Clinical Study of Prevalence of Peripheral Neuropathy, Its Risk Factors and Its Association with Vitamin D3 Level in Type II Diabetes Patients

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Abstract:

Introduction: Diabetes is a major global health crisis, ranking among the leading causes of mortality worldwide, alongside cardiovascular disease, cancer, and respiratory disease. According to the WHO, noncommunicable diseases accounted for 74% of global deaths in 2019, with diabetes contributing to 1.6 million deaths, making it the ninth leading cause of death. By 2035, an estimated 592 million people may die from diabetes. Diabetic peripheral neuropathy (DPN), a common complication of Type 2 Diabetes Mellitus (T2DM), arises from chronic hyperglycemia, leading to peripheral nerve dysfunction.

Material and Methods: This prospective, cross-sectional study was conducted over a year at a tertiary care center in Gujarat to evaluate the prevalence of peripheral neuropathy in T2DM patients, identify risk factors, and assess correlations with Vitamin D3 levels. A total of 403 adult T2DM patients, diagnosed for at least one year, were recruited through systematic random sampling. Patients with other causes of peripheral neuropathy were excluded. Data were collected using structured questionnaires capturing demographic and clinical details, neuropathy assessment via the Michigan Neuropathy Screening Instrument (MNSI), and nerve conduction studies. Vitamin D3 levels were categorized as deficient, insufficient, or sufficient using chemiluminescent immunoassay, and glycemic control was assessed via HbA1c. Risk factors like age, BMI, smoking, hypertension, and dyslipidemia were analyzed. Statistical methods, including Pearson correlation and logistic regression, were used to evaluate the association between Vitamin D3 levels and neuropathy severity. Data analysis was conducted using SPSS, with p-values <0.05 considered significant.

Results: In our study, the prevalence of diabetic peripheral neuropathy (DPN) was 70% among 403 T2DM patients, primarily affecting those aged 51–60 years (50.4%). Patients with DPN were significantly older (p < 0.001), while gender showed no significant influence (p = 0.836). Hypertension, poor glycemic control (FBS: 265.91 ± 19.42 mg/dL, PPG: 285.60 ± 82.38 mg/dL, HbA1c: 9.67 ± 2.12%; p < 0.001), higher BMI, smoking, and dyslipidemia were strongly associated with DPN. Additionally, abnormal waist circumference was prevalent in 69.4% of DPN patients (p < 0.001). Vitamin D deficiency was common across both groups, though a higher proportion of sufficient Vitamin D levels (38.0%) was observed in DPN patients (p = 0.005), underscoring its potential role in DPN severity.

Conclusion: Peripheral neuropathy is a prevalent complication in diabetic patients, particularly those over 50 years of age, with no significant gender predilection. Hypertension, obesity, dyslipidemia, smoking, poor glycemic control, and Vitamin D deficiency are significant risk factors. Routine Vitamin D assessment and supplementation, alongside optimized glycemic and lifestyle management, are crucial for mitigating neuropathy risk and severity.

Keywords: Peripheral neuropathy, Type 2 diabetes mellitus, Vitamin D deficiency, Glycemic control.

Introduction

Diabetes is one of the largest global health emergencies of this century, ranking among the 10 leading causes of mortality together with cardiovascular disease (CVD), respiratory disease, and cancer. According to the World Health Organization (WHO), noncommunicable diseases (NCDs) accounted for 74% of deaths globally in 2019, of which, diabetes resulted in 1.6 million deaths, thus becoming the ninth leading cause of death globally. [1] By the year 2035, nearly 592 million people are predicted to die of diabetes. [2] Diabetic peripheral neuropathy (DPN) is a well-

known microvascular complication of type 2 diabetes mellitus attributed to chronic hyperglycemia and is defined as the presence of peripheral nerve dysfunction after exclusion of other causes. Clinically, diabetic neuropathy is a destructive disease of the peripheral nerve leading to symptoms of pain or paraesthesia or problems arising from neurological deficit. [3]

