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Vitamin D deficiency in patients with type-2 diabetes mellitus attending tertiary care health setting: A hospital-based study

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Abstract: Background: Diabetes mellitus (DM) is a metabolic disorder that has reached epidemic proportions, with India being designated as the diabetic capital. It is a chronic disorder that can lead to many microvascular and macrovascular complications. Vitamin D deficiency has been linked to insulin resistance and impaired insulin secretion. This study aimed to assess the levels of Vitamin D in Type-2 diabetes mellitus and its correlation with microvascular complications and glycemic control.
Methodology: The study was conducted at the Department of General Medicine, SCB Medical College Hospital, Cuttack, Odisha. A total of 50 patients with type 2 diabetes, who were admitted to SCB Medical College hospital, were randomly selected after obtaining informed consent. The detailed medical history was collected through clinical examination and necessary laboratory tests were conducted. Two groups were formed, comprising diabetes patients in group I and healthy subjects in group II.
Results: Of the total 50 cases in group I, 31 (62%) were male and 19 (38%) were female, and in group II, 10 (50%) were male and 10 (50%) were female. The mean level of 25 OH vitamin D was 17.09 $\pm$ 1.36 ng/ml in group I. Out of 50 subjects, 98% were vitamin D deficient, i.e., < 20 ng/ml, 2% were insufficient, and none were sufficient. The mean 25 OH vitamin D level in group II was 18.29 $\pm$ 1.36 ng/ml. Out of 20 controls, 18 (90%) were vitamin D deficient i.e., < 20 ng/ml, and 2 (10%) controls were vitamin D insufficient.
Discussion: This study found that the mean level of vitamin D3 in diabetes patients was 17.09 $\pm$ 1.36 ng/ml compared to the control group. The correlation coefficient between vitamin D level and fasting blood sugar, postprandial blood sugar, and HbA1c was statistically significant, with retinopathy and neuropathy significantly associated with hypovitaminosis.
Conclusion: Given the enormous social and economic costs of type 2 diabetes and its devastating complications, there is an urgent need to develop effective strategies for curbing the epidemic through prevention and early treatment. Further interventional studies may be required to determine the recommended daily allowances of vitamin D.

Keywords: Diabetes; Vitamin D; HbA1c; Hospital based.

1. Introduction

Diabetes mellitus (DM) is a metabolic disorder that has reached epidemic proportions, with India being designated as the diabetic capital. The World Health Organization (WHO) estimates that there are currently 220 million cases of DM worldwide, with 45.5 million people in India having DM in 2010. By 2020, this number is expected to increase to 69.7 million, making India the country with the largest number of cases of DM in the world [1,2].

DM is a chronic disorder with multiorgan involvement that has many microvascular and macrovascular complications. Microvascular complications include diabetic nephropathy, neuropathy, and retinopathy, while macrovascular complications include coronary artery disease, peripheral artery disease, and stroke. Cardiovascular disease is the leading cause of death in individuals with DM [3].

Genetic factors and environmental factors such as sedentary lifestyle, physical inactivity, and obesity contribute to the onset of DM [4]. Of late, many studies have demonstrated an increased association of DM with vitamin D deficiency [4]. Not many such studies have been reported in India. Therefore, this study was undertaken to investigate if vitamin D deficiency is a causative factor in the pathogenesis of type 2 DM and its complications and to examine its correlation with glycemic control. Evidence is also accumulating for a role of vitamin D in maintaining normal glucose homeostasis. For instance, in both animal and human studies, vitamin D depletion was significantly related to insulin resistance and impaired insulin secretion. Furthermore, circulating concentrations of 25-hydroxyvitamin D (25-[OH] D), the primary circulating form of vitamin D, were significantly and inversely related to the risk for type 2 diabetes and related phenotypes in epidemiological studies.

Several Indian studies have shown that vitamin D deficiency is epidemic in India despite plenty of sunshine [5–7]. All Indian studies point to low 25(OH)D levels in the population. It was reported that patients with type 2 DM had lower mean 25 (OH) D concentrations than non-diabetic controls. Hypovitaminosis D may be a significant risk factor for glucose intolerance and the development of various complications. Both vitamin D deficiency and diabetes are common in both urban and rural India.

