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Research Article

Vitamin D Levels and Microvascular Complications in Type 2 Diabetes Mellitus Patients: A Study from North Keral

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Abstract

Introduction: Vitamin D plays an important role in glucose metabolism. Several pleiotropic effects of Vitamin D have been studied like regulation of cell proliferation, suppression of cell mediated immunity, Glial cell line-derived neurotrophic factor, stimulation of nerve growth factor, suppression of Renin-angiotensin-aldosterone system (RAAS), reduction of albuminuria, immunomodulatory effects, and anti-inflammatory effects.(1)Thus, vitamin D is implicated in the pathogenesis of retinopathy, neuropathy and nephropathy.

Materials and Methods*:* A Cross-sectional case-control study of 206 patients (>30 years), who met the American Diabetes Association, 2011 criteria (2) for type 2 DM, was conducted. Subjects were evaluated for the presence of microvascular complications by clinical evaluation, urine examination, fundus examination, clinical neuropathy scoring, and various biochemical tests. 25-OH cholecalciferol levels were done and cut off level for vitamin D deficiency was 30 ng/ml. 72 Vitamin D sufficient and 134 Vitamin D deficient cases were studied.

Results: A total of 134 T2DM cases with Vitamin D deficiency were studied. 72 age matched T2DM patients with sufficient Vitamin D levels served as controls. The mean age of cases under study was 47.58 ± 9.63 years compared to 51.24 ± 8.75 years of controls. 61.2% were females, whereas 38.8% were males in the case group while in the control group, 69.4% were males, and 30.5% were females. The mean duration of diabetes in the cases studied was 57.08 ± 18.13 months. It was 52.69 ± 17.98 months in the Vitamin D sufficient controls. Significant statistical associations were established using Chi square test between Vitamin D status and development of microvascular complications like Diabetic nephropathy, retinopathy and neuropathy in Type 2 Diabetes Mellitus at $p < 0.05$.

Conclusion and Implication: Vitamin D is an important factor in modifying the risk of Type 2 DM and its microvascular complications, especially Diabetic retinopathy, neuropathy and nephropathy. Administration of vitamin D supplements may prove to be a beneficial adjuvant therapy in mitigating microvascular complications. Frequent Monitoring of Vitamin D status can decrease the burden of co-morbidities in T2DM and thus can decrease the mortality rate associated with T2DM. However; the exact role of vitamin D in these processes requires further investigations.

Keywords:
Diabetes, Nephropathy, Neuropathy, Retinopathy, Vitamin D

Introduction

Diabetes Mellitus is a fast growing epidemic and the rising burden of diabetes is a major concern in healthcare worldwide. Its incidence rate is increasing year by year in both developed and developing countries. According to the Diabetes Atlas, 2021(2) of the International

Diabetes Federation, the estimated number of diabetes patients in India in the 20-79 age group is 74.2 million (2021) and is likely to increase to 124.8 million in 2045. It is estimated that around 20% of diabetic cases were under diagnosed and are at higher risk for development of complications such as renal failure, atherosclerosis, stroke, myocardial infarction, diabetic foot amputations etc. On studying the complications of diabetes, 63% of patients with diabetic nephropathy have type II DM and the risk of developing diabetic nephropathy is not constant over the duration of diabetes. On the other hand, the duration of diabetes has a direct relationship with the prevalence of retinopathy. Almost all patients with type 1 diabetes develop signs of retinopathy within 2 years of diagnosis, one – third of those with type 2 diabetes have retinopathy at diagnosis, increasing to two-thirds within 20 years.

Vitamin D is a multifunctional fat soluble vitamin required for human growth and development and its non-classical functions have attracted more attention for studying close association between vitamin D deficiency and complications of DM. The prevalence of vitamin D deficiency is high in type 2 DM and so are its complications [(3)]. This study is undertaken to evaluate the effect of vitamin D deficiency in the development of micro vascular complications like diabetic nephropathy, neuropathy and retinopathy in type 2 DM.