Vitamin D deficiency is a common public health problem all over the world. [4] Vitamin D deficiency contributes significantly to the pathogenesis of the two types of diabetes by impairing insulin secretion from pancreatic beta-cells5 and increasing insulin resistance. Clinical studies reported that vitamin D deficiency is more common in patients with diabetes and plays an important role in pathogenesis of diabetic neuropathies. [6] Clinical observational studies demonstrated a significant association among patients with vitamin D deficiency, and neuropathic pain symptoms, neurological deficits, autonomic dysfunction, and electrophysiological studies in diabetic patients, [7] Also, a prospective clinical study reported the improvement of neuropathic pain in DPN patients with vitamin D supplementation. [8]

Material and Methods

This clinical study was conducted as a prospective, cross-sectional analysis at a tertiary care center in Gujarat, over one year. The research focused on determining the prevalence of peripheral neuropathy among Type II Diabetes Mellitus (T2DM) patients, identifying associated risk factors, and assessing its correlation with Vitamin D3 levels.

The study included adult patients aged 18 years and above diagnosed with T2DM for at least one year. Participants with other causes of peripheral neuropathy, such as chronic alcohol consumption, chronic kidney disease, or hypothyroidism, were excluded. A total of 403 participants were recruited through systematic random sampling from the outpatient department and inpatient wards of the hospital.

Comprehensive data were collected using structured questionnaires, which included demographic details, clinical history, and diabetes duration. Neuropathy was assessed using the Michigan Neuropathy Screening Instrument (MNSI) and nerve conduction studies. Serum Vitamin D3 levels were measured through a chemiluminescent immunoassay, and values were categorized as deficient (<20 ng/mL), insufficient

(20–30 ng/mL), or sufficient (>30 ng/mL). Glycemic control was evaluated using HbA1c levels.

Risk factors analyzed included age, gender, body mass index (BMI), glycemic control (HbA1c), duration of diabetes, smoking status, and comorbidities such as hypertension and dyslipidemia. The association between Vitamin D3 levels and neuropathy severity was evaluated using statistical methods, including Pearson correlation and logistic regression analysis.

All data were analyzed using SPSS software, with descriptive statistics presented as mean ± standard deviation or percentages. Categorical data were compared using the chi-square test, while continuous variables were analyzed using independent t-tests or ANOVA. The strength of associations between risk factors and peripheral neuropathy was assessed through multivariate regression. A p-value of <0.05 was considered statistically significant.

Results

In our study, the prevalence of diabetic peripheral neuropathy was observed in 70% of the total 403 Type II diabetes mellitus patients, highlighting its significant burden. Patients with diabetic neuropathy were significantly older than those without, with a highly significant p-value of <0.001. The majority of affected patients were aged between 51–60 years (50.4%), followed by 61–70 years (21.5%), while no cases were reported in individuals below 40 years of age. Notably, only 2.5% of patients aged above 80 years had diabetic neuropathy. The sex distribution showed a slightly higher prevalence among males (50.4%) compared to females (49.6%); however, this difference was not statistically significant (p = 0.836), indicating that gender does not play a major role in neuropathy prevalence. Hypertension emerged as a significant risk factor, with 57% of patients with diabetic neuropathy being hypertensive, and this association was strongly supported by a p-value of <0.001.

The table 1 compares glycemic parameters, including fasting blood sugar (FBS), postprandial glucose (PPG), and HbA1c levels, between patients with and without diabetic peripheral neuropathy (DNP). Patients with DNP demonstrated significantly higher values for all glycemic parameters compared to those without, as indicated by the p-values, suggesting poor glycemic control as a contributing factor to neuropathy.

