Original Research Article

Study to Assess Various Glycaemic Parameters and Diabetic Peripheral Neuropathy in Patients with Diabetes Mellitus.

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Abstract

Introduction: Chronic hyperglycemia in type 2 diabetes mellitus is associated with macrovascular and microvascular complications. Peripheral neuropathy is one of the known complications of type 2 diabetes.

Objective: To assess correlation between glycemic parameters and age and duration of diabetes with peripheral neuropathy in type 2 diabetes mellitus.

Material and methods: In this observational study, correlation of vibration perception threshold (VPT) was estimated with glycemic parameters i.e. fasting blood glucose (FBG), post-prandial blood glucose (PPG) and glycosylated hemoglobin le (HbA1c) and age and duration of diabetes in patients with type 2 diabetes. Patients were categorized into normal (VPT <15 mV), mild (VPT >15-25 mV), moderate (VPT 26-40 mV), and severe (VPT > 40 mV) types of peripheral neuropathy.

Results: One hundred and ten patients [mean age 59.55 years; mean body mass index (BMI) 24.21 kg/m2; males 63.64%] were included. Significantly higher percentage of patients with BMI $\geq$30 kg/m2 had moderate to severe abnormality in VPT compared to those with BMI $\leq$30 kg/m2 (p=0.0347).There was no significant difference in the severity of results based on the duration of diabetes less than or more than 10 years (p=0.367).Significant difference in VPT was observed in patients with FBG < 160 mg/dl versus > 160 mg/dl (p=0.049), PPG <250 mg/dl versus > 250 mg/dl (p<0.0001) and HbA1 c <10% versus > 10% (p=0.00039).

Conclusion:BMI and glycemic parameters (FBG, PPG and HbA1c) are significantly associated with severity of VPT in patients with type 2 diabetes mellitus.

Keywords: distal peripheral neuropathy, BMI, type 2 diabetes, macrovascularcomplications.

Introduction

Diabetes mellitus (DM) is a chronic disease of hyperglycemia associated with metabolic syndrome, characterized by insulin resistance. [1] Long-standing DM affects many organs leading to severe complications of retinopathy, nephropathy and neuropathy.[2]

Diabetic peripheral polyneuropathy (DPN), which includes peripheral nerve damage, is one of the most common complications of DM, affecting approximately 8% of newly diagnosed patients and more than 50% of patients with long-term DM.[3] More than 80% of amputations occur after ulceration or injury, which can result from diabetic neuropathy.[4] Diabetic patients are 15 times more likely to have an amputation than non-diabetic patients. Early identification of DPN prevents the morbidity and mortality due to diabetic neuropathy.[5]

Assessment of vibration perception threshold (VPT) is one of the recommended standardized quantitative sensory testing methods employed in the diagnosis of DPN.[6] Elevated VPT is an effective predictor of neuropathic foot ulceration, one of the most common causes for hospital admission and lower limb amputations among patients with diabetes.[7]

Plasma glycosylated hemoglobin (HbA1c) is as an index of average glycemic control over the previous 2–3 months and indicates poor diabetic control; furthermore, increased HbA1c concentration is the most important risk factor for predicting DM complications. Maintaining an HbA1c level below 6.5% is critical to decrease the incidence of diabetic complications.[8] Many investigators have examined the correlation of HbA1c levels with DM complications. However, very little research has focused on the critical HbA1c level in diabetic peripheral polyneuropathy.

Hence the aim of the study was to assess the various glycaemic parameters such as fasting blood glucose, post-prandial blood glucose and glycosylated haemoglobin as well as age and duration of diabetes with diabetic peripheral neuropathy in known cases of type 2 diabetes mellitus.

Material and methods:

In this observational, cross-sectional study, patients with diabetes mellitus diagnosed based on American Diabetes Association classification[9] from outpatient department were included. Convenience sampling was used for enrollment of patients. Patients with ulcers or amputation, other diseases affecting peripheral nerve function including malnutrition, alcoholism, familial and chronic liver disease, chronic kidney disease, kidney transplantation, nondiabetic nephropathy kidney diseases, clinical evidence of any other peripheral nerve lesions, lumbosacral radiculopathy, lumbar canal stenosis, patients with cardiac pacemaker or cardiac rhythm abnormalities, unstable medical state such as acute cerebrovascular events, acute coronary events, Charcot foot, thyroid function abnormalities, vitamin B12 deficiency and pregnant women were excluded.

