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ORIGINAL ARTICLE

Unmasking Early Neuropathy: Metabolic Correlates of Peripheral Neuropathy among Newly Diagnosed Patients of Type-II Diabetes

Shayan Muhammad Aslam[1*], Muhammad Umar Khan[2], Iftikhar Haider Naqvi[3]

[1]*FCPS II Trainee, Department of Medicine, DIMC-DUHS, Karachi, Pakistan*
[2]*Assistant Professor, Department of Medicine, Dow University of Health Sciences, Karachi, Pakistan*
[3]*Department of Medicine, Dow University of Health Sciences, Baba-e-Urdu Road, Karachi, Pakistan*
**Correspondence: shayanaslam.doc93@gmail.com*
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ABSTRACT

OBJECTIVE: To evaluate the frequency of peripheral neuropathy in newly diagnosed T2DM patients and the correlation between metabolic indices and peripheral neuropathy.

METHODOLOGY: A cross-sectional study was carried out at the Department of Medicine, Dow University Hospital, Karachi, from January 2025 to June 2025. A total of 175 newly diagnosed patients with type 2 diabetes mellitus were consecutively enrolled. T2DM was diagnosed using the American Diabetes Association's (ADA) criteria, and diabetic neuropathy was assessed using the Michigan Neuropathy Screening Instrument (MNSI) score. Metabolic parameters, including fasting blood sugar (FBS), glycated haemoglobin A levels, lipid profile, and albumin-to-creatinine ratio (ACR), were evaluated. SPSS version 26 was used for statistical analysis of data, and p-values of less than 0.05 were considered statistically significant.

RESULTS: Majority of T2DM patients were males (58.9%, n=103) and 41.1% (n=72) were females, with a mean age of 45.77 ± 8.59 years. Peripheral diabetic neuropathy was present in 41.7% (n=73) of patients. Metabolic indices, including FBS, HbA1c, cholesterol, triglycerides, low-density lipoprotein cholesterol (LDL-C), and ACR, were considerably higher ($p<0.001$). In contrast, high-density lipoprotein cholesterol (HDL-C) was considerably lower ($p<0.001$) in peripheral diabetic neuropathy.

CONCLUSION: The frequency of peripheral neuropathy in newly diagnosed patients with T2DM was high. Higher levels of FBS, HbA1c, cholesterol, triglycerides, LDL-C, and ACR, and lower levels of HDL-C, were significantly associated with peripheral neuropathy.

KEYWORDS: Cholesterol, diabetes mellitus, glycated hemoglobin, peripheral neuropathy, albumin-to-creatinine ratio, Michigan Neuropathy Screening Instrument.

INTRODUCTION

Diabetes is a chronic condition that affects around 11.1% of the world's population[1]. The World Health Organization (WHO) found that the incidence of diabetes is continuously rising throughout the world, especially in developing countries. Diabetes is the leading cause of several serious health issues, which include stroke, blindness, myocardial infarction, lower limb amputations, and kidney failure. The WHO Global Diabetes Compact reports that diabetes is now the ninth leading cause of death throughout the world, showing its growing burden[1,2]. According to recent global estimates, about 589 million individuals are living with diabetes. The International Diabetes Federation (IDF) reports that by 2050, diabetes will reach around 853 million. In 2024, diabetes was responsible for about 3.44 million deaths globally. Within the IDF's Middle East and North Africa (MENA) region, Pakistan ranks among the most affected countries, with a reported 31.4% prevalence of diabetes among adults, making about 34.5 million individuals[1].

Diabetic foot ulcers (DFU) are among the most serious consequences of diabetes, often resulting in infection, amputation, and a higher risk of death. It typically develops because of poorly controlled blood sugar levels, neuropathy, peripheral arterial disease, or negligence in foot care. DFU significantly increases morbidity and mortality, lowers quality of life, and imposes a significant economic burden on both patients and health systems. Diabetic foot ulcers are predicted to occur in 19% to 34% of diabetic patients during their lifetime, and about 18.6 million new cases are diagnosed each year[3,4]. Approximately 20% of individuals with diabetic foot ulcers may require lower-extremity amputation, which can be either major (above the ankle) or minor (below the ankle) or both[4]. Furthermore, it has been reported that between 12% and 17% of individuals with diabetes in Pakistan develop diabetic foot ulcers, with 21% to 48% of these cases resulting in amputations[5-7].

