

## Vitamin D Insufficiency Prevalence and Severity in Type 2 Diabetes Mellitus Patients at IGIMS, Patna: A Case Control Study

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### Abstract

**Aim:** The aim of the study to assess the prevalence and severity of vitamin D insufficiency in type 2 DM patients and to know whether any correlation between level of glycemic control and vitamin D insufficiency.

**Methods:** A case-control study was conducted in the Department of General Medicine, Indira Gandhi Institute of Medical Sciences, Sheikhpura, Patna, Bihar, India. Total 200 participants were included in the study, out of which 100 type 2 diabetic patients were included as case (Group A) and 100 healthy people as controls (Group B). Routine laboratory investigations like CBC, FBS, RBS, PP2BS, HbA1C, blood urea, serum creatinine, lipid profile, urine albumin and Vitamin D3 levels were done by standard methods in central laboratory of Institute.

**Results:** In the study population, the mean age of group A (case) was 50.58±10.55 years while that of group B (control) was 48.82±10.36 years. Total 110 males and 90 females were enrolled in study. 66% of group A were male and 34% female. Group B (control) had 46% males and 54 females. Prevalence of low vitamin D level in healthy population was only 24 % in my study, while prevalence was 85 % in Diabetic group. Among diabetic patients having abnormal Vitamin D level, majority 67%) were having insufficiency, only 18% were having overt vitamin D deficiency in Diabetic patients. In patients with controlled diabetes as per HbA1C criteria, the prevalence of sufficient, Insufficient and Deficient Vitamin D was 20.45%, 65.91% and 13.64% respectively, where in patients with uncontrolled diabetes it was 7.14%, 75% and 17.86% respectively. More number of diabetic patients with uncontrolled status (17.86%) were having overt vitamin D deficiency in comparison to controlled status (13.64%). Hypertension was most common co-morbidity found in diabetic group (12%) followed by ischemic heart disease (7%). Serum vitamin D level was measured in all

participants. 85 of diabetic population was having less than normal vitamin D level, while only 24% had less than normal vitamin D level in group B (control). Mean value of vitamin D in type 2 Diabetic patients was  $28.83 \pm 6.97$  ng/dl and mean value of vitamin D in healthy individuals was  $37.21 \pm 4.89$  ng/dl.

**Conclusion:** We concluded that the control of diabetic status is mandatory in order to prevent vitamin D deficiency.

**Keywords:** Serum vitamin D level, Type 2 diabetes mellitus, Vitamin D deficiency.

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## Background

Vitamin D is a pleiotropic hormone known to play an immunomodulatory role in addition to Calcium and bone metabolism [1]. Receptors for its activated form have been identified on pancreatic  $\beta$ -cells and immune cells [2].

Evidence is available linking vitamin D deficiency with bacterial and viral infections [3]. Foot infection accounts for 20% of hospitalization of diabetic patients annually. Immunological defects in addition to neuropathy and vascular abnormality are the prime contributors in the pathogenesis of diabetic foot and subsequent infections. Different studies have shown that deficiency of vitamin D leads to immune cell dysfunction,  $\beta$ -cell damage and impaired insulin production [3]. In addition to hyperglycaemia, vitamin D deficiency could also be linked to an altered immune system of patients with diabetes, rendering them susceptible to foot infection and unfavourable prognosis.

Although the number of people with type 2 diabetes mellitus is increasing in every country, its major contribution is from developing countries, where it is fast becoming an epidemic. Due to the increasing global burden of type 2 diabetes mellitus, the pathophysiology of this disease is being explored with renewed interest. Insulin resistance and  $\beta$ -cell failure are the core pathophysiologic defects of type 2 diabetes mellitus. It is primarily due to interplay between genetic and environmental factors. Incidence of type 2 diabetes mellitus varies from one geographical region to another due to

differences in lifestyle and risk factors. Apart from conventional environmental risk factors like obesity, physical inactivity, intake of high calorie food and stress, the role of certain nutritional factors in pathogenesis of type 2 diabetes mellitus is an emerging concept at present.