After clinical examination, patients underwent laboratory parameters for estimation of fasting blood glucose (FBG), post-prandial blood glucose (PPG) and glycosylated hemoglobin level (HbA1c).

Vibration perception threshold (VPT) was tested using digital biothesiometer (Biothezi VPT, Kody Medical Electronic Pvt Ltd, India). VPT was measured at six different places (First toe, first, third and fifth metatarsal head, ankle and heal) on both feet. Average of the twelve

readings was considered for analysis. Subjects were initially familiarized with the sensation by holding the probe against the distal palmar surface of hand. VPT was then measured at the distal plantar surface of both soles. The voltage was slowly increased at the rate of 1 mV/sec and the VPT value was defined as the voltage level when the subject indicated that he or she first felt the vibration sense. Patients were rated as having normal vibration perception (VPT <15 mV), mild (VPT >15-25 mV), moderate (VPT 26-40 mV), and severe (VPT > 40 mV).[10] Correlation of VPT with glycemic parameters was estimated. The study was performed from December 2019 to August 2020. Ethics committee approval was obtained before patient enrolment. Informed consent was obtained by patients before enrolling the patients.

Statistical analysis:
Continuous data are presented as mean ± standard deviation whereas categorical data are presented as frequency and percentages. Unpaired t test was used to compare difference in the continuous variables between two groups. Chi-Square test was used for comparison of categorical parameters between groups. Pearson Correlation was used for examining correlation between VPT and glycemic parameters. P value of less than 0.05 was considered as statistically significant.

Results:

Table 1: Baseline characteristics

Parameter	Result
Mean (SD) age in years	59.55 (10.24) (Range 38-78) years
Male n (%)	70 (63.64%)
Female n (%)	40 (36.36%)
Mean (SD) BMI in kg/m2	24.21 (4.76) (Range 13.60-36.78)
Mean (SD) duration of diabetes in years	13.91 (6.02) (Range 3-32) years
Mean (SD) fasting blood glucose mg/dl	188.11 (45.34) (Range 110-287) mg/dl
Mean (SD) postprandial blood glucose mg/dl	250.35 (59.03) (Range 145-389)
Mean (SD) HbA1c	10.78 (2.76) (Range 6-18.4)