Table 1: Glycemic Parameters between Patients with and Without Diabetic Peripheral Neuropathy

Glycemic Parameter	DNP: Yes (Mean ± SD)	DNP: No (Mean ± SD)	P-value
FBS (mg/dL)	265.91 ± 19.42	125.29 ± 7.90	0.001
PPG (mg/dL)	285.60 ± 82.38	146.37 ± 43.94	0.001
HbA1c (%)	9.67 ± 2.118	7.091 ± 0.156	0.004

In our study, diabetic peripheral neuropathy (DNP) was significantly associated with higher BMI, smoking status, and dyslipidemia. Among BMI groups, 37.2% of patients with DNP were obese, and 30.6% were overweight, compared to 3.9% and 17.4%, respectively, in patients without DNP. In contrast, healthy weight individuals comprised 72.0% of patients without DNP and only 32.2% of those with DNP, with no underweight cases observed in the DNP group (p < 0.001). Smoking was another significant factor, with 28.1% of smokers showing DNP, compared to 15.2% of non-smokers, highlighting a significant association (p = 0.003). Dyslipidemia also showed a strong correlation, with 66.1% of patients with DNP having dyslipidemia, compared to only 6.7% in those without DNP (p < 0.001). In our study, waist circumference (WC) was also significantly associated with diabetic peripheral neuropathy (DNP), as 69.4% of patients with DNP had abnormal WC compared to 27.7% without DNP, while 72.3% of patients with normal WC did not have DNP (p < 0.001). The table 2 compares 25-OH Vitamin D levels between patients with and without diabetic peripheral neuropathy (DNP). The majority of patients in both groups were Vitamin D deficient; however, a higher proportion of sufficient Vitamin D levels was observed in patients with DNP (38.0%) compared to those without (33.3%), with a statistically significant association (p = 0.005).

Table 2: Comparison of 25-OH Vitamin D Levels with Diabetic Peripheral Neuropathy

25-OH Vit-D Group	DNP: No (Count, %)	DNP: Yes (Count, %)	Total (Count, %)	P-value
Deficient	188 (66.7%)	75 (62.0%)	263 (65.3%)	0.005
Sufficient	94 (33.3%)	46 (38.0%)	140 (34.7%)	

Discussion

DM and its related complications are increasing worldwide. DPN is considered a major micro-vascular complication, which is estimated to affect up to half of these diabetic patients and represent a main cause of mortality and morbidity in these patients. [9]

Diabetic neuropathy is the most common neuropathy in developing countries. In present study incidence of diabetic peripheral neuropathy was 30%. Prevalence is a function of disease duration, and a reasonable figure, based upon several large studies, is that approximately 50 percent of patients with diabetes will eventually develop neuropathy. [10,11] In study by Katulanda et al. reported the prevalence of DPN according to DNS score among all patients, patients with already established diabetes and newly diagnosed patients were 48.1%, 59.1% and 28.8% respectively. [12] Regarding the prevalence of diabetic neuropathy in T2DM, this was 32.1% in a study performed in the UK, and in the patients over 60 the prevalence was over 50%. [13] The prevalence of diabetic peripheral neuropathy among youths with type 1 diabetes (mean age 15.7 years) was 8.2% in the SEARCH for Diabetes in Youth Study. [14] The possible explication is that, in T2DM, other factors besides hyperglycaemia are implicated in the development and progression of diabetic neuropathy. It appears that metabolic syndrome and its components, obesity, hypertriglyceridemia, low HDL-cholesterol and arterial hypertension are independent factors of diabetic neuropathy. [15] In present study, patients with diabetic peripheral neuropathy were significantly older than those without diabetic peripheral neuropathy. Diabetic peripheral neuropathy was not reported in patients below 40 years of age whereas 2.5% of the patients older than 8-0 years had diabetic peripheral neuropathy in present study. In Bondar et al. [16] study, patients with T2DM had an average age of 56.8 years and the prevalence of diabetic neuropathy was 50.70%, these results being very close to those from the our study. In the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial, peripheral neuropathy was present in 42% of adults with type 2 diabetes at baseline. [17] The burden of diabetic peripheral neuropathy is higher in older age and among adults with long-standing type 1 or type 2 diabetes. [14–16] Most estimates suggest that approximately 50% of adults with diabetes will be affected by diabetic peripheral neuropathy over the course of their lifetime. [18,19]

In present study, hypertension was one of the significant risk factors for developing diabetic peripheral neuropathy in diabetes patients as revealed by the significant p value of <0.001 in 57% of the study subjects. However, the role of hypertension in DPN remains uncertain. [20] A significant relationship has been found between hypertension and the incidence of neuropathy in

patients with type 1 diabetes (T1DM) [15] but not in those with type 2 diabetes (T2DM). [21–23] The current evidence also supports an association between hypertension and neuropathy in T1DM but not in T2DM. [24]

