

# Evaluation of Risk Factors for Diabetic Peripheral Neuropathy Among Saudi Type 2 Diabetic Patients with Longer Duration of Diabetes

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**Background:** Neuropathy is the most common microvascular complications among diabetic patients. Diabetic peripheral neuropathy (DPN) is the predominant variety which may associate with increased in mortality and morbidity among type 2 diabetes mellitus (T2DM).

**Objective:** To assess the prevalence of diabetic peripheral neuropathy and its correlation with risk factors among T2DM.

**Methods:** This was a cross-sectional retrospective study, data was collected from a previous cohort study conducted at the University Diabetes Center, King Saud University Medical City (KSUMC), King Saud University, Riyadh, Saudi Arabia. The data of T2DM patients were collected from case report form, included demographic data, history of chronic diabetes neuropathy, and laboratory reports. Statistical analysis includes Student's *t* test, chi square test, and Pearson correlation and logistic regression were performed.

**Results:** A total of 430 patients with T2DM data was collected and analyzed, and of them 54% were females, with the mean age of 55.88 years. The prevalence of diabetic neuropathy among study participants were 40.2%, and 73.3% of them having the subtype polyneuropathy. The mean BMI;  $p = 0.006$ , FBS;  $p < 0.001$ , HbA1c;  $p < 0.001$ , cholesterol  $p = 0.001$ , LDL;  $p < 0.001$ , and triglyceride;  $p < 0.001$  levels were a significantly higher among participants with diabetic neuropathy than without neuropathy. The male gender (Risk Ratio: 1.294, 95% CI:1.090, 1.536)  $p = 0.003$ , fasting blood glucose (Risk Ratio: 1.157, 95% CI:1.051, 1.273)  $p = 0.003$  Cholesterol (Risk Ratio: 1.588, 95% CI:1.174, 2.147)  $p = 0.003$ , triglyceride (Risk Ratio: 1.290, 95% CI:1.086, 1.538),  $p = 0.004$ , and LDL (Risk Ratio: 1.299, 95% CI:1.073, 1.574),  $p = 0.007$  were found to be significant risk factors for DPN.

**Conclusion:** DPN is highly prevalent among T2DM patients in Saudi Arabia. Poor glycemic control and hyperlipidemia were associated with significantly higher risk for DPN patients among T2DM.

**Keywords:** diabetic peripheral neuropathy, hyperlipidemia, glycemic control, type 2 diabetes

## Introduction

Globally, Diabetes mellitus (DM) is one of the foremost non-communicable diseases that currently affects 463 million adults (20–79 years); a total that is set to reach 700 million by 2045.<sup>1</sup> In Saudi Arabia, Al Rubeaan et al found that the prevalence of diabetes among Saudis aged  $\geq 30$  years was 25.4% with 40.3% being unaware of their disease.<sup>2</sup> Type 2 diabetes mellitus (T2DM) is a disorder of glucose metabolism that involves the regulation of insulin secretion, insulin sensitivity, gluconeogenesis, and glucose uptake at the cellular level. Dysregulation of one or more of these previously mentioned processes due to genetic or environmental factors can result in altering glucose metabolism causing DM.<sup>3,4</sup>

The enormous impact of diabetes, being secondary to its high prevalence, is also significantly related to the high frequency of chronic complications that can affect any organ system in the body. In most societies worldwide, diabetes is considered to be the leading cause of vision loss, amputation, renal dialysis, and high mortality secondary to coronary artery disease (CAD), thereby making it one of the world's most important causes of disability and economic growth loss.

Diabetes risk factors in those the Gulf Cooperation Council (GCC) countries including Saudi Arabia are almost similar in which overweight and obesity are considered to be the most prominent risk factor. It is estimated that the prevalence of overweight ranges between 25% and 50% and the prevalence of obesity ranges between 10% and 50% and is found to be relatively higher in women showing an increase with age.<sup>5</sup> It has been reported that neuropathy is a common complication of diabetes, affecting up to 50% of patients.<sup>6–10</sup> The most common diabetes-related microvascular complications are diabetic peripheral neuropathy (DPN) and diabetic autonomic neuropathy, and they can result in a significant increase in morbidity, such as chronic pain, foot ulcerations, amputations, and mortality.<sup>11</sup>

In a recently published preliminary report, it was found that subjects with DPN had higher body mass index and waist circumference than subjects without DPN.<sup>12</sup> Also, the association of markers of inflammation with microvascular and cardiovascular disease among diabetes has been previously reported. This is because inflammatory activity is increased in individuals with diabetes.<sup>13</sup> Besides, as reported by Pinzur et al there is no doubt that foot ulcers strongly correlated with morbid obesity.<sup>14</sup> Previous studies showed a significant correlation between the early development of DPN and BMI.<sup>15–20</sup>

There is a scarcity of data regarding the association between risk factors and neuropathy among T2DM patients in Saudi Arabia; therefore, we conducted this study in a trial to fill the literature gap in this regard.