Objectives:

To find out the association, if any, between vitamin D levels and micro vascular complications of Diabetes Mellitus like diabetic retinopathy, neuropathy and nephropathy

Material and Methods:

Study Design: This study is an observational Cross-sectional study

Study Setting: The study was conducted in the Department of General medicine at KMCT Medical College, Calicut, and Kerala, India.

Study Period: The study was conducted over a period of 18 months from March 2021 to September, 2022.

Study Population: Patients with Type II Diabetes Mellitus attending the Department of General medicine at KMCT Medical College, Calicut, Kerala, India.

Inclusion Criteria: T2DM patients attending general medicine OPD for glycaemic control and who gave consent for participating in the study.

Exclusion Criteria: Patients on medication affecting vitamin d metabolism phenytoin and glucocorticoids, Patient who is a known case of chronic liver disease, Patient with primary hypoparathyroidism, Patient on vitamin D supplementation, Patient having kidney disease due to any other definite causes other than Type 2 DM or Hypertension

Sample Size

In the study, Vitamin D levels and microvascular complications in type 2 diabetes by -Sarita Bajaj, Raj Pratap Singh, N. C. Dwivedi, Kamaljeet Singh1, Arvind Gupta, Manoj Mathur,[(4)] the prevalence of diabetic neuropathy among Type 2 DM is 35.4% and prevalence of diabetic retinopathy and diabetic nephropathy is found to be 34.2% each. Taking the minimum prevalence as 34.2% (P), Q= 65.8% and 20% allowable error on the expected prevalence,

$$\mathbf{N = \frac{4 * 34.2 * 35.8}{6.84}}$$

The calculated sample size is 195. However, we took a total of 206 patients as samples for our study.

Sampling Technique: Consecutive sampling till the sample size was met.

Study Procedure

Patients with type 2 diabetes coming to General medicine Department underwent tests to access vitamin D levels, glycaemic control and the presence /severity of microvascular

complications. Glycaemic control was assessed by HBA1C level. Retinopathy was assessed using indirect ophthalmoscope and classified as no retinopathy, NPDR (non-proliferative diabetic retinopathy) and PDR (proliferative diabetic retinopathy). Nephropathy was assessed by doing Serum creatinine level and calculating the eGFR by using the CKD Epidemiology Collaboration (CKD-EPI) Creatinine Equation (2009) [(5)]. Urine was tested to look for proteinuria. Neuropathy was assessed using modified Toronto clinical neuropathy score and classified as no neuropathy, mild, moderate and severe neuropathy.

Study Tool

A structured Performa was used to collect patient information and note the results of laboratory investigations and clinical findings of the patients.

Statistical Analysis

Data was analysed using SPSS 21.0 and graphs were depicted using Microsoft excel Spreadsheet. Continuous variables were summarized as Mean ± Standard Deviation or median with interquartile range. Categorical variable were summarized in terms of frequency with percentage. To find association between categorical variables chi square test was used. To compare the average value of vitamin D in different groups‘t’ tests were used. For all statistical tests, a p value less than 0.05 was considered as statistically significant.

Ethical Considerations

The study was formulated only after obtaining approval from the Institutional Research and Ethical committee. Informed consent was obtained from all patients satisfying the inclusion criteria, in the local language. Data safety norms were followed to preserve confidentiality and privacy of the patient. There has been no conflict of interest as well.

Results

A total of 134 T2DM cases with Vitamin D deficiency were studied. 72 age matched T2DM patients with sufficient Vitamin D levels served as controls. The mean age of cases under study was 47.58 ± 9.63 years compared to 51.24 ± 8.75 years of controls. 61.2% were females, whereas 38.8% were males in the case group while in the control group, 69.4% were males, and 30.5% were females. The mean duration of diabetes in the cases studied was 57.08 ± 18.13 months. It was 52.69 ± 17.98 months in the Vitamin D sufficient controls.