In our study, patients with diabetic peripheral neuropathy had significantly higher fasting blood sugar level (265.91±19.42 mg/dL; p=0.001), post prandial glucose level (285.60±82.38 mg/dL; p=0.001) and glycated hemoglobin (9.67±2.11 %; p=0.004) as compared to those without diabetic peripheral neuropathy. Randomized clinical trials have demonstrated the benefit of glucose control of slowing the progression of microvascular disease in diabetes, including peripheral neuropathy.25 In the DCCT trial of 1,441 adults with type 1 diabetesy, intensive insulin therapy (versus conventional therapy) reduced the risk of clinical neuropathy by 60% after 6.5 years of follow-up. [26] The benefits of strict glycemic control persisted long-term, as demonstrated in the observational follow-up of the DCCT/EDIC participants, with a reduction in the risk of diabetic peripheral neuropathy in the intensively treated versus conventional group that persisted after the end of the trial (relative risk reduction of 30% during years 6.5 to 14). [27]

In a recent Cochrane review and meta-analysis of data from 17 randomized trials (7 in people with type 1 diabetes, 8 in people with type 2 diabetes, and 2 in both types) evaluating the association of glucose control with diabetic peripheral neuropathy, enhanced glucose control significantly reduced the risk of clinical neuropathy as well as nerve conduction and vibration threshold abnormalities in type 1 diabetes. The risk of clinical neuropathy was also reduced in type 2 diabetes, although this was not statistically significant (P=0.06). [23]

In present study patients with diabetes with diabetic peripheral neuropathy were overweight (30.6%) and obese (37.2%) than those without diabetic peripheral neuropathy. The association was significant with p value of <0.001. In study by Oh et al. [28] showed among 65 subjects, 44.6% were diagnosed with DPN. Subjects with DPN had higher body mass index and waist circumference than subjects without DPN.

Body composition data showed that fat mass, fat percent, and visceral fat area were higher in subjects with DPN than in subjects without DPN. Previous studies have been reported higher body mass index (BMI) independently associated with the development of polyneuropathies. [29] Both hypertriglyceridemia and obesity increased neuropathy risk two fold, whereas having ≥ 3 risk factors increased risk 3 fold. [30] These risk relationships became more robust when

considering patients with otherwise well controlled diabetes, yielding risk ratios of 4. [30]

The association of elevated fasting triglycerides with DPN supports the emerging idea that hyper-triglyceridaemia contributes to the development and the progression of diabetic neuropathy. [31] Elevated serum triglycerides are commonly associated with insulin resistance and represent a valuable clinical marker of the metabolic syndrome and the resultant atherogenic potential could contribute towards the progression of DPN. [15] On comparing the 25-OH Vit-D in diabetes patients with and without diabetic peripheral neuropathy it was found that majority of the patients with diabetic peripheral neuropathy had 25-OH Vit-D deficiency as revealed by the significant p value of 0.005.

The systematic review and meta-analysis by Qu et al. [32] explored how vitamin D level measured in human blood sample affected the development of DPN in diabetic patients. From the result, there was severe heterogeneity in those ten studies (I2 = 94.1%) to assess the correlation between 25(OH) D level and DPN.

However, after subgroup analysis by study design and race, the heterogeneity was reduced significantly. The cause of these changes may be caused by the low quality study designs and the different regions of studies. When we calculated the standardized mean difference (SMD) of included articles, we found that there was an obvious association between vitamin D and DPN in Caucasian, but no obvious correlation between vitamin D and DPN was observed in Asian.

However, after analyzed all reported OR values of four studies, finally, we find that diabetic patients with vitamin D deficiency are 1.22 times suffering from DPN than those patients without vitamin D deficiency in Asian. Thus, vitamin D may be a high risk factor for the occurrence of DPN in diabetic patients. A previous meta-analysis also has demonstrated that vitamin D is involved in the development of DPN, and vitamin D deficiency is very likely to be associated with increased risk of DPN.33 Appropriate vitamin D supplements can be an effective measurement to prevent the development of DPN in diabetic patients.