BMI: Body mass index; HbA1c: Glycosylated hemoglobin; SD: Standard deviation

Table 2: Gender wise distribution of baseline characteristics

| Parameter	Male (n=70)	Female (n=40)
Mean (SD) age in years	59.37 (10.53) (Range 39-78)	59.87 (9.81) (Range 38-78)
Mean (SD) BMI in kg/m^2	24. 87 (5.18) (Range 13.60-36.78)	23.06 (3.70) (Range 15.46-31.09)
Mean (SD) duration of diabetes in years	14.57 (6.51) (Range 4-32)	12.75 (4.91) (Range 3-24)
Mean (SD) fasting blood glucose mg/dl	185.44 (43.08) (Range 110-287)	192.77 (49.27) (Range 118-287)
Mean (SD) postprandial blood glucose mg/dl	251.54 (58.78) (Range 145-385)	248.27 (60.16) (Range 150-389)
Mean (SD) HbA1c	10.94 (2.99) (Range 6-18.4)	10.52 (2.34) (Range 6.6-16.2)
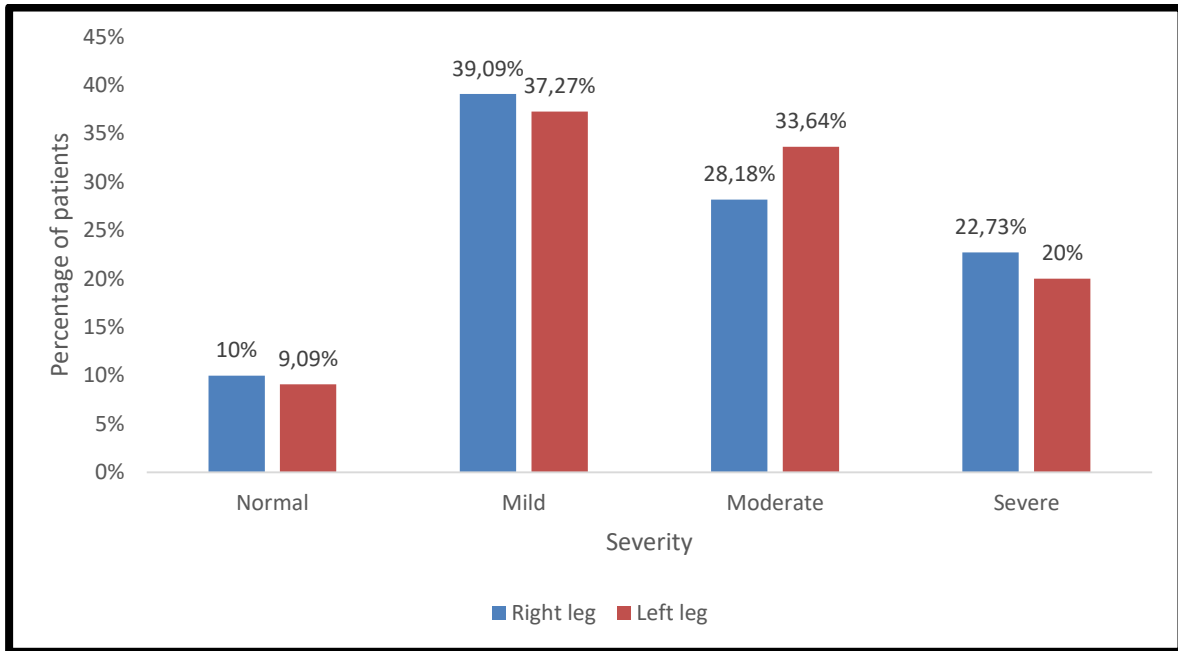
Figure 1: Severity of vibration test in study participants

Table 3: Distribution of cases with vibration test results based on BMI andduration of diabetes

	Normal/Mild	Moderate-severe
BMI		
<30 kg/m2 (n=100)	55 (55%)	45 (45%)
≥30 kg/m2 (n=10)	2 (20%)	8 (80%)
Duration of diabetes		
<10 years (n=28)	14 (50%)	14 (50%)
≥10 years (n=82)	33 (40.24%)	49 (59.76%)

Table 4: Distribution of cases with vibration test results based on the glycemicparameters

	Normal/Mild	Moderate-severe
Fasting blood glucose level		
<160 mg/dl (n=40)	22 (55%)	18 (45%)
≥160 mg/dl (n=70)	25 (35.71%)	45 (64.29%)
Post-prandial blood glucose level		
<250 mg/dl (n=57)	35 (61.40%)	22 (38.60%)
≥250 mg/dl (n=53)	13 (24.53%)	40 (75.47%)
Glycosylated haemoglobin (HbA1c)		

| <10 (n=50) | 31 (62%) | 19 (38%) |
| >10 (n=60) | 17 (28.23%) | 43 (71.67%) |

Discussion
About one third of diabetic people are at risk of foot ulceration because of loss of protective sensation due to peripheral neuropathy. The symptoms of neuropathy and the conventional assessment of it with Cotton wool, Vibrating tuning fork, pin prick and hot and cold sensation can give a qualitative diagnosis. Diabetic neuropathy increases the risk of myocardial infarction and reduces the life span, resulting in death of 25–50% of patients within 5-10 years of disease existence.[2]

DPN is one of the most commonly occurring major complications of diabetes. The disease may manifest in several clinical patterns: most frequently as distal symmetrical sensory polyneuropathy. Guidelines are available for the diagnosis of DPN by the primary care physician. These recommend that a review of diabetic patients, including a questionnaire and inspection and neurological examination of the feet, is undertaken annually. Techniques used for studying the disease process in clinical trials may include nerve conduction and quantitative sensory function tests, autonomic nervous system testing, post-ganglionic sudomotor function and skin biopsy. Current therapies for managing DPN are strict glycemic control, palliative treatments and foot ulcer prevention. Future treatments aim to beneficially affect the underlying disease pathology and putative agents are currently being investigated.

