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Associations between peripheral neuropathy and cardiovascular complications in patients with type 2 diabetes mellitus: a cross-sectional study

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Diabetes mellitus (DM) is a globally prevalent metabolic disorder with rising incidence. Diabetic peripheral neuropathy (DPN), the most common microvascular complication in DM, disrupts autonomic nervous system regulation of cardiac and circulatory functions, thereby increasing susceptibility to cardiovascular and cerebrovascular events. Elucidating the relationship between diabetic DPN and cardiovascular complications is critical for optimizing holistic management of diabetic patients. This study aimed to investigate the correlation between DPN and cardiovascular events in patients attending the Diabetes Clinic of Rafsanjan University of Medical Sciences, Iran. In this cross-sectional study, 260 patients with type 2 diabetes mellitus (T2DM), diagnosed per the American Diabetes Association (ADA) 2023 criteria, were enrolled via convenience sampling. The patients with cardiovascular complications group comprised 121 patients with T2DM and documented cardiovascular events, while the control group included 138 patients with T2DM and no cardiovascular history. Data on demographic characteristics, body mass index (BMI), blood pressure, clinical laboratory parameters, and neuropathy severity (assessed via the Michigan Neuropathy Screening Instrument [MNSI]) were collected. Statistical analysis was performed using SPSS version 22. The patients with cardiovascular complications had significantly higher neuropathy scores ($p = 0.039$), longer diabetes duration ($p < 0.05$), greater prevalence of hypertension ($p < 0.001$), and elevated serum creatinine ($p = 0.020$) compared to those without cardiovascular complications. In multivariable logistic regression, severe diabetic neuropathy (score > 4) was associated with increased odds of cardiovascular complications in the unadjusted model (OR = 1.73, 95% CI: 1.03–2.91) and after adjustment for demographic and lifestyle factors (adjusted OR = 2.07, 95% CI: 1.07–3.97; $p = 0.030$). A significant crude association was also observed for each one-unit increase in continuous neuropathy score (OR = 1.09, 95% CI: 1.01–1.18; $p = 0.021$). A significant association was found between peripheral neuropathy and increased odds of cardiovascular disease in T2DM patients. This underscores the potential role of neuropathy as

a marker for cardiovascular risk. Further longitudinal studies are warranted to explore the mechanistic interplay between neuropathy progression and cardiovascular outcomes.

Keywords Diabetes mellitus, Peripheral neuropathy, Cardiovascular events, Hypertension, Dyslipidemia

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DM is characterized by impaired carbohydrate and lipoprotein metabolism, along with elevated glucose levels, resulting from defects in insulin secretion or action. It is classified into two primary types: type 1 and type 2 diabetes mellitus[1]. DM is a leading cause of morbidity and mortality worldwide, with over 90% of diabetic patients affected by T2DM. Early identification of the disease and its complications facilitates interventions to prevent or mitigate cardiovascular diseases, which are among the principal causes of mortality in these patients[2]. By 2030, an estimated 532 million individuals globally are projected to have diabetes[2]. In China, the world's most populous country, approximately 13% of the adult population has diabetes, with nearly half of cases remaining undiagnosed[1]. Given the dramatic rise in childhood obesity, concerns persist regarding a significant escalation in diabetes prevalence[2]. Puberty and obesity are important risk factors for T2DM, and obese children and adolescents should be carefully screened for T2DM[3]. Since complications of T2DM often develop years prior to clinical diagnosis, their timely recognition is critical. These complications include microvascular outcomes such as neuropathy, retinopathy, and nephropathy, as well as macrovascular complications and severe damage to vital organs[4].

A common complication of diabetes is peripheral neuropathy, whose prevalence varies based on disease duration and the severity of hyperglycemia, and is associated with substantial health and economic burdens[5]. Approximately 50% of diabetic patients eventually develop DPN[4]. The pathogenesis of DPN is highly complex, involving a combination of metabolic, vascular, and hormonal factors that disrupt the balance between nerve fiber damage and repair, favoring injury. In this process, sensory and autonomic nerve fibers are predominantly affected, leading to progressive loss of sensation and motor function, which underlies the clinical manifestations of DPN[6]. The symptoms and signs of DPN vary depending on the specific region of the peripheral nervous system involved[7]. Diabetic DPN is the most prevalent form of DPN in developed countries. Data from multiple large-scale studies indicate that nearly 50% of diabetic patients ultimately develop DPN[8,9]. Risk factors for DPN include the severity and duration of hyperglycemia, dyslipidemia, smoking, and metabolic syndrome[6].