Peripheral neuropathy, immune dysfunction, and vasculopathy are the major mechanisms causing complications related to diabetic foot. Foot ulcers caused by diabetes can arise from diabetic peripheral neuropathy, which impairs sensory, motor and autonomic functions[8]. One of the main contributing factors to foot ulcers is the loss of nerve fibres in the posterior and lateral spinothalamic columns brought on by hyperglycemia. It is estimated that between 6% and 51% of diabetes patients worldwide have peripheral neuropathy. Peripheral neuropathy is thought to be responsible for more than 60% of foot ulcers in diabetic patients[9]. Peripheral neuropathy prevalence rates in early detection type II diabetes mellitus cases have varied according to several studies[9,10].

Pakistan, a country marked by socioeconomic difficulties and inadequate primary healthcare infrastructure, has a higher rate of illness, especially diabetes and its related complications, which has a substantial influence on health economics. Early identification of peripheral neuropathy in diabetic patients and prompt intervention is expected to lower the proportion of diabetic foot ulcers and, in turn, lower the number of amputations. This strategy will also make it easier to create a comprehensive foot care plan that reduces the risk of amputation and, eventually, death.

METHODOLOGY

A cross-sectional study was conducted at the Department of Medicine, Dow University Hospital, Karachi, from January 2025 to June 2025. After obtaining informed consent, all patients aged 20 to 60 years diagnosed with T2DM and treatment-naive were consecutively enrolled. Patients at risk of severe diabetic complications, such as lower limb amputation and those presenting with nephropathy-related symptoms or with a smoking history were also excluded.
The Online Open Epi Sample Size software was used by Akram N 2019[10] to determine the sample size based on the observed 20.67% prevalence of peripheral neuropathy in 20.67% of newly diagnosed type 2 diabetic patients. This calculation was conducted with a 95% confidence interval of 95% and a 6% margin of error. As a result, 175 was found to be the final sample size. Prior permission from the Institutional Review Board (IRB) of Dow University of Health Sciences (DUHS), Karachi, was sought before the commencement of this study (No. IRB-3726/DUHS/Approval/2024/384).

RESEARCH PROTOCOL

Demographic parameters: All demographic parameters will be assessed using a specially structured pro forma for this study.

Clinical and biochemical parameters: All clinical symptoms and metabolic parameters, including FBS, HbA1c, lipid profiles, and ACR, were evaluated and recorded on a pro forma in patients with T2DM.

Diagnosis of T2DM

T2DM was diagnosed according to the ADA criteria. Patients newly diagnosed with type 2 diabetic mellitus were clinically evaluated for polyuria (frequent urination), polyphagia (increased appetite), polydipsia (excessive thirst), weight loss greater than 5% during the previous six months, weakness (decreased strength during daily activities), excessive sweating (increased perspiration), or blurred vision (decreased visual clarity), and the diagnosis was confirmed using ADA criteria[11.]

Diabetic peripheral neuropathy:

Diabetic neuropathy was screened with the Michigan Neuropathy Screening Instrument (MNSI)[12,13]. The MNSI is a validated and reliable tool. Patients were asked the MNSI clinical questions to help determine their clinical level of peripheral neuropathy. The questionnaire section of the MNSI consists of 15 items. If a patient answered "yes" to any of the questions, it was considered indicative of possible peripheral neuropathy, which was then confirmed through the clinical examination, the second component of the MNSI. The second part of the MNSI includes five distinct categories—appearance, vibration sensation, ankle reflex, ulceration, and touch-pressure sensitivity. A score ranging from 0 to 1 was used to assess each of these parameters. An MNSI score ≥ 2.5 was used to diagnose peripheral neuropathy[14].

Statistical analysis: The Statistical Package for the Social Sciences (SPSS) Version 26 was used for analyses after data collection. Peripheral neuropathy was compared across both quantitative and qualitative variables using the chi-square test and the independent-samples t-test, with a significance level of $p \leq 0.05$.

