Association between metabolic syndrome and diabetic peripheral neuropathy in patients with type 2 diabetes mellitus: a cross-sectional study

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Abstract

Background and aims. Diabetic peripheral neuropathy (DPN) is the most prevalent chronic complication of diabetes. Several risk factors have been identified in recent studies, in particular metabolic syndrome (MetS). However, this association remains unclear. We aimed to determine the prevalence of DPN and to study its associated factors, especially the MetS as a potential risk factor of DPN in patients with Type 2 diabetes mellitus (T2DM).

Methods. This was a retrospective and comparative study, with cross-sectional collected data, involving patients with T2DM from North Africa, followed up in the Department of Endocrinology-Diabetology-Nutrition at Mohammed VI University Hospital Center of Oujda, located in the eastern region of Morocco. Patients were grouped according to the presence (T2DM/DPN+, n = 110) or absence of DPN (T2DM/DPN-, n = 290). Data were collected from medical records and analyzed using SPSS software version 21.

Results. DPN was found in 27.5% of the patients. The mean age was similar between the two groups, at 58.96 ± 11.86 years in the T2DM/DPN+ group and 57.10 ± 13.29 years in the T2DM/DPN- group. Males comprised 40.9% of the T2DM/DPN+ group and 31.7% of the T2DM/DPN- group, but this difference was not statistically significant ($p = 0.054$). Patients with DPN had a significantly longer duration of diabetes (median 10 years vs. 5 years, $p < 0.001$). Both groups showed glycemic imbalance, with mean HbA1c values of 10.71 ± 2.31% for T2DM/DPN+ and 10.40 ± 2.87% for T2DM/DPN-, without a significant difference. MetS was a significant predictor of neuropathy presence. The prevalence of DPN was greater in individuals with hypertension ($p = 0.013$), abdominal obesity ($p = 0.010$), elevated triglyceride levels ($p = 0.007$), and low HDLc ($p = 0.013$). Male sex and the duration of diabetes were found to be significant risk factors for the development of DPN.

Conclusion. MetS and its components are strongly associated with the presence of DPN in patients with T2DM. Therefore, screening and optimal control of these risk factors may help prevent DPN in these patients. However, further intervention studies are needed to determine whether comprehensive multifactorial control in patients with T2DM and MetS can effectively prevent DPN.

Keywords: Type 2 Diabetes Mellitus, peripheral neuropathy, metabolic syndrome, risk factors

DOI: 10.15386/mpr-2779

Manuscript received: 02.08.2024
Received in revised form: 12.11.2024
Accepted: 09.02.2025

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Background and aims

Diabetic peripheral neuropathy (DPN) is the most prevalent chronic complication of diabetes [1]. It impacts the quality of life through pain, foot ulceration, and amputations. It is strongly associated with substantial socioeconomic consequences [2]. The incidence and prevalence of DPN are variable. In newly diagnosed type 2 diabetes mellitus (T2DM), DPN is found in 10-15% of cases, while it may be present in 50% after 10 years of diabetes progression [1].

While glycemic control is fundamental in managing diabetes complications, recent studies suggest that it has a limited effect on preventing DPN in T2DM, suggesting the involvement of additional factors in its pathogenesis, in particular metabolic syndrome (MetS), given its high prevalence in patients with T2DM [3]. Although multiple studies have identified an association between MetS and DPN, this relationship remains unclear [4].

The prevalence of DPN and the particularity of the association between DPN and MetS remain unknown in our population. Studying this association is essential to developing effective prevention and treatment strategies, particularly the treatment of modifiable risk factors, including components of MetS. Through this study, we aimed to determine the prevalence of DPN and study its associated factors, especially the metabolic syndrome, as a potential risk factor of peripheral neuropathy in patients with T2DM.

Methods

Study design and study population

This was a retrospective and comparative study, with cross-sectional data collected from reviewing the medical records of 437 patients with type 2 diabetes mellitus, followed up at the Department of Endocrinology-Diabetology and Nutrition at Mohammed VI University Hospital Center of Oujda, located in the eastern region of Morocco, and admitted between September 2016 and July 2024.

We included in this study patients with T2DM aged between 18 and 90 years old, who were admitted to the Department. We excluded participants with a history of neurotoxic treatment (chemotherapy), or toxins (including any level of alcohol consumption). We also had to exclude those with chronic kidney disease, hypothyroidism, vitamin B12 deficiency, infections (HIV), malignancies (bronchogenic carcinoma, multiple myeloma), chronic inflammatory demyelinating neuropathy, vasculitis, and inherited neuropathies.

