ORIGINAL ARTICLE

Association of Vitamin D Level with Diabetic Peripheral Neuropathy

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Abstract

Background: Diabetes mellitus causes a range of nerve damage referring to diabetic neuropathy. Diabetic peripheral neuropathy (DPN) affects over 132 million individuals worldwide (about 1.9% of the population). Diabetes is the largest recognized cause of neuropathy in affluent countries, and the most prevalent consequence and reason for morbidity and mortality. The deficient vitamin D value is one of the newest considerations of the development of diabetes and peripheral neuropathy.

Objective: The objective of this study was to compare vitamin D levels among Type 2 diabetes mellitus patients with/without diabetic peripheral neuropathy and to find an association of Vitamin D levels with diabetic peripheral neuropathy based on the Michigan Neuropathy Screening Instrument (MNSI) score at a tertiary care hospital, Peshawar.

Methods: A case-control study was conducted from August 2021 to October 2021 after taking approval from the ethical committee of Prime foundation Pakistan, Mercy Teaching Hospital Peshawar. Patients with type 2 diabetes were recruited and then divided into two groups using the purposive sampling technique. Type 2 diabetes with neuropathy included group A Patients (Cases), while type 2 diabetes without neuropathy included group B (Controls). Both groups had 49 study subjects each based on convenience. A physical examination was conducted to prove the diagnosis of diabetic peripheral neuropathy (DPN) using the Michigan Neuropathy Screening Instrument (MNSI). Patients screening positive on the MNSI (>2 points out of a 10-point scale) were considered neuropathic. Serum vitamin D levels were assessed in both patients (cases) and controls using a hospital laboratory and labeled as Vitamin D sufficiency (more than 30ng/ml), Vitamin D deficiency (<20 ng/ml), Higher Vitamin D (100 ng/ml) and vitamin D insufficiency (between 20 and 30 ng/ml).

Results: A total of 98 subjects were enrolled in the study with a 1:1 ratio of cases and controls. Median age [57 (IQR 52-65) *versus* 55 (IQR=48-61), p<0.001] and disease duration [10 (IQR=8-16) *versus* 7 (IQR=4-10), p<0.001] were significantly different among cases and control respectively. The proportion of patients with normal vitamin D levels was significantly lower in cases than in control (10.2% *versus* 67.3%, p<0.001). On the multivariable regression model, vitamin D levels were found to be an independent predictor of DPN with a significantly lower risk of DPN among patients with normal vitamin D levels as compared to those who had vitamin d higher than 100 ng/ml (OR=0.19, 95% CI:0.001-0.282, p=0.004).

Conclusion: Our study concluded that patients with Type 2 diabetes mellitus DPN have deficient levels of Vitamin D as assessed by Michigan Neuropathy Screening Instrument. Considerable risk of Diabetic peripheral neuropathy among patients having a deficiency of Vitamin D was proved.

Keywords: *Association, Diabetes mellitus, Diabetic peripheral neuropathy, Vitamin D, Michigan Score.*

INTRODUCTION

Diabetes mellitus (DM); is an impairment of insulin action or a decrease in insulin secretion that results in a metabolic disturbance. It is a major global health concern. As per W.H.O., the number of individuals with diabetes will be 366 million by 2030 [1]. The peripheral nervous system can be damaged in a variety of ways Neuropathy affects roughly 30% of diabetic patients, with up to 50 % developing neuropathy with time [2]. Peripheral neuropathy is a frequent consequence of DM, affecting 50 % of diabetic patients [3]. About 11% of individuals with Diabetic peripheral neuropathy (DPN) have persistent, tormenting symptoms, and it is among the leading causes of morbidity and mortality. Risk factors for Diabetic peripheral neuropathy (DPN) have been named in literature/research, including high blood glucose levels as well as Glycated hemoglobin (HB), Duration of DM, increased albumin excretion, high blood pressure, and obesity [4, 5].

Diabetes mellitus affects more than 27 million Pakistanis [6] and neuropathy affects about half of the population of Karachi Pakistan [7]. More than 1 million Pakistanis suffer from diabetic foot ulcers today, indicating the severity of the disease [8]. Vitamin D has a wide range of functions in the human body, and it is a steroid hormone. The earlier investigation has linked vitamin D to the control of bone metabolism, and other epidemiological studies have linked vitamin D to a vast number of autoimmune illnesses. Progression of type 1 and type 2 diabetes mellitus (T1DM & T2DM) may have a therapeutic impact on Vitamin D intake as it may decrease its severity [9]. 25-hydroxyvitamin D [25(OH) D] as a Vitamin D

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Received: August 01, 2022; Revised: November 22, 2022; Accepted: November 23, 2022
DOI: https://doi.org/10.37184/lnjpc.2707-3521.5.8

  ISSN: 2708-9134 (Online) Liaquat National Journal of Primary Care 2023; 5(1): 26-30

biomarker is tested in the blood of patients to monitor vitamin D levels [10]. Vitamin D deficiency is defined as a Vitamin D 25(OH) D level less than 20 ng/ml or 50 nmol/L. 25-hydroxyvitamin D concentration of 20 to 30 ng/ml (50 to 75 nmol/L) or 50 to 75 nmol/L are considered vitamin D insufficiency [11].

