



Serum Vitamin D Levels in Patients with Type 2 Diabetes Mellitus with and without Peripheral Neuropathy

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Abstract

Introduction: Serum vitamin D levels has been hypothesized to influence the progress of diabetes and its various complications. The role of Vitamin D in diabetic peripheral neuropathy have been debated. **Aim of the Study:** This study was conducted to compare serum vitamin D levels in patients with diabetic peripheral neuropathy and patients with type 2 diabetes mellitus without neuropathy, as well as to assess any possible association between serum vitamin D levels and severity of diabetic peripheral neuropathy. **Subjects and Methods:** This is a case-control study involving 100 cases and 100 controls in which serum vitamin D levels and severity of neuropathy were assessed using Vibration perception threshold (VPT). **Results:** The levels of Vitamin D were significantly lower in cases (patients with diabetes with peripheral neuropathy) compared to controls (patients with diabetes but without peripheral neuropathy). The mean serum levels of 25(OH)D in cases was 14.1 ± 3.2 ng/ml and in controls was 22.3 ± 3.8 ng/ml which was statistically significant (p value < 0.001). The mean serum vitamin D levels in cases with mild neuropathy (VPT 20-24 mV) was 16.8 ± 3.2 ng/ml, moderate neuropathy (VPT 25-39 mV) was 14.5 ± 1.4 ng/ml, and in those with severe neuropathy (VPT > 39 mV) was 11.6 ± 2.1 ng/ml ($p=0.004$). A significant negative correlation was observed between Serum Vitamin D levels and VPT ($r = -0.65$, $p < 0.001$). **Conclusion:** Vitamin D levels were significantly lower among patients of diabetes mellitus with neuropathy as compared to patients of diabetes without any evidence of underlying neuropathy. Vitamin D levels also varied significantly with severity of diabetic peripheral neuropathy. Vitamin D might be used as a valuable marker for prognostication of cases of diabetic peripheral neuropathy and can be advocated as a special test once the patient develops minimal sign and symptoms of peripheral neuropathy. Lifestyle changes and medications to improve Vitamin D levels should be advocated irrespective of glycemic control to reduce the symptoms and incidence of microvascular complications such as diabetic peripheral neuropathy.

Keywords

Type 2 diabetes mellitus, Diabetic Peripheral Neuropathy, Serum 25(OH) Vitamin D level.

Introduction

In non-communicable diseases like diabetes mellitus, the burden of the complications poses more mortality and morbidity than the disease itself. The very diverse nature of diabetic peripheral neuropathy has made even the

classification of its severity even more difficult. Estimates in the literature on prevalence of painful diabetic peripheral neuropathy varied from ten percent to hundred percent.^{1, 21}

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Vitamin D was found to play an extremely crucial role not only in musculoskeletal health, but also immunological and regenerative health of the individual. In both experimental and epidemiological studies, vitamin D insufficiency is linked to type 2 diabetes, insulin resistance, and impaired insulin secretion.^[3] 1,25(OH)₂D₃ stimulates the pancreatic β -cell to release insulin. Moreover, genetic polymorphisms of certain vitamin D related genes may contribute to the process of insulin resistance and subsequent development of diabetes mellitus.^[4] Vitamin-D leads to reduction in the inflammatory processes which are a major pathway in the destruction of beta-cells. It also helps to control concentrations of calcium and reactive oxygen species that are mainly responsible for cell-death.^[5] The relationship between Vitamin D and various complications of diabetes, especially diabetic peripheral neuropathy, needs to be studied extensively. New insight into this relationship can help up mitigate and prevent the deficiency-related complications.

Aim and Objectives

The study was planned to evaluate any possible association between serum Vitamin D levels and peripheral neuropathy in patients with Type 2 Diabetes Mellitus. The objectives were:

1. To estimate the levels of Vitamin D in patients with Type 2 Diabetes Mellitus
2. To compare the serum Vitamin D levels in Type 2 Diabetes mellitus patients with and without peripheral neuropathy.

