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Peripheral Neuropathy and Vasculopathy; Frequency and Associated Risk Factors in Newly Diagnosed Treatment Naive Type 2 Diabetes

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Abstract

Background: The prevalence of diabetes in Pakistan is 11.45%. The reported prevalence of diabetic foot ulceration in Pakistan is between 4% and 10%, with the amputation rate of 8% - 21%. Peripheral neuropathy and vasculopathy are main underlying cause of diabetic foot ulcers. **Methodology:** It was a cross-sectional **non-interventional** cohort study where all newly diagnosed treatment naïve type 2 diabetic patients were enrolled. Peripheral neuropathy and vasculopathy were detected by Michigan neuropathy screening instrument (MNSI) and ankle brachial index (ABI) respectively. Risk factors for peripheral neuropathy and vasculopathy were determined by univariate and multivariate logistic regression analysis. Statistical significance was considered with P value of < 0.05. **Result:** Fifty seven patients (37.7%) had early neuropathy with MNSI score of 3.3 ± 0.4. Thirty seven patients (20.6%) had vasculopathy with ABI score of 0.76 ± 0.11. Age (Odd ratio 1.07 (1.02 - 1.11), p 0.003), duration of symptoms (Odd ratio 1.11 95% CI: 1.05 - 1.17, $p \leq 0.001$), high HbA1C % (Odd ratio 1.94 95% CI: 1.54 - 2.45, $P \leq 0.001$), albumin creatinine ratio (Odd ratio 1.01, 95% CI: 1.00 - 1.01, $P \leq 0.001$) and cholesterol level (Odd ratio 1.01 95% CI: 1.01 - 1.02, $p = 0.001$) were found as risk factors for early neuropathy and vasculopathy. **Conclusion:** Peripheral neuropathy and vasculopathy are frequently reported complications among newly diagnosed treatment naïve patients of type 2 DM. Age, duration of symptoms prior to diagnosis, metabolic parameters like raised HbA1C, hyperlipidemia and spot random albumin creatinine ratio are found to be risk factors for both peripheral neuropathy and vasculopathy.

Keywords

Peripheral Neuropathy, Peripheral Vasculopathy, Type 2 Diabetes Mellitus

1. Introduction

The increasing global prevalence of diabetes has been estimated about 8.5% [1]. Prevalence of diabetes has more rising trend in middle- and low-income countries as reported by World Health Organization. Diabetes has been connected to the major cause of renal failure, blindness, myocardial infarction, stroke and lower limb amputation. In 2030 diabetes will be the 7th leading cause of death as predicted by World Health Organization [2]. The prevalence of diabetes in Pakistan is 11.47% [3]. The reported prevalence of diabetic foot ulceration in Pakistan is between 4 and 10%, with the amputation rate of 8% - 21% [4] [5]. How much amputation contributes in the overall mortality in Pakistan is not known.

Foot problems related to diabetes are a well known complication where approximately 5% of patients may require major amputation. Diabetic foot ulcers have been observed in nearly 25% of patients during their course of illness [6] [7]. Peripheral neuropathy, vasculopathy, and immunopathy are the main underlying mechanism for diabetic foot complications [8] [9]. Peripheral diabetic neuropathy affects sensory, motor and autonomic components and collectively triggers diabetic foot ulcers [10] [11]. Hyperglycemia induced damage to nerve fibers in both lateral spinothalamic and posterior column contributes to foot ulceration. The reported global prevalence of peripheral neuropathy in diabetes is 30% - 50%. Peripheral neuropathy is considered as a main cause (>60%) of diabetic foot ulcers [8].

Apart from neuropathy, the role of diabetic vasculopathy in diabetic foot complications cannot be undermined. Peripheral arterial disease (PAD) is an important risk factor associated with complication related to diabetic foot; poor wound healing, impaired perfusion, deformity and superimposed infections [9]. Peripheral arterial occlusive disease at the bifurcation of abdominal aorta is common among old people [12]. Vasculopathy remains undetected as initially most of the patients are asymptomatic with ankle brachial index < 0.9. Hyperglycemia induced Microvascular complications and loss of demyelinated nerve fibers are possible underlying mechanisms for neurovasculopathy [10] [13]. There are various risk factors associated with diabetic foot like duration of disease, age, gender and poor glycemic control. Foot problems related to diabetes are a common reason for hospitalization which leads to lower limb amputation. It poses a great challenge both in terms of economic and quality of life among patients [14]. Earlier data has shown increase mortality among diabetics from 30% - 70% after lower limb amputation [15] [16] [17].