RESULTS

Of the 175 newly diagnosed type 2 diabetes patients, male patients were 58.9% (n=103) and female patients were 41.1% (n=72), with a mean age of 45.77±8.59 years. The majority of type 2 diabetes patients were married (85.7%, n = 150) and employed (58.3%, n = 102) [**Table I**].

The majority of type 2 diabetes patients were presented with polyuria (97.1%, n=170), followed by polydipsia (84.6%, n=148), fatigue (81.7%, n=143), weakness (72.0%, n=126), polyphagia (59.4%, n=104), sweating (17.7%, n=31), weight loss (17.1%, n=30), and blurred vision (10.9%, n=19) [**Figure 1**]. Peripheral diabetic neuropathy was found in 41.7% (n=73) of patients [**Figure 2**].

Of the 73 peripheral diabetic neuropathy patients, male patients were non-significantly higher than female patients (58.9%, n=43 vs. 41.1%, n=30; p=0.991). Patients with diabetic neuropathy had a considerably higher mean age than those without the diabetic neuropathy (48.88±6.75 vs. 43.55 ± 9.10; p<0.001). The majority of peripheral diabetic neuropathy patients were married (90.4%, n = 66) and employed (53.4%, n = 39) [**Table II**].

Out of the 15 questions of the MNSI, 12 were applicable to our patients, as they were newly diagnosed. All reported questions were more frequently found in patients with diabetic neuropathy than those without the diabetic neuropathy. The most commonly found symptoms in diabetic neuropathy patients were burning pain (97.3%, n=71), weakness (94.5%, n=69), and symptoms worse at night (93.2%, n=68) [**Table III**].

Metabolic indices such as FBS, HbA1c, cholesterol, triglycerides, LDL-C, and ACR were considerably higher, while HDL-C was considerably lower in patients with peripheral diabetic neuropathy. The p-value was <0.001 for each parameter [**Table IV**].

Table I: Demographics of type 2 diabetes Mellitus Patients (n=175)

Demographics		Frequency	Percentage
Gender	Male	103	58.9
	Female	72	41.1
Age (Years)	Mean ± SD	45.77±8.59 (30-60)	
	30-40	55	31.4
	41-50	57	32.6
	51-60	63	36.0
Marital	Single	25	14.3
	Married	150	85.7
Occupation	Housewife	33	18.9
	Employed	102	58.3
	Unemployed	40	22.9

Table II: Demographics of Peripheral Diabetic Neuropathy Patients (n=175)

Demographics		Absent (n=102)	Present (n=73)	P-Value
Gender	Male	60(58.8%)	43(58.9%)	0.991
	Female	42(41.2%)	30(41.1%)	
Age (Years)	Mean ± SD	43.55±9.10	48.88±6.75	<0.001
	30-40	42(41.2%)	13(17.8%)	0.002
	41-50	32(31.4%)	25(34.2%)	
	51-60	28(27.5%)	35(47.9%)	
Marital	Single	18(17.6%)	7(9.6%)	0.133
	Married	84(82.4%)	66(90.4%)	
Occupation	Housewife	16(15.7%)	17(23.3%)	0.402
	Employed	63(61.8%)	39(53.4%)	
	Unemployed	23(22.5%)	17(23.3%)	

Table III: Clinical Features of Peripheral Diabetic Neuropathy Patients (n=175)

Questions	Absent (n=102)	Present (n=73)	P-Value
Are your legs and/or feet numb?	79(77.5%)	65(89.0%)	0.048
Do you ever have burning pain in your legs and/or feet?	87(85.3%)	71(97.3%)	0.008
Are your feet too sensitive to touch?	77(75.5%)	66(90.4%)	0.012
Do you get muscle cramps in your legs and/or feet?	73(71.6%)	62(84.9%)	0.038
Do you ever have any prickling feelings in your legs or feet?	25(24.5%)	45(61.6%)	<0.001
Does it hurt when the bed covers touch your skin?	13(12.7%)	28(38.4%)	<0.001
When you get into the tub or shower, are you able to tell the hot water from the cold water?	64(62.7%)	59(80.8%)	0.010
Have you ever had an open sore on your foot?	0(0.0%)	0(0.0%)	--
Has your doctor ever told you that you have diabetic neuropathy?	0(0.0%)	0(0.0%)	--
Do you feel weak all over most of the time?	76(74.5%)	69(94.5%)	0.001
Are your symptoms worse at night?	70(68.6%)	68(93.2%)	<0.001
Do your legs hurt when you walk?	55(53.9%)	55(75.3%)	0.004
Are you able to sense your feet when you walk?	81(79.4%)	68(93.2%)	0.012
Is the skin on your feet so dry that it cracks open?	10(9.8%)	27(37.0%)	<0.001
Have you ever had an amputation?	0(0.0%)	0(0.0%)	--