Study protocol

We collected socio-demographic parameters (age, sex, smoking status), clinical examination data, including waist circumference measures, blood pressure, the DN4 score, and monofilament testing. Furthermore, data related to diabetes was recorded, along with biological data, including lipid profile and HbA1c assessment results. Additionally, data pertaining to diabetic retinopathy, diabetic nephropathy, and cardiovascular complications were included.

Diabetic peripheral neuropathy diagnosis

Diabetic peripheral neuropathy (DPN) was defined using medical history and simple clinical tests. Symptoms included numbness, tingling, burning sensation, electric shocks, and stabbing. Clinical tests used were: vibration perception, ankle reflexes, 10-g monofilament test, proprioception, pinprick sensation, and thermal discrimination.

Neuropathic pain was evaluated using the DN4 questionnaire, which is comprised of 10 items. Three items are associated with the characteristics of pain (painful cold, burning, and electric shocks), four items consist of symptoms (pins and needles sensation, numbness, tingling, and itching), while three items are obtained from neurological examination (hypoesthesia to touch, hypoesthesia to prick, and brushing). A "No" answer is scored 0, and a "Yes" answer is scored 1. This leads to the final score including all items, with the cut-off score to define neuropathic pain as 4/10.

The diagnosis of DPN is based on clinical criteria. The diagnosis is made in the presence of typical symptoms with symmetrical distal sensory loss, or the presence of typical signs, and in some cases, in the presence of a painless foot ulcer, and may not require further evaluation or referral. In our study, patients with T2DM were considered to have DPN (T2DM/DPN+) if they had signs or symptoms of neuropathy, and/or a DN4 score equal to or higher than 4. Those who did not meet the criteria for DPN were classified in the group of T2DM patients without neuropathy (T2DM/DPN-).

Out of 437 patients with T2DM followed up in our department, we excluded 37 patients who did not meet the criteria of selection and included a total of 400 patients (Figure 1).

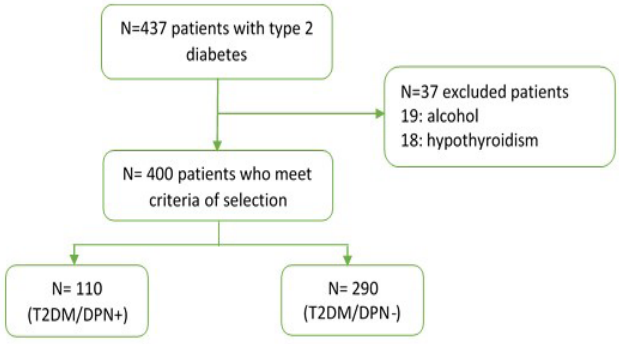

Figure 1. The study population.

Metabolic syndrome diagnosis

The diagnosis of Metabolic syndrome (MetS) is based on three of the following five criteria, according to the International Diabetes Federation (IDF 2009): fasting

blood glucose ≥ 100 mg/dL or specific treatment for hyperglycemia, an elevated waist circumference ≥ 80 cm (women) or ≥94 cm (men), reduced high-density lipoprotein cholesterol (HDLc) <0.5 (women) or < 0.4 g/L (men) or on drug treatment for reduced HDLc, hypertriglyceridemia ≥ 150 mg/dl or on drug treatment for elevated triglycerides, and diastolic blood pressure (DBP) > 85 mmHg or systolic blood pressure (SBP) >130 mmHg or on antihypertensive drug treatment in a patient with a history of hypertension [5]. All T2DM participants were considered to have MetS if they had two other components than T2DM.

Outcomes

The primary outcome was to study MetS as a potential risk factor for DPN by comparison between patients with and without DPN. Secondary outcomes were to evaluate the prevalence of DPN, describe the metabolic profile of patients with T2DM and neuropathy, and study other associated factors to DPN.

Statistical analysis

We used the Statistical Package for the Social Sciences (SPSS), version 21 (IBM, Armonk, NY) for all analyses. Data were described as frequencies, percentages, means +/- standard deviation (SD), and median with quartile Q (Q1; Q3).

A bivariate analysis was initially conducted to identify potential associated factors for DPN, including age, sex, diabetes duration, HbA1c levels, obesity, and the presence of metabolic syndrome and its components. For qualitative variables, we used the Chi-2 test. For quantitative variables, we performed the Student's t test or the Mann-Whitney test respectively for variables with a normal or non-normal distribution, after checking the distribution graphs. In addition, correlation tests (Pearson or Spearman, as appropriate) were conducted for continuous variables to assess the strength of linear associations.