## Methods

This was a cross-sectional retrospective study for which the data was collected from a previous cohort study conducted at the University Diabetes Center, King Saud University Medical City, King Saud University, Riyadh, Saudi Arabia. This study has been approved by institutional review board College of Medicine, King Saud University, Riyadh Saudi Arabia (IRB No. E-19- 4288) and has been conducted in accordance with the principles set forth in the Helsinki Declaration. The consent from patients for this manuscript was waived due to the retrospective nature of the study and mention in the letter of approval in the ethical board. A total of 526 patients' data was collected, all of them were diagnosed with T2DM of them, 434 patients fulfilled the current study inclusion and exclusion criteria, then 4 patients were excluded because of missing data. Therefore, the remaining total patients' number for whom the data was analyzed was 430 patients.

Diabetic peripheral neuropathy examined by the Neuropathy Disability Score (NDS), Diabetic neuropathy symptom score (DNS) scoring system, and electromyography (EMG)/nerve conduction velocity (NCV).<sup>21–24</sup>

The inclusion criteria for the current study were T2DM, Saudi Nationals, both genders, aged between 35 and 70 years, with DM duration of more than two years. While the exclusion criteria were other types of DM, patients aged less than 35 years or more than 70 years, DM duration more than 25 years or less than 2 years, and non-Saudi.

BMI was categorized according to WHO criteria of diagnosis for adult over 20 years by dividing weight by the square of height and categorized below 18.5 considered to be underweight, 18.5 to 24.9 normal healthy weight, 25 to 29.9 considered to be above ideal range "Pre-obesity", 30.0 and above considered to be obesity.<sup>25</sup> Degree of control of diabetes mellitus will be according to ADA Standard of medical care 2021 for glycemic goals in table 6.3, which mentioned that appropriate glycemic goal for many nonpregnant adults of HbA1C <7% which considered to be appropriate control and fasting blood sugar (FBS) from 80 to 130 mg/dl.<sup>26</sup> Hypertension, defined according to ADA standard of medical care 2021, as defined as a sustained blood pressure  $\geq$ 140/90 mmHg.<sup>27</sup>

The data collection tool was a case report form that included the following information: demographic data (age, gender, height, weight, and smoking status), age at diagnosis, history of chronic diabetes neuropathy evaluated by assessing upper and lower extremities of nerve conduction velocity (defined by the presence of different types of Neuropathy "eg sensory and motor polyneuropathy, mononeuropathy), and biochemical analysis (fasting blood glucose (FBS), glycosylated hemoglobin (HbA1c), total cholesterol, low-density lipoprotein (LDL), high-density lipoprotein (HDL), triglyceride).

## Statistical Analysis

Statistical analysis was carried out using the Statistical Package for the Social Sciences (SPSS®) software (version 25) (IBM-SPSS, Armonk, New York, USA). Descriptive statistics was employed to obtain frequencies, mean, and standard deviation for continuous variables and numbers and percentages for categorical variables. Test of normality in the distribution was done using the Shapiro–Wilk Test. Statistical inference to compare and determine the association between groups, independent *T*-test (for continuous variables) and Chi-square test (for categorical variables) were used. The association between diabetic neuropathy and covariates was assessed by Pearson correlation analysis whereby the presence or absence of DN neuropathy was coded as 0-no DM neuropathy and 1-with DM neuropathy. Significant variables were entered into a binary logistic regression analysis. Likelihood ratio with 0.1 probability removal was used to develop the model. Risk ratio (RO) was estimated with 95% CI to show the strength of association and *p*-value  $\leq 0.05$  was used to declare statistical significance.