Material and Methods

This was a case-control study conducted in a tertiary care centre in Bhubaneswar, Odisha. The study was carried out for a period of two years. The study subjects were taken from the patients with Type-2 diabetes mellitus attending General Medicine out-patient department. Based on the prevalence and the Odds of Vitamin-D-deficiency in subjects with diabetes mellitus and peripheral neuropathy, and with a confidence limit of 95% and an allowable alpha error of 5%, a sample size of 200 was calculated, which included 100 cases (patients with diabetes mellitus and peripheral neuropathy) and 100 age and sex matched controls (patients with diabetes mellitus but without any evidence of peripheral neuropathy). Subjects with renal dysfunction (creatinine >1.5mg/dl, eGFR <30ml/min) and liver dysfunction (serum bilirubin >3mg/dl, AST & ALT >40 IU/L), endocrinal abnormalities (Type 1 diabetes mellitus, thyroid abnormalities, metabolic bone diseases), those on supplemental doses of Vitamin

D currently or within past 1 year, having any infectious diseases or any malignant disorders during the study period, currently on medications like antiepileptic, antitubercular, corticosteroids which alters vitamin D levels, with known history of psychiatric disorders, with past or present history of significant alcohol consumption (men more than two drinks or 20 g of pure alcohol a day, women more than one drink or 10 g of pure alcohol a day) and with peripheral neuropathy due to a non-diabetic cause were excluded from the study. Informed and written consent was obtained from all the participants of the study. Relevant history was recorded and detailed clinical examination of all the study participants was done. Biochemical parameters like FBS, PPBS, HbA_{1c}, serum vitamin D levels, complete blood picture, lipid profile, serum TSH, liver function tests, renal function tests, serum calcium were collected from all participants. In the current study, cases included Type 2 diabetes mellitus presenting with neuropathic symptoms, with positive findings on physical examination. In these patients, nerve conduction study (NCS) was done to confirm neuropathy. After confirmation of neuropathy, vibration perception threshold done to assess the severity of neuropathy. Neuropathy was assessed by using Biothesiometer (Biomedical Instrument Co., Newbury, OH, USA). Vibratory perception threshold (VPT) of the great toes was measured in a standardized fashion by a single observer. The biothesiometer probe was applied perpendicular to the test site with a constant and firm pressure and VPT was measured at the distal plantar surface of the great toe in both legs. The voltage was slowly increased and the VPT was defined as the moment when the subject first felt the vibration. The mean value of three measurements of both legs was used for analysis. A cut-off value of 20 mV was considered for the presence of Diabetic peripheral neuropathy (DPN) and classified into three grades of severity - mild (20–24 mV), moderate (25–39 mV) and severe (>39 mV) based on VPT score. The cut-off value of 20 mV of VPT among Indians was found to have better sensitivity compared with Neuropathy Disability Scores (NDS) which is usually taken as the gold standard.^[6]

Data analysis was carried out using SPSS version 22. Data was expressed as means and proportions. The difference of means between groups was tested using Students T test. The association of categorical variables was tested using chi square test. Results with p value less than 0.05 were considered statistically significant.

Results

There was a slight female preponderance showing 52% women and 48% men. Majority of study subjects belonged to the age group of 41-60 years (49%) followed by > 60 years age group (29%). Satisfactory glycemic control (HbA1c <7) was noted in 61%, moderate (HbA1c 7.1-9.9) in 28%, poor glycemic control (HbA1c > 10) in 11% of the study subjects. Majority of the study subjects were reported to be suffering from diabetes for 5-10 years (47%), followed by <5 years (37%) and >10 years (16%) respectively. The average duration of diabetes in cases was 7.8 years and in controls was 5.2 years, and this difference was statistically significant (p=0.01).

Among the cases, 54% had mild neuropathy (VPT - 20–24 mV), 32% had moderate neuropathy (VPT - 25–39 mV) and only 14% had severe neuropathy (VPT

>39 mV). The mean VPT scores in mild, moderate, and severe groups were 24.2 ± 3.1 , 31.8 ± 3.8 , and 44.7 ± 5.3 respectively and the difference was statistically significant (p=0.004). In majority of cases (82%) axonal neuropathy reported in NCS, and in few cases (18%) both axonal & demyelinating neuropathy was observed.