A multivariate analysis was then performed using a binary logistic regression model, with stepwise selection. Variables with a p-value of ≤0.10 were introduced into the initial model, and only significant variables were presented in the final model. Adjusted odds ratios (aOR) with their 95% confidence intervals (95% CI) were measured. A critical value of p<0.05 indicated statistical significance.

Ethical approval

The ethical review committee approved the study design and protocol under the number: Project 16/2020.

Results

A total of 400 participants with T2DM were recruited in the study, including 132 male (33%) and 268 female patients (67%). The mean age was 57.62 ± 12.93 years. The median duration of diabetes was six years, with quartiles of 1 and 15 years. Almost all patients presented with unbalanced diabetes on admission, with a mean HbA1C of 10.49 ± 2.84%. Seventy-eight percent were already on insulin therapy.

In terms of degenerative disease, hypertension was present in 44.5% of patients, and macroangiopathy in 50%, mainly represented by ischemic heart disease (44.3%). With regard to microangiopathy, diabetic retinopathy was present in 25% of cases, while nephropathy was present in 22.3%. DPN was identified in 27.5% of patients.

The subjects were divided into two groups according to the presence (T2DM/DPN+, N = 110) or absence of DPN (T2DM/DPN-, N = 290), as illustrated in figure 1. Table I presents a comparison between the two groups in question.

The proportion of males in the T2DM/DPN+ group was 40.9%, while it was 31.7% in the T2DM/DPN- group, however, there was no significant difference in the distribution of sex (p = 0.054). The mean age in the two groups was almost similar. A longer duration of diabetes was observed in patients with DPN (p < 0.001). Smoking status was significantly associated with the presence of DPN (p = 0.030).While, glycemic imbalance was noted in both groups, with no significant difference.

The presence of MetS (p = 0.026), abdominal obesity (p = 0.010), and hypertension (p = 0.013) were found to be significantly associated with the presence of DPN. However, obesity was not associated to DPN.

Hypertriglyceridemia was noted in 43.5% of patients with DPN, with no observed significant correlation (p=0.213). However, their triglyceride levels were higher (1.68 ± 1.26 g/L vs. 1.29 ± 0.53 g/L in T2DM/DPN- group; p = 0.007). Low HDLc was significantly more frequent in the DPN group (p = 0.013), with a mean level of 0.35 ± 0.11 g/L.

Our analysis identified a significant association between DPN and diabetic nephropathy. However, no significant associations were observed between DPN and other degenerative complications, such as diabetic retinopathy and cardiovascular complications.

Our results indicate that the duration of diabetes is a significant risk factor for DPN. To explore this further, we divided the patients into two subgroups based on diabetes duration (<10 years and ≥10 years) within both the DPN+ and DPN- groups. We observed that 36.58% of patients with a diabetes duration of ≥10 years had DPN, compared to 21.18% among those with a duration of <10 years. This stratification is detailed in tables IIa and IIb.

A multivariate logistic analysis was performed to ascertain whether MetS is an independent risk factor for the occurrence of DPN. This analysis included sex and duration of diabetes as variables.The results are presented in table III. MetS was a significant risk factor for DPN (aOR = 1.844; 95% CI = 1.090-3.118; p = 0.022). The male sex (aOR = 1.759; 95% CI = 1.082-2.860; p = 0.023) and diabetes duration (aOR = 1.050; 95% CI = 1.023-1.076; p<0.001) were found to be associated factors of DPN.

Table I. The clinical, demographic, and biological characteristics of the patients with and without DPN.

		T2DM/DPN+	T2DM/DPN-	p-value
Number (%)		110 (27.5%)	290 (72.5%)	
Age, years ± SD		58.96 ± 11.86	57.10 ± 13.29	0.177
Sex	Male, N (%)	45 (40.9)	92 (31.7)	0.054
	Female, N (%)	65 (59.1)	198 (68.3)	
Smoking status, N (%)		96 (87.2)	31 (10.7)	0.030
Diabetes duration, median years (Q1; Q3)		10 (2.0-18.0)	5 (0.5-14.0)	<0.001
Hba1c, % ± SD		10.71 ± 2.31	10.40 ± 2.87	0.281
Participants on insulin, N (%)		91 (82.72)	224 (77.2)	0.503
Abdominal obesity, N (%)		75 (68.2)	159 (54.8)	0.010
Obesity, N (%)		41 (37.3)	88 (30.3)	0.115
Triglycerides, mean g/l ± SD		1.68 ± 1.26	1.29 ± 0.53	0.007
Hypertriglyceridemia, N (%)		40 (43.5)	102 (38.1)	0.213
LDLc, mean g/l ± SD		1.13 ± 1.03	1.03 ± 0.36	0.113
HDLc, mean g/l ± SD		0.35 ± 0.11	0.41 ± 0.12	<0.001
Low HDLc, N (%)		82 (82.8)	179 (70.8)	0.013
Hypertension, N (%)		59 (54.1)	119 (41.0)	0.013
MetS, N (%)		82 (74.5)	185 (63.8)	0.026
Diabetic retinopathy, N (%)		33 (30)	67 (23)	0.099
Diabetic nephropathy, N (%)		41 (37.2)	52 (17.9)	0.030
Cardiovascular disease, N (%)		63 (57.3)	119 (41)	0.050

