PERIPHERAL NEUROPATHY AMONG PATIENTS WITH TYPE 2 DIABETES USING MICHIGAN NEUROPATHY SCREENING INSTRUMENT

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ABSTRACT

Objective: To determine the frequency of peripheral neuropathy and associated factors among patients with type 2 diabetes mellitus (T2DM), attending a tertiary care hospital via Michigan Neuropathy Screening Instrument (MNSI).

Methodology: This cross-sectional study was conducted in the department of endocrinology and metabolic diseaes, Medical Teaching Institute, Lady Reading Hospital Peshawar, from March to December 2019. A total of 365 patients with T2DM were included in the study. All patients were evaluated for peripheral neuropathy using the two sets of MNSI (symptoms and examinations).

Results: Mean age of the patients was 49.0±7.52 years. Mean body mass index (BMI) was 28.1±5.21 kg/m^2, and mean glycated haemoglobin (HbA1c) was 10.1±1.56%. There wew 150 (41.10%) males and 215 (58.90) females. Based on the scoring of MNSI questionnaire, 239 (65.5%) had diabetic peripheral neuropathy (DPN) while using MNSI examination 252 (69.0%) had DPN. By combining both questionnaire and examination, DPN was present in 290 (79.5%) of the study participants. The factors associated with DPN after controlling for potential confounders were age of > 50, high levels of total cholesterol (TC) and low density lipoproteins (LDL).

Conclusion: The frequency of DPN was found to be higher in our study population; the burden being high among males. Age, TC and LDL were found to have significant association.

Key Words: Diabetes Mellitus; Peripheral neuropathy; Michigan neuropathy screening instrument (MNSI)

INTRODUCTION

Diabetes mellitus (DM) is a global public health issue and has developed as a major socioeconomic problem for low income countries.[1] In 2017, worldwide, 451 million people were diabetic, and by 2045 the number is expected to surpass 693 million.[2] According to latest Pakistan national diabetes survey, about 26.3% (overall weighted prevalence) of the local population aged above 19 is diabetic.[3] However, a similar study, named Diabetes Prevalence Survey of Pakistan (DPS-PAK) reported this prevalence to be 16.98%.[4]

Among the long-term diabetes associated complications, neuropathy is the most prevalent chronic and debilitating complication.[5-9] It has varying presentations and is thus sometimes difficult to diagnose.[7] In a vast majority of patients, it is asymptomatic. Distal symmetrical polyneuropathy (DSPN), also known as diabetic peripheral neuropathy (DPN), is the commonest presentation. It affects the lower limbs mostly and contributes to ulcers formation and ultimately amputations or even death.[10] It is therefore important to screen patients periodically and develop preventive and therapeutic measures in a timely fashion to prevent excess morbidity and mortality.

DPN is caused by persistent hyperglycemia leading to other metabolic abnormalities like polyol flux, increased oxidative stress and advanced glycation end-products formations along with dyslipidemia and other risk factors.[6,11,12] The Toronto Diabetic Neuropathy Expert group defines DPN as symmetrical, length-dependent sensorimotor polyneuropathy, attributable to metabolic and micro-vessel alterations as a result of chronic hyperglycemia exposure and cardiovascular risk covariates, and divides it into possible, probable, confirmed and subclinical.[8,13]

The diagnosis of DPN is difficult because of lack of clear diagnostic guidelines.[14] Different screening tools have been used to identify neuropathy. However a confirmed diagnosis requires complete nerve conduction study (NCS) or small fiber functions measurement. NCS is regarded as the gold standard for diagnosing neuropathy but requires special instruments and qualified personnel, which are not available in most of our setups. Therefore, it cannot be practiced for screening in all settings. The Michigan Neuropathy Screening instrument (MNSI) is a simple, non-invasive and valid tool for assessment of DPN in diabetic patients.[15]

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Screening for DPN in clinical practice using such simple objective tool may be much helpful, as the detection of the various soft and subtle signs of DPN at the earliest could minimize the damaging effects of this serious microvascular complication and, in turn, improve the quality of life of such patients. Considering this, we conducted this study to determine frequency of peripheral neuropathy using MSNI.

METHODOLOGY

This cross-sectional study was conducted in the department of endocrinology and metabolic diseases from March to December 2019. A total of 365 T2DM patients, diagnosed according to American Diabetes Association criteria[14], aged ≥ 30 years, having HbA1c of ≥ 6.5%, and willing to participate in the study, were included. All those with history of alcohol intake, drug abuse, history of nerve root compression, cerebral vascular diseases and hypothyroidism were excluded.