Numerous studies have investigated the prevalence and incidence of diabetic polyneuropathy, demonstrating a positive correlation between DPN prevalence and the duration of diabetes[10,11]. Approximately 50% of patients with DPN are asymptomatic and may present with complications such as foot ulcers. DPN increases the odds of infection, lower limb ulcers, non-traumatic amputations, and lifelong disability, significantly impairing quality of life[1]. Therefore, early diagnosis of diabetic DPN is crucial for initiating timely interventions to reduce disability, prevent amputations, and improve quality of life in diabetic individuals. Concurrently, identifying risk factors for diabetes-related cardiovascular diseases plays a pivotal role in enhancing preventive strategies and the early detection of diabetic DPN[12].

Hyperglycemia leads to vascular endothelial cell dysfunction. Inefficient endothelial cells promote vascular smooth muscle proliferation, inflammatory cell infiltration, and platelet aggregation, resulting in ischemia secondary to endothelial dysfunction caused by vascular constriction. These combined factors represent key events in cardiovascular diseases. DPN is associated with an elevated risk of cardiac events, and atherosclerotic diseases and cardiovascular events remain the primary cause of mortality in diabetic patients[13]. Notably, cardiovascular diseases are prevalent globally in the general population. In 2019, the American Heart Association reported that 48% of adults over 20 years old in the United States suffer from cardiovascular diseases, including coronary artery disease, hypertension, and heart failure[14]. Cardiac events account for nearly one-third to half of all cardiovascular disease cases, with ischemic heart disease being the leading cause of mortality worldwide[14]. Diabetic individuals are more prone to hypertension, obesity, hypercholesterolemia, hypertriglyceridemia, and elevated plasma fibrinogen levels. The risk of cardiovascular events in diabetic patients escalates with the severity of these factors[15].

Several studies emphasize the critical link between diabetes and coronary heart disease (CHD), demonstrating that diabetes doubles the risk of cardiovascular diseases in men and triples it in women as they age[16]. In another study, among 5,163 individuals with T2DM, 9.7% died from cardiovascular diseases over a 12-year period, compared to a 2.6% cardiovascular mortality rate in 342,815 non-diabetic individuals. However, among diabetics, the addition of each risk factor markedly amplified cardiovascular events relative to non-diabetic individuals[17]. A study involving 229,460 participants without prior cardiovascular events found that diabetic patients faced

twice the risk of coronary artery disease (CVD). The CVD risk in T2DM depends on the accumulation of risk factors and the efficacy of their management[18].

DM induces progressive vascular damage and microvascular/macrovascular complications. Recent studies highlight the necessity for further research to understand the impact of patient-specific characteristics during diabetic DPN treatment[19]. Autonomic neuropathy, a serious complication in diabetic patients, can adversely affect heart rate and blood pressure regulation[9,13,20]. Given the high prevalence of diabetes in Iran and the limited studies investigating the association between DPN and cardiovascular diseases in this population, the present study aimed to determine the correlation between DPN and cardiovascular events in patients with DM. This research seeks to enhance clinical insights for managing diabetic patients and preventing disease complications.

Methods

Study type and setting

This cross-sectional study aimed to investigate the association between DPN and cardiovascular complications in patients attending the Diabetes Clinic of Rafsanjan University of Medical Sciences in southeastern Iran. The clinic is located at Ali Ibn Abitaleb Hospital, affiliated with Rafsanjan University of Medical Sciences, and operates six days a week with two endocrinology subspecialists managing diabetic patients. Two trained nurses routinely measure patients' blood pressure, height, weight, and waist circumference prior to physician consultations. All data are recorded in electronic medical files, which include patients' medical history, longer duration of diabetes, presence of microvascular/macrovascular complications, BMI, and relevant laboratory results.

Sample size and sampling

A total of 260 eligible individuals were enrolled via convenience sampling. Diagnosis of T2DM was confirmed based on clinical history, physical examination, laboratory results, and the 2023 ADA criteria. (a) *patients with cardiovascular complications group*: 121 patients with T2DM and a history of cardiovascular complications (including coronary artery disease or myocardial infarction or ischemic heart disease or heart failure or coronary angioplasty or cerebrovascular diseases). History of cardiovascular complications was ascertained through a combination of patient self-report, review of medical records, and verification against documented from hospitalization records. (b) *Control Group*: 139 patients with T2DM but no history of cardiovascular complications. Groups were matched for age, sex, and disease duration using individual matching[21].

Inclusion criteria

For both groups: age ≥ 18 years and consent to participate; in patients with cardiovascular complications group: confirmed cardiovascular complications (as defined above); in control group: absence of cardiovascular complications.