SD: Standard deviation, N: number of patients, Q: Quartile, LDLc: low-density lipoprotein cholesterol, HDLc: high-density lipoprotein cholesterol, MetS: Metabolic Syndrome, HbA1c: glycated haemoglobin.

Table IIa. Patients' characteristics stratified by duration of diabetes (<10 years) in DPN+ and DPN- Groups.

		T2DM/DPN+	T2DM/DPN-	p-value
Number (%)		50 (21.18)	186 (78.81)	
Age, years ± SD		55.48 ± 13.93	54.37 ± 13.77	0.753
Sex	Male, N (%)	20 (40)	55 (29.6)	0.109
	Female, N (%)	30 (60)	131 (70.4)	
Hba1c, % ± SD		11.21 ± 2.50	10.60 ± 3.09	0.160
Abdominal obesity, N (%)		33 (66)	94 (50.5)	0.063
Obesity, N (%)		14 (28)	53 (28.5)	0.549
Triglycerides, mean g/l ± SD		1.90 ± 1.63	1.29 ± 0.56	0.029
Hypertriglyceridemia, N (%)		20 (40)	63 (33.9)	0.057
LDLc, mean g/l ± SD		1.00 ± 0.32	1.02 ± 0.34	0.325
HDLc, mean g/l ± SD		0.34 ± 0.12	0.40 ± 0.11	0.663
Low HDLc, N (%)		35 (70)	119 (64)	0.248
Hypertension, N (%)		18 (36)	64 (34.4)	0.442
MetS, N (%)		36 (72)	117 (62.9)	0.152

SD: Standard deviation, N: number of patients, LDLc: low-density lipoprotein cholesterol, HDLc: high-density lipoprotein cholesterol, MetS: Metabolic Syndrome, HbA1c: glycated haemoglobin.

Table IIb. Patients' characteristics stratified by duration of diabetes (≥10 years) in DPN+ and DPN- Groups.

		T2DM/DPN+	T2DM/DPN-	p-value
Number (%)		60 (36.58)	104 (63.41)	
Age, years ± SD		61.87 ± 8.93	62.00 ± 10.84	0.367
Sex	Male, N (%)	25 (41.7)	37 (35.6)	0.271
	Female, N (%)	35 (58.3)	67 (64.4)	
Hba1c, % ± SD		10.27 ± 2.06	10.03 ± 2.41	0.345
Abdominal obesity, N (%)		42 (70)	65 (62.5)	0.212
Obesity, N (%)		27 (45)	35 (33.7)	0.101
Triglycerides, mean g/l ± SD		1.49 ± 0.89	1.29 ± 0.50	0.022
Hypertriglyceridemia, N (%)		20 (33.3)	39 (37.5)	0.438
LDLc, mean g/l ± SD		1.24 ± 1.35	1.04 ± 0.40	0.096
HDLc, mean g/l ± SD		0.35 ± 0.11	0.43 ± 0.13	0.440
Low HDLc, N (%)		47 (78.3)	60 (57.7)	0.073
Hypertension, N (%)		41 (68.3)	55 (52.9)	0.076
MetS, N (%)		46 (76.7)	68 (65.4)	0.075

SD: Standard deviation, N: number of patients, LDLc: low-density lipoprotein cholesterol, HDLc: high-density lipoprotein cholesterol, MetS: Metabolic Syndrome, HbA1c: glycated haemoglobin.

Table III. Bivariate logistic regression model analyzing the risk factors of DPN.

	aOR	95% CI	p-value
Sex	1.779	1.077-2.939	0.024
Diabetes duration	1.004	1.002-1.007	<0.001
MetS	1.928	1.113-3.340	0.019
HbA1c	1.067	0.976-1.165	0.152

OR: adjusted odds ratio, CI: confidence interval. Statistically significant $p<0.05$. MetS: Metabolic Syndrome.