2. Methodology

The present study aimed to assess the Vitamin-D level in Type-2 diabetes mellitus and its correlations with microvascular complications and glycemic control. The study was conducted in the Department of General Medicine, SCB Medical College Hospital, Cuttack, Odisha. A total of 50 patients with type 2 diabetes who were admitted to SCB Medical college hospital were randomly selected and included in the study after obtaining informed consent. The study was approved by the Medical Ethical committee. The detailed medical history was collected as per Proforma through clinical examination and necessary laboratory tests. Group I comprised of diabetes patients admitted to the Medicine ward. Group II (controls) included 20 healthy subjects with no long-standing medical illness or history of drug intake affecting vitamin D metabolism. They were selected randomly and matched for age and gender.

2.1. Inclusion criteria

Type 2 Diabetes mellitus patients aged 30 to 70 years (as per WHO and American Diabetic Association guidelines).

2.2. Exclusion criteria

Patients with type I diabetes mellitus, chronic kidney disease, chronic liver disease, hyperparathyroidism, on dialysis, diabetic nephropathy, epilepsy, drugs that affect vitamin D metabolism, and Vit-D supplementation.

Blood samples were collected to estimate FBS, PPBS, Sr calcium, serum phosphorus, serum urea, serum creatinine, and vitamin D. Plasma for sugar and serum for vitamin D were obtained after centrifugation. FBS, PPBS, serum calcium, serum phosphorus, serum urea, serum creatinine were estimated using an automated analyzer (Erba Mannheim EM 360). 24-hour urinary protein estimation was done by spot urine analysis. Blood for HbA1c was tested using the HPLC method with the VARIANT II TURBO Haemoglobin Testing System, Bio-Rad Laboratories. Serum 25 OH vit D was estimated by radioimmunoassay. The subjects were classified as vitamin D-deficient, insufficient, and sufficient based on 25(OH) D concentrations of < 20, 20 to 30, and >30 ng/ml, respectively. Fundoscopy was performed by an experienced ophthalmologist in the department of Ophthalmology after dilatation of the pupil. Nerve conduction velocity was measured in the department of neurology. Statistical analysis was done using Microsoft Excel version-2007 and SPSS software. With the help of this software, mean, standard deviation, standard error of mean, confidence interval, and p-value were calculated.

All the data collected from both groups were analyzed in tabular form, and statistical significance was determined by ANOVA method. Data are presented as mean $\pm$ standard deviation. Student's 't' test was used to compare the differences between the case and control subjects. Pearson's coefficient was calculated for the correlation. $P<0.05$ was considered significant.

3. Results

In the case group, a total of 50 individuals were studied, out of which 31 (62%) were males and 19 (38%) were females. In the control group, 20 individuals were studied, out of which 10 (50%) were males and 10 (50%) were females. Both cases and controls were well-matched for age, sex, and BMI. The mean level of vitamin D3 in diabetes patients was 17.09 ± 1.36 ng/ml, compared to a serum level of 18.29 ± 1.26 ng/ml in the control group. This study shows that the population in Odisha is deficient in serum vitamin D levels, and in diabetes patients, it is lower than in the non-diabetic control group. A t-test comparing these two groups was significant (P = 0.001).

Figure 1 indicates the age and sex distribution of 50 diagnosed type 2 DM cases, of whom 31 (62%) were male and 19 (38%) were female. The maximum number of cases were in the 41-50-year age group, i.e., 20 (40%), out of which 11 were male and 9 were female.

Figure 2 indicates the age and sex distribution of 20 controls, of whom 10 (50%) were male and 10 (50%) were female. The maximum number of cases were in the 41-50-year age group, i.e., 11 (55%), out of which 6 (30%) were male and 5 (25%) were female.

The mean age of cases was 50.7 ± 8.78 years and controls was 49 ± 8.32 years. The mean BMI of cases was 24.81 ± 3.09 Kg/m^2, and controls was 25.19 ± 3.23 Kg/m^2. The mean HbA1c of cases was 8.15 ± 0.08, and controls was 5.27 ± 0.22. The mean FBS of cases was 179 ± 33.49 mg/dl, and controls was 92.20 ± 7.56 mg/dl. The 2Hr PPBS of cases was 226 ± 49.12 mg/dl, and controls was 120 ± 11.46 mg/dl. The mean level of 25 OH vitamin D in cases and controls was 17.09 ± 1.36 ng/dl and 18.29 ± 1.26 ng/dl, respectively, with P < 0.01.

Figure 3 indicates that vitamin D deficiency is more prevalent in diabetes cases (98%) than in controls (90%). Vitamin D deficiency is equally prevalent in both males and females, with females being slightly more deficient than males, but this difference is not significant. The maximum number of cases, i.e., 33 (66%), had serum vitamin D levels between 16-18 ng/ml, and the maximum number of controls, i.e., 14 (70%), had serum vitamin D levels between 16-18 ng/ml.