The purpose of the current study was to assess the diabetic peripheral polyneuropathy with respect to age and the duration of the DM and various glycemic parameters which are routinely done in the outpatient basis. It can also be used to verify their value as a screening tool to diagnose diabetic polyneuropathy.

In this study, a total of 110 patients were included. Of them, 70 (63.64%) were male patients and 40 (36.36%) were females. The mean age of patients in the study was 59.55 years. The mean body mass index of the patients in the study was 24.21 kg/m^2. Mean fasting blood glucose, postprandial blood glucose and HbA1c levels were found out. (Table 1)

Gender wise distribution of baseline characteristics is shown in table 2. There was no significant difference in the age (p=0.805), BMI (p=0.054), duration of diabetes (p=0.127), fasting blood glucose (p=0.417), postprandial blood glucose level (p=0.781) and HbA1c (p=0.453) between male and female patients.

In present study vibration perception threshold (VPT) was tested using digital biothesiometer. Francisco Javier DM et al in their study noted that the relative reliability results of the vibration perception threshold test in people with type 2 diabetes mellitus is excellent, both for the general group and for the sex and obesity subgroups.[11]

Catherine L. Martin et al determined VPT in 1,177 adults with type 1 diabetes and found that abnormal VPT was associated with older age. They concluded that VPT was a sensitive measure of confirmed clinical neuropathy (87%) and of definite clinical neuropathy (80%) and a specific measure of abnormal nerve conduction (62%).[12]
Hwu CM et al carried out a study in 1400 healthy and 273 diabetic. VPT was higher in diabetic subjects as compared to nondiabetics.[13]

Jay M Sosenko et al measured the vibratory perception threshold in young type I diabetic patients (N = 55) and nondiabetic control subjects (N = 34) of similar age. Values were significantly higher in the diabetic patients (P < 0.01) especially postpubertal group and persisted with allowances for age and gender in an analysis of covariance.[14]

Figure 1 shows the distribution of normal and abnormal vibration test (based on the severity) in right and left leg. A total of 11 (10%) and 10 (9.09%) patients had normal vibration test in right and left leg respectively. In the right leg 31 (28.18%) and 25 (22.73%) patients had moderate and severe abnormality whereas 43 (39.09%) patients had mild abnormality. In left leg, 37 (33.64%) and 22 (20%) patients had moderate and severe abnormality respectively whereas 41 (27.27%) patients had mild abnormality.

With reference to table 3, significant difference in the severity of VPT results based on BMI was observed. Significantly higher percentage of patients with BMI 30 or more had moderate to severe abnormality in vibration test compared to those with BMI of less than 30 kg/m2 (Chi-square test p=0.0347).

Hwu CM et al in his study observed that BMI was positively associated with VPT in men.[13]
Dan Ziegler et al noted that abdominal obesity may constitute important targets for strategies to prevent diabetic polyneuropathy.[15]

Shan Gao et al in their study found that obesity was associated with an increased risk of neuropathy. The question arises whether weight reduction in individuals who are overweight or with obesity by interventions, such as lifestyle modification or bariatric surgery, have an influence on the prevention of neuropathy.[16]

There was no significant difference in the severity of results based on the duration of diabetes less than or more than 10 years (Chi square test p=0.367) as shown in table number 3.
Jay M Sosenko et al measured the vibratory perception threshold in young type I diabetic patients (N = 55) and nondiabetic control subjects (N = 34) of similar age. There found associations of the vibratory perception threshold with diabetes duration (r = 0.36, P < 0.01).[14]

The development and long term progression of diabetic peripheral neuropathy was studied by D V Coppini et al using vibration perception threshold (VPT) as a validated measure in three hundred and ninety-two patients. Over 80% retained a "normal" VPT after a mean diabetes duration of 16 years despite only average glycaemic control, suggesting that non-ideal long term glycaemic control leads to neuropathy in a subset of predisposed patients.[17]
Lakshmana Kumar N et al showed duration of diabetes was associated with DPN in urban and rural population.[18]

There was significant difference in the vibration test between those with fasting blood glucose level of less than 160 mg/dl versus more than 160 mg/dl (Chi square t test p=0.049), post-prandial blood glucose of less than 250 mg/dl versus more than 250 mg/dl (Chi square t test p<0.0001) and HbA1 c of less than 10% versus more than 10% (Chi square test p=0.000392; Table 4).