Table IV: Metabolic Indices and Peripheral Diabetic Neuropathy (n=175)

Metabolic Indices	Absent (n=102)	Present (n=73)	P-Value
HbA1c (%)	6.66±0.17	7.01±0.59	<0.001
FBS (mg/dl)	134.19±9.37	148.96±17.12	<0.001
Cholesterol (mg/dl)	162.01±19.99	179.15±18.02	<0.001
Triglycerides (mg/dl)	164.68±30.82	188.26±36.39	<0.001
LDL (mg/dl)	147.75±28.05	159.74±12.72	0.001
HDL (mg/dl)	38.51±4.45	33.40±5.24	<0.001
ACR (mg/g)	3.88±1.81	4.90±1.06	<0.001

HbA1c: Glycated Haemoglobin; FBS: Fasting Blood Sugar; LDL: Low-Density Lipoprotein Cholesterol; HDL: High-Density Lipoprotein Cholesterol; ACR: Albumin Creatinine Ratio.

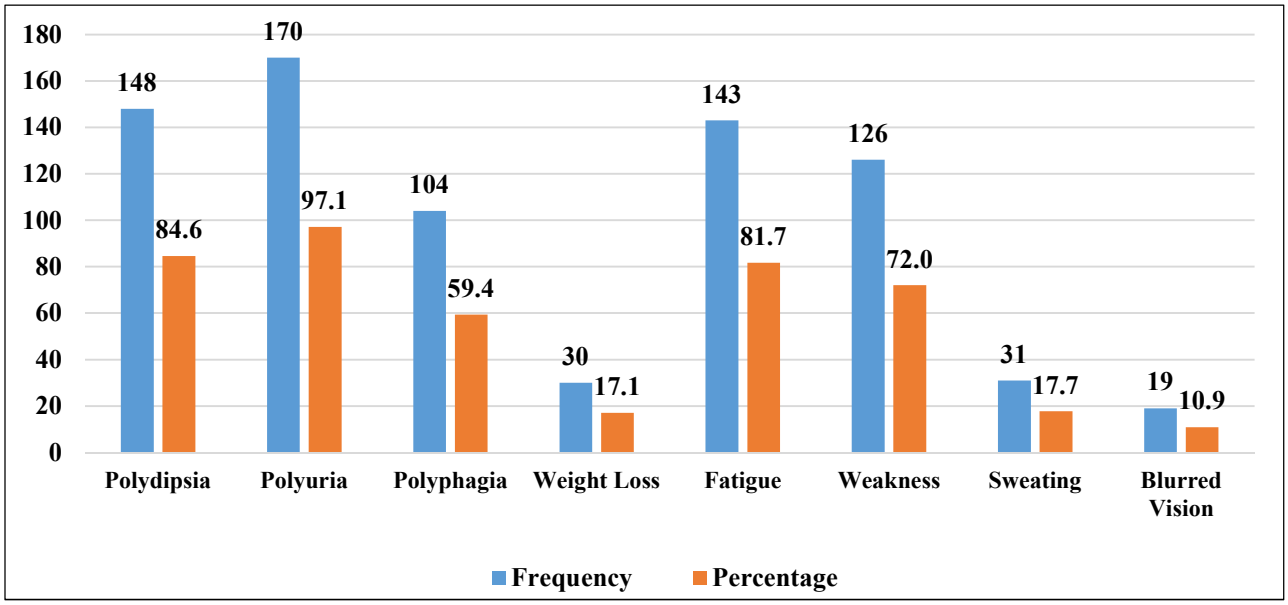

Figure 1: Clinical Features of Type 2 DM

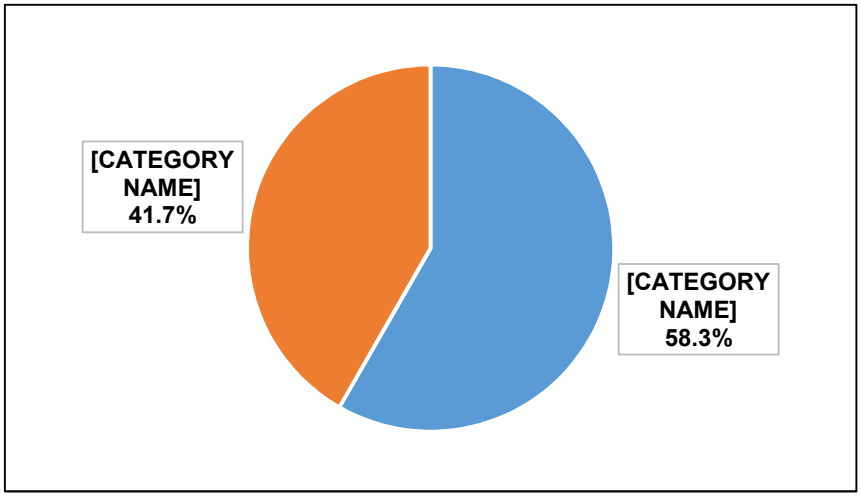

Figure 2: Peripheral Diabetic Neuropathy

DISCUSSION

Early diagnosis of diabetic peripheral neuropathy is of vital importance in newly diagnosed type 2 diabetes patients for immediate treatment and prevention of complications and worse outcomes. Globally, the prevalence of peripheral neuropathy in newly diagnosed type 2 diabetes patients is continuously increasing, indicating the significance of early screening upon diagnosis. Metabolic indices, such as lipid profiles, ACR, FBS, and HbA1c levels, have been identified as significant risk factors for the onset and progression of peripheral neuropathy[15,16].

This research was conducted at a hospital to assess peripheral neuropathy among those recently diagnosed with type 2 diabetes and to examine the correlation between metabolic indices and peripheral neuropathy using the MNSI score. In this study, 175 newly diagnosed type 2 diabetes patients were evaluated for peripheral neuropathy, of whom peripheral neuropathy was found in 41.7% (n = 73) of patients. Similarly, studies from Pakistan reported a higher prevalence of peripheral neuropathy, at 59.6%, 39.3%, and 37.7% amid newly diagnosed