doi:10.2478/enr-2025-0025

LDL/HDL ratio and HOMA-IR as markers of severity of peripheral neuropathy in diabetic population

Anand Nisintha, Kumar Bhargavi, Thangavelu Saravanan

Department of General Medicine, PSG Institute of Medical Sciences and Research, Peelamedu, Coimbatore, India
E-mail: kmcbhargavi@gmail.com

Objective. Diabetic peripheral neuropathy (DPN) is a common complication of type 2 diabetes mellitus (T2DM) that substantially impairs quality of life. This study aimed to assess the relationship between metabolic parameters and DPN severity in T2DM patients.

Methods. A prospective observational study was conducted at PSG Institute of Medical Sciences and Research (Peelamedu, Coimbatore, India) from August 2023 to August 2024, enrolling 90 adults with T2DM on oral hypoglycemic agents after ethical approval and informed consent. Blood samples were analyzed for fasting glucose, HbA1c, lipid profile, and plasma insulin. The LDL/HDL ratio and HOMA-IR were calculated to evaluate metabolic status. DPN severity was measured using a biothesiometer.

Results. The higher HbA1c levels significantly correlated with increased neuropathy severity (severe: 12.1±1.3% vs. mild: 8.4±2.0%; p=0.002). LDL/HDL ratio was elevated in patients with severe DPN (3.6±1.8) compared to mild DPN cases (2.5±1.0), but this difference was not significant (p=0.12). Severe DPN cases also showed higher HOMA-IR (10.2±2.8) suggesting a possible link to insulin resistance though not statistically significant (p=0.23).

Conclusion. HbA1c strongly associates with DPN severity, while LDL/HDL ratio and HOMA-IR showed no significant correlation. Further research is needed to clarify these metabolic relationships and their clinical relevance.

Keywords: type 2 diabetes mellitus, diabetic peripheral neuropathy, HbA1c; LDL/HDL ratio; insulin resistance

According to the International Diabetes Federation (IDF) Diabetes Atlas 11th Edition (2025), the prevalence of diabetes (in adults aged 20–79 years) in 2024 was 11.1% (588.7 million people) and it is projected to be 13% by 2025. The mortality attributed to diabetes is about 3.4 million as until 2024. The total health expenditure due to diabetes mellitus (DM) stands at around 1 trillion US Dollars (IDF Diabetes Atlas 2025).

Diabetes mellitus is one of the most prevalent metabolic illnesses worldwide with diabetic peripheral neuropathy (DPN) as its most frequent consequence. DPN is a microvascular consequence of DM that results in irreversible anatomical and functional alterations in the nerves due to demyelination, axonal atrophy, and diminished regeneration (Uslu and Yilmaz 2025). A report by the International Diabetes Federation in 2021 characterizes diabetes as a rapidly expanding global pandemic of the 21st century, projecting an increase in prevalence from 10.5% (536.6 million individuals) in 2021 to 12.2% (783.2 million individuals) by 2045 (Atmaca et al. 2024).

Among the consequences of DM, neuropathy results in the highest morbidity and significantly diminishes the patient's quality of life if inadequately

Corresponding author: Kumar Bhargavi, M.D., Associate Professor, PSG Institute of Medical Sciences and Research, Peelamedu, Coimbatore, India; phone: 9855478899; e-mail: kmcbhargavi@gmail.com.

controlled. DPN may manifest asymptomatically and remain undiscovered or it may present with gradually progressing signs and symptoms potentially leading to severe problems. Moreover, DPN is linked to gait irregularities and worse balance, which can lead to impairment and diminish the patient's quality of life (Dhillon et al. 2023). The pathophysiology is intricate, mostly associated with the activation of the polyol pathway, oxidative stress, chronic low-grade inflammation, immune system impairment, excessive glycosylation of neural tissue, and deficiency of neurotrophic factors (Sun et al. 2022; Ma 2023).

Insulin resistance quantified by Homeostatic Model Assessment of Insulin Resistance (HOMA-IR) intensifies neuropathy by various mechanisms. Hyperinsulinemia diminishes neurotrophic factors such as nerve growth factor (NGF) and insulin-like growth factor-1 (IGF-1) hindering axonal regeneration. Furthermore, insulin resistance impairs microvascular function by diminishing nitric oxide (NO) bioavailability resulting in persistent neuronal hypoxia. Clinically, each 1-unit increment in HOMA-IR is associated with a 56% increased probability of DPN in obese diabetic patients. Individuals with prediabetes exhibiting HOMA-IR values exceeding 2.8 demonstrate a 43% prevalence of neuropathy in contrast to 18% among insulin-sensitive individuals indicating that metabolic dysregulation predates overt diabetes in contributing to nerve injury (Han et al. 2015; Singh et al. 2019; Gonzalez-Gonzalez et al. 2022; Mehta et al. 2024).

Lipid abnormalities, especially modified low-density lipoprotein/high-density lipoprotein (LDL/HDL) ratios, have become significant indicators of microvascular problems. This ratio integrates both atherogenic (LDL) and protective (HDL) elements offering a comprehensive perspective on cardiovascular and neurological risk in contrast to standalone lipid measures. Increased LDL/HDL ratios are associated with endothelial dysfunction in the vasa nervorum leading to diminished nerve perfusion and facilitating ischemia. The anti-inflammatory effects of HDL encompassing its function in reverse cholesterol transport and the suppression of LDL oxidation are essential for preserving brain health (Sun et al. 2022).

The combined effect of dyslipidemia and insulin resistance markedly increases the risk of neuropathy. The effect of lipid-lowering medications on the course of neuropathy, independent of diabetic management, remains inadequately investigated. The present therapy is predominantly glucocentric, frequently neglecting the dysmetabolic origins of nerve injury. However, there is a lack of evidence on the effect of LDL/HDL ratio and HOMA-IR on DPN severity.

