were unaware of the allocation.

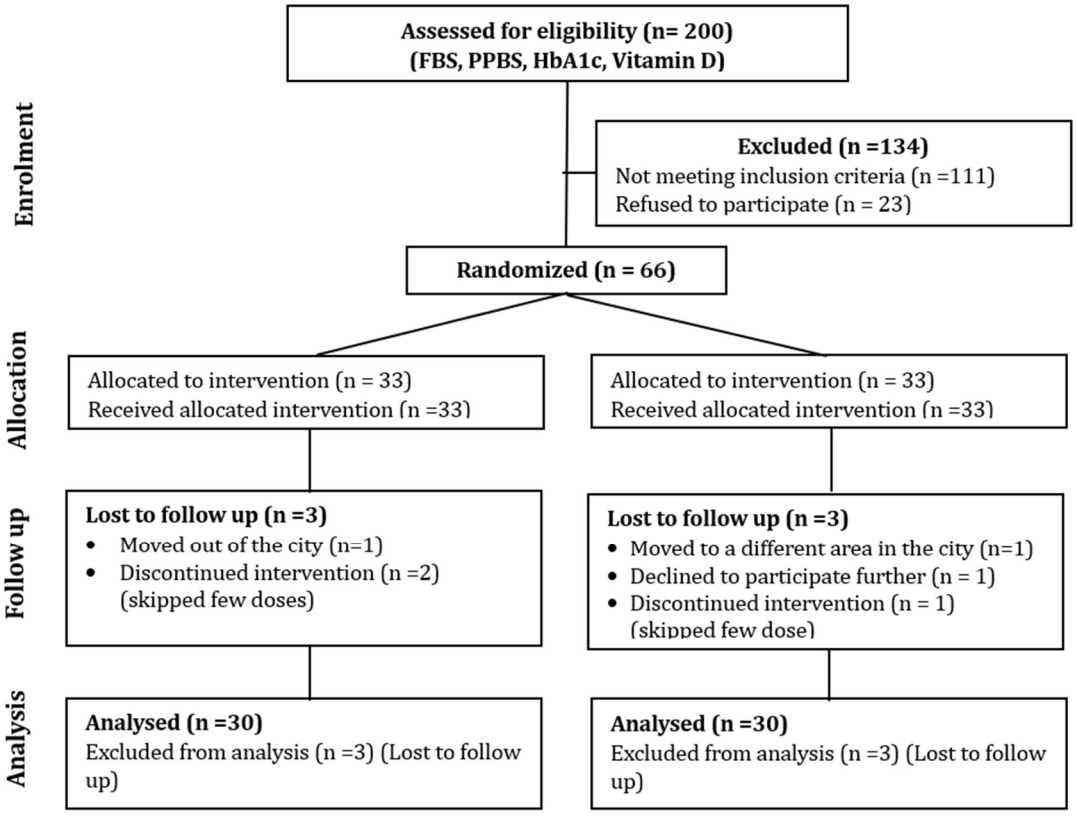

Figure 1: CONSORT diagram showing the flow of participants through each stage of the trial

Statistical methods: Data were entered into MS Excel and analyzed using SPSS 21.0 software. Continuous variables were presented as mean ± standard deviation. Student's independent t-test was employed to compare the two groups of interest. The Pearson chi-square test was utilized to compare differences in distribution between groups. The significance level was set at 5% ($P < 0.05$). The analysis focused on glycaemic control, quality of life domains, and their associations with demographic and clinical variables. The statistical approach was aimed to comprehensively assess the impact of vitamin D supplementation on study outcomes.

RESULTS

This study was conducted among 66 participants who were equally divided into intervention and control groups among which 6 were lost due to attrition. In the intervention group, there were three losses during follow-up as one moved out of the city and the other two discontinued medication as they missed a few doses. In the control group, there were three losses to follow up as one moved to a different area of the city, and one discontinued medication as they missed a few doses. One was not willing to participate further (Figure 1).