Pakistan being a poor country with socioeconomic constrains having improper primary health care system has a high burden of diseases where diabetes and

its complications cause severe impact on health economics thus magnifying the importance of reaching out to the suffering families having been long ignored on this subject like many others. This epitaph alone has enough reason for paying importance to family medicine in this part of the world. The prevalence of diabetes in Pakistan is 11.45% [3]. The reported prevalence of diabetic foot ulceration in Pakistan is between 4 and 10%, with the amputation rate of 8% - 21% [4] [5]. Early detection or screening of peripheral neuropathy and vasculopathy with timely intervention or institution of their treatment among diabetics will definitely reduce diabetic foot ulcers and eventually the frequency of amputations. It also aids to strategize comprehensive foot care programme to minimize rate of amputation and eventually mortality. The study is aimed to determine the frequency of early diabetic neuropathy and vasculopathy among patients attending tertiary care public hospital. The study further aims to determine the risk factors associated with peripheral neuropathy and vasculopathy.

2. Methodology

Prior to the commencement of research the approval was taken from the Institutional review board (IRB). It was a cross sectional **non interventional** cohort study where all diabetic patients attending Medical OPD of medical unit 1, CHK and DUHS from November 2017 to January 2018 were enrolled. A sample of 155 diabetic will be included considering 11.5% prevalence [3] of diabetes in Pakistan.

2.1. Research Participant

All cases of newly diagnosed treatment naïve T2DM with age ≥ 20 years to 60 years were enrolled. T2DM was diagnosed in accordance to ADA criteria where any of the following criteria met as FPG ≥ 126 mg/dL (7.0 mmol/L) or 2-h PG ≥ 200 mg/dL (11.1 mmol/L) during OGTT or A1C ≥ 6.5% (48 mmol/mol) or a patient with classic symptoms of hyperglycemia or hyperglycemic crisis, a random plasma glucose ≥ 200 mg/dL (11.1 mmol/L). Patients with type 1 DM along with patients who already have serious diabetic complications like lower limb amputation were excluded. Patients with any symptoms suggesting nephropathy as well as known smokers will also be excluded.

2.2. Research Instruments

2.2.1. Demographic Profile

All demographic details of patients like age, gender, marital status, and duration of diabetes, any previous screening for neuropathy, and previous history of foot ulcer and history of any comorbids were recorded through specially designed proforma.

2.2.2. Peripheral Diabetic Neuropathy

Diabetic neuropathy *was* measured by the Michigan neuropathy screening instrument (MNSI) a reliable and validated tool for this purpose where a total score of 0 - 10 was obtained [18] [19]. Vibration sensations were determined on

the dorsum of the big toe by a turning fork (128-Hz) which could help to determine even early neuropathy [20]. Each participant feet was assessed by MNSI scoring for five defined parameters which includes appearance, ulceration, vibration sensations, ankle jerk and touch pressure modality of sensation. Each above parameter has 0.1 and 1.5 points. Peripheral neuropathy was confirmed or diagnosed when patient on a 10-point scale has MNSI score of ≥2.5.

2.2.3. Peripheral Vasculopathy

Vascular status of extremity was determined by ankle brachial index (ABI). Peripheral vasculopathy was labeled when ABI values of ≤0.89 against 0.9 of normal [15].

2.2.4. Metabolic Indicators

Fasting blood sugar (FBS), lipid profile and creatinine is determined by Auto analyzer. Glycated haemoglobin (HbA_1C determined by high performance liquid chromatography (HPLC), urinary albumin was determined by a radioimmunoassay technique (Immunotech, Prague, Czech Republic). Spot urinary albumin creatinine ratios (ACR) were calculated for all patients.

2.2.5. Statistical Analysis

The data of the study will be analyzed through SPSS version 21 where Data was conveyed as mean ± SD and respective frequencies. Data was evaluated by Student's t-test and χ^2 analyses for proportions and continuous variables, respectively. Risk factors for peripheral neuropathy and vasculopathy were determined by multivariate logistic regression analyses. Statistical significance was considered with P value of <0.05.