The present study was conducted to examine the individual and combined effects of the LDL/HDL ratio and HOMA-IR on the severity of neuropathy. This study aimed to assess the correlation between the LDL/HDL ratio, insulin resistance (measured by HOMA-IR), and the severity of peripheral neuropathy in a diabetic cohort.

Subjects and Methods

Subjects. The present study was a prospective observational study, which was conducted among patients with type 2 diabetes mellitus (T2DM) who attended the outpatient department of the Department of General Medicine of the PSG Institute of Medical Sciences and Research (Peelamedu, Coimbatore, India) or were admitted to the hospital between August 2023 and August 2024. The study was conducted after obtaining clearance from the Institutional Human Ethics Committee (IHEC) with reference number PSG/IHEC/2023/Appr/Exp/FB/041 as well as informed consent from the participants.

Patients aged ≥18 years diagnosed with T2DM and on oral hypoglycemic agents for glycemic control were included in the present study. Patients on insulin therapy and diagnosed with type 1 diabetes mellitus (T1DM) were excluded from the present study.

A consecutive sampling technique was employed, wherein all eligible patients attending the PSG Institute of Medical Sciences and Research (Peelamedu, Coimbatore, India) during the study period were approached for inclusion in the study until the required sample size was achieved. The participants were included after they satisfied both the inclusion and exclusion criteria.

Ethical approval. The study was conducted after obtaining clearance from the IHEC with reference number PSG/IHEC/2023/Appr/Exp/FB/041 as well as informed consent from the participants.

Sample size estimation. The sample size was calculated based on the prevalence of diabetes in India, which is approximately 9% as per the National Noncommunicable Disease Monitoring Survey (NNMS). The sample size was calculated using the formula n=4pq/d2 where p=9%, q=100-p=91%, d=absolute precision=7%. The initial calculated sample size was 67. Anticipating a 20% non-response rate and 10% loss to follow-up, the required sample size was calculated to be 88 participants. Finally, the data was collected from a total of 90 study participants.

Procedure. Participants underwent blood sample collection for fasting plasma glucose, glycated hemoglobin (HbA1C), lipid profile, and plasma insulin levels. The LDL/HDL ratio was derived from the lipid profile, and HOMA-IR was calculated to assess insulin resistance. The severity of DPN was graded using a biothesiometer, which measures the vibration perception threshold (VPT) on the patient's foot. Data were collected using a structured data sheet that included demographic details, clinical history, and laboratory results. The HOMA-IR was calculated using the following formula: (fasting insulin (mU/L) x fasting glucose (mg/dL))/405.

Statistical analysis. The collected data were entered into Microsoft Excel for initial tabulation. Data were analyzed using SPSS software version 24.0. Categorical variables are presented in a frequency table and continuous variables are presented as Mean ± SD or Median (Min, Max). For continuous variables, the normality of data was assessed using the Kolmogorov-Smirnov test, then independent t-test or Mann-Whitney U test were used to assess a significance between two groups. For more than two groups, the one-way analysis of variance (ANOVA) or Kruskal-Wallis test were used to assess a significance between the groups. For categorical variables, Pearson's chi-square test verified the relationship between the characteristics in two groups. When this test did not meet its requirements (n>20, all expected values in the table are greater than 1 and at least 80% of these are greater than or equal to 5), we used Fisher's exact test. The $p<0.05$ was considered statistically significant.

Results

The study population had a mean age of 57.2±11.8 years with a slight male predominance (53.3%). Duration of diabetes varied with 52.2% having DM for ≤5 years and 47.8% for more than 5 years. The mean fasting blood sugar (FBS) was 161.3±62.5 mg/dL and the postprandial blood sugar (PPBS) was 222.4±85.2 mg/dL suggesting poor glycemic control. HbA1c levels averaged 8.4±2.0% reinforcing chronic hyperglycemia and suboptimal disease management. Lipid profiles indicated a mean total cholesterol of 161.4±47.2 mg/dL, triglycerides at 153.9±81.5 mg/dL, and an LDL/HDL ratio of 3.0±1.3. The HOMA-IR index (8.6±6.4) reflected significant insulin resistance (Table 1).

The highest proportion of patients (29%) had diabetes for 2–5 years followed closely by those with a 6–10-year history (27%) (Figure 1). Peripheral neuropathy severity varied with mild cases being the most prevalent (61.1%) followed by moderate (26.7%) and severe neuropathy (5.6%), while 6.7% had no neuropathy (Figure 2).

Table 1
Demographic characteristics of the study sample

Variables	Sub-category	Number of subjects (%)
Age (years)	Mean ± SD	57.2±11.8
Gender	Male	48 (53.3%)
	Female	42 (46.7%)
Comorbidities		
Diabetes duration	0–5 Years	47 (52.2%)
	>5 Years	43 (47.8%)
Other comorbidities	No	29 (32.2%)
	Yes	61 (67.8%)
Smoker	No	72 (80.0%)
	Yes	18 (20.0%)
Alcoholic	No	72 (80.0%)
	Yes	18 (20.0%)
FBS (mg/dL)	Mean ± SD	161.3 ± 62.5
PPBS (mg/dL)	Mean ± SD	222.4 ± 85.2
HbA1C (%)	Mean ± SD	8.4 ± 2.0
Total cholesterol (mg/dL)	Mean ± SD	161.4 ± 47.2
Triglycerides (mg/dL)	Mean ± SD	153.9 ± 81.5
LDL/HDL ratio	Mean ± SD	3.0 ± 1.3
HOMA-IR	Mean ± SD	8.6 ± 6.4
Severity of peripheral neuropathy	Normal	6 (6.7%)
	Mild	55 (61.1%)
	Moderate	24 (26.7%)
	Sever	5 (5.6%)

Abbreviations: FBS – fasting blood sugar; HDL – high-density lipoprotein; HOMA-IR – Homeostatic Model Assessment of Insulin Resistance; LDL – low-density lipoprotein; PPBS – postprandial blood sugar.