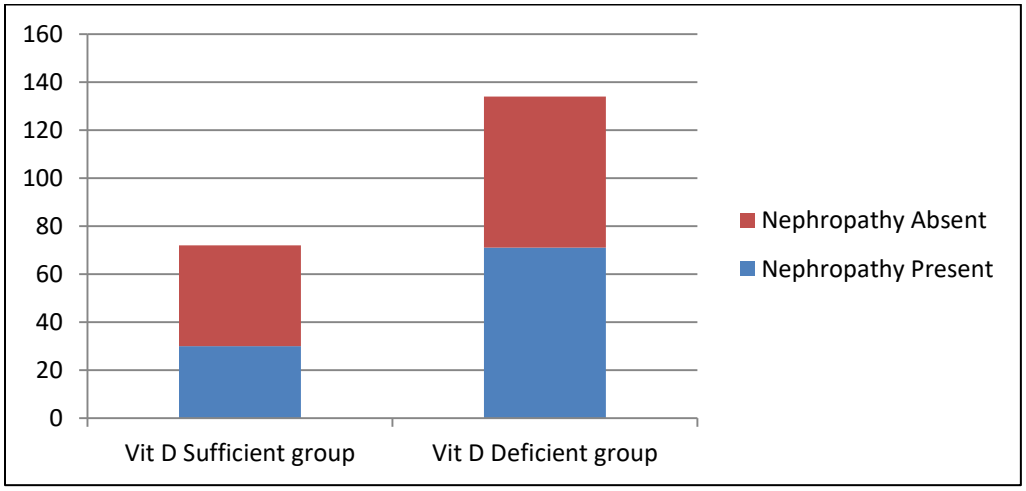

Chart 1: Association between Diabetic Nephropathy and Vitamin D Status

Table 1: Association between Diabetic Nephropathy and Vitamin D Status

Comparison between Diabetic Nephropathy with Vitamin D Status							
			Vitamin D		Total	Chi Squarevalue	P-value
			> 30 ng/ml	< 30 ng/ml			
Diabetic Nephropathy	N	Count	52	53	105	20.0028	<0.001
		%	72.2%	40.0%	51.0%		
	Y	Count	20	81	101		
		%	27.8%	60.0%	49.0%		
Total		Count	72	134	206		
		%	100.0%	100.0%	100.0%		
# Significant at P < 0.05 level							

Here, 81 patients with vitamin D deficiency which constitutes about 60%, was found to have diabetic nephropathy and in vitamin D sufficient patients, 20 patients which constitutes about 27.8% was found to have diabetic nephropathy with a 'p' value of <0.001 which is highly statistically significant.

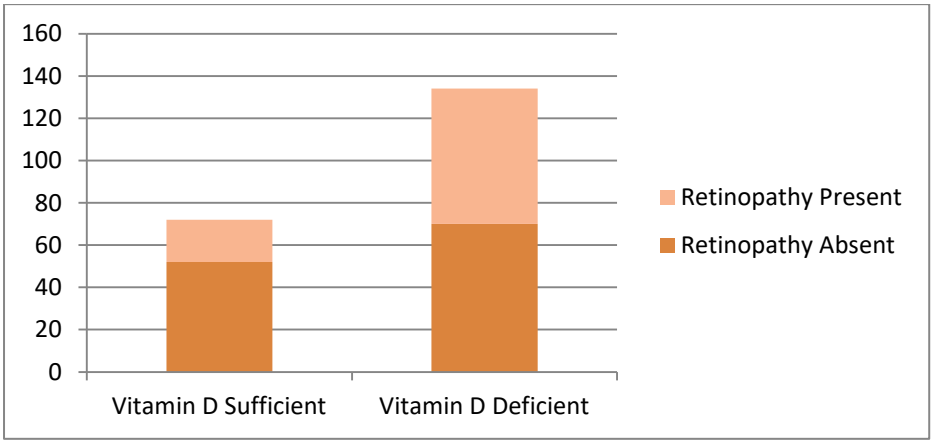

Chart 2: Association of Diabetic Retinopathy and Vitamin D Status

Table 2: Diabetic Retinopathy and Vitamin D Status

Diabetic Retinopathy and Vitamin D Status							
			Vitamin D		Total	Chi Square value	P-value
			> 30 ng/ml	< 30 ng/ml			
Diabetic Retinopathy	No	Count	52	70	122	7.745	0.005
		%	72.2%	52.2%	59.2%		
	Yes	Count	20	64	84		
		%	27.8%	47.8%	40.8%		
Total		Count	72	134	206		
		%	100.0%	100.0%	100.0%		
* Significant at P < 0.05 level							