Exclusion criteria

(Applied to both groups): History of lower limb amputation, thyroid disorders, vitamin B12 deficiency, glucocorticoid use, malignancy, congenital neurological diseases, lumbar/cervical discopathy, carpal tunnel syndrome, alcoholic neuropathy, or hereditary neuropathies.

The sample size was calculated using the formula for comparing proportions between two groups, based on data from Ybarra-Muñoz et al.[22]. Parameters included: $Z1 - \alpha/2 = 1.96$ (95% confidence level), $Z1 - \beta = 0.84$ (80% power), P1 = 30% (prevalence of DPN in diabetic patients with cardiovascular complications), P2 = 14.7% (prevalence in those without complications) and P1 − P2 = 15.3%. A target sample size of 116 participants per group was required. Accounting for anticipated incomplete questionnaires, 140 participants per group were recruited. For the final analysis, 121 patients with cardiovascular complications and 139 controls were included due to incomplete questionnaires (Fig. 1).

$$n = 2\frac{\left(z_1 - \frac{\alpha}{2} + z_1 - \beta\right)^2 \overline{pq}}{\left(p_1 - p_2\right)^2}$$

Data collection tools

A demographic questionnaire was used to collect information on age, sex, regular quarterly physician visits, smoking/waterpipe use, occupation, and weekly physical activity. Physical activity was categorized into three groups: (a) regular: 30-minute walks, 4–7 days/week, (b) irregular: 30-minute walks, 1–3 days/week and, (c) no physical activity: less than once/week[23]. Clinical data on diabetes duration, medication history, nephropathy, hypertension, dyslipidemia, cardiovascular disease, BMI, and HbA1c were extracted from medical records and laboratory tests. Weight and height were measured using a digital scale (accuracy: 0.1 kg) and stadiometer (accuracy: 0.5 cm), respectively, without shoes and in minimal clothing. BMI was calculated as weight (kg) divided by height squared (m^2).

Laboratory and diagnostic criteria

(a) HbA1c: Measured via high-performance liquid chromatography (HPLC). (b) Hypertension and dyslipidemia (HDL < 40 mg/dL (men)/HDL < 50 mg/dL (women), LDL > 100 mg/dL, and triglycerides > 150 mg/dL): Diagnosed according to ADA criteria[23]. (c) Nephropathy: Defined as persistent albuminuria (299–300 mg/24 h or ≥ 300 mg/24 h in a 24-hour urine)[23]. (d) Cardiovascular disease: Confirmed by a cardiologist based on documented coronary angiography, electrocardiogram (ECG), or current coronary artery disease treatment.