Accumulating evidence from several cross-sectional studies suggests that vitamin D has an important role in the homeostasis of blood glucose, and its deficiency may cause development of type 2 diabetes mellitus. Vitamin D, originally described merely as a vitamin, is indeed a misnomer as it is now well-established that its active form is a hormone which is not only involved in bone metabolism but also in a plethora of non-skeletal physiological processes. Several mechanisms have been proposed, indicating a positive effect of vitamin D on insulin secretion and sensitivity, which include its direct effect via activation of vitamin D receptor on pancreatic  $\beta$ -cells and insulin sensitive organs and indirect effect via regulation of calcium homeostasis [3]. In the largest epidemiological study from the NHANES population, a dose-dependent inverse relationship has been observed between vitamin D and type 2 diabetes mellitus with the highest number of metabolic syndrome patients having the lowest quartiles of vitamin D [4]. The main source of vitamin D in humans is exposure to sunlight, natural diet and dietary supplements. Vitamin D from the skin and diet are metabolised in the liver to 25-hydroxy vitamin D [25 (OH)D] which is

used to determine the patient's vitamin D status.

Although there is no definite consensus about the normal level of vitamin D, most experts define vitamin D deficiency as less than 20 ng/ml. A level of 20 - 29 ng/ml is considered to indicate a relative insufficiency of vitamin D and a level of 30 ng/ml or greater can be considered as sufficient [5,6]. According to this definition, 1 billion people worldwide are suffering from vitamin D deficiency or insufficiency. Various studies done in different geographical region and cultural background have shown varied range of prevalence of vitamin D deficiency in diabetic group ranging from 67%-98.8% [7-10].

Even in the sunniest countries including India, vitamin D deficiency is very common as most of the body surface is shielded from the sun. The prevalence of vitamin D deficiency in India is around 50-90% in normal healthy population [7]. India is already declared as 'Capital of Diabetes'. Diabetes mellitus is accepted as major emerging epidemic in India. India has an estimated 77 million people with diabetes which makes it the second most affected in the world after China. The number is projected to grow by 2045 to become 134 million per the International Diabetes Federation [11]. The majority of diabetes cases are of type 2 diabetes [12]. As vitamin D has been shown to have an effect on pathophysiology of diabetes and there is very high prevalence of vitamin D insufficiency, so we have taken up this study to see the effect of both high prevalence diseases on each other.

### Material and Method

A case-control study was conducted in the Department of General Medicine, Indira Gandhi Institute of Medical Sciences, Sheikhpura, Patna, Bihar, India.

Total 200 participants were included in the study, out of which 100 type 2 diabetic patients were included as case (Group A)

& 100 healthy people as control (Group B).

The participants were selected as per following inclusion and exclusion criteria.

### Inclusion Criteria

1. Patients with type2 diabetes mellitus visited in General Medicine OPD or admitted in wards of General Medicine department, IGIMS Patna, as Group A.
2. Healthy individuals including patient's attendants, health care workers of IGIMS etc. as Group B.

### Exclusion Criteria

1. Patients with chronic kidney disease
2. Patients taking calcium supplements or vitamin D supplements within last 3 months
3. Patients suffering from any known chronic illness
4. Type1 diabetes mellitus patients

After selecting the participants as per inclusion and exclusion criteria, informed consent was taken.

The participants were subjected for routine laboratory investigations like CBC, FBS, RBS, PP2BS, HbA1c, blood urea, serum creatinine, lipid profile, urine routine examination and Vitamin D3 level by standard methods in central laboratory of the Institute.

The value of serum vitamin D level was further divided in the following category: sufficient = 30-100ng/ml, insufficient = 20-29ng/ml, deficiency = less than 20ng/ml.

### Results

In the study population, the mean age of group A (case) was  $50.58 \pm 10.55$  years while that of group B (control) was  $48.82 \pm 10.36$  years. Total 110 males and 90 females were enrolled in study. 66% of group A were male and 34% female. Group B (control) had 46% males and 54 females. On evaluation of investigation profile of both group A and group B, mean values of haematological parameters in form of haemoglobin, total count and platelet were within normal limit and

comparable in both groups. Surprisingly mean value of renal function test parameters, blood urea and serum creatinine were within normal range for diabetic group also, though 11% of patients had abnormal serum creatinine value and it range from 2.33 to 4.4 mg/dl.

Mean value of all lipid profile component was in normal limit in both the group, but 39% of diabetic patients had dyslipidaemia and commonest dyslipidaemia was hyper-

triglyceridemia in 30% patients. Frequency Distribution of Participants according to Severity of Vitamin D level noted. Prevalence of low vitamin D level in healthy population was only 24 % in our study, while prevalence was 85 % in Diabetic group. Among diabetic patients having abnormal Vitamin D level, majority 67%) were having insufficiency, only 18% were having overt vitamin D deficiency in Diabetic patients (table 1.)

