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Original Research Article

Hypovitaminosis D and effect of vitamin D supplementation in type 2 diabetes mellitus: a rural population based study

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ABSTRACT

Background: Deficiency of Vitamin D in general population and its association with various disease conditions have been studied worldwide. Type 2 Diabetes mellitus is increasing at an alarming rate in Indian subcontinent, contributing to increased morbidity and mortality. This study aimed to estimate level of Vitamin D and its association with patients with type 2 diabetes mellitus of rural origin. This study objective was to estimate the Vitamin D level of patients with Type 2 Diabetes mellitus and the effect of Vitamin D supplementation on glycemic status
Methods: This study was conducted at the Department of General medicine for a period of 1 year. Eighty patients with type 2 Diabetes mellitus were recruited in the study and baseline parameters of glycemic control and Vitamin D levels were assessed. Only 36 patients complied with the recommendation and evaluated further.
Results: All the patients included in the study had insufficient or deficient levels of Vitamin D. The mean vitamin D levels before and after supplementation were 17.75±6.30 and 29.33±6.34 respectively. The mean plasma HbA1c level before and after supplementation were 7.78 and 7.30 respectively. Patients after vitamin D replacement showed significant improvement in their glycaemic status.
Conclusions: Vitamin D supplementation of 2000 IU/day had shown to improve the glycaemic status. The beneficial effect of Vitamin D on diabetes was evident in a short period of supplementation.

Keywords: Diabetes mellitus, Glycemic status, Vitamin D deficiency, Vitamin D supplement

INTRODUCTION

Vitamin (Vit) D is crucial for metabolism of calcium and its homeostasis. It is estimated that 1 billion people worldwide have vitamin D deficiency or insufficiency. Vit D deficiency is still an undertreated nutritional disorder. Vit D deficiency has been noted in 70-100% of healthy persons. There is a varying degree (50-90%) of Vitamin D deficiency with low dietary calcium intake in Indian population according to a study published by Londhey V.[1] Apart from low dietary intake, people suffering from hepatic, renal, dermatological disorders, alcoholics and inflammatory rheumatologic conditions also have Vitamin D deficiency. A growing number of studies have reported widespread vitamin D deficiency and insufficiency in both apparently healthy population and patients with various pathologies.[2] Type 2 Diabetes mellitus (DM) which is increasing at an alarming rate in developing countries like India is a major public health problem accounting for significant morbidity and mortality. The prevalence of Diabetes Mellitus in India is estimated to be around 62.4 million cases in a recent study.[3] Low levels of vitamin D have been associated with an increased risk of cardiovascular mortality in the general population as well as in patients with type 2 Diabetes mellitus.[4,5]

The prevalence of Diabetes mellitus is high in Southern parts of India but there is a paucity of literature regarding the association of Vitamin D and diabetes mellitus.

Although India is a tropical country, there is widespread vitamin D deficiency among the indigenous population probably due to highly pigmented skin (melanin) and dressing practices.[6]

The present study is designed to detect patients with Type 2 Diabetes mellitus with vitamin D deficiency and to assess the effect of supplementation on glycemic status.

The primary objective was to estimate blood glucose, glycosylated haemoglobin (HbA1c) and serum vitamin D in patients with Type 2 diabetes mellitus.

The secondary objective was to assess the glycemic status after supplementation with vitamin D among patients with deficiency.

METHODS

This study was conducted at the Outpatient Department of General Medicine, Sri Manakula Vinayagar Medical College and Hospital, Puducherry, India. It is an interventional study involving 80 patients with Type 2 Diabetes mellitus over a period of one year. The patients were mostly from rural or semiurban background. After getting informed consent, blood sample was collected for fasting, postprandial blood glucose, blood urea, serum creatinine, fasting lipid profile, HbA1c and serum Vitamin D3 levels. In patients found to be Vitamin D deficient or insufficient, supplementation was given for a period of 3 months. Patients received 2000 IU of Vitamin D3 daily orally.

After ensuring drug compliance, patients were again tested for the same and the results interpreted. Patients with osteoporosis, Type 1 Diabetes mellitus, postmenopausal, pregnant women, renal failure, malignancy, patients on medications that affect Vit D metabolism like phenytoin, rifampicin, INH etc., malnutrition and already on Vitamin D supplements were excluded from the study.

Serum Vitamin-D3 levels was estimated by ELISA method. In this study, 25-OH vitamin D ELISA kit which has 100% specificity and high sensitivity up to 1.5 ng/dl was used. According to the vitamin D level the patients were divided into three groups namely patients with vitamin D deficiency (<20 ng/ml), insufficiency (21-29 ng/ml) and sufficiency (>30 ng/ml).