## Results

This retrospective cross-sectional study assessed the association between risk factors and DPN. A total of 430 T2DM patient's data were analyzed, 54% of them were female: with a mean age of  $55.88 \pm 6.68$  years. Sixty-one percent of the participants have diabetes duration of  $>15$  years with a mean duration of  $17.3 \pm 4.48$ , and 4.5% were smokers. Sixty percent of the study participants were obese, and 30.8% were pre-obese. Ninety-six percent of study participants have uncontrolled blood sugar with mean HbA1c  $10.08 \pm 1.82$ . The prevalence of DPN among the studied sample was 40.2%, and 68.2% of them were of subtype polyneuropathy (Table 1).

**Table 1** Demographic, Biochemical, and Clinical Characteristics of Type 2 Diabetic Patients

Parameters	
n	430
Age, years (mean $\pm$ SD)	$55.88 \pm 6.683$
Sex, (n) % M/F	(198/232) 46/54
Diabetes duration, years (mean $\pm$ SD)	$17.33 \pm 4.48$
FBS, mg/dL (mean $\pm$ SD)	$191.96(138.05-237.34)$
FBS, mg/dL ( $> 130$ ) (n)% yes	(331)78.6
HbA1c, % (mean $\pm$ SD)	$10.08 \pm 1.82$
HbA1c, % ( $\geq 7$ ) (n)% yes	(410) 96.0
Total cholesterol, mg/dL (mean $\pm$ SD)	$174.76(147.45-204.27)$
LDL, mg/dL (mean $\pm$ SD)	$118.35(91.31-153.84)$
HDL, mg/dL (mean $\pm$ SD)	$43.24(36.89-50.19)$
Triglycerides, mg/dL (mean $\pm$ SD)	$155.29(111.47-217.57)$
BMI, kg/m <sup>2</sup>	
Underweight, (n)%	(1)0.2
Normal body weight, (n)%	(37)8.6
Pre-obesity, (n)%	(132)30.8
Obesity, (n)%	(258)60.3
Hypertension, (n) % yes	(161)37.4
Smoking, (n) % yes	(19)4.5
Diabetic neuropathy, (n) % yes	(173)40.2
Neuropathy subtypes	
Mononeuropathy, (n)%	(43) 24.9
Polyneuropathy, (n)%	(118) 68.2
Undefined neuropathy, (n)%	(12) 6.9

**Note:** Data are presented as percentage and mean  $\pm$  standard deviation, Median, IQR.

**Abbreviations:** FBS, fasting blood sugar; LDL, low density lipoprotein; HDL, high-density lipoprotein; BMI, body mass index.

Comparison of risk factors in T2DM patients with and without neuropathy is shown in Table 2. The mean BMI;  $p=0.006$ , FBS;  $p<0.001$ , HbA1c;  $p<0.001$ , cholesterol  $p=0.001$ , LDL;  $p<0.001$ , and triglyceride;  $p<0.001$  levels were significantly higher among participants with DPN than without neuropathy. There was no significant association between age, diabetes duration, and HDL with the risk of DPN.

Correlations between diabetic neuropathy and risk factors of diabetes are shown in Table 3. DPN showed a significant relationship with BMI ( $r=0.133$ ;  $p=0.006$ ), the glycemic parameters; FBS ( $r=0.174$ ;  $p<0.001$ ) and HbA1c ( $r=0.190$ ;  $p<0.001$ ) and lipid parameters; cholesterol ( $r=0.164$ ;  $p=0.001$ ), triglyceride; ( $r=0.193$ ;  $p<0.001$ ) and LDL; ( $r=0.039$ ;  $p<0.001$ ).

In binary logistic regression model, the male gender (Risk Ratio: 1.294, 95% CI:1.090, 1.536)  $p=0.003$ , fasting blood glucose (Risk Ratio: 1.157, 95% CI:1.051, 1.273)  $p=0.003$  cholesterol (Risk Ratio: 1.588, 95% CI:1.174, 2.147)  $p=0.003$ , triglyceride (Risk Ratio: 1.290, 95% CI:1.086, 1.538),  $p=0.004$ , and LDL (Risk Ratio: 1.299, 95% CI:1.073, 1.574),  $p=0.007$  were found to be significant risk factors for DPN (Table 4).