**Table 1: Severity grading of vitamin D deficiency in cases and controls**

	Case =100	%	Control=100	%
Deficiency	18	18	nil	
Insufficient	67	67	24	24
Sufficient	15	15	76	76

**Table 2: The association of severity of vitamin D level with the category of diabetes control**

Diabetes control	Vitamin D Level			p-value
	Sufficient	Insufficient	Deficiency	
Controlled Diabetic (N = 44)	9(20.45%)	29 (65.91%)	6(13.64%)	0.002
Uncontrolled Diabetic (N= 56)	4(7.14%)	42(75%)	10(17.86%)	

In patients with controlled diabetes as per HbA1C criteria, the prevalence of sufficient, Insufficient and Deficient Vitamin D was 20.45%, 65.91% and 13.64% respectively, where in patients with uncontrolled diabetes it was 7.14%, 75% and 17.86% respectively. More number of diabetic patients with uncontrolled status (17.86%) were having overt vitamin D deficiency in comparison to controlled status (13.64%). There is a significant association between the maintenance of euglycemia and severity of Vitamin D level in diabetic patients, as the p value is less than 0.05 (Table 2).

Pearson correlation test showed negative correlation between HbA1C level and mean vitamin D level in Diabetic group as  $r = -0.221$ ,  $p \text{ value} = <0.001$ . It suggests as HbA1c level increase, the level of vitamin

D decreases, so more severe the hyperglycaemia and poorer the control of diabetes status, there was more severe the vitamin D deficiency.

We also compared the mean value of vitamin D deficiency with the duration of Diabetes, but there was no significant relation between duration of diabetes and serum vitamin D deficiency ( $P \text{ value} >0.5$ ).

Diabetic nephropathy was the most common microvascular complication seen in type 2 diabetic patients. it was found that all three important microvascular complications: - diabetic retinopathy, diabetic nephropathy and peripheral neuropathy did not have any significant correlation with serum Vitamin D level as p value is greater than 0.05 for all three parameters (Table 3).

**Table 3: Comparison of mean vitamin D level with duration and micro vascular complication of diabetes mellitus**

Parameters		Mean value of vitamin D (ng/dl)	p value
Duration of diabetes	0-5 years	27.21±6.73	0.21
	5-10 years	29±5.77	
	>10 years	26.94±3.87	
Micro-vascular complication	Diabetic retinopathy	Present	0.077
		Absent	
	Diabetic nephropathy	Present	0.055
		Absent	
	Peripheral neuropathy	Present	0.101
		Absent	

Hypertension was most common co-morbidity found in diabetic group (12%) followed by ischemic heart disease (7%). Serum vitamin D level was measured in all participants. 85 of diabetic population was having less than normal vitamin D level, while only 24% had less than normal vitamin D level in group B(control). Mean value of vitamin D in type 2 Diabetic patients was 28.83±6.97 ng/dl and mean value of vitamin D in healthy individuals was 37.21±4.89 ng/dl.

**Table 4: Subgroup analysis- mean vitamin D level in diabetes patients in relation with age, gender and associated co-morbidities**

Parameters (Number of patients)	Mean value of vitamin D	p value
Age group	Below 35(79)	0.221
	Above 35 (21)	
Gender	Male (66)	0.025
	Female (34)	
HTN	Yes (12)	0.034
	No (88)	
IHD	Yes(7)	0.123
	No (93)	

## Discussion

The literature on the role of 25(OH) vitamin D in vascular calcification is ambiguous. Experimentally higher 25(OH) vitamin D level have been associated with increased vascular calcification while in vivo, lower level of 25(OH) vitamin D seems to have this effect. This suggests that 25 (OH) vitamin D may have a biphasic relation with risk promoting Vascular Calcification in both excess and deficiency [13].

However, the prevalence of vitamin D deficiency in India is around 50-90% in normal healthy population [7]. In our study, prevalence of vitamin D deficiency

is 24% in normal population which is similar to worldwide prevalence but very less in comparison to prevalence shown in Indian studies. This low prevalence in healthy population was contradictory to other Indian studies. Another on-going study on vitamin D level done in similar region had also showed 16% prevalence of vitamin D deficiency in healthy population. Vitamin D exerts its effect on calcium metabolism and hence affects skeletal system; however, it also has extra skeletal effects like that on cardiovascular system, endocrine disorders and autoimmune disorder. Several reports have ascribed an active role to vitamin D in the

functional regulation of the endocrine pancreas, particularly the beta-cells.