Evidence favoring low vitamin D levels other than causing rickets in newborns and adults leading to chondrosteoma may play a potential part in DM and its underlying disease progression [12, 13]. Deficiency of Vitamin D, a predominant symptom of diabetes along with microvascular/macrovascular complications [14]. Vitamin D deficiency is among the newest causes of the development of diabetes and peripheral neuropathy [12]. Vitamin D appears to be vital not just in preventing islet cell death but also in increasing nerve gro [12] Vitamin levels, according to research [13].

Multiple studies have also found a connection between vitamin D insufficiency and DPN in people with type 1 or type 2 diabetes [12, 15]. In Egyptian patients with T2DM, vitamin D insufficiency plays a significant impact on the severity of DPN [16]. Vitamin D insufficiency commonly affects prediabetics and could be a risk factor for painful PN among them. Improvement in glycemic indices and the severity of peripheral neuropathy linked with improved vitamin D levels [17]. According to a meta-analysis, vitamin D deficiency is associated with the onset and progression of DPN in Caucasian diabetes patients with T2DM, and diabetic patients with vitamin D deficiency are 1.22 times more likely to develop DPN than diabetic patients with normal vitamin D levels. To avoid the development of Diabetic peripheral neuropathy in people with T2DM, vitamin D supplementation is critical [18]. Meanwhile, Investigations proved a connection between vitamin D insufficiency and the neuropathy emergence in T2DM. Due to limited sample size, the disparity in methodology as well as the populace and territorial studies, no distinct result regarding the link between vitamin D levels and DPN in individuals with diabetes has been reached [19].

This study was designed to find updated data on the comparison of Vitamin D levels and (MNSI) scores among type 2 diabetes mellitus (T2DM) with and without diabetic peripheral neuropathy (DPN) as well as to see the association of Vitamin D levels with DPN. As far as our knowledge is concerned, no study has been conducted in the district of Peshawar on this topic. As type 2 diabetes mellitus is prevalent worldwide, there is a dire need to conduct this study involving this population to get knowledge and in turn, try to save the people from its consequences through awareness and lifestyle modifications.

The objective of this study was to compare vitamin D levels among Type 2 diabetes mellitus patients with/ without diabetic peripheral neuropathy and to find an association of Vitamin D levels with diabetic peripheral neuropathy based on the Michigan Neuropathy Screening Instrument (MNSI) score at a tertiary care hospital, Peshawar.

METHODS

A case-control study was conducted after taking approval from the ethical committee of Prime foundation Pakistan, Mercy Teaching Hospital, Peshawar (IRB Approval Number: Prime/IRB/2021-240). Data were collected from August 2021 to October 2021. Patients aged 40-65 years with type 2 diabetes mellitus visiting the endocrinology outpatient department (OPD) of Mercy Teaching Hospital were recruited in this study. Those patients with established complications of diabetes were excluded from the sample. Consent from the patients was obtained before the conduct of the study.

With the aid of the purposive sampling method, patients were split into two groups. Group A (Cases) included Type 2 diabetes mellitus individuals with diabetic neuropathy. Group B (Controls) included Type 2 diabetes mellitus patients without diabetic neuropathy. The sample size was calculated through an online available calculator Open-Epi by setting a confidence interval of 95% with the power of 80, OR 3.7, and the population in control is 35%. The total sample size is 90 with a 1:1 ratio of cases and controls [16].

Data was collected through a proforma. The first part has demographic variables and Vitamin D (outcome variable) while the second part is the Michigan Neuropathy Screening Instrument (MNSI) Form filled out by the principal investigator and health professional (instrument attached). Vitamin D values were recorded as Vitamin D sufficiency (more than 30 ng/ml), Vitamin D deficiency (below 20 ng/ml), Higher Vitamin D levels (100 ng/ml) and vitamin D insufficiency (between 20 and 30 ng/ml). The diagnosis of diabetic peripheral neuropathy (DPN) was confirmed by MNSI physical assessment. Inspection of the feet for deformities, dry skin, callous or infection, fissures, ulceration, ankle reflexes, vibration, and monofilament testing was performed by the principal investigator as well as the health care provider involved in the treatment of diabetes patients. Patients screening positive on the MNSI (greater than 2 points on a 10-point scale) were considered neuropathic and included in this study as Cases [20].