Lakshmana Kumar N et al observed that fasting plasma glucose and HbA1C, were associated with DPN. However, according to them age and HbA1C are strong predictors of changes in VPT.[18]

According to Dan Ziegler et al, the prevalence of polyneuropathy is slightly increased in individuals with impaired glucose tolerance (IGT) and impaired fasting glucose (IFG) compared with those with normal glucose tolerance (NGT).[15]

C E Kullberginvestigated the impact of long-term glycaemic control, assessed as HbA1c for 5 years or more, on vibration perception threshold (VPT) in Type 1 (insulin-dependent) diabetes. Impaired VPT was strongly associated with high long-term HbA1c.[19]

Jay M Sosenko et al observed a highly significant positive relationship between the vibratory perception threshold and hemoglobin A_1 in postpubertal diabetic patients (r = 0.72, P < 0.001).[14]

A study was done byWon-Jae Lee et al showsIncreased HbA1c level indicative of a state of chronichyperglycemia was a risk factor for polyneuropathy in diabetic patients and a quantitative measure of its severity.[20]

While P.Jayaprakash, A. B et al shows Vibration perception threshold (VPT) is considered as a gold standard for diagnosis of diabetic peripheral neuropathy. He observed observed significant correlations between the VPT score and the DNE (Diabetic Neuropathy Examination)(r = 0.532, *P*<0.001) and DNS (Diabetic Neuropathy Symptom) (r = 0.546, *P*<0.001) scores of 1044 patients.[21]

According to Solomon Tesfaye & Dinesh Selvarajah et al Glycaemic control is the central component of treatment, but it is difficult to achieve for many patients because cardiovascular risk factors play a major role in diabetes and the pathogenesis of DPN, they should be controlled as well.[22]

Our study is associated with some limitations. Considering single center study, small sample size and no follow up, results of our study should be carefully extrapolated. Larger, prospective studies are necessary to confirm these findings. Moreover, evaluation lipid profile, blood pressure and ankle brachial index may help in detailed evaluation.

Conclusion:
Management of neuropathic complications in diabetes poses significant clinical challenge. Symptomatic treatments are beneficial but may be insufficient. These complications severely affect the quality of life in patients especially in late stages. Early screening and diagnosis of neuropathic complications assumes crucial importance.

References:
1. Gallagher EJ, Leroith D, Karnieli E. The metabolic syndrome: from insulin resistance to obesity and diabetes.Med Clin North Am 2011;95:855-73.
2. Gionfriddo MR, McCoy RG, Lipska KJ. The 2013 American Association of Clinical Endocrinologists' diabetes mellitus management recommendations: improvements needed. JAMA Intern Med 2014; 174: 179-80.
3. Deli G, Bosnyak E, Pusch G, Komoly S, Feher G. Diabetic neuropathies: diagnosis and management. Neuroendocrinology 2013; 98: 267-80.
4. Boulton AJM, Vinik AI, Arezzo JC, Bril V, Feldman EL, Freeman R, et al. Diabetic neuropathies: a statement by the American Diabetes Association. Diabetes Care 2005; 28: 956-962.