**Table 2** Comparison of Risk Factors on Diabetic Peripheral Neuropathy in Type 2 Diabetes Patients with and without Neuropathy

Risk Factors	Non-Neuropathy	Neuropathy	p values*
	Mean $\pm$ SD	Mean $\pm$ SD	
Number (n)	257	173	
Age	56.12 $\pm$ 7.2	55.50 $\pm$ 5.9	0.365
Diabetes duration	17.44 $\pm$ 4.6	17.17 $\pm$ 4.2	0.540
BMI	31.50 $\pm$ 5.3	33.09 $\pm$ 6.4	<b>0.006</b>
FBS	188.96 $\pm$ 75.1	218.31 $\pm$ 90.7	<b>&lt;0.001</b>
HbA1C	9.79 $\pm$ 1.8	10.50 $\pm$ 1.8	<b>&lt;0.001</b>
Cholesterol	172.93 $\pm$ 39.7	187.80 $\pm$ 49.9	<b>0.001</b>
Triglyceride	161.79 $\pm$ 74.3	194.54 $\pm$ 92.3	<b>&lt;0.001</b>
HDL	44.01 $\pm$ 11.4	44.89 $\pm$ 10.8	0.424
LDL	119.32 $\pm$ 43.9	135.47 $\pm$ 48.1	<b>&lt;0.001</b>

**Note:** \*independent samples t-test significant at  $p\leq0.05$  shown in bold.

**Abbreviations:** BMI, body mass index; FBS, fasting blood sugar; HDL, high-density lipoprotein; LDL, low density lipoprotein.

**Table 3** Correlation of Diabetic Neuropathy with Risk Factors of Diabetes

	Diabetic Peripheral Neuropathy	
	Correlation Coefficient (r)	p values*
Age	-0.044	0.365
Gender	0.139	0.004
DM duration	-0.030	0.540
BMI	0.133	<b>0.006</b>
FBS	0.174	<b>&lt;0.001</b>
HbA1C	0.190	<b>&lt;0.001</b>
Cholesterol	0.164	<b>0.001</b>
Triglyceride	0.193	<b>&lt;0.001</b>
HDL	0.039	0.424
LDL	0.039	<b>&lt;0.001</b>

**Note:** \*Correlation is significant at the p values  $\leq0.05$  shown in bold.

**Table 4** Binary Logistic Regression Analysis Using Diabetic Peripheral Neuropathy as Dependent Variable in Diabetic Subjects

Variables	Risk Ratio	95% CI	p values*
Constant	0.027	–	–
Age			
Reference: ≤ 50 years	0.995	0.907, 1.092	0.918
Gender, male	1.294	1.090, 1.536	0.003
Duration of diabetes			
Reference: ≤ 15 years	0.981	0.841, 1.144	0.807
BMI	1.113	0.955, 1.297	0.171
FBS	1.157	1.051, 1.273	0.003
HbA1c	1.019	0.981, 1.058	0.329
Cholesterol	1.588	1.174, 2.147	0.003
Triglycerides	1.292	1.086, 1.538	0.004
HDL	1.021	0.963, 1.083	0.483
LDL	1.299	1.073, 1.574	0.007

Note: a Variable(s) entered on step 1: Gender, BMI, FBS, HbA1C, Cholesterol, Triglyceride, HDL, LDL, BMI.

\*p ≤ 0.05 significant.

Abbreviations: BMI, body mass index; SBP, systolic blood pressure; FBG, fasting blood glucose; LDL, low density lipoprotein; HDL, high-density lipoprotein; CI, Confidence Interval.

## Discussion

We conducted this study aiming to assess the prevalence of DPN and its correlation with risk factors of diabetes among T2DM patients in Saudi Arabia. The results of the current study revealed that the prevalence of DPN was 40.2%, and there is a significant positive correlation between BMI, FBS, HbA1c, cholesterol, triglycerides and LDL level were significantly associated with DPN. Binary logistic regression showed that male gender, FBS, cholesterol, triglyceride and LDL has also a significant higher risk for DPN.

In general, the estimated overall prevalence of DPN in the current study is considered within the range of several recent studies from Middle East countries in which the prevalence of diabetic neuropathy was 45, 93.5%, 31.9%, 25.6%, and 29.2% in Saudi Arabia, Jordan, Iran, United Arab Emirates (UAE) and India, respectively.<sup>28–32</sup> However, a far lower prevalence of DPN among Chinese patients was reported was 17%, putting into consideration that those patients were newly diagnosed, without cerebrovascular disease or foot ulcers, and were diagnosed using monofilament and tuning fork.<sup>33</sup> On the other hand, a higher prevalence was reported in another study among T2DM patients with angiographically documented coronary artery disease, at 51%.<sup>16</sup>

In regard to BMI, the result of the current study showed that there was a significant correlation between BMI and the presence of DPN, and this is supported by several previous studies.<sup>17–20,34</sup> There is a shred of evidence that supports the theory that metabolic syndrome and obesity are risk factors for diabetic neuropathy. The suggested mechanisms for nerve damage include extracellular protein glycation, oxidative stress, fat deposition, mitochondrial dysfunction, and counter-regulatory signaling pathways activation causing chronic metabolic inflammation.<sup>35,36</sup> Even though, in this study, BMI was no more associated to the risk for DPN in patients with T2DM, may be because 91% of our study subject were in overweight or in obese category.