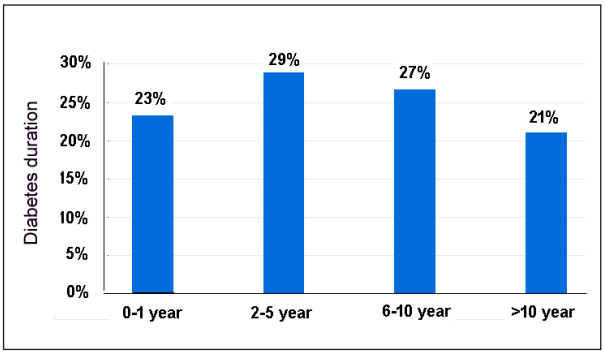

Figure 1. Duration of the diabetes and patient outcomes of the study sample.

Among the 90 diabetic patients, mild neuropathy was more common in females (71.4%) than males (52.1%), whereas moderate (33.3%) and severe (8.3%) neuropathy was more prevalent in males. The results indicate that males had a higher proportion of moderate and severe neuropathy, but the association was not statistically significant (p=0.214) (Table 2). Patients with diabetes for more than 5 years had higher rates of moderate (32.6%) and severe (9.3%) neuropathy than those with diabetes for 0–5 years (21.3% moderate, 2.1% severe). Mild neuropathy was more frequent in patients with shorter diabetes duration (70.2%). Although there was a trend of worsening neuropathy with prolonged diabetes duration, the association was not statistically significant (p=0.216) (Table 2). Patients with other comorbidities had a higher proportion of moderate neuropathy (31.1%) compared to those without (17.2%), but the association was not statistically significant (p=0.471). Smokers and alcohol users had higher rates of mild neuropathy (72.2% and 66.7%, respectively) though severe cases remained relatively low (5.6%). No statistically significant association was found between neuropathy severity and smoking (p=0.738) or alcohol consumption (p=0.892) (Table 2).

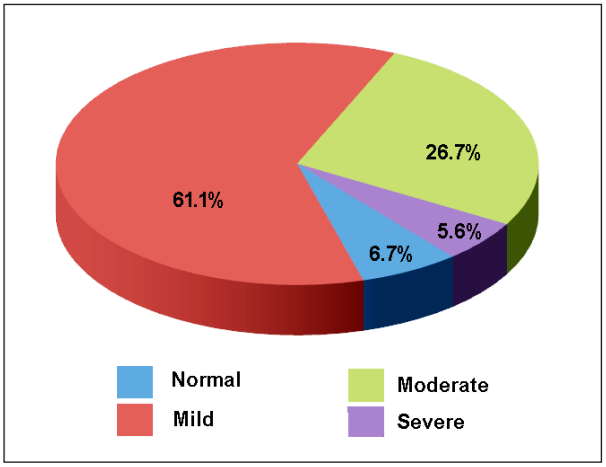

Figure 2. Patients' outcomes severity of peripheral neuropathy of the study sample.

The mean age across all groups was similar with no significant difference (p=0.94) indicating that age alone may not be a determining factor for neuropathy progression. FBS was significantly higher in the severe neuropathy group (218.4±77.0 mg/dL) compared to milder cases (p=0.03) suggesting that poor fasting glucose control may contribute to neuropathy progression. PPBS was also highest in the severe group (348.2±106.2 mg/dL) indicating worsening neuropathy with poor post-meal glucose regulation (p=0.05) (Table 3). HbA1c levels were significantly elevated in severe cases (12.1±1.3%) highlighting chronic hyperglycemia as a major risk factor for advanced neuropathy (p=0.002). Total cholesterol, triglycerides, and LDL/HDL ratio did not show statistically significant associations with neuropathy

Table 2
Association between severity of peripheral neuropathy and demographic factors used in this study

Variables	Categories	Severity of peripheral neuropathy				p-value
		Normal	Mild	Moderate	Severe	
Gender	Male	3 (6.3%)	25 (52.1%)	16 (33.3%)	4 (8.3%)	0.214
	Female	3 (7.2%)	30 (71.4%)	8 (19.0%)	1 (2.4%)	
Diabetes duration	0–5 Year	3 (6.4%)	33 (70.2%)	10 (21.3%)	1 (2.1%)	0.216
	>5 Year	3 (7.0%)	22 (51.2%)	14 (32.6%)	4 (9.3%)	
Other comorbidities	No	3(10.3%)	19 (65.5%)	5 (17.2%)	2 (6.9%)	0.471
	Yes	3 (4.9%)	36 (59.0%)	19 (31.1%)	3 (4.9%)	
Smoker	No	5 (6.9%)	42 (58.3%)	21 (29.2%)	4 (5.6%)	0.738
	Yes	1 (5.6%)	13 (72.2%)	3 (16.7%)	1 (5.6%)	
Alcoholic	No	5 (6.9%)	43 (59.7%)	19 (26.4%)	5 (6.9%)	0.892
	Yes	1 (5.6%)	12 (66.7%)	5 (27.8%)	–	

Data are presented as number (%) and were statistically analyzed by Fisher's exact test; # indicates statistical significance.

severity (p>0.05). However, patients with severe neuropathy had higher LDL/HDL ratios (3.6±1.8). HOMA-IR values were highest in severe neuropathy cases (10.2±2.8) indicating a strong association between insulin resistance and neuropathy progression although not statistically significant (p=0.23) (Table 3).