Limitations of the current study are the small sample size, lack of quantification of sunlight exposure or daily activity and comparison with a non-neuropathic diabetic cohort.

Conclusion

Peripheral neuropathy is a common complication observed in both diabetic and prediabetic individuals, with a higher prevalence among elderly diabetic patients over 50 years of age. The condition affects both sexes equally, with no

observed gender predilection. Hypertension, obesity, and dyslipidemia significantly contribute to the risk of developing peripheral neuropathy in diabetics, highlighting the importance of addressing these modifiable factors. Additionally, smokers and individuals with poorly controlled blood sugar, as indicated by higher HbA1c values, are at increased risk. Emerging evidence, including findings from this study, underscores the independent association of Vitamin D deficiency with peripheral neuropathy. Vitamin D levels also correlate with neuropathy severity, supporting the recommendation for routine assessment of 25-OH Vitamin D levels in diabetic patients and appropriate supplementation in cases of insufficiency, alongside optimized blood sugar control and lifestyle interventions.

Bibliography

1. Becker R, Silvi J, Ma Fat D, L'Hours A, Laurenti R. A method for deriving leading causes of death. Bull World Health Organ. 2006; 84(4):297–304.

2. Tao Z, Shi A, Zhao J. Epidemiological perspectives of diabetes. Cell Biochem Biophys. 2015; 73(1):181–5.

3. Veves A, Backonja M, Malik RA. Painful diabetic neuropathy: epidemiology, natural history, early diagnosis, and treatment options. Pain Med. 2008; 9(6):660–74.

4. Hilger J, Friedel A, Herr R, Rausch T, Roos F, Wahl DA, et al. A systematic review of vitamin D status in populations worldwide. Br J Nutr. 2014; 111(1):23–45.

5. Reis A, Hauache O, Velho G. Vitamin D endocrine system and the genetic susceptibility to diabetes, obesity and vascular disease. A review of evidence. Diabetes Metab. 2005; 31(4):318–25.

6. Bell DS. Reversal of the symptoms of diabetic neuropathy through correction of vitamin D deficiency in a type 1 diabetic patient. Case Rep Endocrinol. 2012; 2012.

7. Soderstrom L, Johnson S, Diaz V, Mainous Iii A. Association between vitamin D and diabetic neuropathy in a nationally representative sample: results from 2001–2004 NHANES. Diabet Med. 2012; 29(1):50–5.

8. Lee P, Chen R. Vitamin D as an analgesic for patients with type 2 diabetes and neuropathic pain. Arch Intern Med. 2008; 168(7):771–2.

9. Cannell JJ, Grant WB, Holick MF. Vitamin D and inflammation. Dermatoendocrinol. 2014; 6(1):e983401.

10. Sun J, Wang Y, Zhang X, Zhu S, He H. Prevalence of peripheral neuropathy in patients with diabetes: A systematic review and meta-analysis. Prim Care Diabetes. 2020; 14(5):435–44.

11. Sobhani S, Asayesh H, Sharifi F, Djalalinia S, Baradaran HR, Arzaghi SM, et al. Prevalence of diabetic peripheral neuropathy in Iran: a systematic review and meta-analysis. J Diabetes Metab Disord. 2014; 13(1):1–7.

12. Katulanda P, Ranasinghe P, Jayawardena R, Constantine GR, Sheriff M, Matthews DR. The prevalence, patterns and predictors of diabetic peripheral neuropathy in a developing country. Diabetol Metab Syndr. 2012; 4(1):1–8.

13. Young M, Boulton A, MacLeod A, Williams D, Sonksen P. A multicentre study of the prevalence of diabetic peripheral neuropathy in the United Kingdom hospital clinic population. Diabetologia. 1993; 36(2):150–4.

14. Jaiswal M, Lauer A, Martin CL, Bell RA, Divers J, Dabelea D, et al. Peripheral neuropathy in adolescents and young adults with type 1 and type 2 diabetes from the SEARCH for Diabetes in Youth follow-up cohort: a pilot study. Diabetes Care. 2013; 36(12):3903–8.