Table 1: Baseline Characteristics of Participants

Category	Intervention (%) (n=30)	Control (%) (n=30)	p-Value
Gender			
Male	10 (33.3)	8 (26.7)	0.389
Female	20 (66.7)	22 (73.3)	
Age (Years)			
<40	3 (10)	4 (13.3)	0.686
41-50	9 (30)	7 (23.3)	
51-60	8 (26.7)	12 (40)	
61-70	7 (23.3)	6 (20)	
>70	3 (10)	1 (3.3)	
Family history			
Father	3 (10)	5 (16.7)	0.211
Mother	4 (13.3)	8 (26.7)	
Grandparent	0 (0)	2 (6.7)	
Both parents	3 (10)	3 (10)	
None	20 (66.7)	12 (40)	
Co-morbidities			
No comorbidities	12 (40)	11 (36.7)	0.450
Hypertension	10 (33.3)	16 (53.3)	
CAD	2 (6.7)	2 (6.7)	
Thyroid	2 (6.7)	0 (0)	
CKD	1 (3.3)	0 (0)	
Dyslipidemia	1 (3.3)	0 (0)	
Multiple Co-morbidities	2 (6.7)	1 (3.3)	
Complications			
Absent	23 (76.7)	26 (86.7)	0.316
Present	7 (23.3)	4 (13.3)	
Glycemic Control			
Good*	4 (13.3)	6 (20)	0.365
Poor#	26 (86.7)	24 (80)	

*Good Glycemic Control is Hba1c 7% or less than 7%,
#Poor Glycemic Control is Hba1c more than 7.1%
CAD - Coronary Artery Disease; CKD - Chronic Kidney Diseases

The study was concluded after completing both follow-ups during the 3rd and 6th months as planned. The data was analyzed for the 60 participants 30 in each group. No unintended effect was found during the trial both in the intervention group and the control group.

The baseline characteristics of the participants were addressed in Table 1. In the intervention group and control group, the mean age of the participants was 55.8 (±12.3) and 52.7(±12.2) respectively and years with diabetes were 10.1 (±5.14) and 7.9 (±7.06) respectively. Totally 18 males and 42 females were included in the study among which 10 males and 20 females were in the intervention group and 8 males and 22 females were in the control group. The majority of the participants were in the 51 to 60 years age group. 20 participants from the intervention group and 12 from the control group did not have any relevant family history. The most common comorbidity observed in each group was hypertension. Participants with complications were 11 and 4 in the intervention group and control group respectively.

Investigations such as Hba1C, Fasting blood sugar (FBS), post-prandial blood sugar (PPBS), and vitamin D levels were analyzed at baseline, at the end of 3rd month and 6th month. Mean Hba1c values were 9.2 (± 1.9) and 9.51(± 2.62) at baseline, 9.41 (± 2.9) and 9.14 (± 3.83) at the end of 3rd month, and 10.94 (± 3.53) and 10.57 (± 4.72) at the end of 6th month among interventional and control group respectively. Mean FBS values were 121.03 (± 23.3) and 126.8 (± 28.03) at baseline, 126.6 (± 26.9) and 134.3 (± 34.2) at the end of 3rd month, and 136.3 (± 31.6) and 138.7 (± 38.8) at the end of 6th month among interventional and control group respectively. Mean PPBS values were 293.8 (± 78.28) and 315.5 (± 73.27) at baseline, 275.7 (± 79.1) and 292.9 (± 80.6) at the end of 3rd month, and 248.7 (± 87.8) and 264.3 (± 80.4) at the end of 6th month among interventional and control group respectively. Mean Vitamin D levels were 21.89 (± 6.9) and 24.4 (± 12.9) at baseline, 24.7 (± 7.5) and 23.16 (± 12.84) at the end of 3rd month, and 27.6 (± 7.85) and 23.4 (± 12.7) at the end of 6th month among interventional and control group respectively. There was no significant statistical difference between the interventional and control groups [Table 2]. Good glycemic control association was compared among different variables only the comorbidities factor was statistically significant (P value 0.009) and other variables like gender, age, family history, and complication were found not to be significantly associated [Table 3.].

At enrolment Quality of life difference between the control and intervention groups was statistically significant in three domains (Domains 1,2 and 3). At the end of the study Quality of life difference between the control and intervention group was statistically significant in only one domain (Domain 1) [Table 4.]. Quality of life was tested for association with other variables and all the variables were not significantly associated with Quality of life [Table 5].