Table 4 provides the results of multinomial logistic regression analysis examining predictors of peripheral neuropathy severity. Since the "severe" category had insufficient observations, results for that category are not available. All variables did not show significant associations (p<0.05), meaning none of the predictors have a confirmed strong association with mild or

Table 3
Effect between metabolic parameters with severity of peripheral neuropathy used in this study

Parameter	Severity of peripheral neuropathy			
	Normal	Mild	Moderate	Severe
Age (years)				
Mean±SD	57.0±10.8	56.7±12.2	58.8±12.2	55.2±5.9
Median (Min, Max)	54.0 (44, 76)	57.0 (28, 83)	57.0 (41, 94)	57.0 (48, 61)
	value = 0.384; p-value = 0.94**			
FBS (mg/dL)				
Mean±SD	146.2±39.7	158.3±61.8	151.4±50.5	218.4±77.0
Median (Min, Max)	141.5 (90, 203)	144.0 (77, 369)	138.0 (94, 283)	195.0 (129, 401)
	value = 8.74; p-value = **0.03****#			
PPBS (mg/dL)				
Mean±SD	221.0±76.3	212.9±80.6	218.4±77.0	348.2±106.2
Median (Min, Max)	251.0 (99, 291)	197.0 (86, 479)	195.0 (129, 401)	300.0 (232, 483)
	value = 7.75; p-value = **0.05****#			
HbA1C (%)				
Mean±SD	8.0±1.5	8.0±1.6	8.8±2.1	12.1±1.3
Median (Min, Max)	8.1 (6.0, 9.6)	7.7 (4.9, 12.6)	8.3 (5.5, 13.6)	12.0 (10.5, 13.9)
	value = 14.61; p-value = **0.002****#			
TC (mg/dL)				
Mean±SD	169.7±55.2	158.8±40.5	158.9±54.8	191.6±71.2
Median (Min, Max)	160.0 (107, 234)	156.0 (98, 271)	159.0 (85, 282)	209.0 (76, 261)
	value = 2.27; p-value = 0.519**			
TGs (mg/dL)				
Mean±SD	145.2±75.4	150.9±80.3	157.2±90.5	182.0±71.3
Median (Min, Max)	130.0 (67, 279)	130.0 (66, 418)	143.0 (52, 484)	200.0 (73, 260)
	value = 1.77; p-value = 0.622**			
LDL/HDL ratio				
Mean±SD	2.9±1.2	2.8±1.2	3.1±1.5	3.6±1.8
Median (Min, Max)	3.1 (1.1, 4.2)	2.8 (1.0, 7.5)	3.1 (0.5, 5.9)	4.5 (1.0, 5.1)
	value = 1.47; p-value = 0.689**			
HOMA-IR				
Mean±SD	12.6±10.4	8.0±6.5	8.5±5.6	10.2±2.8
Median (Min, Max)	9.4 (3.6, 28.8)	6.3 (0.7, 31.0)	8.7 (0.8, 27.9)	9.0 (7.3, 14.3)
	value = 4.21; p-value = 0.239**			

Abbreviations: FBS – fasting blood sugar; HDL – high-density lipoprotein; HOMA-IR – Homeostatic Model Assessment of Insulin Resistance; LDL – low-density lipoprotein; PPBS – postprandial blood sugar; TC – total cholesterol; TGs – triglycerides. Data were statistically analyzed by *one-way ANOVA or **Kruskal-Wallis H Test; #indicates statistically significant differences at p<0.05.

moderate peripheral neuropathy. HbA1C [1.10 (0.41, 2.94 for mild and 2.33 (0.81, 6.69) for moderate] and LDL/HDL ratio [0.97 (0.28, 3.39) for mild and 2.54 (0.67, 9.66) for moderate] showed potential trends toward significance suggesting that they may play a role in peripheral neuropathy severity. HOMA-IR had a protective effect in mild neuropathy, but was not significant.

Discussion

Diabetic peripheral neuropathy is a condition characterized by damage to peripheral nerves leading to symptoms such as pain, numbness, and paralysis. The etiology of DPN is complex with chronic hyperglycemia, dyslipidemia, and insulin resistance playing key roles in its development and progression (Ma 2023). This study investigates the relationship between metabolic parameters and the severity of peripheral neuropathy in diabetic patients. The findings aim to elucidate the roles of glycemic control, lipid profiles, and insulin resistance in the progression of neuropathy.

With a mean age of 57.2±11.8 years and a male predominance of 53.3% the study cohort conforms to high-risk diabetic groups due to aging and male

Table 4
Multinominal logistic regression analysis for predictors of severity of peripheral neuropathy among the study participants