The average glycemic control (HbA1c) did not differ significantly between the cases (mean HbA1c = 8.2%) and

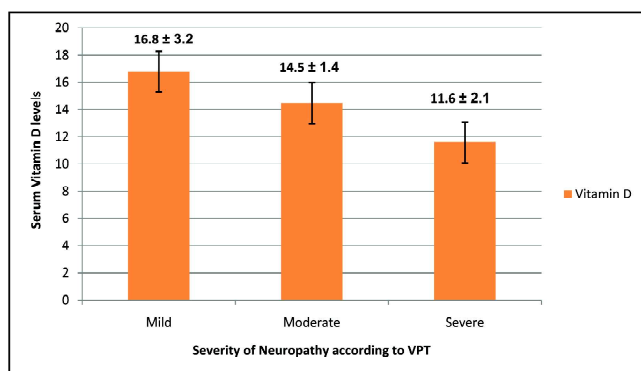


Fig 1 : Showing Vitamin D Levels in Cases according to Severity of DPN

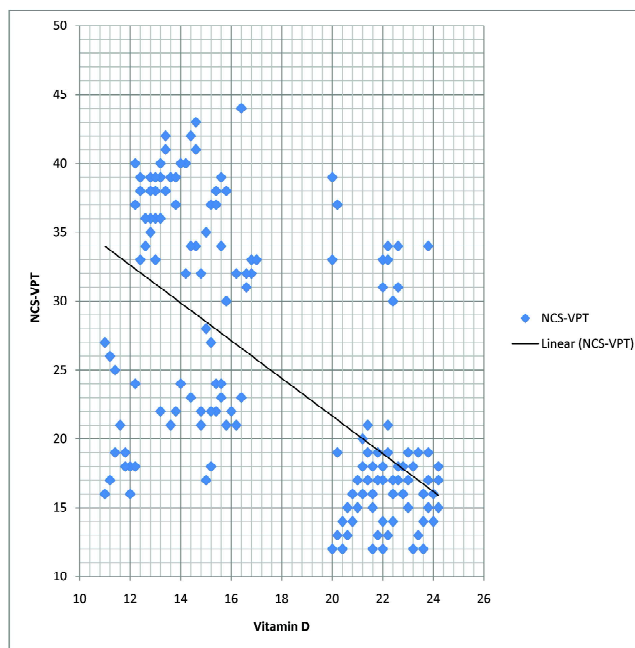


Fig 2 : Showing the negative correlation between VPT and Vitamin D (r value= -0.65, p value=<0.001).

Table 1 : Showing baseline biochemical parameters in Cases and Controls

Baseline Biochemical Parameters in Cases and Controls			
	Cases (Mean ± SD)	Controls (Mean ± SD)	p-value
Vitamin D (mg/dl)	14.1 ± 3.2	22.3 ± 3.8	<0.001
Total Cholesterol (mg/dl)	173.6 ± 19.5	162.3 ± 22.4	0.07
Triglycerides (mg/dl)	177.9 ± 15.1	144.8 ± 18.8	0.03
HDL (mg/dl)	39.2 ± 5.1	38.3 ± 4.2	0.62
LDL (mg/dl)	92.1 ± 11.4	87 ± 10.1	0.12
Serum Calcium (mg/dl)	9.6 ± 1.6	9.4 ± 1.2	0.26
TSH	3.6 ± 0.9	3.3 ± 0.7	0.34
FBS (mg/dl)	137.6 ± 15.4	118.6 ± 22.4	0.06
PPBS (mg/dl)	208.0 ± 22.8	176.6 ± 8.2	0.02
HbA1c	8.2%	7.4%	0.08

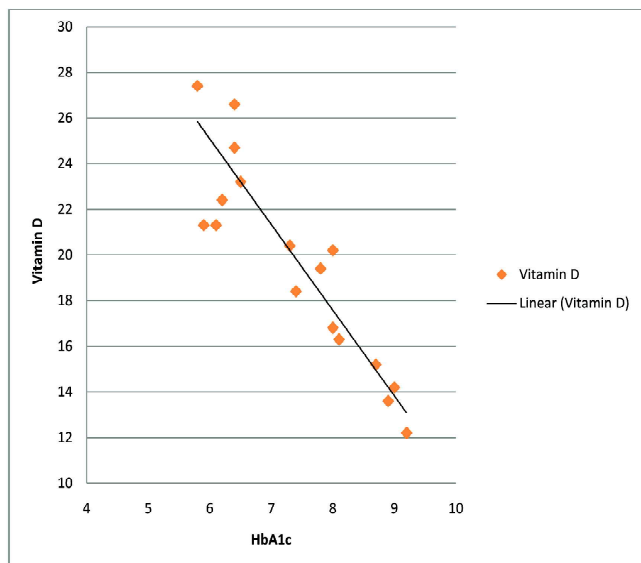


Figure 3 : Showing the negative correlation between HbA1c and Vitamin D levels ($r = -0.93$; $p < 0.001$)