Statistical analysis

All results were expressed as Mean±SD. Mean difference in all analyte before and after vitamin D supplementation was analyzed using 'paired student t test'. Comparison of mean HbA1c with Vitamin D Deficiency and Insufficiency was done using Independent Student t test. Correlation between vitamin D and HbA1c was done using Pearson's correlation. A 'P value less than 0.05' was considered statistically significant. All analysis were done using Statistical Package for the Social Sciences (SPSS) version 16 for windows.

RESULTS

All the patients studied were over 30 years of age. All the parameters studied, and their statistical details are shown in Table 1, 2 and 3. Interestingly all the 80 patients recruited in the study were either Vitamin D deficient or insufficient. Vitamin D levels were insufficient in 31% of female and 69% of male, and the levels were deficient in 82% male and 18% of female (Table 4).

Table 1: Results of the different parameters studied before vitamin D supplementation (n=80 male: Female-62:18).

Variables	Mean±SD	Min	Max
Age (in years)	51.78±9.85	33	77
FBS (mg/dl)	136.05±43.69	65	244
PPBS (mg/dl)	227.74±77.82	105	438
HbA1c (%)	7.77±0.88	6.1	9.9
Serum vitamin D (ng/ml)	17.38±5.95	6	28
Serum urea (mg/dl)	24.24±6.42	16	40
Serum creatinine (mg/dl)	0.82±0.17	0.5	1.2

Table: 2: Age distribution in subgroups of study population.

Age distribution (in years)	No. of patients before vitamin-D supplementation (n=80)	No. of patients after vitamin-D supplementation (n=36)
30-40	14	8
41-50	25	12
51-60	22	7
61-70	16	8
>70	3	1

Table: 3: Results of the different parameters studied after vitamin D supplementation (n=36).

Parameter	Mean±SD	Min	Max
Age (in years)	50.44±0.12	35	72
FBS (mg/dl)	123.00±19.78	91	171
PPBS (mg/dl)	184.19±59.12	112	457
HbA1c (%)	7.30±0.70	6.1	9.1
Serum vitamin D3 (ng/mL)	29.33±6.34	17	41
Serum urea (mg/dl)	25.81±7.29	15	41
Serum creatinine (mg/dl)	0.78±0.19	0.5	1.1

Out of the 80 patients (male:female 62:18) recruited in the study, only 36 patients (45%), complied with the recommendation and included for post supplementation

analysis. Thirty-two patients stopped vitamin D supplementation before the recommended period of treatment and 12 did not turn up for the follow up study.

Table 4: Levels of vitamin D deficiency among the study group (n=80).

Vitamin D	Study population	
	Male	Female
Insufficiency	20	9
Deficiency	42	9

Table: 5: Serum vitamin D levels before and after supplementation.

Serum Vitamin D levels	Serum vitamin D levels (ng/ml) (n=36)	
	Before	After
Mean±SD	17.75±6.30	29.33±6.34
Paired student t test	P <0.001*	

P value less than 0.05 is considered statistically significant.

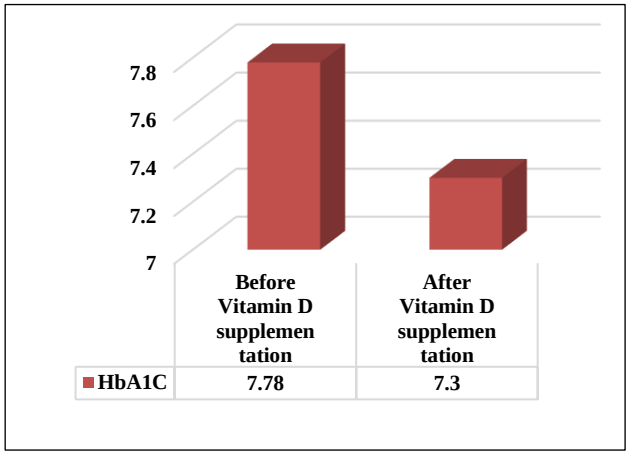

Figure: 1: Plasma HbA1c levels before and after supplementation (n=36).

The mean vitamin D levels before and after supplementation were 17.75±6.30 and 29.33±6.34 respectively (Table 5). The mean HbA1c levels among patients with Vitamin D deficiency and insufficiency was found to be 7.93 and 7.53 respectively before supplementation. The difference is found to be statistically significant (Figure 2).

The mean plasma HbA1c level before and after supplementation were 7.78 and 7.30 respectively. Patients after vitamin D supplementation showed significant improvement in their glycemic status (Figure 1, Table 6). There was a negative correlation of vitamin D levels with HbA1c.

The fasting, postprandial glucose and glycosylated haemoglobin levels decreased to statistically significant values after vitamin D supplementation as depicted in Table 4 and Table 7.