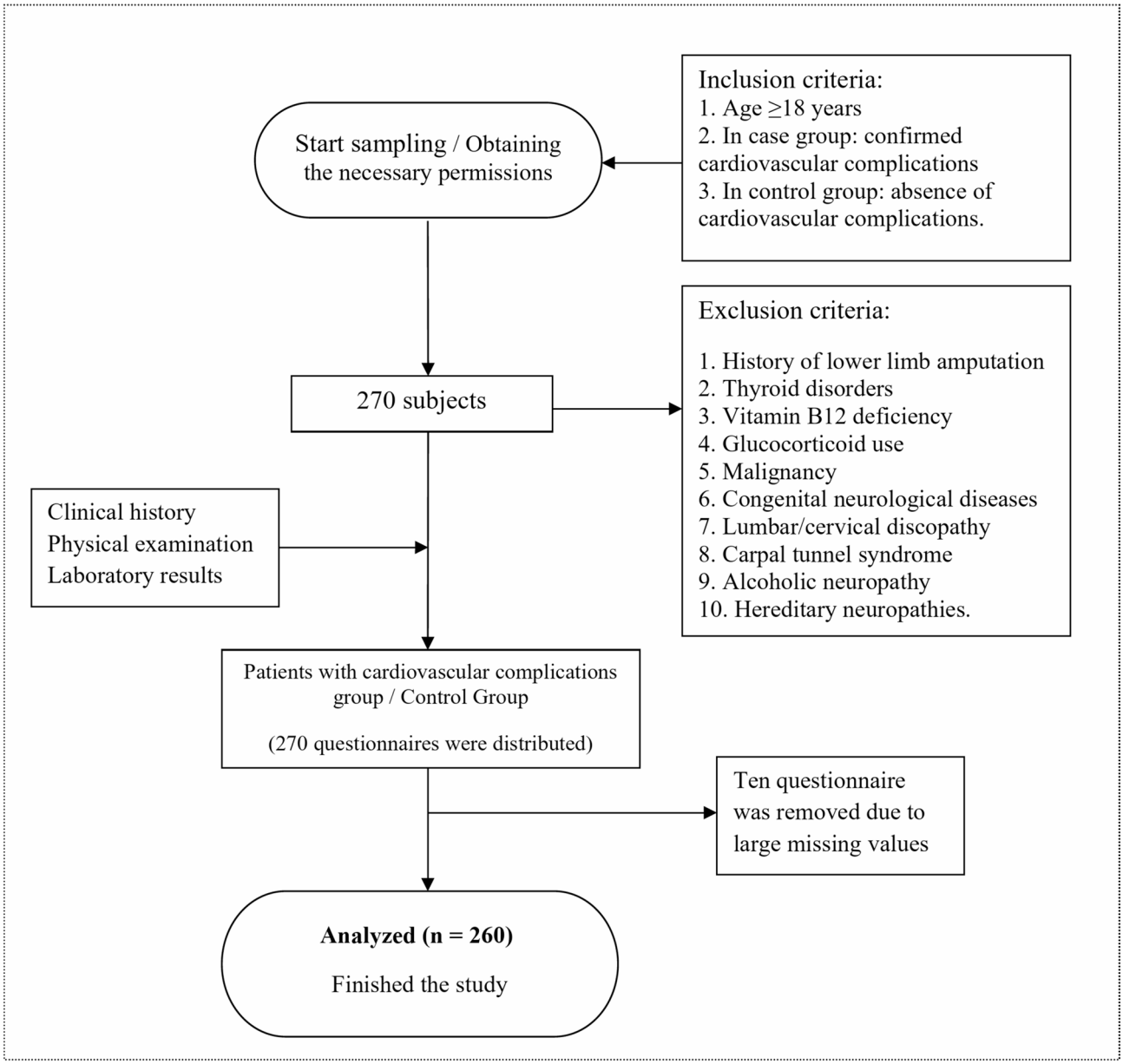

Fig. 1. The study flowchart.

Michigan neuropathy screening instrument (MNSI)

The MNSI, a validated tool for DDPN screening, was administered. This 15-item questionnaire assesses DPN symptoms through yes/no responses. Scores range from 0 to 15, with two items scored inversely (negative responses indicate neuropathy). A score > 4 indicates diabetic peripheral neuropathy. The MNSI has 80% sensitivity and 95% specificity for detecting DPN in T2DM patients and is widely used for early identification. The questionnaire was translated into Persian, and all items were culturally adapted[24].

Data collection

Following the acquisition of ethical approval code from Rafsanjan University of Medical Sciences and obtaining consent from the hospital director and physicians, the researcher visited the diabetes clinic. Data were obtained from patients attending the diabetes clinic from September to December 2024. The patients were initially briefed face-to-face about the research protocol, and written informed consent was obtained prior to their participation. For patients who agreed to join the study, demographic data (age, gender, occupation, regular medical visits, weekly physical activity, and tobacco/waterpipe use) were collected. Additionally, assessments for DPN (as a risk factor) were conducted using the MNSI. Clinical characteristics, including BMI, nephropathy, and CVD, were extracted from medical records and documented in a researcher-designed checklist. After necessary coordination, 3 cc of blood was collected from each patient in the morning (prior to breakfast) and sent to

the laboratory for analysis of serum lipid profile, FBS, HbA1C, and creatinine levels. All collected data were subsequently entered into SPSS software (IBM® SPSS® Statistics 22) for statistical analysis.

Statistical analysis

Data were analyzed using SPSS version 22. Qualitative variables were reported as frequency (percentage), while quantitative variables were summarized as mean ± standard deviation (SD). Normality of quantitative variables was assessed using skewness (−1 to +1) and kurtosis (−1.96 to +1.96), with histograms providing visual confirmation. Homogeneity of variance was evaluated via Levene's test. (a) quantitative variables: Analyzed using the Chi-square test (if assumptions were met) or Fisher's exact test (for small sample sizes or unmet assumptions). (b) Quantitative variables: Compared via the independent t-test (for normally distributed data) or the Mann-Whitney U test (non-parametric alternative). A binomial logistic regression model was employed to estimate the effect of CVD-related variables, calculate odds ratios (OR) with 95% confidence intervals (CI), and adjust for confounders. Regression analysis followed a two-stage approach: (a) Univariate analysis: Variables with a p-value ≤ 0.25 in the bivariate analysis, along with certain variables of established clinical relevance (e.g., gender), were included in the multivariate logistic regression model. (b) Multivariate analysis: Adjusted for confounders to identify independent predictors. Statistical significance was set at $p < 0.05$ (two-tailed). All results were reported as OR (95% CI).