In the vitamin D deficient groups, 64 patients i.e. 47.8% of the study population were found to have diabetic retinopathy whereas in vitamin D sufficient group 20 patients i.e., 27.8% were found to have diabetic retinopathy with 'p' value of 0.005 which is statistically significant.

Diabetic Neuropathy and Vitamin D Status

Association of Diabetic Neuropathy and Vitamin D Status

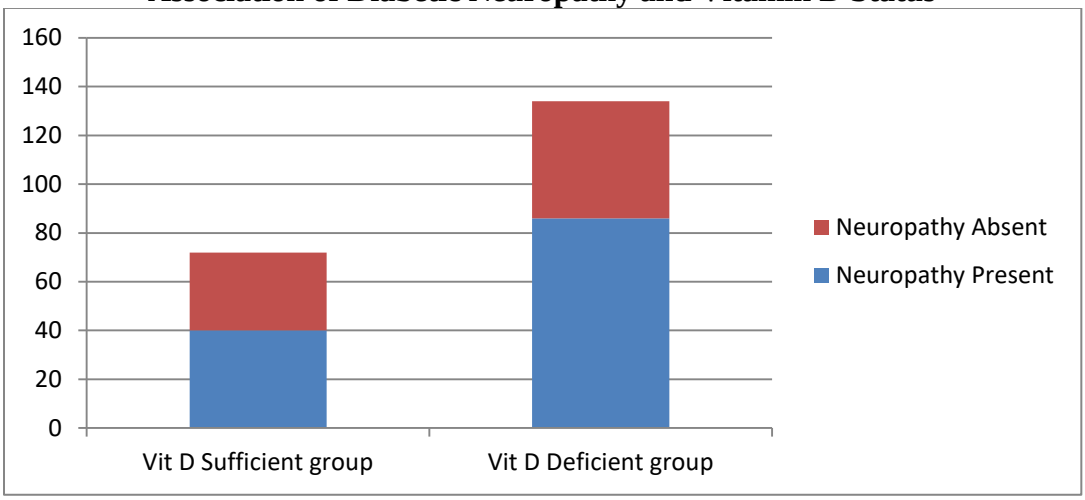

Table 3: Diabetic Neuropathy and Vitamin D Status

Association Of Diabetic Neuropathy And Vitamin D Status							
			Vitamin D		Total	Chi Square value	P-value
			> 30 ng/ml	< 30 ng/ml			
Diabetic Neuropathy	No	Count	32	48	80	7.745	0.005
		%	44.4%	35.8%	38.8%		
	Yes	Count	40	86	126		
		%	55.6%	64.2%	61.2%		
Total		Count	72	134	206		
		%	100.0%	100.0%	100.0%		

In the vitamin D deficient group, 86 patients i.e. 64.2 % of the study participants were found to have diabetic neuropathy whereas in vitamin D sufficient group, 44 patients i.e. 55.6% were found to have diabetic neuropathy with 'p' value of 0.005, which is statistically significant.

Discussion:

In this cross sectional study, conducted among patients who attended our general medicine outpatient clinics and inpatients of the medical wards, an association was tested between circulating 25-hydroxy vitamin D levels and the presence of microvascular complications in type 2 diabetes mellitus. Our study included 206 patients which included two groups, one group of 72 patients with 25(OH) D <30ng/ml and

another group of 134 patients with 25(OH)D>30ng/ml.