Table 2: Mean HbA1c values at the Baseline, 3 months and 6 months in both groups

Variables	Baseline			At 3 months			At 6 months		
	Intervention (n=30)	Control (n=30)	p-value	Intervention (n=30)	Control (n=30)	p-value	Intervention (n=30)	Control (n=30)	p-value
Duration of Diabetes (yrs)	10.1±5.14	7.9±7.06	0.173						
Age (Years)	55.8±12.3	52.7±12.2	0.342						
Hba1C	9.28±1.9	9.51±2.62	0.699	9.41±2.9	9.14±3.83	0.763	10.94±3.53	10.57±4.72	0.738
FBS	121.03±23.3	126.8±28.03	0.39	126.6±26.9	134.3±34.2	0.339	136.3±31.6	138.7±38.8	0.822
PPBS	293.8±78.28	315.5±73.27	0.273	275.7±79.1	292.9±80.6	0.408	248.7±87.8	264.3±80.04	0.474
Vitamin D	21.89±6.9	24.4±12.9	0.336	24.7±7.5	23.16±12.84	0.569	27.6±7.85	23.4±12.7	0.128

Table 3: Glycemic control at the baseline in relation to other variables

	Good Glycemic Control (n=10) (%)	Poor Glycemic Control (n=50) (%)	p-Value
Gender			
Male	3 (30)	15 (30)	0.657
Female	7 (70)	35 (70)	
Age			
≤40	7 (70)	6 (12)	0.988
41-50	3 (30)	13 (26)	
51-60	3 (30)	17 (34)	
61-70	2 (20)	11(22)	
>70	1 (10)	3 (6)	
Family history			0.835
Parents/Grandparents	4 (40)	24 (48)	
None	6 (60)	26 (52)	
Co-morbidities			0.009*
No comorbidities	2 (20)	21 (42)	
Hypertension/ Coronary Artery Disease/Any other comorbidity	8 (80)	29 (58)	
Complications			0.219
Absent	9(90)	36 (72)	
Present	1 (10)	14 (28)	

Table 4: 4 Domains of Quality of Life in Both the Groups

Domains of Quality of Life	Control	Intervention	p-value
Quality of Life at 0 months (Base scores)			
Domain 1 Physical health	49.7 ± 21.1	38.5 ± 12.7	0.016
Domain 2 Psychological health	55.4 ± 21.3	43.6 ± 13.2	0.013
Domain 3 Social relationships	66.3 ± 19.2	54.7 ± 18.9	0.021
Domain 4 Environmental health	57.8 ± 24.09	55.8 ± 18.8	0.723
Quality of Life at 6 months			
Domain 1 Physical health	40.2 ± 12.7	50.01 ± 21.3	0.035
Domain 2 Psychological health	47.8 ± 14.2	56.7 ± 21.7	0.066
Domain 3 Social relationships	55.7 ± 18.4	66.8 ± 19.5	0.072
Domain 4 Environmental health	57.02 ± 18.8	59.1 ± 24.1	0.707