control (mean HbA1c = 7.4%) ($p = 0.08$). Also, the mean fasting blood sugar level in controls was 118.6 ± 22.4 mg/dl and in cases was 137.6 ± 15.4 mg/dl with p-value of 0.06. However, the mean post-prandial blood glucose level was 208 ± 22.8 mg/dl in cases and 176.6 ± 8.2 mg/dl in controls, which was statistically significant with a p-value of 0.02.

Various biochemical parameters were compared between cases and controls. (Table 1) Only Vitamin D and triglycerides were found to have significant difference with p-values < 0.001 and 0.03 respectively. The Vitamin-D levels in cases (14.1 ± 3.2) was found to be significantly lower than the controls (22.3 ± 2.8). The levels of Vitamin-D also varied significantly in subjects with mild (16.8 ± 3.2), moderate (14.5 ± 1.4), and severe diabetic neuropathy (11.6 ± 2.1) with a p value of < 0.001 . (Fig 1) Serum vitamin D levels in subjects with good, moderate, and poor glycemic control were 19.4 ± 4.4 , 16.3 ± 2.7 , and 15.2 ± 3.1 respectively and the difference was statistically significant with a p value of 0.02.

In this study, a significant negative correlation was observed between Vibration Perception Threshold (VPT) and serum Vitamin-D levels (r value = -0.65 , p value = < 0.001). (Fig 2) There was also an inverse correlation between HbA1c, and serum Vitamin D levels (r value = -0.93 , p value = 0.04). (Fig 3) Similarly the correlation between HbA1c and VPT was found to be positive (r value = 0.8 , p value = < 0.001). (Fig 4)

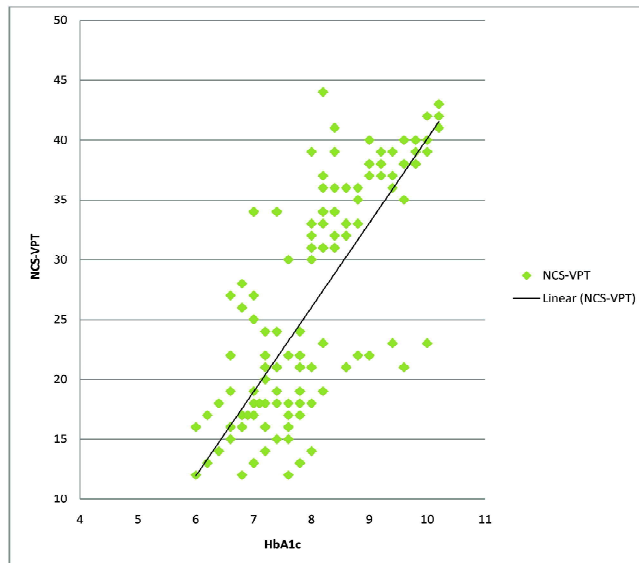


Figure 4 : Showing the positive correlation between VPT and HbA1c ($r = 0.8$, $p < 0.001$)

Discussion

The role of Vitamin D is of immense research interest. Apart from regulation of calcium in maintaining musculoskeletal health, its role is being established in immunity and regenerative processes in the body. As diabetes mellitus causes micro and macro vascular complications, the role of vitamin D in relation to mitigating and managing various complications of diabetes mellitus is being actively investigated. The present study is a case control study undertaken at a tertiary care teaching hospital in Bhubaneswar, Odisha.

The present study showed slight female predisposition with respect to gender, but this difference was not statistically significant. Though conventionally, non-communicable diseases were postulated to be higher in men, the gender gap is fast closing. The higher rate of complications in women compared to men may suggest that proper glycemic control was lacking in women compared to men. This may be due to lack of awareness in women or poor compliance to medication among women, or totally, poor health seeking behavior in women compared to men. Hence it is imperative to be extra cautious in screening women for diabetes and its complications during hospital visits for any purpose. Shehab et al, reported that gender did not have any significant association with diabetic neuropathy in the study subjects.^[7] Our study was in tune with the findings from the studies done by Shehab *et al* regarding gender



disparity.