DPN assessment was done by principal investigator using MNSI. Part one (history version) comprised of 15 questions to asses the history of neuropathic symptoms. These are simple questions based on "Yes "or "No" responses. The responses were used in evaluating the patients for the presence of numbness, temperature and other foot sensation. Part two of MNSI (examination version) comprised of a brief physical examination for the inspection of feet, ankle reflexes by tendon hammer, vibration by using 128 Hz tuning fork and fine touch sensation done by 10 gm Semmes-Weinstein Monofilament (SWM). Neuropathy was defined as seven or more positive responses on the MNSI questionnaire or a score >2.0 on the MNSI examination.[15]

A structured data collection sheet was used to record all the demographic and clinical characteristics of the patients including age, sex, body mass index (BMI), duration of diabetes and laboratory parameters. The analysis was done using SPSS version 20. Presence or absence of DPN was reported in percentages. Means of variables were compared using independent t-test while Chi square test was used to determine the association between categorical variables. Binary logistic regression analysis was run to determine the Odds Ratio (OR). A p-value of <0.05 was considered significant.

RESULTS

There were 150 (41.10%) males and 215 (58.90%) females enrolled in the study. The mean age of the patients was 49.0±7.52 years with 259 (70.96%) patients of age 50 or below and 106 (29.04%) patients of above 50 years of age. The mean height was 161.0±8.27 cm, weight was 74.0±13.83 kg and BMI was 28.1±5.21 kg/m^2. Mean total cholesterol (TC) level was 199.4±47.78 mg/dl, low density lipoprotein (LDL) level was 134±24.63 mg/dl, high density lipoprotein (HDL) level was 35.0±3.01 mg/dl, triglyceride (TG) level was 234.5±95.59 mg/dl and mean glycated hemoglobin (HbA1c) was 10.1±1.56 % as shown in table 1. There was a family history of diabetes in 266 (72.88%) patients.

The most frequently reported symptoms were numbness (85.7%), followed by burning sensation in feet (76.1 %). The individual examination of MNSI showed that 125 (34.25%) patients were having abnormal appearance, 157 (43.01%) were having ulceration, 156 (42.74%) were having absent ankle reflex, 191 (52.33%) had absent vibration and 210 (57.53%) had absent monofilament perception. MNSI symptoms showed peripheral neuropathy in 239 (65.5%) and MNSI examination showed peripheral neuropathy in 252 (69.0%) patients. By combining both, DPN was present in 290 (79.5%) of the study participants.

Table 2 shows association of age, anthropometric and laboratory parameters with DPN status. BMI and LDL were significantly higher in Non DPN patients as compared to DNP patients (p<0.005). People of age ≤50 years were significantly more in number in DPN group as compared to those with no DPN (p=0.009).

Table 3 shows the odds ratios (ORs) for factors associated with DPN. Parameters with a p-value ≤ 0.2 in the univariate analysis were included in the multivariate logistic regression analysis. The factors associated with DPN were found to be age group >50 (OR: 2.1, CI: 1.03-4.26, p=0.042), total cholesterol (OR: 1.02, CI: 1.01-1.03, p <0.001) and LDL (OR: 0.97, CI: 0.96-0.99, p<0.001), after controlling for potential confounders.

DISCUSSION

Our study showed the presence of Diabetic Peripheral Neuropathy (DPN) in 290 (79.5%) patients. Almost comparable results have been reported in another study that found 69 % prevalence of DPN by MNSI.[16] Another study found that 51 % of the T2DM patients with cardiovascular manifestations had DPN on this instrument.[17] Contrary to our findings, Herman et al, only showed 30% confirmed clinical neuropathy cases by this instrument, 18% were having ≥ 4 and 5% were having ≥ 7 abnormal response to MNSI symptoms while 33% were having abnormal examination (≥ 2.5 score).[18] However, his study was done on patients with type 1 diabetes only. The difference in prevalence of DPN among these studies may be due to the differences in the duration and type of diabetes, study designs, type of study population and difference in types of scales used to assess the magnitude of DPN. High frequency of DPN in our patients may be due to the presence of other undetected complications like coronary artery disease (CAD) and retinopathy, as diabetic patients having other microvascular and macrovascular complications are more likely to have DPN. This can be due to common pathogenic mechanisms as the toxic effect of hyperglycemia in the form of increasing thickness of endo-neural micro vessels, accumulation of advanced glycation end products, activation of the polyol pathway and oxidative stress.[6,11,12] Moreover, this can also be due to inter subjects variability in signs and symptoms of DPN and the differences in sample selected.

We evaluated many risk factors for diabetic neuropathy. Statistically significant association was observed between age and DPN (being more common in less than 50 years of age group) in univariate analysis, while in multivariate analysis, the likelihood of DPN was higher in the age group >50 years. Similar results have been described by previously published studies.[18, 19] In our study, mean BMI and LDL were higher in non-DPN as compared to DPN patients in univariate analysis. The high BMI in patients with non

Table 1: Demographic and anthropometric characteristics of patients

Variables	Mean ± SD
Age (years)	49.0 ± 7.52
Duration of diabetes (years)	6.58 ± 4.02
Height (m)	161.0 ± 8.27
Weight (kg)	74.0 ± 13.83
Body Mass Index (kg/m2)	28.1 ± 5.21
Cholesterol (mg/dl)	199.4 ± 47.76
Low Density Lipoprotein (mg/dl)	134.0 ± 24.63
High Density Lipoprotein (mg/dl)	35.0 ± 3.01
Triglyceride (mg/dl)	234.5 ± 95.59
Glycated Hemoglobin [HbA1c] (%)	10.1 ± 1.56