In our study, in vitamin D deficient group, 64 patients that is 47.8% of the study population were found to have diabetic retinopathy whereas in vitamin D sufficient group 20 patients which is of 27.8% were found to have diabetic retinopathy with 'p' value of 0.005 which is statistically significant. So this study revealed that there is a significant association between vitamin D deficiency and Diabetic Retinopathy. The two main biochemical mechanisms underlying this association are neoangiogenesis and chronic inflammation. The effect of vitamin D on angiogenesis is mediated by Vitamin D receptors which are present in human retina and the Vitamin D receptor Polymorphisms have been associated with increased risk of retinopathy in diabetic patients. Robinson *et al*. in his study found that vitamin D were significantly lower in those diabetics who had microvascular complications.(6) Payne *et al*. showed that patients with Diabetic Retinopathy were deficient in vitamin D and that diabetic subjects, especially those with proliferative diabetic retinopathy (PDR).(7)Aksoy *et al*. also showed that the mean vitamin D3 concentrations reduced with increasing severity of diabetic retinopathy.[8] Even in a study on type 1 diabetes, Kaur *et al*. found that retinopathy prevalence was higher in cases with vitamin D deficiency versus sufficiency.[9]

Among the vitamin D deficients, 86 patients i.e. 64.2 % were found to be suffering from diabetic neuropathy whereas in vitamin D sufficient group, 44 patients i.e. 55.6% were found to have diabetic neuropathy with 'p' value of 0.005, which is statistically significant. These findings are consistent with other similar studies, done elsewhere. Chaychi *et al*. in his study found that patients with diabetic polyneuropathy had a lower mean serum vitamin D level. [10] Soderstorm *et al*. demonstrated vitamin D insufficiency is associated with the adjusted composite measure of neuropathy.[11] Lee and Chen in their study on use of vitamin D as analgesic for neuropathic pain found that all patients were vitamin D insufficient.[12]

81 (60%) patients with vitamin D deficiency were found to have diabetic nephropathy and in vitamin D sufficient patients, 20 patients (27.8%) were found to have diabetic nephropathy with a 'p' value of <0.001 which is statistically highly significant. Hence this study revealed that there is significant association between vitamin D deficiency and Diabetic nephropathy, among diabetics. Diaz *et al*. in their study found that 30.7% of adults with diabetes have nephropathy, 48.9% have vitamin D deficiency and 36.6% have vitamin D insufficiency.[13] Kim *et al*. in their study found that mean vitamin D level was 18.4 ± 9.8 in diabetic nephropathy and 86% of subjects were vitamin D insufficient and 46% were deficient.[14] Oh *et al*. demonstrated that in early stage 3 CKD mean vitamin D level was 20.4 ng/ml and 29.9% were deficient in vitamin D.[15]

The results obtained in our study compare well with those obtained in above studies. Thus in conclusion, mean vitamin D levels are significantly lower in type 2 diabetics, vitamin D deficiency (<30 ng/ml) in type 2 diabetes is significantly associated with any of the individual microvascular complications, i.e. neuropathy, retinopathy, and nephropathy and type 2 diabetics with decreasing vitamin D levels have significantly increasing prevalence of combination of microvascular complications.

Conclusion

Vitamin D is known to be an important factor in modifying the risk of Type 2 diabetes mellitus and its microvascular complications especially Diabetic retinopathy, neuropathy and nephropathy, which has been further evidenced by our study too. Based on the above results, administration of vitamin D supplements may prove to be a beneficial adjuvant therapy in mitigating neuropathy, nephropathy and retinopathy. Identifying the immune mediators having an impact on the development of these might be important, as later on these could

become the focal points of targeted therapy. However, the exact role of vitamin D in these processes requires further investigations. Until then, in the event of diabetic microvascular complications, vitamin D deficiency should definitely be estimated and, if present, vitamin D supplementation should be considered.

Limitations

We have taken the WHO recommendations as the standard for Vitamin-D levels which can be variable in case of the south-East Asian population. As there is no regional standardized value, the WHO standards have been taken as the standard markers. This may not be an appropriate standard for our Indian Population and more specifically, the Kerala population.

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