Variables		B	p–value	OR (95% CI)
Mild peripheral neuropathy	Age	–0.008	0.86	0.99 (0.91, 1.09)
	Gender (female)	1.60	0.22	4.96 (0.38, 64.93)
	Duration of diabetes mellitus (0 – 5 years)	0.35	0.74	1.42 (0.18, 11.02)
	Other comorbidities (No)	–0.40	0.71	0.67 (0.08, 5.54)
	Smoker (No)	–1.12	0.55	0.33 (0.008, 12.90)
	Alcoholic (No)	–0.81	0.62	0.45 (0.02, 11.38)
	FBS	0.03	0.16	1.03 (0.99, 1.07)
	PPBS	–0.013	0.31	0.99 (0.96, 1.01)
	HbA1C	0.097	0.85	1.10 (0.41, 2.94)
	Total cholesterol	–0.015	0.35	0.99 (0.95, 1.02)
	Triglycerides	0.004	0.60	1.004 (0.99, 1.02)
	LDL/HDL ratio	–0.036	0.96	0.97 (0.28, 3.39)
	HOMA-IR	–0.14	0.054	0.87 (0.76, 1.003)
	Constant	4.70	0.35	
Moderate peripheral neuropathy	Age	0.018	0.73	1.018 (0.92, 1.13)
	Gender (female)	–0.99	0.49	0.37 (0.023, 6.00)
	Duration of diabetes mellitus (0 – 5 years)	–0.78	0.50	0.46 (0.05, 4.31)
	Other comorbidities (No)	–1.82	0.14	0.16 (0.015, 1.79)
	Smoker (No)	1.84	0.39	6.30 (0.099, 399,79)
	Alcoholic (No)	0.37	0.83	1.44 (0.05, 43.26)
	FBS	0.003	0.90	1.003 (0.96, 1.04)
	PPBS	–0.009	0.49	0.99 (0.97, 1.02)
	HbA1C	0.85	0.12	2.33 (0.81, 6.69)
	Total cholesterol	–0.032	0.09	0.97 (0.93, 1.005)
	Triglycerides	0.013	0.13	1.013 (0.99, 1.03)
	LDL/HDL ratio	0.93	0.17	2.54 (0.67, 9.66)
	HOMA-IR	–0.094	0.24	0.91 (0.78, 1.07)
	Constant	–4.19	0.46	

Abbreviations: FBS – fasting blood sugar; HDL – high-density lipoprotein; HOMA-IR – Homeostatic Model Assessment of Insulin Resistance; LDL – low-density lipoprotein; PPBS – postprandial blood sugar. # indicates statistically significant differences at $p<0.05$.

sex being recognized risk factors for DPN due to cumulative microvascular injury and gender-specific metabolic variations (Amour et al. 2019). Long-term diabetes (>5 years in 47.8%) and poor glycemic control (HbA1c 8.4±2.0%, FBS 161.3±62.5 mg/dL, PPBS 222.4±85.2 mg/dL) may have accelerated neuropathy by promoting advanced glycation end-products and oxidative stress, increasing the odds of DPN by 7.8 times per year (Nisar et al. 2015). Due to impaired vasa nervorum perfusion and adipokine-mediated inflammation, comorbidities and lifestyle factors like smoking and alcohol intake worsen neurovascular injury (Mokhtarpour et al. 2024).

The study population exhibited mild dyslipidemia characterized by a mean total cholesterol of 161.4±47.2 mg/dL, triglycerides at 153.9±81.5 mg/dL, and an elevated LDL/HDL ratio of 3.0±1.3. Dyslipidemia is a recognized contributor to DPN as elevated LDL and triglycerides exacerbate oxidative stress, inflammation, and lipotoxicity, while reduced HDL impedes reverse cholesterol transport and anti-inflammatory mechanisms (Dinh Le et al. 2022; Ponirakis et al. 2022). The mean HOMA-IR index of 8.6±6.4 signifies considerable insulin resistance, which is intricately associated with DPN through processes such as oxidative stress and cytokine production (Dinh Le et al. 2022). Insulin resistance exacerbates dyslipidemia by increasing very low-density lipoprotein (VLDL) production, hence exacerbating atherogenic lipid profiles (Dinh Le et al. 2022; Liu et al. 2022; Yu et al. 2024).

This study indicated that mild peripheral neuropathy was the most common affecting 61.1% of participants followed by moderate instances at 26.7% and severe cases at 5.6%, while 6.7% exhibited no neuropathy. This distribution highlights the persistent character of DPN, wherein mild symptoms frequently precede more severe manifestations, consistent with other research indicating a cumulative increase in neuropathy severity correlated with the duration of diabetes (Zhu et al. 2024).

The results demonstrate that mild neuropathy occurred more frequently in females (71.4%) than in males (52.1%), although intermediate (33.3%) and severe neuropathy (8.3%) were more prevalent in males. Nevertheless, these differences lacked statistical significance (p=0.214). This corresponds with other research indicating that although males may exhibit more severe manifestations of DPN, gender disparities in neuropathy severity frequently lack statistical significance (Javed et al. 2014; Abosrea et al. 2020). Furthermore, patients with diabetes for over five years demonstrated elevated rates of moderate (32.6%) and severe neuropathy (9.3%) relative to those with a shorter duration of diabetes reinforcing the hypothesis that extended hyperglycemia leads to nerve damage. However, this trend did not achieve statistical significance (p=0.216). The significant occurrence of mild neuropathy in individuals with a shorter period of diabetes (70.2%) indicates early-stage nerve impairment underscoring the necessity for prompt diagnosis and care to avert development (Vinik et al. 2006). Lifestyle factors including smoking and alcohol intake were linked to increased instances of mild neuropathy, but did not exhibit significant relationships with severity (p=0.738 and p=0.892, respectively). These findings underscore the intricate interactions among gender, diabetes duration, comorbidities, and lifestyle factors in the onset of DPN necessitating additional research to elucidate these connections and enhance management options.