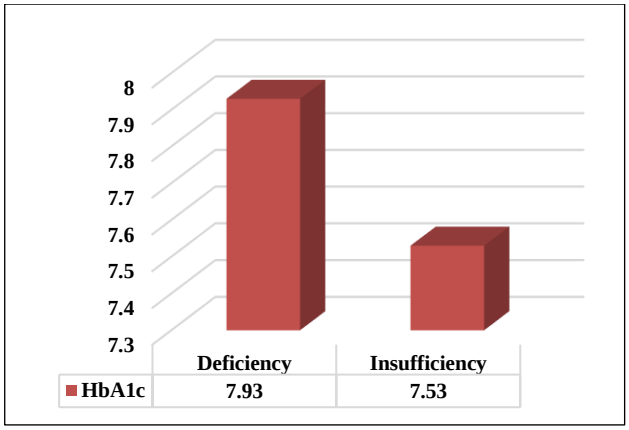

Figure 2: Comparison of HbA1c in vitamin D deficiency and insufficiency.

Table: 6: Paired t test for FBS, PPBS and HbA1c.

Glycemic parameters	Before vitamin D supplementation	After vitamin D supplementation	P value
FBS (mg/dl)	135.36±36.38	123±19.78	0.03*
PPBS (mg/dl)	218.58±62.26	184.19±59.12	0.01*
HbA1c (%)	7.78±0.81	7.30±0.70	0.01*

P value less than 0.05 is considered statistically significant.

Table: 7: Correlation between Vitamin-D and HbA1c (before and after treatment).

Levels of Vitamin D	HbA1c		P value
	N	Pearson Correlation r value	
Vitamin D (Before)	36	-0.36	0.03*
Vitamin D (After)	36	-0.60	<0.001*

P value less than 0.05 is considered statistically significant.

DISCUSSION

The present work is an interventional study on 80 patients more than 18 years of age with Type 2 Diabetes mellitus. Patients of all body Mass Index (BMI) and both gender were included. Those found to have hypovitaminosis D were supplemented with 2000 IU/day of Vitamin D for a period of 3 months and glycemic status was reassessed.

Vitamin D requirements of the body is met through diet and exposure to sun light for adequate time. Vitamin D facilitates calcium absorption in the small intestine and works with parathyroid hormone in skeletal mineralization and controls calcium homeostasis in the blood.

Vitamin D deficiency is observed in association with various disease states in epidemiologic studies. The protective effect could be attributed to the anti-

inflammatory, immune-modulating properties of Vitamin D and possible effects on cytokine levels.[7]

It was observed in this study that fasting blood Glucose (FBS), post prandial blood glucose (PPBS) and the Glycated haemoglobin (HbA1c), correlated negatively with the Vitamin D3 status.

Vitamin D exerts its action in all nucleated cells. Vitamin D and its analogues exert their actions through the nuclear VDR, which is responsible for transducing the action of the active form of vitamin D, 1,25(OH)2D3, the gene of which is located on chromosome 12q12-q14 in humans.[8] Vitamin D receptors (VDR) exist in more than twenty different tissues. Polymorphisms within the VDR gene may be associated with altered gene expression or gene function.[9]

Many reports revealed their association with different physiologic and pathologic phenotypes. Insulin producing pancreatic β cells contain vitamin D receptor (VDR) and Vitamin D binding protein (DBP). Treatment with 1,25 (OH)2D is reported to protect against β cell death.[10] Vitamin D can improve the β cell function directly or indirectly by increasing the intracellular ionized calcium and thereby enhancing insulin release, increase insulin sensitivity related to expression of insulin receptor or via calcium dependent pathways in target cells leading to increase in glucose utilization. Several observational studies have explained a strong association between the onset of Diabetes mellitus and Vitamin D deficiency in the recent past.[11,12]

Vitamin D acts as an immune-modulator and has anti-inflammatory effect that reduces inflammatory reaction in pancreatic islets and decrease auto-immune insulinitis. Hypovtaminosis D has been implicated with metabolic syndrome and an inverse relationship exists according to some population-based studies.[13,14]

Studies have found an inverse correlation between vitamin D levels and fasting blood glucose and after oral glucose load. It is also suggested that in vitamin D deficient populations with IGT and with type-2 DM, vitamin D replenishment may improve insulin secretion and glucose tolerance as well as HbA1c levels.[15-17]

The inverse association between serum 25(OH)D3 and HbA1c suggests that vitamin D supplementation could be a possible way of glycemic control of type 2 diabetes. However, some intervention studies have shown inconclusive results on the effect of vitamin D on HbA1c and type 2 diabetes.[18]

1,25(OH)2D3 exerts antiapoptotic effects on the cytokine-induced pancreatic β-cells apoptosis. It induces and maintains high levels of A20 gene protein, which leads to decreased nitric oxide (NO) levels, thus preventing beta cell dysfunction and death. and indirectly, through the induction of Fast expression which facilitates apoptosis.[19]