patients with type 2 diabetes[14,17,18]. In contrast, other studies from Pakistan and other countries, reported a lower prevalence of peripheral neuropathy, at 20.67%, 26.52%, 20%, and 29% amid newly diagnosed patients with type 2 diabetes[12,19-21]. It is more common among newly diagnosed type 2 diabetics in Pakistan, possibly due to delayed diagnosis, poor glycaemic control, and restricted access to healthcare facilities as compared to other countries.

In this study, of the 73 peripheral neuropathy patients, male patients were non-significantly higher than female patients (58.9%, n=43 vs. 41.1%, n=30; p=0.991). A similarly higher male prevalence among peripheral neuropathy patients was reported by previous researchers who reported male proportions of 54.9%, 56%, 59.6%, and 58.6%, respectively, among diabetic neuropathy patients[10,17,18,21]. These findings suggest that male diabetic patients experience a higher prevalence of diabetic neuropathy due to greater exposure to risk factors such as poor glycaemic control, lifestyle- or occupation-related stress, smoking, and higher comorbidities.

The mean age in peripheral neuropathy patients was significantly higher at 48.88±6.75 years. Most of the patients fell in the age group of 51-60 years (47.9%, n=35), followed by the age groups of 41-50 years (34.2%, n=25) and 30-40 years (17.8%, n=13). A similarly higher age among peripheral neuropathy patients was reported by previous researchers, such as Qureshi EF et al.[17], who reported that 65% of peripheral neuropathy patients were above 50 years of age, and Naqvi IH et al.[18] and Mairaj MK 2024[20], who reported higher mean ages of 51.4 and 55.6 years among peripheral neuropathy patients, respectively. These findings suggest that older age is among the most common risk factors of diabetic neuropathy, and the risk continues to increase with advancing age.

