SPECTRUM OF VITAMIN D IN TYPE 2 DIABETES MELLITUS: A HOSPITAL BASED STUDY

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ABSTRACT

BACKGROUND

Vitamin D deficiency has been found to have an inverse relationship with the occurrence of type-2 diabetes mellitus. The aim of this study was to assess serum vitamin D level in patients with type 2 DM and correlate its finding with healthy controls, and to ascertain the relationship between low 25(OH) vitamin D levels and the marker of glycemic control, glycated hemoglobin A_1c (HbA_1c).

MATERIALS AND METHODS

Total 100 patients of type 2 diabetes mellitus were selected as cases with an equal number of non-diabetic persons without chronic renal failure, coronary artery disease, chronic liver disease, patients not on calcium and vitamin D supplementation were taken as controls. Serum 25 hydroxyvitamin D3 level was estimated and compared with fasting blood glucose and glycosylated HbA_1C in both the cases and controls.

RESULTS

The prevalence of vitamin D insufficiency was significantly higher among diabetic patients than among the controls. Patients with poor glycemic control had a higher prevalence of low vitamin D status than those with good glycemic control ($HbA_1c \leq 7\%$). Mean vitamin D levels was significantly lower in obese than the cases with normal BMI and in patients with longer duration of diabetes.

CONCLUSION

A low vitamin D status is present in more than two thirds of patients with DM type 2, more so amongst diabetics with poor glycemic control, high BMI and those with longer diabetes durations.

KEYWORDS

Vitamin D, Type 2 Diabetes Mellitus, Glycemic Control.

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BACKGROUND

Type 2 diabetes mellitus (DM) is a chronic metabolic disorder the prevalence of which has been increasing steadily all over the world.[1] According to International Diabetes Federation estimates, the prevalence of diabetes in 2015 was around 415 million in the world and this number is expected to rise to 642 million by 2040.[2] around 75% of subjects with DM live in low and middle-income countries (LMICs). World Health Organization (WHO) projects that the 7th leading cause of death will be diabetes in 2030.[3] India is home to 69.1 million people with DM and is estimated to have the second highest number of cases of DM in the world after China in 2015.[2] The high incidence of the disease is attributed to a combination of genetic susceptibility plus adoption of a high-calorie, low-activity lifestyle by India's growing middle class.[4]

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Vitamin D, known to everyone as the "sunshine hormone" is the essential vitamin for good health and is involved in different immune functions besides skeletal and muscle development.[5] Vitamin D deficiency is pandemic, yet it is the most under-diagnosed and under-treated nutritional deficiency in the world.[6,7] Recently, Vitamin D has sparked widespread interest in the pathogenesis and presentations of diabetes. In vitamin D-deficient individuals an increased prevalence of type 2 diabetes has been described and it is seen that insulin synthesis and secretion is impaired in beta cells from vitamin D-deficient animals.[8] There are also several studies which have ascribed that there is an active role of vitamin D in the functional regulation of the endocrine pancreas, particularly the beta cells. Not only are receptors for 1,25 dihydroxy vitamin D3 found in beta cells, but also the effector part of the vitamin D pathway is present in the form of vitamin D-dependent calcium-binding protein, which is known as calbindin-D28k. Evidences also suggests polymorphisms in the Vitamin D receptor (VDR) gene may be associated with insulin resistance, insulin secretion, and fasting glucose concentrations, suggesting that vitamin D is likely to contribute to glucose metabolism.[9] The aim of this study was to assess serum vitamin D level in patients with type 2 DM and correlate its finding with healthy controls, and to ascertain the relationship between low 25 (OH) vitamin D levels and the marker of glycemic control, glycated haemoglobin A1c (HbA1c).