5. Bild DE, Selby JV, Sinnock P, Browner WS, Braveman P, Showstack JA. Lower extremity amputation in people with diabetes: epidemiology and prevention. Diabetes Care 1989; 12: 24-31.
6. Consensus Development Conference on Standardised Measures in Diabetic Neuropathy. Proceedings of a consensus development conference on standardised measures in diabetic neuropathy. Diabetes Care 1992; 15(3): 1080-1107.
7. Abbott CA, Vileikyte L, Willimason S, Carrington AL, Boulton AJM. Multicenter study of the incidence of and predictive risk factors for diabetic neuropathic foot ulceration. Diabetes Care 1998; 21: 1071-1075.
8. International Expert Committee. International Expert Committee report on the role of the A1C assay in the diagnosis of diabetes. Diabetes Care 2009; 32: 1327-34.
9. Executive summary: Standards of Medical Care in Diabetes-2010. Diabetes Care 2010; 33: S4-S10. (Accessed from **https://doi.org/10.2337/dc10- S004 on 14/12/2021**)
10. Kapoor N, Kirubah D, Saravanan B. Approach to diabetic neuropathy. Current
11. Medical issues 2017; 15: 189-199.
12. Francisco Javier Domínguez-Munoz , José Carmelo Adsuar , Santos Villafaina, Miguel Angel García-Gordillo, Miguel Ángel Hernández-Mocholí, Daniel Collado-Mateo and NarcísGusi. Test-Retest Reliability of Vibration PerceptionThreshold Test in People with Type 2 Diabetes Mellitus. Int. J. Environ. Res. Public Health 2020: 17; 1773.
13. Catherine L. Martin, Barbara H. Waberski, Rodica Pop-Busui, Patricia A. Cleary, Sarah Catton, James W. Albers, Eva L. Feldman, William H. Herman. Vibration Perception Threshold as a Measure of Distal Symmetrical Peripheral Neuropathy in Type 1 Diabetes. Diabetes Care December 2010; 33(12): 2635-41.
14. Hwu CM, Chang HY, Chen JY, Wang SL, Ho LT, Pan WH. Quantitative vibration perception thresholds in normal and diabetic Chinese: Influence of age, height and body mass index. Neuroepidemiology 2001; 21:271-78.
15. Jay M Sosenko, Andrew J M Boulton, Denise B Kubrusly, Jagdish K Weintraub, B.A., Jay S Skyler.The Vibratory Perception Threshold in Young Diabetic Patients: Associations with Glycemia and Puberty. Diabetes Care 1985 Nov; 8(6): 605-607.
16. Dan Ziegler, Wolfgang Rathmann, Thorsten Dickhaus, Christa Meisinger, Andreas Mielck, KORA Study Group Prevalence of polyneuropathy in pre-diabetes and diabetes is associated with abdominal obesity and macroangiopathy: the MONICA/KORA Augsburg Surveys S2 and S3 DIABETES CARE, VOLUME 31, NUMBER 3, MARCH 2008 Mar;31(3):464-9.
17. Shan Gao, Hongliang Zhang, Chen Long, Zhenhua Xing. Association Between Obesity and Microvascular Diseases in Patients With Type 2 Diabetes Mellitus Front Endocrinol (Lausanne). 2021; 12: 719515.
18. **D V Coppini** , **A Wellmer**, **C Weng**, **P J Young**, **P Anand**, **P H Sönksen**. The natural history of diabetic peripheral neuropathy determined by a 12 year prospective study using vibration perception thresholds. J Clin Neurosci2001 Nov; 8(6): 520-4.
19. Lakshmana Kumar N., Mallikarjuna Rao K.V.N, Srinivas Ch , Kishore K.,KiranDeedi M. Lakshmana Rao N. Evaluation Of Diabetic Peripheral Neuropathy In Known Cases Of Type 2 Diabetes In Urban And R912ural Population . International journal of research and review. 2013; 05 (12) :51-56.
20. **C E Kullberg** , **H J Arnqvist**. Impaired vibration perception threshold and long-term mean HbA1c in patients with type 1 diabetes mellitus. Diabet Med 1996 Dec; 13(12): 1027-32.
21. Won-Jae Lee, Sol Jang, Seung-Hwa Lee, Hyun-Seok Lee. Correlation between the severity of diabetic peripheral polyneuropathy and glycosylated hemoglobin levels: A quantitative study. Ann Rehabil Med 2016; 40: 263-270.

22. P.Jayaprakash, Anil Bhansali, Shobhit Bhansali*, Pinaki Dutta, R. Anantharaman, G. Shanmugasundar, M. Ravikiran Validation of bedside methods in evaluation of diabetic peripheral neuropathy. Indian J Med Res June 2011; 133: 645-649.
23. Solomon Tesfaye, Dinesh Selvarajah. Advances in the epidemiology, pathogenesis and management of diabetic peripheral neuropathy.DIABETES/METABOLISM RESEARCH AND REVIEWS Diabetes Metab Res Rev 2012; 28(Suppl 1): 8–14.