Table 2: Association of age, anthropometric and laboratory parameters with DPN

	DPN [n (%)]	Non-DPN [n (%)]	P-value
≤50 Years	197 (53.97)	62 (16.99)	0.009
>50 Years	93 (25.48)	13 (3.56)	
Male	123 (33.70)	27 (7.40)	0.312
Female	167 (45.75)	48 (13.15)	
Family History of T2DM	206 (56.44)	60 (16.44)	0.145
No family history of T2DM	84 (23.01)	15 (4.11)	
	DPN (Mean ± SD)	Non-DPN (Mean ± SD)	P-value
Height (m)	161.0 ± 8.41	159.0 ± 7.64	0.180
Weight (kg)	73.0 ± 13.73	76.0 ± 14.09	0.107
Body Mass Index (kg/m2)	27.8 ± 5.00	29.5 ± 5.80	0.011
Cholesterol (mg/dl)	201.1 ± 43.94	193.0 ± 60.24	0.193
LDL (mg/dl)	132.2 ± 24.54	141.0 ± 23.87	0.005
HDL (mg/dl)	35.2 ± 3.04	34.4 ± 2.85	0.062
Triglyceride (mg/dl)	234.4 ± 99.32	234.9 ± 80.15	0.964
HbA1c (%)	10.0 ± 1.62	10.3 ± 1.29	0.209
Duration of diabetes	6.36 ± 4.08	7.41 ± 4.58	0.053
Total MNSI Score	7.82 ± 2.49	3.45 ± 1.59	<0.001

DPN: Diabetic Peripheral Neuropathy
T2DM: Type 2 Diabetes Mellitus
LDL: Low density Lipoprotein
HDL: High density Lipoprotein
HbA1c: Glycated hemoglobin
MNSI: Michigan Neuropathy Screening Instrument

Table 3: Determinates of DPN in our study population

Variable	OR	95% CI	p
Cholesterol [mg/dl (mean)]	1.02	1.01-1.03	<0.001
LDL [mg/dl(mean)]	0.97	0.96-0.99	<0.001
Age groups (years) (%)			
≤50	1		
>50	2.1	1.03-4.26	0.042

DPN: Diabetic Peripheral Neuropathy
LDL: Low density Lipoprotein

DPN may be explained by the confounding effect of Insulin use, leading to weight gain. On the other hand, in multivariate regression, after controlling for potential confounders, TC and LDL were found to be associated with DPN. Literature supports that high BMI and LDL cholesterol are positively related to the development of DPN.[20, 21]

Won et al showed that age, female gender, duration of diabetes, low HbA1c, presence of retinopathy, history of peripheral arterial disease or stroke, presence of hypertension, dyslipidemia and foot ulcers were independently associated with the occurrence of DPN.[13] Some of the variables like increasing age and dyslipidemia leading to DPN are consistent with our findings. Our study argues for multifactorial nature of neuropathy and hence supports the need for managing multiple metabolic abnormalities. The combination of older age and injurious effects of high blood glucose can bring an increased frequency of DPN as one gets older.[22]

Although the prevalence of microvascular complications like neuropathy is strongly related to the degree of glycemic control, we did not find an association between DPN and HbA1c. This is consistent with the study done by Khawaja et al.[22] However, a single reading of HBA1c at the time of presentation does not reflect the true status of long-term glycemic control. Moreover, this does not mean that proper glycemic control has no influence on the development of neuropathy. Although longer duration of DM with poor glycemic control is well known determinant for DPN, we did not find any difference in the mean duration of diabetes in DPN and non-DPN patients in both univariate and multivariate analysis. Similar to our study, no such association was observed by D'Souza et al in their study.[20]

This limitations of the study include lack of inquiry about smoking, physical activity, presence of cardiovascular disease, retinopathy and nephropathy, Furthermore, denial of alcohol use by patients and causality determination for neuropathy like B12 and folic acid deficiency was not elucidated that may lead to overestimation of DPN frequency. Moreover, this was a single hospital study, which may limit the generalization of findings. Also, since MNSI is a screening instrument and not a diagnostic one; the score of >2 means fur-

ther testing is needed for diagnosing neuropathy through nerve conduction studies.

CONCLUSION

The frequency of DPN was found to be higher in our study population; the burden being high among males. Age, TC and LDL were found to have significant association. Our data highlights the need for assessment and detection of DPN in routine screening in the initial and follow-up visits. Moreover, measures should be adopted to prevent the development and progression of DPN.

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Author's Contribution

AH Conceived the idea, made a plan, carried out data collection, script writing and statistical compilation according to the research proposal. IA Data collection as per methodology, refining the manuscript and statistical analysis. MN Data collection as per methodology, refining the manuscript and statistical analysis. AZ Executed the project plan, helped in data collection, literature search and bibliography. SS Executed the project plan, helped in data collection, literature search and bibliography. Authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Conflict of Interest

Authors declared no conflict of interest

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None

Data Sharing Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.