MATERIALS AND METHODS

The present prospective case control study was conducted at tertiary care hospital in Silchar, located in the Cachar district, Assam for a period of 6 months, upon approval by the Institutional Ethics Committee of the Silchar Medical College and Hospital. In this study, 100 type 2 diabetic subjects constituted the study group and 100 age, sex and BMI matched healthy nondiabetic subjects constituted the control group. Subjects with age ≤ 18 years, type 1 DM, cardiovascular disease, chronic liver and kidney disease, history of taking medication that altered vitamin D metabolism and status, and use of sunscreen lotion were excluded from the study. None of the females were pregnant. Informed consent was obtained from all study participants. Detailed history of the patients was taken regarding occupation, sunlight exposure, duration of diabetes, treatment, and family history of diabetes. Informed consent was taken from the eligible patients before doing thorough physical examination. Direct sunlight exposure was assessed by average daily duration of exposure and percentage of body surface area exposed. Body weight was measured without wearing shoes and heavy clothes using a digital scale and height was measured in standing position using a stadiometer. Body mass index were calculated by using formula weight in kilogram/height in meter square. Blood samples were collected from cases and controls to measure the serum 25 hydroxyvitamin D3 and the method used for analysis was electrochemiluminescence immunoassay.

Serum 25-hydroxy vitamin D levels were interpreted as follows[10]

1. Less than 20 ng/ml---vitamin D deficiency
2. 20 to <30 ng/ml--- vitamin D insufficiency
3. 30-100 ng/ml---normal levels
4. >100 ng/ml----vitamin D toxicity

Serum levels of parathyroid hormone were not estimated.

Statistical evaluation of the results was performed using the statistical package SPSS21. Student's t-test was used to compare the patient group with the control group. Pearson correlation coefficient was computed between vitamin D and other parameters and their partial correlation was analysed. A chi-squared test was performed to compare the number of subjects with vitamin D deficiency and insufficiency within the patient and control groups. In all analyses, a p-value of <0.05 was considered significant.

RESULTS

Equal number of males (67) and females (33) were enrolled in case and control groups. The mean age of the case group was 57.04±8.6 years and in control group was 56.22±8.8 years. The socio-demographic parameters, BMI and duration of diabetes have been described in table1 and figure 1, 2. To determine the economic status for the study, beneficiaries of the below poverty line (BPL) cards was considered as the objective criteria as other criteria would have carried subjective biases. It was found that 34 of the case were BPL card holders. The number of BPL card holders is 33 in control group. Of the total number of subjects studied in cases 59% were from Hindu community and 41% were from Muslim community whereas in controls 56% were from Hindu community and 44% were from Muslim community. The mean concentration of vitamin D in diabetic patients was 19.78 ± 8.04 ng/ml and in the non-diabetic patients was 25.52 ± 8.53 ng/dl (p<0.00001) (Table 3). Amongst cases, 71% of were vitamin D deficient i.e. (<20ng/ml) whereas in the control group 45% were found to be vitamin D deficient (Table 2), 70.4% of deficient patients were working indoors and 29.6% were working outdoors and 75% of vitamin D insufficient group were working indoors and 25% were working outdoors. In control group 62.3% of deficient patients were working indoors and 37.7% were working outdoors, 35.5% of vitamin D insufficient group were working outdoors and 64.5% were working indoors (Table 4).

The mean ± SD of serum 25 (OH) D levels with respect to some variables has been shown in Table 5. Table 6 shows the mean levels of different parameters in vitamin D deficient group and vitamin D non-deficient group. On using the Pearson's correlation coefficient (r), a significant inverse relationship between serum 25 (OH) D concentrations and HbA1c % (r= -0.528 and P= <0.0001), and also with BMI (r= -0.355 and P= 0.0029) was found (figure 1, 2). The correlations between serum 25 (OH) D concentrations and age, and duration of diabetes were not statistically significant (r= -0.095, p= 0.34 and r= -0.12 p= 0.23 respectively).