The data were analyzed by using SPSS version 22. Quantitative variables including age, Duration of diabetes mellitus, MNSI score, and vitamin D levels presented as mean+/- standard deviation. Shapiro Wilk test was used to check the normality of data. Logistic regression analysis was used to see the association between quantitative attributes. Qualitative variables including gender and MNSI form variables were expressed as frequencies and percentages. P-values < 0.05 was taken as significant.

RESULTS

A total of 98 study subjects were taken, and data were analyzed. Median age and diabetes duration were 56 (50-62) years and 10 (6-12) years, respectively. Table **1** displays the frequency distribution of demographic variables.

Table 1: Frequency distribution of demographic Variables (n=98).

Variables	Groups	Count	Percentage
Gender	Male	38	38.8
	Female	60	61.2
Education	Illiterate	55	56.1
	Literate	43	43.9

Median age (p=0.019), duration of diabetes (p<0.001), and MSNI score (p<0.001) were significantly higher in DPN patients as compared to patients without DPN. The frequency of vitamin d deficiency was significantly higher in DPN patients than in non-DPN patients. The proportion of DPN patients with normal vitamin D levels was significantly lower than patients without DPN (p<0.001) (**Table 2**).

In univariate analysis, age was significantly associated with DPN with a significantly lower risk among the 38-48 years age group than among 60-70 years. The odds of DPN were significantly lower in patients with normal vitamin D levels as compared to those who had higher vitamin D levels. On the multivariable regression model when the effects of other covariates were adjusted, Vitamin D levels were associated with DPN with the same direction of association observed in univariate analysis (**Table 3**).

Table 2: Comparison of median interquartile & frequency (%) of quantitative variables among Group A and Group B.

Variable	Type 2 DM with DPN (Group A) n=49 median (IQR)	Type 2 DM without DPN (Group B) n=49 median (IQR)	p-value
Age (In years)	57 (52-65)	55 (48-61)	*0.019
Duration of type 2 diabetes mellitus (in years)	10 (8-16)	7 (4-10)	**<0.001
MNSI Score (Foot Examination)	11 (9-12)	2 (1-2)	**<0.001
Vitamin D status	**Frequency (%)**	**Frequency (%)**	
Vitamin D Deficiency (0 to 19.9 ng/ml)	29 (59.2)	4 (8.2)	**<0.001
Vitamin D insufficiency (20 to 29.9 ng/ml)	10 (20.4)	2 (4.1)	
Normal Vitamin D (30 to 99.9 ng/ml)	5 (10.2)	33 (67.3)	
Higher Vitamin D levels (100 ng/ml)	5 (10.2)	10 (20.4)	

DPN: Diabetic peripheral neuropathy, DM: Diabetes mellitus, MNSI: Michigan neuropathy screening instrument
*Statistically significant at p<0.05, **Statistically significant at p<0.01

Table 3: Association of Vitamin D level with Diabetic peripheral neuropathy.

Variables	OR (95% CI)	p-value	aOR (95% CI)	p-value
Age				
38-48 years	0.196 (0.053-0.723)	0.014*	2.249 (0.172-29.417)	0.537
49-59 years	0.665 (0.273-1.1619)	0.369	3.900 (0.695-21.882)	0.122
60-70 years	Ref		Ref	
Gender				
Male	1.41 (0.624 - 3.19)	0.408	-	-
Female	Ref		-	-
Education				
Illiterate	0.660 (0.296-1.472)	0.310	-	-
Literate	Ref		-	-
Duration of diabetes				
1 to 10 Years	0.217 (0.021-2.197)	0.196	0.067 (0.001-3.948)	0.194
11 to 20 years	0.833 (0.075-9.252)	0.882	1.449 (0.026-81.478)	0.857
21 to 30 years	Ref		Ref	
Vitamin D level				
Vitamin D Deficient 0 to 19.9 ng/ml	5.8 (0.310-108.58)	0.240	14.972 (0.624-359.19)	0.095
Vitamin D insufficient 20 to 29.9 ng/ml	0.024 (0.031-3.579)	0.364	0.615 (0.040-9.429)	0.727
Vitamin D Normal 30 to 99.9 ng/ml	0.024 (0.002-0.253)	0.002*	0.19 (0.001-0.282)	0.004*
Vitamin D High greater than 100 ng/ml	Ref		Ref	

CI: Confidence interval, aOR: Adjusted odds ratio, OR: Odds ratio* Statistically significant

DISCUSSION

Diabetic neuropathy is a chronic effect of diabetes that causes significant sickness and lowers the well-being of individuals in general. Vitamin D deficiency is common in diabetic patients, and low levels are associated with the occurrence and severity of neuropathy. Diabetic patients should have their vitamin D levels evaluated because vitamin D insufficiency is connected to diabetic peripheral neuropathy (DPN) as a separate potential cause. To comprehend the causes of DPN and determine the precise role of vitamin D, more study is required [21].