3. Results

3.1. Demographic Profiles

Demographic profiles along with clinical details of patients are shown in **Table 1**. Male gender predominates 58% in this study. Patients had mean age of 49.6 (8.5±) years with 8.0 (IQR 38) months duration of symptoms related to diabetes prior to diagnosis. Metabolic indicators at presentation are as median serum cholesterol of 185 mg/dL (IQR 171), median random spot urinary albumin to creatinine ratio (ACR) 192 (IQR 492) μg/mg and median HbA1C of 8 (IQR 8).

3.2. Peripheral Neuropathy

MNSI score was calculated in all patients and patients were segregated with and without neuropathy on the basis of MNSI score. 57 patients (37.7%) had early neuropathy with MNSI score of 3.3 ± 0.4 whereas 98 (63.3%) patients had no neuropathy with MNSI score of 1.2 ± 0.7 as shown in **Table 2**.

3.3. Peripheral Vasculopathy

ABI was determined in all patients where patients were divided into vasculopathy

Table 1. Demographic profile of patients.

Characteristics	Statistics (N = 155)
Mean age in years (SD)	49.6 (8.5)
Gender, n males (%)	90 (58.1)
Duration of symptoms in months, Median (IQR)	8 (10)
Total cholesterol level in mg/dL, Median (IQR)	185 (83)
HbA1C level (%), Median (IQR)	8.3 (3.2)
Albumin to Creatinine ratio in μg/mg, Median (IQR)	192 (231)
MNSI score for early neuropathy, Median (IQR)	2.0 (2.0)
ABI score for early vasculopathy, Median (IQR)	1.0 (0.2)

MNSI (Michigan neuropathy screening instrument); ABI (Ankle brachial index); IQR (inter quartile range).

Table 2. Demographic characteristics of patients with and without early neuropathy and vasculopathy.

Characteristics	Patients with Peripheral neuropathy and vasculopathy (n = 89)	Patients without Peripheral neuropathy and vasculopathy (n = 66)	P value[¥]
Mean age in years (SD)	51.4 (8.6)	47.2 (7.6)	0.002
Gender, n males (%)	53 (59.6)	37 (56.1)	0.66
Duration of symptoms in months, Median (IQR)	10 (14)	7 (7)	0.012
Total cholesterol level in mg/dL, Median (IQR)	189 (82)	174 (87)	0.001
HBA1C level (%), Median (IQR)	9.3 (2.4)	7.0 (2.4)	<0.001
Albumin to Creatinine ratio in μg/mg, Median (IQR)	255 (197)	97 (186)	<0.001
MNSI score for early neuropathy, Median (IQR)	3.0 (1.0)	1.0 (1.0)	<0.001
ABI score for early vasculopathy, Median (IQR)	0.9 (0.2)	1.1 (0.1)	<0.001*

versus no vasculopathy. 32 patients (20.6%) had vasculopathy with ABI score of 0.76 ± 0.11 whereas 123 (79.4%) patients had no peripheral vasculopathy with ABI score of 1.05 ± 0.08 as shown in Table 2.

3.4. Albumin Creatinine Ratio (ACR)

ACR was determined among all patients with and without neuropathy and vasculopathy. Patients with detected neuropathy and vasculopathy had ACR of 255 (μg/mg) with median of 197 (μg/mg) whereas ACR of 97 (μg/mg) with median of 186 (μg/mg) was found in patients without peripheral neuropathy and vasculopathy.

3.5. Associations of Early Neuropathy and Vasculopathy

Various demographic and metabolic parameters were compared among patients

with and without early neuropathy and vasculopathy as shown in Table 2. Increasing age (p = 0.002), duration of symptoms (p = 0.012) among demographic parameters had significant associations amongst patients with and without early neuropathy and vasculopathy. MNSI score for peripheral neuropathy (p ≤ 0.001) and ABI score for peripheral vasculopathy (p < 0.001) were also found to be significant in patients with and without peripheral neuropathy and vasculopathy. Among metabolic parameters, high HbA1C % (p ≤ 0.001), ACR (P ≤ 0.001) and high cholesterol (p = 0.00) had shown significant association between patients with and without peripheral neuropathy and vasculopathy.