Table 3 shows various microvascular complications studied in 50 cases, in which nephropathy was present in 41 cases (82%) with a mean vitamin D level of 17.08 ± 1.37 ng/ml, and absent in 9 cases (18%) with a mean vitamin D level of 17.08 ± 1.32 ng/ml. Neuropathy was present in 25 cases (50%) with a mean vitamin D level of 16.52 ± 1.31 ng/ml and absent in 25 cases (50%) with a mean vitamin D level of 17.66 ± 1.18 ng/ml. Simple retinopathy was present in 19 cases (38%) with a mean vitamin D level of 16.89 ± 1.26 ng/ml, while proliferative retinopathy was present in 13 cases (26%) with a mean vitamin D level of 16.41 ± 1.01 ng/ml and absent in 18 cases (36%) with a mean vitamin D level of 17.79 ± 1.41 ng/ml. The p-value was 0.012, which is statistically significant.

Figure 4 illustrates a scatter plot, where the X-axis represents the serum vitamin D level in ng/ml, the Y-axis represents HbA1C in %, and the Pearson's correlation coefficient was -0.094.

Table 1. Baseline characteristics of the 70 subjects

Characteristics	Non-DM (n=50)	T2DM (n=98)	p value
Age (years)	49± 8.32	50.70 ± 8.78	-
Gender (Male : Female)	10:10	31:19:00	-
BMI (kg/m2)	25.19±3.23	24.81±3.09	-
HbA1C (%)	5.27±0.22	8.15±0.80	<0.01
FPG (mg/dl)	92.20±7.56	179±33.49	<0.01
PPBS (mg/dl)	120±11.46	226±49.12	<0.01
25(OH)D (ng/ml)	18.29±1.26	17.09±1.36	<0.01

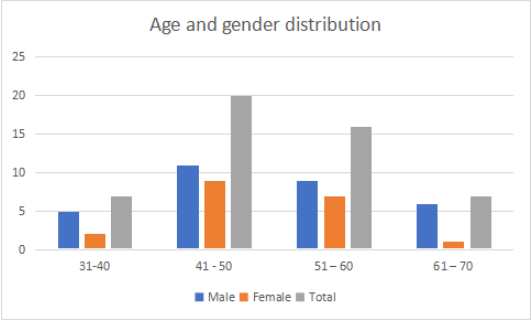

Figure 1. Age and sex distribution

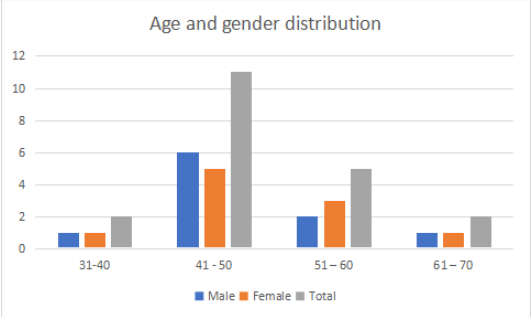

Figure 2. Age and sex distribution (Control)

Table 2. Mean distribution among case and control group

Mean	Case	Control
Age	50.7±8.78Yrs	49±8.32Yrs
BMI	24.81±3.09Kg/m2	25.19±3.23Kg/m2
HbA1c	8.15±0.80	5.27±0.22
FBS in mg/dl	179±33.49	92.20±7.56
2Hr PPBS in mg/dl	226±49.12	120±11.46
Level of 25 OH vit D in ng/ml	17.09±1.36	18.29±1.26

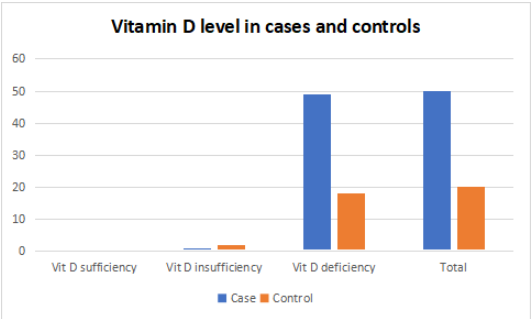

Figure 3. Vitamin D level in cases and controls

Table 3. Various micro vascular complications of cases

Complication		Number	%	Mean Vitamin D in ng/ml	P value
Nephropathy	Present	41	82%	17.08±1.37	0.946
	Absent	9	18%	17.08±1.32	
Neuropathy	Present	25	50%	16.52±1.31	0.002
	Absent	25	50%	17.66±1.18	
Retinopathy	Simple	19	38%	16.89±1.26	0.012
	Proliferative	13	26%	16.41±1.01	
	Absent	18	36%	17.79±1.41	