Among 98(100%) study participants 45 (45.9%) belong to 49 to 59 years, 60 (61.2%) were females and 38(38.8%) were males. 55 (56.1%) were illiterate and 47(48%) had duration of diabetes mellitus 6-10 years. For vitamin D levels, Group A had 29 (59.2%) vitamin D deficiencies (0 to 19.9 ng/ml), followed by 10 (20.4%) vitamin D insufficiencies (20 to 29.9 ng/ml). In Group B, 33 (67.3%) had normal Vitamin D levels (30 to 99.9 ng/ml), 10 (20.4%) had high Vitamin D levels (greater than 100 ng/ml), in addition, only 4(8.2%) were Vitamin D Deficient (0 to 19.9 ng/ml) like our study's previous study by Seham E. Abdelsadek *et al.* in 2018, it was also revealed that 73.3 percent of the T2DM study groups and 35% of the control group overall, both had vitamin D deficiency [16]. Our results are in line with those of Bayani and colleagues [22], who found that only 10.3 percent of participants had a normal level of vitamin D, 25 percent of respondents had vitamin D insufficiency and 64.2 percent had vitamin D deficiency. Our study by Oraby MI *et al.* 2019 concluded that Vitamin D insufficiency was common among diabetes individuals with peripheral neuropathy [13]. Another study Assy MH *et al.* in 2021 showed findings in line with our study as 60% of DPN patients were vitamin D deficient [23]. Contradictory findings were observed by Halawa MR *et al.* 2021 [17]; they found for both DPN and without DPN groups, none of the clients' vitamin D levels were adequate. Both groups were deficient in vitamin D, with 79.8% and 89.9% deficient, respectively; 20.2 percent and 10.1 percent insufficient in-group A and B, respectively.

Mean Vitamin D for Group A is significantly low as compared to Group B (15.5±8.39 & 41.91±18.4 respectively) Like our study previous study by Seham E. Abdelsadek *et al.* in 2018 also found that Subjects with DPN had plasma concentrations of 25(OH) vitamin D that was lower (21.09 ± 8.38) compared to those in participants without DPN (31.12 ± 14.85) [16]. Similar to our study, another study by Noor e Jabeen in 2021 found vitamin D deficiency in Group A, with average serum vitamin D values of 17.50 5.08 ng/ml and 26.33 4.43 ng/ml, respectively [21]. In line with our findings, Oraby MI *et al.* 2019 discovered significantly lower serum vitamin D levels among Type 2 diabetes with DPN patients [13]. Moreover study by Assy MH *et al.* in 2021 also observed similar findings as mean levels were found to be 17.4 ± 10.9. 70% and 18.9 ± 8.49 among painful and without pain DPN respectively [23]. Our study's mean Vitamin D level in the patient group was 19.216 + 7.59. In contrast, the control group's average score was 34.15 ± 13.35. Chaychi *et al.* reported this in 2011 as well, with similar findings (21.36 ± 8.56 for cases and 31.68± 7.56 for controls) [24]. Vitamin D is linked to type 2 diabetic peripheral neuropathy (DPN), according to Zhang *et al.* in 2019 A lack of vitamin D can raise the chance of developing type 2 diabetic peripheral neuropathy. Peripheral neuropathy (DPN) in persons with type 2 diabetes is now treated and prevented by measuring the blood level of of 25 (OH) D [25]. Furthermore, in the present study, the odds of DPN were significantly lower in patients with normal vitamin D levels as compared to those who had higher vitamin D levels. The finding is against our expectations. This study was conducted in a single hospital of the district of Khyber Pakhtunkhwa so its results cannot be generalized to the whole population of the province. Another limitation of this study was its small sample size due to time constraints. Studies with larger sample size are needed to further explore this association.

CONCLUSION

Our study concluded that patients with Type 2 diabetes mellitus DPN have deficient levels of Vitamin D as assessed by Michigan Neuropathy Screening Instrument. Considerable risk of Diabetic peripheral neuropathy among patients having a deficiency of Vitamin D was proved.

ETHICS APPROVAL

Ethical approval was taken from the IRB of mercy Teaching Hospital. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the Helsinki declaration.

CONSENT FOR PUBLICATION

Written informed consent was taken from the participants.

AVAILABILITY OF DATA

Data is available from the corresponding author on a reasonable request.

FUNDING

No Funding.

CONFLICT OF INTEREST

None of the authors has any conflict of interest.

ACKNOWLEDGEMENTS

I am highly thankful to Dr. Muhammad Faisal Akbar (Registrar plastic surgeon, Northwest general hospital & RC, and Dr. Sobia Sabir (Endocrinologist-Mercy Hospital) who were so much cooperative with me during my entire research work period.

AUTHOR'S CONTRIBUTION

All the authors contributed to the publication of this article.

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