15. Tesfaye S, Chaturvedi N, Eaton SE, Ward JD, Manes C, Ionescu-Tirgoviste C, et al. Vascular risk factors and diabetic neuropathy. N Engl J Med. 2005; 352(4):341–50.

16. BONDAR AC, POPA AR. Diabetic neuropathy prevalence and its associated risk factors in two representative groups of type 1 and type 2 diabetes mellitus patients from Bihor County. Maedica. 2018; 13(3):229.

17. Gislén A, Dacke M, Kröger RH, Abrahamsson M, Nilsson DE, Warrant EJ. Superior underwater vision in a human population of sea gypsies. Curr Biol. 2003; 13(10):833–6.

18. Taylor R. Insulin resistance and type 2 diabetes. Diabetes. 2012; 61(4):778–9.

19. Boulton AJ. The pathway to foot ulceration in diabetes. Med Clin. 2013; 97(5):775–90.

20. Ziegler D, Papanas N, Vinik AI, Shaw JE. Epidemiology of polyneuropathy in diabetes and prediabetes. Handb Clin Neurol. 2014; 126:3–22.

21. Pradeepa R, Mohan V. Prevalence of type 2 diabetes and its complications in India and economic costs to the nation. Eur J Clin Nutr. 2017; 71(7):816–24.

22. Kamenov ZA, Parapunova RA, Georgieva RT. Earlier development of diabetic neuropathy in men than in women with type 2 diabetes mellitus. Gend Med. 2010; 7(6):600–15.

23. Callaghan BC, Little AA, Feldman EL, Hughes RA. Enhanced glucose control for preventing and treating diabetic neuropathy. Cochrane Database Syst Rev. 2012; (6).

24. Grisold A, Callaghan BC, Feldman EL. Mediators of diabetic neuropathy-is hyperglycemia the only culprit? Curr Opin Endocrinol Diabetes Obes. 2017; 24(2):103.

25. Ang L, Jaiswal M, Martin C, Pop-Busui R. Glucose control and diabetic neuropathy: les-

sons from recent large clinical trials. Curr Diab Rep. 2014; 14(9):1–15.

26. Nathan D, Genuth S, Lachin J, Cleary P, Crofford O, Davis M, et al. The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. N Engl J Med. 1993; 329(14):977–86.

27. Martin C, Albers J, Pop-Busui R. DCCT/EDIC Research Group: Neuropathy and related findings in the diabetes control and complications trial/epidemiology of diabetes interventions and complications study. Diabetes Care. 2014; 37(1):31–8.

28. Oh TJ, Lee JE, Choi SH, Jang HC. Association between body fat and diabetic peripheral neuropathy in middle-aged adults with type 2 diabetes mellitus: a preliminary report. J Obes Metab Syndr. 2019; 28(2):112.

29. Jambart S, Ammache Z, Haddad F, Younes A, Hassoun A, Abdalla K, et al. Prevalence of painful diabetic peripheral neuropathy among patients with diabetes mellitus in the Middle East region. J Int Med Res. 2011; 39(2):366–77.

30. Smith AG, Singleton JR. Obesity and hyperlipidemia are risk factors for early diabetic neuropathy. J Diabetes Complications. 2013; 27(5):436–42.

31. Wiggin TD, Sullivan KA, Pop-Busui R, Amato A, Sima AA, Feldman EL. Elevated triglycerides correlate with progression of diabetic neuropathy. Diabetes. 2009; 58(7):1634–40.

32. Qu GB, Wang LL, Tang X, Wu W, Sun YH. The association between vitamin D level and diabetic peripheral neuropathy in patients with type 2 diabetes mellitus: An update systematic review and meta-analysis. J Clin Transl Endocrinol. 2017; 9:25–31.

33. Lv W, Zhao W, Gong S, Fang D, Wang B, Fu Z, et al. Serum 25-hydroxyvitamin D levels and peripheral neuropathy in patients with type 2 diabetes: a systematic review and meta-analysis. J Endocrinol Invest. 2015; 38(5):513–8.