Table 4. Number of Micro vascular complications in cases:

Complication	Nos.	Mean vit D in ng/ml	P value
No complication	4	18.30±0.90	0.016
One complication	11	17.86±1.04	
Two complications	18	16.85±1.51	
Three complications	17	16.57±1.14	

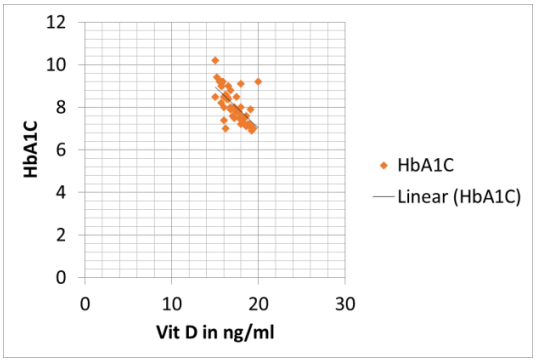

Figure 4. scatter plot of relation between Vit D Vs HbA1c

4. Discussion

Type 2 diabetes is the most common non-communicable disease globally, and its prevalence is increasing due to the worldwide obesity epidemic. Insulin resistance is a significant risk factor for diabetes, which in turn is a major risk factor for cardiovascular disease (CVD). Therefore, understanding the role of various modifiable risk factors, including nutrition, in the pathogenesis of diabetes and impaired glucose tolerance is crucial to combat the rising incidence of diabetes and CVD worldwide.

Numerous studies have investigated the potential causes of diabetes, and many diabetes risk factors have been identified. Vitamin D deficiency has recently received considerable attention as a novel association with diabetes. There is mounting evidence that vitamin D deficiency is prevalent worldwide and is usually caused by low dietary vitamin D intake and reduced cutaneous production of vitamin D. This latter condition is associated with reduced sunlight exposure due to geographic location, genetic background affecting skin color, age, and cultural or religious practices. Consistent with the hypothesis that vitamin D deficiency and diabetes are related, areas with a high prevalence of vitamin D insufficiency and deficiency have been associated with a higher prevalence of diabetes and associated complications.

Several reports have demonstrated that vitamin D status is associated with insulin sensitivity, glucose tolerance, and β-cell function [8,9]. Additionally, a low serum 25(OH)D level is related to increased complications and mortality in patients with type 2 diabetes mellitus. However, less is known about the clinical implications of vitamin D status in the management of type 2 diabetes mellitus. Further studies are needed to clarify how vitamin D is involved in the pathophysiology, progression, and complications of type 2 diabetes mellitus. Although some epidemiological studies have shown an inverse relationship between HbA1C and serum 25(OH)D, and some studies show an association between hypovitaminosis D and stages of type 2 diabetes mellitus and its complications, more studies are necessary to prove this [9,10].

In this study, we examined 50 cases of type 2 diabetes mellitus and 20 healthy controls. Both cases and controls were well-matched for age, sex, and BMI. The mean level of vitamin D3 in diabetes patients was 17.09 ± 1.36 ng/ml, with a vitamin D deficiency prevalence of 98%, as compared to the control group serum level of vitamin D3, which was 18.29 ± 1.26 ng/ml, with a vitamin D deficiency prevalence of 90%. This study shows that the Odisha population is deficient in serum vitamin D levels, and in diabetes patients, it is even lower than the non-diabetic control group. A t-test comparing these two groups was significant (P = 0.0001). The low serum vitamin D levels were negatively correlated with HbA1c (r = -0.668), FBS (r = -0.339), as well as the postprandial blood sugar levels (r = -0.226).

We also studied the correlation between the duration of diabetes and levels of vitamin D3 (r = -0.094, p = 0.514), which was not significant. Similarly, the correlation between BMI and levels of vitamin D3 (r = -0.059, p = 0.683) was also not significant. This case-control study shows that there is a significant correlation between the serum level of vitamin D and glycosylated hemoglobin level, but no significant correlation with the duration of diabetes and BMI of the patients. This result suggests that blood glucose control affects vitamin D metabolism regardless of the duration of diabetes and BMI.

A study by Shanthi *et al.*, [10] showed similar results with the age of participants ranging between 43.42 ± 7.877 years with 25(OH)D insufficiency (18.49 ± 3.497 ng/ml) and assessed glycaemic control with FBS (146.22 ± 45.007 mg/dl) r = -0.090, PPBS (275.28 ± 66.400mg/dl) r = -0.095, and HBA1C (8.326 ± 1.15843) r = -0.173.