Ethical considerations

The study was approved by the ethics committee of Rafsanjan University of Medical Sciences, with the code of ethics No. IR.RUMS.REC.1403.011. Prior to the study's commencement, ethical approval was obtained from the Ethics Committee of Rafsanjan University of Medical Sciences. Written informed consent was acquired from all participants. All participant information remained confidential, and individuals were provided access to their data upon request. Patient data were collected solely for research purposes, and the final results were reported to all participants at the conclusion of the study. Participants retained the right to withdraw from the study at any time without penalty.

Results

This study examined the association of diabetic DPN in 260 patients. Table 1 compares demographic characteristics (gender, education level, occupation, smoking, and waterpipe use) between two groups: diabetic patients with cardiovascular events (CVD) and diabetic patients without CVD. Among the 260 participants, 32 (12.4%) had a university education. Of these, 22 individuals (68.8%) were free of CVD, suggesting that higher education levels correlate with a lower prevalence of CVD in diabetic patients ($p < 0.05$). Additionally, 24 out of 38 smokers (63.2%) had concurrent CVD ($p < 0.05$). As shown in Table 1, statistically significant associations were observed between CVD and the following variables: education level ($p = 0.008$), cigarette smoking ($p = 0.024$), and waterpipe use ($p = 0.005$).

Based on Table 2, only 75 patients (29.0%) out of 260 studied individuals reported engaging in regular weekly physical activity ($p = 0.006$). Among the 55 patients using insulin to manage their DM, 33 (60.0%) had concurrent CVD, whereas only 87 out of 204 patients (42.6%) on oral antidiabetic medications exhibited CVD

Characteristic	Total = 260 *n* (%)	CVD = 121 *n* (%)	No-CVD = 139 *n* (%)	*P*-value
Gender†				0.32*
Male	112 (43.2)	56 (50)	56 (50)	
Female	147 (56.8)	64 (43.8)	83 (56.2)	
Education				0.008**
Illiterate	9 (3.5)	8 (88.9)	1 (11.1)	
Primary/High school/diploma	219 (84.2)	103 (47.2)	116 (52.8)	
Bachelor's degree and above	32 (12.3)	10 (31.3)	22 (68.8)	
Job†				0.65**
Free	80 (30.9)	40 (50)	40 (50)	
Employ	37 (14.3)	17 (45.9)	20 (54.1)	
Homeworker	141 (54.4)	62 (44.3)	79 (55)	
Retired	1 (0.4)	1 (100)	0 (0)	
Cigarette smoking†				0.024*
Never	220 (85.3)	95 (43.4)	125 (56.6)	
Yes (5 cigarettes a day)	38 (14.7)	24 (63.2)	14 (36.8)	
Waterpipe				0.005*
No	244 (93.8)	119 (49)	125 (51)	
Yes (once a day)	16 (6.2)	2 (12.5)	14 (87.5)	

Table 1. Demographic characteristics 260 of subjects stratified by baseline CVD status. Data reported as number (%). *Chi square test. **Fisher's exact test. †Missing data.

Characteristic	Total = 260	CVD = 121	No-CVD = 139	
	n (%)	*n* (%)	*n* (%)	*P*-value*
Physical activity				0.006
Yes	75 (28.8)	45 (60)	30 (40)	
No	185 (71.2)	76 (41.3)	109 (58.7)	
Drug (%)†				0.024
Oral	204 (78.8)	87 (42.9)	117 (57.1)	
Insulin	55 (21.2)	33 (60)	22 (40)	
Renal dysfunction†				0.135
No	221 (85.4)	99 (44.8)	122 (55.2)	
Yes	38 (14.6)	22 (57.9)	16 (42.1)	
Hypertension				< 0.001
No	84 (32.4)	17 (20.2)	67 (79.8)	
Yes	176 (67.6)	104 (59.4)	72 (40.6)	
Regular referral				0.74
≤ 3mo	123 (47.4)	59 (48)	64 (52)	
3mo <	137 (52.6)	62 (45.9)	75 (54.1)	

Table 2. Clinical characteristics 260 of subjects stratified by baseline CVD status. Data reported as number (%). *Chi square test. †Missing data.