	Cases, n =100	Control, n=100	P
Age (mean ± SD)	57.04 ± 8.6	56.22 ± 8.8	0.50 (NS)
Male (%)	67	67	1 (NS)
Female (%)	33	33	
Hindu (%)	59	56	0.546 (NS)
Islam (%)	41	44	
Literate (%)	75	74	0.82 (NS)
Illiterate (%)	25	26	
BPL (%)	34	33	0.832 (NS)
NBPL (%)	66	67	
BMI (mean ± SD)	24.48 ± 3.3	24.12 ± 3.3	0.44 (NS)
Sunlight Exposure	47.79 ± 51.8	47.79 ± 49.8	0.99(NS)

Table 1. Socio-Demographic Profile and BMI of the Study Participants

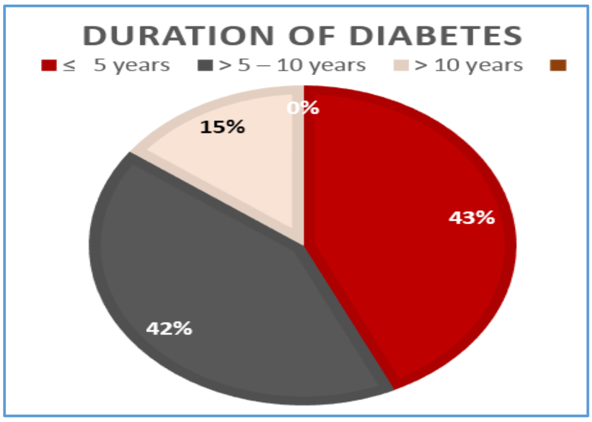

Figure 1. Pie Diagram Showing Distribution of Duration of Diabetes among Cases Including Males and Females

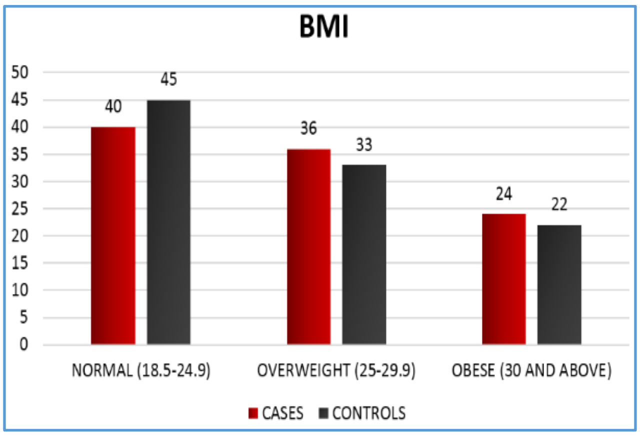

Figure 2. Bar Diagram Showing BMI Distribution of the Studied Groups

Vitamin D	Case	Control	p- value
Deficiency (<20ng/ml)	71	45	<0.001
Insufficiency (20-30 ng/ml)	16	31	
Sufficiency (30-100 ng/ml)	13	24	

Table 2. Distribution of Study Groups Based on Vitamin D Status

Parameters	Cases (n=100)	Controls (n=100)	p-value
FPG (mg/dl)	191.66 ± 56.22	80.33 ± 10.08	<0.00001 (S)
PPPG (mg/dl)	256.37 ± 76.57	101.48 ± 11.88	<0.00001 (S)
HbA_1C (%)	9.01 ± 2.02	5.08 ± 0.46	<0.00001(S)
Calcium (mg/dl)	8.71 ± 0.59	8.68 ± 0.83	0.77 (NS)
Albumin (g/dl)	4.06 ± 0.5	4.07 ± 0.5	0.83(NS)
25(OH)D	19.78 ± 8.04	25.52 ± 8.53	<0.00001

Table 3. Analysis of Biochemical Parameters among Study Groups

FPG= fasting plasma glucose, PPPG=2 hr post prandial plasma glucose, 25 (OH) D=25 hydroxy cholecalciferol.

Occupation Cases	Vitamin D Deficiency (71)		Vitamin D Insufficiency (16)	
	N	%	N	%
Outdoor	21	29.6	4	25
Indoor	50	70.4	12	75
Controls				
Outdoor	17	37.7	11	35.5
Indoor	28	62.3	20	64.5

Table 4. Distribution of Low Vitamin D Status Based on Occupation in Cases and Controls