Vitamin D replenishment in vitamin D deficient healthy adults may improve insulin sensitivity by as much as 60%.[20]

On other hand, some studies found no benefit in vitamin D replenishment on fasting blood glucose, glucose tolerance, or insulin sensitivity.[21,22] The discrepancy in results were explained by the different populations studied and that there may be a different response to vitamin D among different ethnic groups and the existence of DNA sequence variations (polymorphisms) for the VDR gene which may account for a variability in the endocrine action of vitamin D.[23]

Observational studies have shown that glycemic control in patients with type-2 diabetes has a seasonal variation, being worse in the winter.[24]

Vitamin D deficiency is associated with increased inflammatory markers in diabetics including CRP, monocyte toll-like receptor (TLR) 2, TLR4, and nuclear factor-κB (NFκB) expression predicting increased microvascular complications. Cardiovascular diseases increased with low 25-OH D levels in the general population but these results have not been specifically studied in patients with diabetes.[25]

An inverse relation between HbA1c and Vitamin D was noted by Kositsawat and associates in US, as in our study.[26] A study conducted in Canada by Kayaniyil and associates, demonstrated the positive correlation between Vitamin D and β-cell function which means, the Vitamin D preserved B cell function.[27]

After Vitamin D supplementation, the HbA1c value reduced from a pre supplementation value of 7.7±0.81 to 7.30±0.70 in the present study. A study conducted on Arab-Americans showed similar result that the Vitamin D levels has a positive correlation with better glycaemic status.

A recent article revealed that supplemental intake of 400 IU per day of vitamin D, increased 25(OH)D concentrations by only 2.8 to 4.8 ng/mL (7-12 nmol/L) and that daily intake of approximately 1700 IU is needed to raise these concentrations from 20 to 32 ng/mL (50–80 nmol/L). Responses to vitamin D supplementation or exposure to sunlight may vary with patient.[28]

A study conducted in Minnesota US, which used low dose Vitamin D (400 IU/day) has stated that there was no correlation between glycemic improvement and additional calcium supplement along with Vitamin D.[29,30] Hence, in our study participants received only Vitamin D of 2000 IU/day without Calcium supplements.[31] Study by Pittas et al, said that the Vitamin D intake of 700 IU/day improved the glycaemic control in persons with impaired

fasting glucose and not on fasting glucose of a diabetic patient.[13] This improvement was noted after supplementing Vitamin D over a period of 3 years. But, in this study, author are used high dose Vitamin D for a period of 3 months only and significant improvement was observed.

Another study by Shankar et al, also stated that Vitamin D has positive correlation between Pre-Diabetes and Vitamin D.[32]

One more study conducted in Ohio, US by Robinson et al said that there was lack of association between Vitamin D and glycemic status in post-menopausal Women when 400 IU/day of Vitamin D was given.[33]

The present study has excluded women in the post-menopausal status as they might be having baseline deficiency of Vitamin D. Since all the female patients in our group had showed improvement, the same benefit could be expected in the post-menopausal women as well. Further studies on post-menopausal women and supplementation of high doses of Vitamin D is needed.

Gupta et al, who conducted a study on individuals with Pre-Diabetes, Pre Hypertension and combined Pre Diabetes, Pre Hypertension suggested that Vitamin D supplements would increase the glycemic control and prevent conversion to established status.[34]

Datas showed significant improvements in serum FPG, insulin and in HOMA-IR after treatment with vitamin D, suggested that vitamin D supplementation could reduce insulin resistance in Type 2 Diabetes mellitus.[35]

Our study participants had either Vitamin D insufficiency or deficiency suggesting that level of Vitamin D deficiency is relatively high even in rural population. Clothing pattern and vegetarianism limit the Vitamin D absorption. UV–B rays which aid in the synthesis of Vitamin D in the skin is available in the middle of the day, do not penetrate cloth, requires sufficient duration of exposure and vary with the amount of pigment in the skin. These factors should also be considered while supplementing Vitamin D.

The limitations of the study were poor compliance of the patients, small sample size, short study period and inequal representation of gender.

CONCLUSION

Vitamin D supplementation of 2000 IU/day given daily had shown to improve the glycemic status. The beneficial effect of Vitamin D was evident in a short period of supplementation. Though some patients did not attain the normal Vitamin D status within 3 months they still showed better glycemic control indicating the beneficial effect of Vitamin D supplementation, without Calcium supplementation. Serum Vitamin D levels were not adequate even in the rural population where there is abundant sunlight and agriculture, the main occupation. Serum Vitamin D may be assessed for patients with Diabetes routinely and if found deficient may be supplemented with Vitamin D to achieve a better glycemic control and obtain various other benefits of normal Vitamin D levels.

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