3.6. Risk Factors for Early Neuropathy and Vasculopathy

All significant associations among patients with and without peripheral neuropathy and vasculopathy were assessed for risk factors by applying univariate logistic regression analysis. Age (Odd ratio 1.07 (1.02 - 1.11), p = 0.003), duration of symptoms (Odd ratio 1.11 95% CI: 1.05 - 1.17, p ≤ 0.001), high HbA1C % (Odd ratio 1.94 95% CI: 1.54 - 2.45, P ≤ 0.001), ACR (Odd ratio 1.01, 95% CI: 1.00 - 1.01, P < 0.001) and cholesterol level (Odd ratio 1.01 95% CI: 1.01 - 1.02, p = 0.001) were all found to be risk factors for peripheral neuropathy and vasculopathy among newly diagnosed treatment naïve patients as shown in Table 3. Increasing age (Odd ratio 1.08, 95% CI: 1.02 - 1.14, P = 0.012), duration of symptoms (Odd ratio 1.10, 95% CI: 1.02 - 1.19, P = 0.01), high HbA1C % (Odd ratio 4.32, 95% CI: 2.44 - 7.66, p ≤ 0.001), ACR (Odd ratio 1.01, 95% CI: 1.00 - 1.01, P = 0.004) were also found to be independent risk factors for both peripheral neuropathy and vasculopathy as shown in Table 4.

Table 3. Risk factors for early diabetic peripheral neuropathy and vasculopathy.

Variables	Odds Ratio (95% CI)	P-value
Age	1.07 (1.02 - 1.11)	0.003
Gender	1.15 (0.61 - 2.20)	0.663
Duration of symptoms	1.11 (1.05 - 1.17)	<0.001
Total cholesterol level	1.01 (1.01 - 1.02)	0.001
HBA1C level	1.94 (1.54 - 2.45)	<0.001
Albumin to creatinine ratio	1.01 (1.00 - 1.01)	<0.001

Table 4. Multivariate logistic regression analyses of variables associated with Peripheral neuropathy and vasculopathy.

Variables	Odds Ratio (95% CI)	P-value
Age	1.08 (1.02 - 1.14)	0.012
Duration of symptoms	1.10 (1.02 - 1.19)	0.01
Total cholesterol level	0.96 (0.94 - 0.98)	<0.001
HBA1C level	4.32 (2.44 - 7.66)	<0.001
Albumin to creatinine ratio	1.01 (1.00 - 1.01)	0.004

4. Discussion

The current study determined frequency of peripheral neuropathy and vasculopathy among newly diagnosed treatment naïve patients of type 2 DM along with associated risk factors. Male gender (58%) predominates in this study which is similar to earlier studies [21] [22]. Mean age of patients were 49.6 (8.5±) which is again in agreement to earlier study where mean ages were 51.3 ± 12.3 and 52.39 ± 10.03 years respectively [21] [22]. Patients in this study had 8 months (median 10 IQR) duration of symptoms prior to diagnosis of DM which is in accordance to reported data of Gill HK *et al.* [21] where duration of symptoms was 8.4 ± 9.9 months.

Peripheral neuropathy was detected in 57 patients (37.7%) with MNSI score of 3.3 ± 0.4 in newly diagnosed type 2 patients of DM with cut off score ≥2.5. Lee *et al.* [23] in their study found 34.5% peripheral neuropathy detected by same MNSI instrument with same cut off ≥2.5. Chen *et al.* [13] has shown 22.5% peripheral neuropathy however they used MNSI score cut off >3. A European study [24] has shown higher frequency (43.5%) of peripheral neuropathy compare to this study. A large cross sectional study [22] of 2000 newly diagnosed type 2 diabetics has shown peripheral neuropathy of 52% but it was detected by neuropathy disability score (NDS) rather than MNSI. Vasculopathy was found in (20.6%) of patients with ABI score of 0.76 ± 0.11 in this current study. Lee *et al.* [23] has also shown 17.5% of peripheral vasculopathy in newly diagnosed type 2 patients. The earlier reported prevalence of peripheral vasculopathy among type 2 diabetic patient in Asia (20%), Taiwan (17.7%) and United States (20%) [25] [26].