Characteristic	CVD = 121	No-CVD = 139	
	Mean ± SD	Mean ± SD	*P*-value*
Age (years)			< 0.001
	64.9 ± 9.1	56.5 ± 10.96	
BMI (kg/m²)			0.640
	29.5 ± 5.0	29.2 ± 4.7	
Diabetes duration (years)			0.050
	9.3 ± 7.6	7.5 ± 6.2	
Neuropathy			0.032
	3.7 ± 3.5	2.8 ± 2.8	
Neuropathy Score	n (%)	n (%)	
≤ 4	74 (42.3)	102 (57.7)	0.039
> 4	47 (56)	37 (44)	

Table 3. Clinical characteristics 260 of subjects stratified by baseline CVD status. The data in table are reported as mean ± standard deviation. *Independent T Test; CVD: Cardiovascular disease; BMI: Body mass index.

events ($p = 0.024$). Additionally, 104 out of 175 hypertensive diabetic patients (59.4%) were diagnosed with CVD ($p < 0.001$).

Table 3 compares quantitative variables (neuropathy score, BMI, and duration of diabetes) between the patients with cardiovascular complications group and the control group (patients without cardiovascular events), presented as mean ± SD. The mean age of patients with cardiovascular events was 64.9 ± 9.1 years, significantly higher ($p < 0.001$) than the control group (56.5 ± 10.96 years). In the patients with cardiovascular complications group, the mean neuropathy score was 3.7 ± 3.5, diabetes duration was 9.3 ± 7.6 years, and BMI was 29.95 ± 5.0 kg/m². All these variables exhibited statistically significant differences between the two groups ($p < 0.05$). Among 121 diabetic patients with cardiovascular events, 47 (56%) had a neuropathy score > 4 ($p < 0.039$). The analysis revealed a significant association between higher mean neuropathy scores (≥ 3.7) and increased incidence of cardiovascular events ($p < 0.032$).

Table 4 examines the association between diabetic neuropathy and cardiovascular events using logistic regression models. In the univariate model, patients with a diabetic neuropathy score > 4 exhibited a 1.73-fold higher odds of cardiovascular events compared to the reference group (score ≤ 4), indicating a 73% increased odds (OR: 1.73, 95% CI: 1.03–2.91, $p = 0.020$). When neuropathy score was analyzed as a continuous variable, each 1-unit increase in score was associated with a 9% increased odds of cardiovascular events (OR: 1.09, 95% CI: 1.01–1.18, $p = 0.021$). After adjusting for age, gender, education level, smoking, waterpipe use, physical activity, BMI, and occupation (Multivariate Model 1), patients with neuropathy scores > 4 had a 2.07-fold higher odds of cardiovascular events (107% increased odds) compared to the reference group (OR: 2.07, 95% CI: 1.07–3.97, $p = 0.030$). However, the continuous neuropathy score showed a non-significant 10% increased odds per 1-unit increment (OR: 1.10, 95% CI: 0.99–1.21, $p = 0.067$).

Diabetic neuropathy and CVD	Crude mModel		Adjusted model 1		Adjusted model 2		Adjusted model 3	
	OR (CI)	*P* Value	OR (CI)	*P* Value	OR (CI)	*P* Value	OR (CI)	*P* Value
Neuropathy								
≤4	1		1		1		1	
>4	1.73 (1.03–2.91)	0.020	2.07 (1.07–3.97)	0.030	2.17 (1.012–4.64)	0.046	1.52 (0.65–3.57)	0.33
Neuropathy score	1.09 (1.01–1.18)	0.021	1.10 (0.99–1.21)	0.067	1.11 (0.99–1.25)	0.080	1.05 (0.93-1.19)	0.45

Table 4. Results of multivariate logistic regression model assessing inter-score correlation of diabetic neuropathy with cardiovascular variables. The crude model is stratified on the status of neuropathy. The adjusted model 1 is adjusted for confounding variables age (continuous variable), gender (male/ female), education, cigarette smoking, waterpipe, BMI, physical activity, job. The adjusted model 2 is adjusted for confounding variables in adjusted model 1 and hypertension (yes/no) diabetes duration, Type of medicine, status of renal. The adjusted model 3 is adjusted for confounding variables in adjusted model 2 and cholesterol, triglyceride, HDL, and blood sugar levels. CVD: Cardiovascular disease.

Further adjustment for blood pressure, diabetes duration, medication type, and kidney function (Multivariate Model 2) strengthened the association: patients with neuropathy scores > 4 had a 2.17-fold higher odds of cardiovascular events (117% increased odds; OR: 2.17, 95% CI: 1.012–4.64, $p = 0.046$). The continuous neuropathy score remained non-significant, with an 11% increased odds per 1-unit increase (OR: 1.11, 95% CI: 0.99–1.25, $p = 0.080$). In logistic regression model 3, the inclusion of blood cholesterol, triglyceride, HDL, and blood sugar eliminated the association between nephropathy and cardiovascular disease, which was present in model 2.