For the correlation between dyslipidemia and diabetic neuropathy, despite being weak, our results are consistent with previous studies in that patients with dyslipidemia are more likely to have DPN<sup>18,29,37–39</sup> Also, a cohort study showed that, among patients with mild to moderate diabetic neuropathy, elevated triglycerides correlated with myelinated fiber density loss independent of patient age, disease duration, and control.<sup>40</sup>

The present study identified males gender having higher risk to have diabetic neuropathy. Previous study identified a higher proportion of males to be affected by neuropathy.<sup>41</sup> The present study was in contrary with previous findings who reported that there were no sex-specific differences.<sup>42</sup> In addition, the present study was in contrary with previous findings who reported that Diabetic neuropathy was more prevalent in the advanced age groups and among those with

longer duration of the disease.<sup>43–46</sup> This might be due to this study population were with older age and are with longer duration of diabetes and were accompanied with other microvascular diabetes complications.

Previous study reported a significant correlation between poor glycemic control (FBS) was associated to the risk of painful DPN in patients with T2DM.<sup>47</sup> Yang et al, reported that FPG-CV and HbA1c  $\geq 7\%$  were potent predictors of DPN in T2DM patients.<sup>48</sup> This study finding was also in line with previous findings that hyperglycemia (FBS) was significantly associated with increased risks of DPN among T2DM patients. Besides, these studies above highlighted that the progression of diabetic polyneuropathy can be slowed by glycemic control.<sup>37,49</sup>

The risk factors for DPN among T2D included older age, and a cardiovascular-metabolic risk profile (obesity, hypertension, low HDL-c levels, elevated triglycerides, low physical activity and limited range of motion).<sup>50</sup> Also, other studies showed that risk factors for DPN include diabetes duration.<sup>51–53</sup> Kiani et al found that diabetes duration is significantly associated with increased risk of diabetic polyneuropathy among diabetic patients while BMI did not indicate any risks of increasing diabetic polyneuropathy.<sup>54</sup> In contrast to above study results, this study did not show any relation with duration of diabetes and older age. This might be due to this study population were with older age and longer duration of diabetes and were accompanied with other microvascular diabetes complications.

The common risk factors include uncontrolled blood glucose (FBS) and hyperlipidemia (cholesterol, LDL and triglycerides), suggest that measures aimed at the prevention, control and treatment of CVD, can also help prevent DPN development. This emphasizes the importance of implementing a health program to educate diabetic patients about the development and prevention of macrovascular complications and neuropathy in specific. T2DM patients with longer duration of diabetes and the need for regular examination of the feet and provide proper education on foot care.

## Limitations

The current study also has some limitations. First, definitive diagnostic tests test for all sub types of neuropathy were not performed. Second, as our study data having lack of data on duration of diabetic neuropathy. Third, we did not evaluate other causes of DPN other than diabetes such as vitamin B12 and folic acid deficiency, hypothyroidism, inflammatory diseases, drugs as well as autoimmune, hereditary, or neoplastic disorders. Finally, this is a cross-sectional study, which cannot evaluate long-term effects of risk factors concerning the development of DPN. However, with the establishment of our register, we aim to possibly implement those longitudinal measures in future studies.

## Conclusions

The results herein showed a high prevalence of diabetic neuropathy among T2DM patients in Saudi Arabia. This study identified severe hyperglycemia and hyperlipidemia were significantly associated with increased risks of diabetic neuropathy among T2DM patients with longer duration of diabetes. This suggested the measures aimed at the prevention, control and treatment of DPN development and emphasizes the importance of implementing a health program to educate diabetic patients about the development and prevention of macro vascular complications in T2DM patients with longer duration of diabetes.

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## Author Contributions

All authors made substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; took part in drafting the article or revising it critically for important intellectual content; agreed to submit to the current journal; gave final approval of the version to be published; and agree to be accountable for all aspects of the work.



## Disclosure

The authors report no conflicts of interest in this work.

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