India is already declared as 'Capital of Diabetes'. Diabetes mellitus is accepted as major emerging epidemic in India, as India is having 77 million of diabetic patients currently and it is projected to grow up to 134 million by year 2045. As vitamin D has been shown to have effect on pathophysiology of diabetes and have very high prevalence of vitamin D deficiency, so we have taken up this study to see effect of both high prevalence diseases on each other.

Various studies done in different geographical region and cultural background have shown varied range of prevalence of vitamin D deficiency in diabetic group ranging from 67%-98.8% [7-10]. Our study along with Bashir *et al* and Ifigenia-Kostoglou A *et al* studies had shown higher prevalence of vitamin D deficiency in diabetes mellitus patients compared to healthy individuals, but two other studies had shown no difference of prevalence between diabetic and healthy population [8-10,14]. So, we have compared the mean value of serum vitamin D level in diabetic patients and in healthy population of various study. Various studies including our study had low mean level of vitamin D for diabetic patients in comparison to healthy population [7,14,15].

In patients with controlled diabetes as per HbA1C criteria, the prevalence of sufficient, Insufficient and Deficient Vitamin D was 20.45%, 65.91% and 13.64% respectively, where in patients with uncontrolled diabetes it was 7.14%, 75% and 17.86% respectively. More number of diabetic patients with uncontrolled status (17.86%) was having overt vitamin D deficiency in comparison to controlled status (13.64%). There is a significant association between the maintenance of euglycemia and severity of Vitamin D level in diabetic patients, as the p value is less than 0.05. Similar results were shown by Mukherjee B *et al*. Mean

level of vitamin D is low in uncontrolled diabetic patients ( $19.47 \pm 4.76$ ) as compared to controlled diabetic patients ( $23.63 \pm 3.71$ ) [14]. Modi KD *et al* found that vitamin D levels in patients with controlled diabetes was  $22.4 \pm 18.6$  while in uncontrolled diabetic patients it was lower,  $19.9 \pm 18.3$  which is statistically significant [15]. Overall insufficiency is more common than deficiency state in diabetic patients regardless of diabetic control status, but severe vitamin D deficiency is more prevalent when patients were having uncontrolled diabetes than controlled diabetes (17.86% and 13.64% respectively). On Pearson correlation, the study has demonstrated negative correlation between HbA1C level and serum vitamin D level. It suggests that as HbA1C level increase, there is decrease in serum vitamin D level. Ifigenia-Kostoglou A *et al* had also found that 25(OH) D3 levels were inversely associated with HbA1c when the patient and control groups were analysed together ( $p = 0.008$ ,  $r^2 = 0.058$ , linear regression analysis) [10]. Study by Mukherjee B *et al* also indicates there is a definite negative correlation between Vitamin D levels and diabetes ( $r = -0.94$  and  $-0.97$ ) and poorly controlled diabetics have further lower values of Vitamin D [14]. A study by Akshay kumar SV *et al* showed a negative negligible co-relation between vitamin D levels and HbA1C, which was not statistically significant ( $r = 0.017$ , p value 0.741) [9]. The inverse relationship between vitamin D level and glycaemic control in this study support an active role of vitamin D in pathogenesis of type 2 diabetes mellitus.

Duration of diabetes and presence of micro-vascular complication do not have effect on serum vitamin D level. No effect of increasing age was observed on vitamin D status in diabetic patients and we could not able to find such association in other studies. Female diabetic patients were having lower vitamin D level compared to male counterparts; the reason might be less exposure to sun due to household activity.

Hypertension was the most common comorbidity found in diabetic patients (12%) in our study. Study by Shalini P *et al* found that Vitamin D deficiency is more prevalent (80.4%) in hypertensive patients than healthy (67.7%) individuals [16]. Hypertensive diabetic patients had lower vitamin D level than non-hypertensive diabetic patients in my study, which is statistically significant as p-value was 0.034. Ischemic heart disease was another comorbidity found with diabetes, but there was no significant difference in mean Vitamin D level was recorded in diabetic patients with or without ischemic heart disease.

### Conclusion

Diabetic individuals have a higher rate of vitamin D insufficiency than healthy people and vitamin D deficiency is more prevalent in uncontrolled diabetes than controlled diabetes. Therefore, all type 2 diabetes patients must be checked for vitamin D levels and given supplements if deficient. To avoid vitamin D insufficiency, diabetes must be strictly controlled. We recommend greater research to identify vitamin D insufficiency in our community, particularly in type-2 diabetes patients, and active initiatives to supplement our population with vitamin D.

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