Discussion

The present study was a case-control investigation aimed at examining the association between DPN and cardiovascular events in patients with T2DM. Our findings revealed that the prevalence of diabetic neuropathy in the study population was 32.43%. In contrast, a 10-year follow-up study by Ybarra-Muñoz et al. (2016) reported a cumulative incidence of DPN of 18.3%[22]. Similarly, Bjerg et al., utilizing the MNSI with a cutoff score of ≥ 4 to define DPN, documented a neuropathy prevalence of 40.7% among Danish T2DM patients[25]. A 2024 study by Pető et al. in Hungary identified distal sensory-motor polyneuropathy (DSPN) the earliest and most common microvascular complication of diabetes in 71.7% of participants[19]. These discrepancies in reported prevalence across studies highlight the influence of regional and methodological factors, warranting further exploration in future research.

A review of the literature revealed that various tools and methods have been utilized for the assessment of DPN. These instruments include the MNSI[25,26], the Neuropathy Disability Score (NDS)[20], the Neuropathy Symptom Score (NSS)[27], the Toronto Clinical Scoring System (TCSS)[21], the 10-g monofilament examination[12,13], and assessment based on neurological clinical examination[22]. Although all these tools are valid and acceptable, caution is required in interpreting and comparing results, and due attention must be given to these differences.

A recent Hungarian study reinforced the link between DSPN and CVD[19]. Previous studies have confirmed that diabetic neuropathy is more prevalent in individuals with a history of myocardial infarction, and DSPN is independently associated with an elevated risk of primary cardiovascular events in T2DM[27,28]. Our results align with these findings. Brownrigg et al. reported that DPN correlates with increased cardiovascular risk in diabetic populations[28]. Pető et al. further observed higher rates of myocardial infarction, ischemic heart disease, peripheral arterial disease, and atherosclerosis in patients with DSPN (18). A 2023 UK cohort study found diabetic polyneuropathy significantly associated with both all-cause mortality and cardiovascular mortality[29]. Chung et al. (2011) concluded that DSPN increases the incidence of cardiovascular events, including hypertension, in T2DM[30]. Similarly, a 2020 Saudi Arabian study by Ghassan Alghamdi revealed higher neuropathy rates in patients with comorbid diabetes and CVD compared to those with diabetes alone[31]. Karvestedt et al. demonstrated that DSPN triples the risk of cardiovascular events[32], while Brownrigg et al. (2013) identified DPN as an independent risk factor for CVD in diabetes patients without prior cardiovascular history[33]. Kuo et al.'s study demonstrated that DPN is a risk factor for coronary artery disease[34]. Independently, DPN is a predictor of primary CVD in patients with T2DM[28]. The association between DPN and cardiovascular events likely indicates the involvement of shared pathways, including systemic inflammation[35] and lipid dysmetabolism[36]. The observed association between DPN and CVD likely reflects shared pathophysiological pathways, particularly low-grade chronic inflammation and autonomic neuropathy[37,38]. Diabetic autonomic neuropathy especially vagal withdrawal and sympathetic overactivity leads to impaired heart rate variability, endothelial dysfunction, increased vascular tone, and arrhythmogenicity, all of which contribute to heightened cardiovascular risk[39,40]. This neuroautonomic dysregulation, often coexisting with somatic DPN, may serve as a critical mechanistic link between peripheral nerve damage and adverse cardiac events[41]. Khawaja et al.'s study found that DPN was significantly associated with dyslipidemia and cardiovascular diseases[26]. Although early diagnosis and appropriate intervention among high-risk groups are imperative, multiple complex factors influence the association between DPN and CVD; nevertheless, these must be taken into account by healthcare managers.

Cardiac autonomic neuropathy (CAN), characterized by dysfunction of the autonomic innervation of the heart, is a common diabetic complication. CAN disrupts heart rate regulation and vascular dynamics, contributing to acute myocardial injury and diabetic heart failure[42]. Our findings are consistent with this pathophysiological

framework. Additionally, microvascular complications such as retinopathy, nephropathy, and neuropathy play a critical role in diabetic heart failure, underscoring the need for cardiac screening in these patients[43].

Our study further highlights the bidirectional relationship between micro- and macrovascular complications. For instance, a longitudinal study with a median 11.6-year follow-up found that individuals experiencing a macrovascular event faced twice the odds of subsequent microvascular complications[44]. The study by Shillah et al.[45] demonstrated that a significant proportion of microvascular complications were present in a cohort of patients with T2DM. Factors such as lack of regular physical activity, obesity, hypertension, and long disease duration were significantly associated with microvascular complications[45]. Arnold et al.'s study of 11,357 individuals with T2DM across 33 countries found that at enrollment, 19% had at least one microvascular complication (predominantly neuropathy) and 13.2% had at least one macrovascular complication (predominantly coronary artery disease). At the end of the 3-year follow-up period, 31.5% of patients had developed at least one microvascular complication and 16.6% had developed at least one macrovascular complication[46]. These results emphasize the importance of early identification and management of both micro- and macrovascular complications to mitigate cardiovascular morbidity in diabetes.