The study by Yu *et al.*, [11] showed that mean 25(OH)D serum levels were quite low in both control and T2DM subjects (15.4 ± 0.5 and 12.9 ± 0.4 ng/ml, respectively), p < 0.01 [11]. A Korean study by Lee *et al.* showed that the mean concentration (±SD) of 25(OH)D in patients with T2DM was 11.2 (±6.1) ng/ml with a prevalence of Vitamin D deficiency of 85.9%. A Japanese study by Suzuki [12] showed that the mean serum 25(OH)D concentration (±SD) in patients with T2DM was 17.0 (±7.1) ng/ml in the winter and was not statistically different from that in a normal population (17.5 ± 3.6 ng/ml) with a Vitamin D deficiency prevalence of 70.6%. Two reports on the serum 25(OH)D levels of patients with T2DM in the United States [13,14] revealed higher mean values, 22.9 ng/ml and 22.3 ng/ml.

These results suggest that the 25(OH)D level in patients with T2DM varies widely according to ethnic or other backgrounds. Pittas *et al.* have systematically reviewed world literature related to (1) the association between Vitamin D deficiency (VDD) and prevalence/incidence of type 2 DM in different populations, and (2) randomized trials assessing the role of vitamin D supplementation on glucose metabolism [15].

In most case-control studies reviewed by Pittas et al. [15], patients with type 2 diabetes showed a lower mean 25(OH)D concentration than the non-diabetic controls 67-70. However, some of the case-control studies have failed to show such an association 71, 72. Two prospective studies also examined the association of vitamin D intake with incident type 2 DM. In the Women's Health Study, subjects with daily vitamin D intake >511 IU had a lower risk of incidence of DM when compared to a cohort with daily vitamin D intake of <159 IU per day (2.7% vs. 5.6%). Pittas et al. also examined the association between combined vitamin D and calcium intake and incidence of type 2 DM among 83,806 women in the Nurses' Health Study. After adjusting for age, BMI, and non-dietary covariates, a significant inverse association was observed between vitamin D intake and calcium intake on one hand, and risk of type 2 DM on the other73, 74.

In the largest cross-sectional study to date from the National Health and Nutrition Examination Survey (NHANES) data, serum 25-OHD concentration (after multivariate adjustment) was inversely associated with diabetes prevalence in a dose-dependent pattern in non-Hispanic whites and Mexican-Americans. In the same study, 25-OHD concentration also correlated with measures of insulin resistance [estimated by homeostatic model assessment (HOMA-IR) based on fasting glucose and insulin levels] but did not correlate with β-cell function (estimated by HOMA-β). No correlation between 25-OHD and diabetes prevalence or measures of insulin resistance or cell function was seen in non-Hispanic blacks. This lack of association may be explained by the observation that non-whites exhibit different vitamin D, calcium, and PTH homeostasis compared with whites 75. Combining data from all studies that reported on the association between 25-OH vitamin D level and prevalent type 2 DM, Pittas et al. [15] in the meta-analysis review summarised the OR as 0.54 (95% CI, 0.23-1.27) for the highest vs. the lowest 25-OHD concentration (25-38 vs. 10-23 ng/ml, respectively), but with significant heterogeneity among studies. Hence, we found retinopathy and neuropathy significantly associated with hypovitaminosis D but not with nephropathy.

5. Conclusion

The study found that the mean serum vitamin D3 level in diabetes patients was 17.09 $\pm$1.36ng/ml, which was lower than the control group's level of 18.29$\pm$ 1.26ng /ml. This indicates that the general population is deficient in serum vitamin D levels, and diabetes patients have even lower levels than non-diabetic individuals. The correlation coefficient between vitamin D level and FBS, PPBS, and HbA1c was statistically significant, indicating that lower vitamin D levels were associated with more complications. Retinopathy and neuropathy were significantly associated with hypovitaminosis D, but not with nephropathy. These findings reinforce previous research suggesting that vitamin D deficiency may play a role in the development of diabetes and its complications. Given the significant social and economic costs of type 2 diabetes and its complications, it is urgent to develop effective strategies for prevention and early treatment. Further interventional studies may be necessary to determine the recommended daily allowances of vitamin D or calcium to prevent the development of diabetes and its complications and improve glycemia.

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Conflicts of Interest: "Authors declare that they do not have any conflict of interests."

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