	Serum 25(OH)D Level		
	N	Mean ± SD	p-value
Age			
≤ 60 years	64	20.84 ± 8.04	0.07 (NS)
> 60 years	36	17.89 ± 7.8	
Gender			
Male	67	20.53 ± 8.02	0.18(NS)
Female	33	18.26 ± 7.99	
Body Mass Index (kg/m^2)			
Normal (<25)	60	22.66 ± 8.77	0.000023(S)
Over weight (25-29.9)	36	15.68 ± 3.93	
Obese (≥30)	4	13.47 ± 4.3	
Glycemic Control (HbA_1C)			
≤ 7%	18	32.4 ± 5.92	<0.00001(S)
>7%	82	17.00 ±5.34	
Diabetes Duration			
< 5 years	40	22.03 ± 9.27	0.02(S)
≥ 5 years	60	18.27 ± 6.8	

Table 5. Serum Vitamin D Levels in Diabetic Patients With Respect to Age, Gender, BMI, HbA1c and Duration of Diabetes

Parameters	<20 ng/ml n = 71	≥20 ng/ml N = 29	p-value
Age (years)	57.02 ± 8.5	57.06 ± 8.8	0.98(NS)
BMI (kg/m^2)	25.17 ± 3.3	22.78 ± 3.3	0.0008(S)
FPG (mg/dl)	209.55 ± 56.69	147.86 ± 57.72	<0.00001(S)
HbA_1C (%)	9.75 ± 2.01	7.19 ± 1.93	<0.00001(S)

Table 6. Findings of Different Parameters in Cases According to their Serum Vitamin D Levels

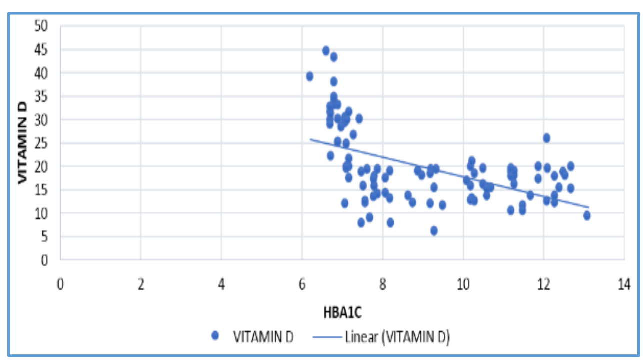

Figure 3. Graph Showing Correlation Between HbA1c and vitamin D levels

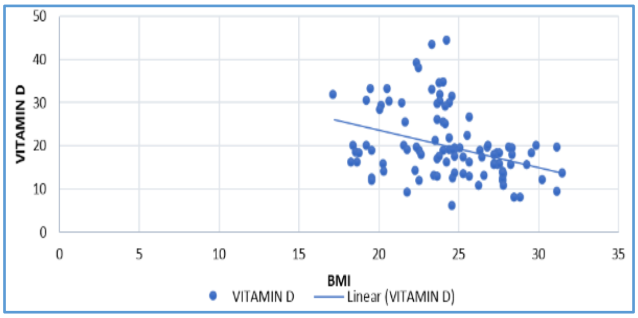

Figure 4. Graph Showing Correlation between Vitamin D Levels and BMI

DISCUSSION

The mean blood level of serum 25 (OH) cholecalciferol in type 2 diabetic cases in this study was found to be (19.78 ± 8.04) ng/ml and (25.52 ± 8.53) ng/ml in controls (P value <0.00001). Vitamin D deficiency is detected in 71% of the diabetic cases compared to only 45% in the control group. Only 13% of the cases and 24% of the controls were having sufficient vitamin D levels. None were found to be in toxic range group i.e. 25 (OH) D levels >100 ng/ml. Similar observations were made by Nayak Chitralekha et al in Goa, who observed that 72% of the study population being severely vitamin D deficient, while 26% being vitamin D insufficient and the remaining 2% having normal vitamin D levels.[11]