The mean age of patients with cardiovascular events was 64.9 years, with a neuropathy score of 3.7 and a diabetes duration of 9.3 years. Salinero-Fort et al. identified age ≥ 75 years as a cardiovascular risk factor in diabetic patients[47]. Pető et al. similarly demonstrated that advanced age and cardiovascular complications may increase the risk of DSPN[19]. Existing literature highlights age as an independent risk factor for DSPN progression in T2D, likely due to vascular aging, endothelial dysfunction, atherosclerosis, and cumulative axonal damage over time[48,49]. A meta-analysis further confirmed age as an independent risk factor for DPN in T2D[50]. In our study, cardiovascular odds appeared to increase with diabetes duration. Contrary to these findings, Pető et al. reported no association between diabetes duration and cardiovascular complications[19]. This discrepancy may stem from the fact that both groups in Pető et al.'s cohort had long-term diabetes[19]. Routine screening for diabetic neuropathy may facilitate early detection of peripheral nerve dysfunction in diabetic patients. Emphasizing glycemic control, enhanced monitoring of microvascular complications, and integrating neuropathy screening into diabetes care protocols may improve the identification and mitigation of cardiovascular risks in T2D populations.

Limitations

The strengths of this study include data collection from a sufficiently large sample of Iranian patients with T2DM, confirmed through validated instrumental examinations, which enabled a comprehensive assessment of risk factors, cardiovascular diseases, and microvascular complications. However, interpreting these findings requires careful consideration of several limitations. This study was a single-center study with a small sample size. Second, the study population was ethnically Iranian, limiting the generalizability of results to other ethnic groups. Also, due to unmatched age and gender, residual confounding may be present. Additionally, due to patients' ongoing pharmacological treatments, such as lipid-lowering drugs, we could not fully control for the effects of triglycerides and other clinical laboratory parameters. For future studies, we recommend enrolling pre-diabetic individuals not on medication and also on lipid-lowering drugs to evaluate better the effects of lipid profiles, FBS, HbA1C, and other laboratory parameters. Prospective studies should also focus on diabetic patients without a history of cardiovascular events and neuropathy scores less than 4 to examine the association between these variables. Monofilament testing was not used in the present study. Therefore, for a more accurate assessment of peripheral neuropathy in future studies, it is recommended to use standard tools such as the 10-gram monofilament and dermatome sensory testing. These methods provide more precise information about neuropathic status. Cardiovascular disease confirmation relied on cardiac records (e.g., ECG, angiography). We therefore propose the use of more sensitive tests (e.g., stress testing, echocardiography) in future studies. In the present study, the MNSI cutoff point is set at 4; however, some studies have adopted lower cutoff values, which should be further investigated in future research. Our definition of cardiovascular disease encompassed a composite endpoint including coronary artery disease, heart failure, stroke, and peripheral arterial disease. While this approach enhances statistical power by capturing clinically relevant endpoints, it may mask differential associations between specific CVD subtypes and DPN. Future prospective studies with subtype-specific analyses are warranted.

Conclusion

This study provides preliminary insights into the prevalence of DPN and its association with cardiovascular events in southeastern Iran. Our central finding is that patients with cardiovascular events exhibited significantly higher neuropathy scores, confirming a significant correlation between DPN and cardiovascular disease in T2DM patients. Although other comorbid factors were observed at higher rates in the affected group, the strong association with neuropathy highlights its potential importance as a key indicator or risk factor. Further prospective studies are essential to validate this correlation and to unravel the pathophysiological mechanisms linking DPN to cardiovascular outcomes.

Data availability

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

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Author contributions
MP, ZK, MS, PK and MK conceptualized, designed, analyzed, and interpreted the data, prepared a draft manuscript and edited the manuscript. MAZ, AHH, SKH and IJ conceptualized and edited the manuscript. MK, MP and MAZ contributed equally to this work. All authors read and approved the final manuscript.

Declarations

Competing interests
The authors declare no competing interests.

Ethical approval and consent to participate
The study was approved by the ethics committee of Rafsanjan University of Medical Sciences, with the code of ethics No. IR.RUMS.REC.1403.011. All procedures followed were in accordance with ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2000. Informed consent was obtained from all participants before participating in this study. All participants agreed to be included in the study anonymously.

Additional information
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