Values with ± indicate mean ± SD

Table 5: Association of QOL with other variables at baseline

	Domain 1 Physical health	Domain 2 Psychological health	Domain 3 Social relationships	Domain 4 Environmental health
Glycemic control				
Good control*	45.71 ± 13.23	58.33 ± 19.22	69.15 ± 20.8	48.76 ± 23.2
Poor Control*	43.85 ± 19.13	47.76 ± 18.14	58.83 ± 19.37	58.45 ± 20.99
p-Value	0.77	0.10	0.13	0.20
Age (years)				
<40	52.01 ± 23.32	51.8 ± 16.47	63.1 ± 21.96	62.06 ± 23.41
41-50	43.08 ± 17.08	48.96 ± 21.32	61.98 ± 21.29	60.18 ± 19.42
51-60	44.47 ± 18.71	49.59 ± 20.41	53.75 ± 18.42	52.2 ± 21.96
61-70	44.23 ± 18.35	50.32 ± 17.87	63.44 ± 20.57	59.41 ± 25.8
>70	33.03 ± 9.38	44.8 ± 3.97	75 ± 0	49.23 ± 1.55
p-Value	0.59	0.98	0.30	0.67
Co-morbidities				
No comorbidities	50.77 ± 21.24	54.36 ± 21.07	61.23 ± 19.55	64.14 ± 21.11
Hypertension	38.33 ± 14.31	45.51 ± 14.99	60.24 ± 18.9	50.75 ± 20.09
Coronary Artery Disease	46.43 ± 11.3	58.33 ± 23.78	68.75 ± 24.88	59.38 ± 13.49
Thyroid	44.6 ± 17.68	56.25 ± 14.78	75 ± 0	68.75 ± 26.52
Chronic Kidney Diseases	71.40	62.50	83.30	93.80
Dyslipidaemia	39.30	41.70	33.30	25.00
Multiple Co-morbidities	33.33 ± 19.68	29.17 ± 11	38.87 ± 17.33	40.63 ± 14.32
p-Value	0.16	0.22	0.20	0.05
Complications				
Absent	46.27 ± 19.75	50.74 ± 20.49	62.4 ± 20.61	57.52 ± 22.43
Present	37.85 ± 10.61	45.85 ± 10.79	55 ± 16.6	54.8 ± 18.89
p-Value	0.12	0.38	0.21	0.68

*Good Glycemic Control is Hba1c 7% or less than 7%, Poor Glycemic Control is Hba1c more than 7.1%; Values with ± indicate mean ± SD

DISCUSSION

This study was not able to demonstrate a positive effect on glycemic control for participants who received vitamin D. There were no major side effects caused due to vitamin D supplementation. Similarly to this finding a study conducted by Jorde et al and Pittas et al. did not demonstrate any positive effect on glycemic control and type 2 diabetes mellites.[18,19] In a study conducted among pre-diabetic participants vitamin d level had a favorable outcome with type 2 diabetes mellites this difference in results might be because our study was conducted on uncontrolled type 2 diabetes mellites.[20]

In our study quality of life was not found to be better in the intervention group after the stipulated time when compared to the control group. Similar to this finding in a study conducted by Westra et al. there was no effect of vitamin d supplementation on the quality of life except in the domain "role limitation due to physical problem" which was statistically significant.[21] A systematic review from Hoffmann et al. categorized fifteen articles (among which seven were randomized placebo-controlled trials) contrasting to our finding four out of seven studies showed a positive effect on the quality of health in participants with diabetes.[22] A study conducted in 2020 had a positive association with quality of life in all domains when Vitamin D supplementation and this association was statically significant.[23]

There was no adverse effect observed with the supplementation of Vitamin D but in another study in Tabriz City Vitamin D supplementation caused hypervitaminosis and increased diastolic blood pressure. The complications associated with diabetes did not improve significantly in our which was also the case in various similar studies conducted in different places.[17-23]

The strength of our study was blinding both the investigator and the participants and this double blinding was followed effectively throughout the study. Also, this study was done on uncontrolled diabetic patients which throws light on the new population as other studies focused on pre-diabetic and early diabetic patients. The limitation of the study was it was not a multicentric study as it was confined to a particular demographic area and can be generalized to only the patients visiting tertiary hospitals. The study was registered in the Clinical Trial Registry of India (CTRI) CTRI/2022/10/046193 and the protocol of the study is available in CTRI. Funding for this study was provided by the Chettinad Academy of Research and Education under the CARE Seed Grant (Ref. No.004/Regr./AR-Research/2022-13)

CONCLUSION

In conclusion, our study did not reveal significant benefits of vitamin D supplementation on glycemic control or quality of life among Type 2 Diabetes Mellitus (T2DM) patients with vitamin D deficiency. Despite robust methodology and adherence to blinding, our findings align with certain previous trials that reported inconclusive results regarding the efficacy of vitamin D in managing T2DM. These results underscore the complexity of T2DM management and highlight the need for further exploration into alternative interventions or underlying factors influencing glycemic control and quality of life in this patient population. While our study contributes valuable insights, its single-center nature necessitates caution in generalizing findings, emphasizing the importance of additional research in diverse settings to elucidate optimal strategies for addressing vitamin D deficiency in T2DM patients.

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