In this study, metabolic indices such as FBS, HbA1c, cholesterol, triglycerides, LDL-C, and ACR were considerably higher, while HDL-C was considerably lower in patients with peripheral diabetic neuropathy. Higher FBS and HbA1c indicate poor glycaemic control, whereas higher cholesterol, triglycerides, and LDL-C and lower HDL-C indicate dyslipidaemia and vascular dysfunction. Increased levels of ACR indicate early kidney damage. Nozawa K 2022[22] showed that higher 3-year mean HbA1c levels were significantly associated with diabetic peripheral neuropathy. Zhang H et al.[23] reported elevated levels of LDL-C and HbA1c levels. They linked these to reduced motor fibre conduction velocities of the Ulnar and common peroneal nerves in the neuropathy group. Wang W 2023[24] have shown that diabetic patients with lipid metabolism impairment have an increased risk of developing diabetic peripheral neuropathy and that total serum cholesterol, triglycerides, HDL, and LDL cholesterol are predictors of neuropathy. Hoque

S 2016[25] have shown that HbA1c > 7.0% was significantly associated with increased prevalence of diabetic peripheral neuropathy. Lai YR 2024[26] reported that HbA1c variability was a robust predictor of the emergence of new diabetic sensory peripheral neuropathy independent of age and diabetes duration. Zhang H 2024[27] also reported that elevated HbA1c and urinary ACR levels are risk factors for diabetic peripheral neuropathy and may be considered as a potential biomarker for it in T2DM patients. Fukuda T et al.[28] have shown a significant association between diabetic peripheral neuropathy and urinary albumin excretion in patients having type 2 diabetes. A study by Naqvi et al. [18] reports that increased cholesterol, ACR, and HbA1c levels are substantial risk factors for the early development of peripheral neuropathy. Similarly, Qureshi EF et al.[17] and Akhtar S 2023[19] found the noteworthy association of peripheral neuropathy with increased levels of HbA1c. Another study by Mairaj MK 2024[20] establishes the significant association of peripheral neuropathy with increased levels of HbA1c, cholesterol and albuminuria. These similar studies' findings suggest that poor metabolic control directly interferes with both vascular and neurological pathways, increasing the risk of the development of peripheral neuropathy.

In this study, we use the MNSI screening tool to determine peripheral neuropathy. D'Souza M 2015[29] among Bangladeshi patients have shown the occurrence of diabetic peripheral neuropathy identified through the MNSI history version and the MNSI examination of 18.3% and 32.2%, respectively and shown correlation with male gender and smoking. An earlier study on Iranian patients has also shown the mean neuropathy score of MNSI 2.3 (1.7) with a significant relationship between the number of neuropathies and the mean of diabetes duration and retinopathy[30]. Kaymaz S 2020[31] have also shown an MNSI score of 8.5 (11.25) for peripheral neuropathy among Turkish diabetic patients.

This research has several limitations. First, the study was conducted at a single tertiary care facility with a small sample size, which limits the results' generalisability of the results. Second, information about the various risk factors that affect the association of peripheral neuropathy and metabolic indices was not collected, including body mass index and other comorbidities.

CONCLUSION

The frequency of peripheral neuropathy in newly diagnosed patients with type 2 diabetes mellitus was high. Higher levels of FBS, HbA1c, cholesterol, triglycerides, LDL-C, and ACR, and lower levels of HDL-C, were significantly associated with peripheral neuropathy. These findings propose that poor metabolic control contributes to the early development of diabetic neuropathy, indicating the need for early screening and metabolic management in newly diagnosed diabetic patients.

Ethical permission: Dow University of Health Sciences, Karachi, Pakistan, IRB approval letter No. IRB-3726/DUHS/Approval/2024/384.
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Data Sharing Statement: The corresponding author can provide the data proving the findings of this study on request. Privacy or ethical restrictions bound us from sharing the data publicly.

AUTHOR CONTRIBUTION

Aslam SM: Contribution to concept, manuscript drafting.
Khan MU: Critical review, has given final approval of the version to be published.
Naqvi IH: Contribution to interpretation of data analysis and manuscript formation.

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