Discussion

In our study, MetS was identified as a significant risk factor for DPN in patients with T2DM. The prevalence of DPN was greater in individuals with hypertension, abdominal obesity, elevated triglyceride levels, and low HDLc. Furthermore, male sex and the duration of diabetes were found to be significant risk factors for the development of DPN.

The prevalence of DPN varies among studies, depending on the duration of diabetes and the methods used for diagnosis [6]. In newly diagnosed T2DM, DPN is found in 10-15% of cases, while it may be present in 50% after 10 years of diabetes progression [1]. In our study, 27.5% of patients had DPN, with a median duration of diabetes of 10 years (Q1=2.0- Q3=18.0). Our results also showed that the prevalence of DPN increases significantly with the duration of diabetes. Specifically, in patients with a diabetes duration of less than 10 years, DPN was present in 21.18% of cases, whereas 36.58% of patients with a diabetes duration of 10 years or more had DPN. These findings suggest that longer diabetes duration is associated with a higher likelihood of developing DPN, supporting the notion that chronic hyperglycemia and associated metabolic changes contribute significantly to neuropathy development.

The pathogenesis of DPN is multifactorial [1]. Emerging evidence now supports the role of MetS and its components to increase the risk of DPN [7]. However, the contribution of each component is unclear [4].

In our study, MetS was a strong predictor of DPN. These findings have also been reported in other studies [8,9]. Issar et al. [10] studied the pathophysiological mechanisms of DPN in the context of MetS in patients with T2DM and found that subjects with T2DM and MetS had major alterations in nerve structure and function than patients with T2DM alone, due to reduced activity of the sodium-potassium pump. In addition, nerve injury can be explained by fatty deposition in nerves, mitochondrial dysfunction, oxidative stress, and extracellular protein glycation. Moreover, the activation of signaling pathways induces chronic metabolic inflammation [11].

Our study results showed that while the percentage of patients with hypertriglyceridemia was higher in the DPN+ group, this difference was not statistically significant. However, triglyceride values were significantly higher in the DPN+ group (Table I). The same correlation

was found in a recent meta-analysis published in 2021 [12]. The Utah Diabetic Neuropathy Study revealed that hypertriglyceridemia was associated with the loss of small unmyelinated axons [13]. Additionally, low HDLc was also an associated factor for DPN in our patients (p=0.048) (Table I). This finding was observed in several past studies [12,14,15]. HDLc has protective effects, by inhibiting inflammation, oxidation, thrombosis, and vasodilatation via endothelial release of nitric oxide. HDLc also, via its effects on reverse cholesterol transport, removes lipids from peripheral cells [16].

Furthermore, our findings indicated that the prevalence of neuropathy was higher in individuals with abdominal obesity. These results are in accordance with several studies [17–21]. The precise mechanisms responsible for this association remain incompletely understood, one potential mediator of this relationship may be related to an associated inflammatory state [20].

Our data indicate that hypertension may be more prevalent among patients with DPN. The relationship between hypertension and DPN has been explored in various studies, with mixed results. Some studies found no significant association [19]. While others found a positive correlation, such as the Eurodiab study and others [22,23]. This association may be attributed to oxidative damage and a reduction in Schwann cells, reduced nerve blood flow, small-fiber neuropathy and axonal atrophy [24].

The present study did not find a correlation between glycemic imbalance and the increased occurrence of DPN. This finding may be explained by the fact that all patients recruited were hospitalized for major glycemic imbalance. This result is in accordance with some studies [25,26], while, a high level of hba1c is considered as an important risk factor in other studies [27,28]. The benefit of intensive glycemic control on the risk of developing DPN in patients with T2DM remains less clear in the literature [29–31].

As a secondary finding in our study, we observed a significant association between smoking and DPN, which is consistent with the conclusion of a recent meta-analysis [32]. Furthermore, existing literature suggests that diabetic neuropathy often correlates with other complications like retinopathy and nephropathy, likely due to shared pathogenic factors [33,34]. In line with this, our results showed a significant association with diabetic nephropathy, although no significant association was found with diabetic retinopathy and cardiovascular diseases.

The strengths of our study lie in providing insights into the prevalence of DPN in our country and describing the associated factors in our patients. It should be noted that the present study had some limitations, as it was retrospective, making it difficult to evaluate certain missing factors.

Conclusion

We conducted a retrospective study to evaluate the association between DPN and MetS. We found that MetS and its components, notably, hypertension, abdominal obesity, low HDLc, and high level of triglycerides were strongly associated with the presence of DPN in patients with T2DM. Therefore, the implementation of screening and optimal control of these risk factors could pave the way for new prevention strategies for DPN in these patients.

Acknowledgments

The authors would like to acknowledge Dr. Asmae Lekfif.

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