Several risk factors like age, bad glycemic control, gender, prolong duration of diabetes, hypertension, retinopathy, smoking, and alcohol consumption were previously determined for peripheral neuropathy among type 2 newly diagnosed DM [27] [28] [29] [30]. In current study, age at diagnosis and duration of symptoms prior to diagnosis were found to be significant risk factors for peripheral neuropathy and vasculopathy. Earlier studies [31] [32] on the subject have also shown similar findings. Previously Smith AG *et al.* and Dyck PJ *et al.* [33] [34] did not find the similar results and contrasted our study.

The current study has shown significant association of hyperlipidemia where it is found to be a risk factor for peripheral neuropathy when compared between patients with and without peripheral neuropathy. Hyperlipidemia is not only found to be a risk factor but early dyslipidemia among type 2 diabetics has shown a main independent risk factor for the development of diabetic peripheral neuropathy as evidenced from emerging data of various large scale trials [35] [36] [37]. An earlier study also supported this current study and showed that obesity and hypertriglyceridemia is a risk factor for early peripheral neuropathy independent to glucose control [38].

The current study has shown high HbA1C as a risk factor for peripheral neuropathy with odds of 4.32, 95% CI: 2.44 - 7.66 when compared among groups

with and without peripheral neuropathy. Previous study [39] has shown similar results where high levels of glycated haemoglobin were found to be a risk factor for peripheral neuropathy. A large recent study [40] has shown high HbA1C as an early marker of peripheral neuropathy among type 2 diabetics. The above referred study determined both the coefficient of variability of HbA1C and mean HbA1C in their patients. A previous study [21] contrasted to this current study and did not confirm high HbA1C as a risk factor for peripheral neuropathy.

ACR with odds of (1.01, 95% CI: 1.00 - 1.01) were found to be a risk factor for peripheral neuropathy in this study when compared between patients with and without peripheral neuropathy and vasculopathy. Earlier study [21] has shown prevalence of albuminuria of 7.9% but did not find it as a risk factor for peripheral neuropathy. Spijkerman AM *et al.* and Shaw JE *et al.* [29] [41] have shown variable association between peripheral neuropathy and albuminuria.

Peripheral vasculopathy in this study has also shown significant association with various parameters like age, duration of symptoms prior to diagnosis as discussed earlier. High HbA1C levels are found to risk factor for peripheral vasculopathy among type 2 diabetic in this study. Lee CM *et al.* [23] has shown raised HbA1C as a risk factor for peripheral vasculopathy in newly diagnosed type 2 DM. Hyperlipidemia was found to be significantly associated as a risk factor for peripheral vasculopathy in this study. Solanki *et al.* [42] has shown significant association between hyperlipidemia with peripheral vasculopathy which is in agreement with our study. ACR (Odd ratio 1.01, 95% CI: 1.00 - 1.01, P = 0.004) found to risk factors for peripheral vasculopathy in this study. Wattanakit K *et al.* [43] in their study concluded that presence but not the quantification of albuminuria, is an important risk factor for peripheral vasculopathy in diabetics. The above referred study is in agreement with our study.

By multivariate logistic regression applied to risk factor for peripheral neuropathy and vasculopathy in this study has shown duration of symptoms prior to diagnosis, age, raised HbA1C, ACR and hyperlipidemia were found to be independent factors for neuropathy and vasculopathy. Earlier study [21] has also shown duration of symptoms and age to be an independent risk factor.

There are certain limitations of this study as neuropathy and vasculopathy group should have been compared with healthy control which would have further strengthen the study. The peripheral neuropathy was not confirmed by nerve conduction studies.

5. Conclusion

Peripheral neuropathy and vasculopathy are frequently detected complications among newly diagnosed treatment naïve patients of type 2 DM. Age, duration of symptoms prior to diagnosis, metabolic parameters like raised HbA1C, hyperlipidemia and spot random albumin creatinine ratio are found to be risk factors for both peripheral neuropathy and vasculopathy. The study recommends early detection of peripheral neuropathy and vasculopathy is of paramount impor-

tance as its timely intervention or institution of their treatment among diabetics will definitely reduce diabetic foot ulcers and eventually the frequency of amputations.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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