The study indicates that age did not significantly affect the course of neuropathy (p=0.94), suggesting that age alone may not be a decisive factor for DPN. FBS levels were markedly elevated in the severe neuropathy group (218.4±77.0 mg/dL) relative to milder cases (p=0.03) indicating that inadequate fasting glucose regulation exacerbates neuropathy severity. PPBS was highest in the severe group (348.2±106.2 mg/dL) underscoring the contribution of post-meal hyperglycemia to the exacerbation of neuropathy (p=0.05). In severe cases, elevated HbA1c values (12.1±1.3%) underscore chronic hyperglycemia as a significant risk factor for progressive neuropathy (p=0.002). A retrospective analysis conducted between 2016 and 2021 demonstrated a significant correlation between HbA1c levels and hematological parameters, suggesting that effective glycemic control may prevent or delay neuropathy in diabetic patients (AlShareef et al. 2024). Similarly, a prospective cohort study revealed that long-term glycemic variability, measured by HbA1c coefficient of variation (CV), is linked to painful DPN with higher HbA1c-CV tertiles showing increased odds ratios for neuropathic pain (Su et al. 2018). This also resonated with the real-world data reported by Nozawa et al. (2022), who have shown that the development or progression of DPN in patients with T2DM was associated with the 3-year mean HbA1c level in real-world data. Conversely, a 6-year follow up study by Chang et al. (2024) reported that HbA1c-CV did not show a significant association with the risk of painful DPN. While another 10-year follow up study reported that individuals who developed neuropathy had significantly higher mean levels of glycemic

indices (HbA1c, FBS, and PPBS), urinary albumin excretion, mean creatinine levels, and a longer duration of diabetes (Firouzabadi et al. 2023).These findings correspond with previously published data which states that prolonged hyperglycemia interferes with nerve-associated metabolic pathways, resulting in oxidative stress, inflammation, and neuroischemia, which collectively facilitate the evolution of DPN (Mayeda et al. 2020; Jia et al. 2024; Wang et al. 2024).

While total cholesterol, triglycerides, and LDL/HDL ratio did not correlate with neuropathy severity ($p>0.05$) individuals with severe neuropathy had elevated ratios (3.6±1.8) suggesting vascular issues affecting nerve health. Despite low statistical significance ($p=0.23$), severe neuropathy cases had elevated HOMA-IR values (10.2±2.8) suggesting a link between insulin resistance and neuropathy progression warranting additional research. Research suggests that dyslipidemia, particularly high triglycerides, and insulin resistance may cause and progress DPN (Vincent et al. 2009; Afshinnia et al. 2022). Although numerous studies have not found a direct link between all lipid markers and diabetic neuropathy, increased LDL/HDL ratios may signal nerve health issues due to vascular malfunction (Vincent et al. 2009). A prior study found that patients without DPN had lower LDL-C levels than those with DPN ($p=0.052$) (Zhang et al. 2023). Another study found that lower HDL-C was linked to DPN, but not LDL-C, total cholesterol, or triglycerides. After controlling for sex, age, and BMI, the significance decreased, although factors like lipid-lowering drug reduction were excluded (Sanchez-Pozos et al. 2021). In another study, diabetics with neuropathy had greater HDL-C values than healthy controls and diabetics without neuropathy. In general, diabetics without neuropathy had the lowest HDL-C. Although not statistically significant, diabetics with neuropathy had greater mean total cholesterol than controls and those without neuropathy. The diabetic group without neuropathy had a higher mean LDL-C value than those with neuropathy and the control group, but the difference was not significant. All lipid profile variables were negligible between diabetics with and without neuropathy (Huma et al. 2021). Although not statistically significant, severe instances of diabetic nephropathy had raised HOMA-IR suggesting that insulin resistance, possibly mediated by oxidative stress and inflammation, is essential (Afshinnia et al. 2022; Kristensen et al. 2024). Further research should use larger sample sizes and more complete lipidomic profiling to identify lipid species that cause nerve damage in diabetes (Cai et al. 2021; Afshinnia et al. 2022). The multinomial logistic regression analysis found no significant associations between mild or moderate peripheral neuropathy and any of the evaluated predictors ($p<0.05$) suggesting that factors like HbA1c and LDL/HDL ratio may not be a reliable predictor. HbA1c readings show that prolonged hyperglycemia may affect neuropathy consistent with prior findings on the negative effects of high blood glucose on nerve health (Barbosa et al. 2019). The higher LDL/HDL ratio in severe neuropathy patients suggests circulatory issues affecting nerve function, but more research is needed. Although not statistically significant ($p=0.23$), severe neuropathy cases had higher HOMA-IR values suggesting a protective effect in mild neuropathy. This finding may be underpowered due to broad confidence intervals (0.78, 1.07) and should be investigated. Insulin resistance may play multiple roles in diabetic complications like neuropathy (Cho et al. 2014; Eid et al. 2023). Wide confidence intervals in regression results show that low event counts in the severe neuropathy category may limit statistical power. Larger cohort studies with balanced severity distribution are needed. Although no significant associations were found, the observed trends suggest deeper inquiry into their potential role in neuropathy severity.

Despite existing limitations, this study sheds light on metabolic indicators and DPN severity. The cross-sectional methodology makes causal inferences about glycemic management, lipid profiles, and neuropathy progression difficult and the sample size may limit generalizability. Self-reported lifestyle factors including smoking and alcohol intake may be biased and longitudinal data is needed to evaluate neuropathy's progression. Subgroup analysis for age, BMI and comorbidities would have given better clarity. Some of these studies did not adequately address relevant confounders like statin or metformin use raising the likelihood of residual bias. Confounding variable adjustments are not stated in regression model results. Despite these limitations, the study's use of particular neuropathy evaluation tools improves reliability and the identification of HbA1c and LDL/HDL ratio changes as neuropathy severity markers is clinically noteworthy.

The findings highlight the importance of improving glycemic control and managing dyslipidemia to reduce the incidence of severe neuropathy. Prompt evaluation for neuropathy in persons with prolonged diabetes duration or insufficient metabolic control is crucial for preventing complications. Future research should focus on comprehensive longitudinal studies

to determine causal relationships and investigate specific lipid species that may influence neuron health. Examining lifestyle interventions for glucose regulation and cholesterol management is crucial for developing comprehensive solutions to alleviate DPN.