Similar results were also observed in the studies by Bashir et al[12] and Bayani MA et al [13] where the mean vitamin D level was 18.81 ± 15.18 ng/ml in diabetes cases compared to 28.46 ± 18.89 ng/ml in healthy controls and 18.7 ± 10.2 in diabetic cases compared to 24.6 ± 13.5 in controls respectively. Al-Timimi DJ et al, showed that a low vitamin D status is present in two thirds of patients with Type 2 DM.[14] in a recently published study from Kashmir, Vitamin D deficiency was found in 91% of the patients with diabetes and 58% of the healthy controls in the age group of less than 25 years. Vitamin D was significantly low, 7.88 ± 1.20 ng/ml in people with diabetes against 16.63 ± 7.82 ng/ml in healthy controls.[15] In contrast, one study in Japanese population having as high as 70% prevalence of Vitamin D deficiency, has not shown any difference in 25 (OH) D between patients with diabetes (17.0 ± 7.1 ng/ml) compared to normal population (17.5 ± 3.6 ng/ml).[16] Majority of the studies available in literature shows higher incidence of vitamin D deficiency in type 2 diabetics in comparison to general population. The present series showed that the serum 25 (OH) D was lower in females than in males (18.26 ± 7.99 and 20.53 ± 8.02 respectively) however statistically not significant.

In the present study vitamin D showed inverse significant correlations with blood HbA_1C (r=-0.528 and P= <0.0001). Patients with poor glycemic control (HbA1c >7%) the mean serum 25 (OH) D is 17.00 ± 5.34 ng/ml whereas in patients with good glycemic control (HbA1c ≤ 7%) it is 32.4 ± 5.92 ng/dl (p < 0.00001). This finding is in agreement with Al-Timimi et al, who reported mean serum 25 (OH) D value of 31.5 ± 12.9 ng/ml and 24.7 ± 12.0 ng/ml in patients with good and poor glycemic control respectively.

In the present study, mean HbA_1c is 9.75 ± 2.01% and 7.19 ± 1.93% in vitamin D deficient group (<20 ng/dL) and vitamin D non-deficient group (≥20 ng/dL) respectively (p<0.00001). Similar observations were made by Farshad et al, who reported that mean HbA_1c value was 6.7 ± 1.0% in vitamin D sufficiency, 7.3 ± 1.5% in insufficiency, and 8.4 ± 2.0% in deficiency subjects ($P < 0.0001$) and that there was a negative correlation between vitamin D and HbA_1c levels ($r = -0.387$, $P < 0.0001$).[17] The inverse relationship of vitamin D with HbA_1c may indicate that hypovitaminosis D may be associated with the long-term abnormal carbohydrate metabolism in type 2 diabetes. In this context, it is suggested that supplementation of vitamin D may be useful in the management of diabetes.

The mean serum 25(OH) D was also significantly lower in patients with a diabetes duration of more than 5 years (18.27 ± 6.8 ng/ml) than those with a duration of less than 5 years (22.03 ± 9.27 ng/ml). This finding is similar to the study by Al-Timimi. This reflects that chronic hyperglycaemia results in diabetic nephropathy which leads to a low vitamin D status by decreasing the rate of vitamin D3 hydroxylation in the kidney.

The findings in this study indicated that serum concentration of 25 (OH) D correlated inversely with body mass index (BMI) in diabetic patients ((r=-0.355 and P= 0.00029). Taheri et al reported that serum level of 25 (OH) D has an inverse relationship with BMI among adult population with and without T2DM in Iran.[18] Fondjo et al, in their study, reported that in the diabetic cases, in whom vitamin D deficiency was higher percentage-wise, were in the overweight range.[19] similarly in the study by Paul. A. Oakley, BMI was negatively correlated with vitamin D (r = -0.21, p < 0.05).[20] The inverse relationship between vitamin D and obesity may be multifactorial – genetic, increased metabolic clearance, negative feedback, and reduced production due to relatively lesser exposure to sunlight.[21]

CONCLUSION

It is concluded from the present study that a low vitamin D status is present in more than two thirds of patients with type 2 DM, more so amongst diabetics with poor glycemic control, high BMI and those with longer diabetes durations. It is reasonable to conclude that normal vitamin D level in blood may influence glucose control and hence, replacement therapy of vitamin D may be an effective public health intervention, to improve vitamin D status in the population.

Limitation

The limitation of the study is that it is a hospital based study with a small sample size conducted over a limited period of time. Hence, to extract more detailed information regarding the relation of vitamin D with type 2 diabetes mellitus, a broader study covering a larger number of patients over a longer time period is required. Our study also did not take into account few confounding factors like dietary habits and parathyroid hormone levels.

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