The age group of 40-60 years is usually the commonest age group for presentation with diabetes. However, of late, the incidence of diabetes in 2nd and 3rd decade age group is increasing swiftly. So that is reflected in the present study where 22% of the study subjects were aged 18-40 years. The higher age group of older than 60 is more likely to develop diabetic peripheral neuropathy owing to possible longer duration of diabetes. But probably due to low health-seeking behavior in older age group and relatively late onset of the disease along with multiple comorbidities and chronic diseases (fulfilling the exclusion criteria), their proportion was lesser than 40-60 age group in our study. Niu *et al* reported that elderly age group over sixty is a major risk factor for developing diabetic neuropathy.^[8] However, Shehab *et al*, did not find any significant association between age and diabetic neuropathy.^[7]

The average glycemic control (HbA1c) did not differ significantly between the cases (mean HbA1c = 8.2%) and control (mean HbA1c = 7.4%) ($p=0.08$). However, the FBS, PPBS, HbA1c values were numerically higher in the cases, but the difference was not statistically significant which could be explained by the fact that both the groups consisted of patients with underlying diabetes. The average duration of diabetes in cases was 7.8 years and in controls was 5.2 years, and this difference was statistically significant ($p=0.01$) which could partially explain about the increased prevalence of neuropathy symptoms among the cases.

The present study found significant difference in Vitamin D levels in subjects with various grades of diabetic peripheral neuropathy. The serum Vitamin D levels worsened with increase in the severity of neuropathy. The Vitamin-D levels in cases was found to be significantly lower than the controls ($p<0.001$). The levels of Vitamin-D also varied significantly in subjects with mild, moderate, and severe diabetic neuropathy with a p value of <0.001 . Serum vitamin D levels also decreased significantly in subjects with poor glycemic control across in both cases and control group and the difference was statistically significant with a p value of 0.02.

In this study, a significant negative correlation was observed between Vibration Perception Threshold (VPT) and serum Vitamin-D levels (r value = -0.65, p value = <0.001). There was also an inverse correlation between HbA1c, and serum Vitamin D levels (r value = -0.93, p value = 0.04). Similarly the correlation between HbA1c and VPT was found to be positive (r value = 0.8,

p value = <0.001). The findings of the present study were in direct line with the findings of He *et al*, who in his study found poor Vitamin D levels in subjects with diabetic peripheral neuropathy.^[9] These findings were also echoed by Shillo *et al*, who concluded that low Vitamin D levels add to a major risk of diabetic peripheral neuropathy.^[10] Darlington *et al*, did not find any significant difference between the patients with or without diabetic foot. This is a significant finding since diabetic peripheral neuropathy is the beginning step and one of the root causes of diabetic foot.^[11] However, the study reported that those with sufficient Vitamin D levels only healed well. This again concurs with the findings of the present study. Shehab *et al* studied the impact of Vitamin D supplementation in diabetic peripheral neuropathy. This was found to be beneficial and improved the rate of recovery from symptoms.^[7]

This study holds strength in assessing prevalence of vitamin D deficiency in patients of DPN. The analysis of two groups gave better understanding of vitamin D levels in type 2 diabetes mellitus patients with and without peripheral neuropathy. The present study is an analytical cross-sectional study. The exposure to risk factor (deficiency of Vitamin-D) in both the groups was analyzed. The matching was also done for subjects of both groups with respect to age, gender, and glycemic control. Thus, every effort was made to limit the confounders. The main limitation of case control study is being unable to establish the course and precedence of events, cause, and effect. Hence a long-term prospective study should be ideally followed up with.

Conclusion

Vitamin D levels were significantly lower among patients of diabetes mellitus with neuropathy as compared to patients of diabetes without any evidence of underlying neuropathy. Vitamin D levels also varied significantly with severity of diabetic peripheral neuropathy. Vitamin D might be used as a valuable marker for prognostication of cases of diabetic peripheral neuropathy and can be advocated as a special test once the patient develops minimal sign and symptoms of peripheral neuropathy. Lifestyle changes and medications to improve Vitamin D levels should be advocated irrespective of glycemic control to reduce the symptoms and incidence of microvascular complications such as diabetic peripheral neuropathy.

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Nil.

Conflicts of Interest

There are no conflicts of interest.

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