Conclusion

The present study emphasizes the significant correlation between glycemic management and the degree of peripheral neuropathy in diabetic patients indicating implications for HbA1c and LDL/HDL ratios. The results emphasize the importance of early screening of DPN and comprehensive therapeutic approaches aimed at metabolic factors to prevent the development of DPN and improve patient outcomes. Larger prospective studies are required to establish the predictive value of LDL/HDL ratio and HOMA-IR.

Conflict of interest: *The authors declare no conflict of interest.*

References

Abosrea M, Elmasry HA, Oraby MI. Gender differences in diabetic peripheral neuropathy. Egyptian J Med Res 1, 55–64, 2020.

Afshinnia F, Reynolds EL, Rajendiran TM, Soni T, Byun J, Savelieff MG, Looker HC, Nelson RG, Michailidis G, Callaghan BC, Pennathur S, Feldman EL. Serum lipidomic determinants of human diabetic neuropathy in type 2 diabetes. Ann Clin Transl Neurol 9, 1392–1404, 2022.

AlShareef AA, Alrawaili MS, Almutairi SA, Ayyad MM, Alshora W. Association of hematological parameters and diabetic neuropathy: a retrospective study. Diabetes Metab Syndr Obes 17, 779–793, 2024.

Amour AA, Chamba N, Kayandabila J, Lyaruu IA, Marieke D, Shao ER, Howlett W. Prevalence, patterns, and factors associated with peripheral neuropathies among diabetic patients at tertiary hospital in the Kilimanjaro region: descriptive cross-sectional study from North-Eastern Tanzania. Int J Endocrinol 2019, 5404781, 2019.

Atmaca A, Ketenci A, Sahin I, Sengun IS, Oner RI, Tilki HE, Adas M, Soyleli H, Demir T. Expert opinion on screening, diagnosis and management of diabetic peripheral neuropathy: a multidisciplinary approach. Front Endocrinol 15, 1380929, 2024.

Barbosa M, Saavedra A, Oliveira S, Reis L, Rodrigues F, Severo M, Sittl R, Maier C, Carvalho DM. Prevalence and determinants of painful and painless neuropathy in type 1 diabetes mellitus. Front Endocrinol 10, 402, 2019.

Cai Z, Yang Y, Zhang J. A systematic review and meta-analysis of the serum lipid profile in prediction of diabetic neuropathy. Sci Rep 11, 499, 2021.

Chang KC, Pai YW, Lin CH, Lee IT, Chang MH. Glycemic variability's impact on painful diabetic peripheral neuropathy in type 2 diabetes patients. Sci Rep 14, 22276, 2024.

Cho YN, Lee KO, Jeong J, Park HJ, Kim SM, Shin HY, Hong JM, Ahn CW, Choi YC. The role of insulin resistance in diabetic neuropathy in Koreans with type 2 diabetes mellitus: a 6-year follow-up study. Yonsei Med J 55, 700–708, 2014.

Dhillon S, Fithrie A, Batubara CA. The association between waist hip ratio and severity of diabetic peripheral neuropathy in diabetes mellitus type 2 by using Toronto Clinical Scoring System. J Social Med 2, 107–116, 2023.

Dinh Le T, Phi Thi Nguyen N, Thanh Thi Tran H, Luong Cong T, Ho Thi Nguyen L, Do Nhu B, Tien Nguyen S, Van Ngo M, Trung Dinh H, Thi Nguyen H, Trung Nguyen K, Le DC. Diabetic peripheral neuropathy associated with cardiovascular risk factors and glucagon-like peptide-1 concentrations among newly diagnosed patients with type 2 diabetes mellitus. Diabetes Metab Syndr Obes 15, 35–44, 2022.

Eid SA, Rumora AE, Beirowski B, Bennett DL, Hur J, Savelieff MG, Feldman EL. New perspectives in diabetic neuropathy. Neuron 111, 2623–2641, 2023.

Firouzabadi MD, Poopak A, Sheikhy A, Samimi S, Nakhaei P, Firouzabadi FD, Moosaie F, Rabizadeh S, Nakhjavani M, Esteghamati A. Glycemic profile variability: An independent risk factor for diabetic neuropathy in patients with type 2 diabetes. Prim Care Diabetes 17, 38–42, 2023.

Gonzalez-Gonzalez JG, Violante-Cumpa JR, Zambrano-Lucio M, Burciaga-Jimenez E, Castillo-Morales PL, Garcia-Campa M, Solis RC, Gonzalez-Colmenero AD, Rodriguez-Gutierrez R. HOMA-IR as a predictor of health outcomes in patients with metabolic risk factors: a systematic review and meta-analysis. High Blood Press Cardiovasc Prev 29, 547–564, 2022.

Han L, Ji L, Chang J, Wen J, Zhao W, Shi H, Zhou L, Li Y, Hu R, Hu J, Lu B. Peripheral neuropathy is associated with insulin resistance independent of metabolic syndrome. Diabetol Metab Syndr 7, 14, 2015.

Huma K, Mehboob K, Rashid A, Fuad F, Mujahid MM, Arshad A. Comparison of lipid profile in patients with diabetic neuropathy and without neuropathy; a cross sectional study. Pakistan Armed Forces Med J 71, 2021.
IDF Diabetes Atlas 11th Edition 2025. Online version available at diabetesatlas.org.
Javed A, Furqan A, Zaheer M, Kasuri N. Gender based differences in diabetic peripheral neuropathy. Pakistan J Neurol Sci 9, 20–24, 2014.
Jia Y, Long D, Yang Y, Wang Q, Wu Q, Zhang Q. Diabetic peripheral neuropathy and glycemic variability assessed by continuous glucose monitoring: A systematic review and meta-analysis. Diabetes Res Clin Pract 213, 111757, 2024.
Kristensen FPB, Christensen DH, Callaghan BC, Nielsen JS, Hojlund K, Andersen H, Dekkers OM, Groenwold RHH, Sorensen HT, Thomsen RW. Lipid levels and risk of diabetic polyneuropathy in 2 Danish type 2 diabetes cohorts. Neurology 103, e209538, 2024.
Liu J, Yuan X, Liu J, Yuan G, Sun Y, Zhang D, Qi X, Li H, Zhang J, Wen B, Guo X. Risk factors for diabetic peripheral neuropathy, peripheral artery disease, and foot deformity among the population with diabetes in Beijing, China: a multicenter, cross-sectional study. Front Endocrinol 13, 824215, 2022.
Ma Q. Analysis of factors related to type 2 diabetic peripheral neuropathy based on flash glucose monitoring system. Med Sci Monit 29, e939157, 2023.
Mayeda L, Katz R, Ahmad I, Bansal N, Batacchi Z, Hirsch IB, Robinson N, Trence DL, Zelnick L, de Boer IH. Glucose time in range and peripheral neuropathy in type 2 diabetes mellitus and chronic kidney disease. BMJ Open Diabetes Res Care 8, e000991, 2020.
Mehta M, Shah J, Joshi U. Understanding insulin resistance in NAFLD: a systematic review and meta-analysis focused on HOMA-IR in South Asians. Cureus 16, e70768, 2024.
Mokhtarpour K, Yadegar A, Mohammadi F, Aghayan SN, Seyedi SA, Rabizadeh S, Esteghamati A, Nakhjavani M. Impact of gender on chronic complications in participants with type 2 diabetes: evidence from a cross-sectional study. Endocrinol Diabetes Metab 7, e488, 2024.
Nisar MU, Asad A, Waqas A, Ali N, Nisar A, Qayyum MA, Maryam H, Javaid M, Jamil M. Association of diabetic neuropathy with duration of type 2 diabetes and glycemic control. Cureus 7, e302, 2015.
Nozawa K, Ikeda M, Kikuchi S. Association between HbA1c levels and diabetic peripheral neuropathy: a case-control study of patients with type 2 diabetes using claims data. Drugs Real World Outcomes 9, 403–414, 2022.
Ponirakis G, Elhadd T, Al Ozairi E, Brema I, Chinnaiyan S, Taghadom E, Al Kandari J, Al Wotayan R, Al Ozairi A, Aljohani N, AlMistehi W, Al Qahtani N, Khan S, Dabbous Z, Siddique MA, Petropoulos IN, Khan A, Almuhannadi H, Ashawesh KA, Dukhan KM, Mahfoud ZR, Zirie MA, Jayyousi A, Malik RA. Prevalence and risk factors for diabetic peripheral neuropathy, neuropathic pain and foot ulceration in the Arabian Gulf region. J Diabetes Investig 13, 1551–1559, 2022.
Sanchez-Pozos K, Monroy-Escutia J, Jaimes-Santoyo J, Granados-Silvestre MLA, Menjivar M, Ortiz-Lopez MG. Risk factors associated with diabetic neuropathy in Mexican patients. Cir Cir 89, 189–199, 2021.
Singh A, Chauhan A, Goyal P, Kaur J, Ramesh P. Insulin resistance as a predictor of sensory neuropathy in prediabetes. Indian J Med Special 10, 95–98, 2019.
Su JB, Zhao LH, Zhang XL, Cai HL, Huang HY, Xu F, Chen T, Wang XQ. HbA1c variability and diabetic peripheral neuropathy in type 2 diabetic patients. Cardiovasc Diabetol 17, 47, 2018.
Sun T, Chen M, Shen H, PingYin Fan L, Chen X, Wu J, Xu Z, Zhang J. Predictive value of LDL/HDL ratio in coronary atherosclerotic heart disease. BMC Cardiovasc Disord 22, 273, 2022.
Uslu MF, Yilmaz M. Are inflammatory markers important for assessing the severity of diabetic polyneuropathy? Medicina 61, 400, 2025.
Vincent AM, Hinder LM, Pop-Busui R, Feldman EL. Hyperlipidemia: a new therapeutic target for diabetic neuropathy. J Peripher Nerv Syst 14, 257–267, 2009.
Vinik A, Ullal J, Parson HK, Casellini CM. Diabetic neuropathies: clinical manifestations and current treatment options. Nat Clin Pract Endocrinol Metab 2, 269–281, 2006.
Wang CS, Pai YW, Lin CH, Lee IT, Chen HH, Chang MH. Diabetic peripheral neuropathy: age-stratified glycemic control. Front Endocrinol 15, 1377923, 2024.
Yu Z, Zhao S, Cao J, Xie H. Analysis of risk factors for painful diabetic peripheral neuropathy and construction of a prediction model based on Lasso regression. Front Endocrinol 15, 1477570, 2024.
Zhu J, Hu Z, Luo Y, Liu Y, Luo W, Du X, Luo Z, Hu J, Peng S. Diabetic peripheral neuropathy: pathogenetic mechanisms and treatment. Front Endocrinol 14, 1265372, 2024.
Zhang H, Chen Y, Zhu W, Niu T, Song B, Wang H, Wang W, Zhang H. The mediating role of HbA1c in the association between elevated low-density lipoprotein cholesterol levels and diabetic peripheral neuropathy in patients with type 2 diabetes mellitus. Lipids Health Dis 22, 102, 2023.