

Article

Comparison of Diabetic Polyneuropathy and Cardiac Autonomic Neuropathy in Type 1 and Type 2 Diabetes Mellitus

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Abstract

Aim: To compare diabetic polyneuropathy (DPN) and cardiac autonomic neuropathy (CAN) between T1DM and T2DM patients. **Methods:** This study enrolled 66 T1DM and 79 T2DM patients. DPN was evaluated using three different methods: clinical examination, using neuropathy symptom score (NSS) and neuropathy disability score (NDS), current perception threshold (CPT) using Neurometer, and nerve conduction studies (NCSs). CAN was assessed by cardiovascular autonomic reflex tests (CARTs). **Results:** The prevalence of DPN did not differ between T1DM and T2DM ($p > 0.05$ for all), however, the proportion of DPN depended on the method used and was highest with CPT (53.0% vs. 46.8%), followed by NCSs (44.1% vs. 41.2%) and clinical examination (25.8% vs. 31.6%). T2DM vs. T1DM patients were more often diagnosed with painful DPN (51.9% vs. 27.3%, $p = 0.004$), reduced perception of vibration (72.2% vs. 48.5%, $p = 0.006$), and autonomic neuropathy (59.5% vs. 32.3%, $p = 0.001$), while NCSs revealed more prevalent motor nerve dysfunction in T1DM compared to T2DM (41.2% vs. 19.6%). Multivariate regression analysis showed increased DPN risk with age and CAN risk with worsening of eGFR in T1DM. No significant associations remained after multivariate adjustment for T2DM. **Conclusions:** The prevalence of DPN is highly varied and depends on the diagnostic method used. T2DM patients more often had symptoms and signs of diabetic neuropathy. However, stronger associations with risk factors were observed in T1DM.

Keywords: diabetes; diabetic polyneuropathy; cardiac autonomic neuropathy; neuropathy risk factors



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1. Introduction

Diabetes mellitus (DM) is a complex and heterogeneous disease classified as a group of metabolic disorders characterized by chronic hyperglycemia resulting from defects in insulin secretion, insulin action, or both [1]. Type 1 (T1DM) and type 2 (T2DM) are the most prevalent DM forms, and it is now well recognized that these two types are distinct disorders with certain different aspects of etiology, pathogenesis, clinical presentation, and complications [2,3].

Chronic microvascular complications are the most burdensome consequence of diabetes, associated with significant patient disability and an enormous load on healthcare systems worldwide. The most prevalent but also the most underdiagnosed microvascular

complication in both T1DM and T2DM is diabetic neuropathy (DN) [4]. DN is characterized by symptoms and/or signs of nerve dysfunction due to metabolic and microvascular alterations caused by chronic hyperglycemia and other cardiovascular risk factors [5,6]. The most common forms of diabetic neuropathy are diabetic polyneuropathy (DPN) and cardiac autonomic neuropathy (CAN). Both of these complications are associated with increased patient morbidity and mortality. DPN in symptomatic cases manifests as pain, paresthesias, or dysesthesias, which often leads to sleep disorders, depression, and overall reduced quality of life [7,8]. Ultimately, it may cause foot ulceration, infection, and lower limb amputation, significantly increasing mortality risk [9,10]. CAN clinically manifests as resting tachycardia, exercise intolerance, and nocturnal hypertension, which may progress to orthostatic hypotension, silent myocardial ischemia, cardiac arrhythmia, and sudden death [11–13].

Despite decades of clinical and experimental investigations, there are many knowledge gaps regarding DPN and CAN, which preclude the successful prevention and treatment of these complications. An individualized approach considering differences in risk factors, pathophysiological mechanisms, and clinical presentation of T1DM and T2DM seems to be one of the critical factors to success [4,14]. Previous studies report differences between T1DM and T2DM in the regulation of molecular pathways involved in the pathogenesis of DN [15], blood biomarkers [16], and structural nerve damage [14,17,18]; however, data on differences in clinical presentation are scarce and inconsistent. Our study aimed to compare CAN and DPN in T1DM and T2DM patients assessed by different methods used in clinical practice.

2. Materials and Methods

2.1. Patients and Study Design

A cross-sectional study was conducted at Vilnius University Hospital Santaros Klinikos Endocrinology Department from August 2019 to June 2022. All patients with T1DM and T2DM, aged 18 years and older, were informed about the study, and those who agreed to participate were included. Patients with malignant, severe, uncontrolled systemic, metabolic, inflammatory, infectious, hereditary, or hematological diseases, mental illnesses, pregnancy, or breastfeeding were excluded to minimize potential confounding factors that could influence the outcomes.

There were 66 T1DM and 79 T2DM patients enrolled in the study. All patients underwent physical examination, biochemical assessment, clinical neurological evaluation, and current perception threshold (CPT) measurement. Cardiovascular autonomic reflex tests (CARTs) were performed in 136 patients, and the remaining 9 patients were not examined due to cardiac arrhythmia, pacemaker implantation, or severe myocardial damage after myocardial infarction. Nerve conduction studies (NCSs) were performed in a random subset of 85 patients due to the need for specific expertise and limited resources. Importantly, patients in the NCS subgroup were comparable to the rest of the cohort regarding age, diabetes duration, and other key clinical characteristics.

The study was approved by Vilnius Regional Biomedical Research Ethics Committee (registry number 2019/6-1146-635), and all participants gave written consent.

2.2. Physical Examination and Laboratory Assessment

Medical history was collected from medical records, and a trained endocrinologist interviewed patients. Heart rate, systolic and diastolic blood pressure (SBP and DBP), body weight (BW), body height (BH), and body mass index (BMI) were measured during physical examination. Obesity was defined as a BMI of 30 kg/m² or higher. Hypertension was diagnosed if blood pressure was at or above 140/90 mmHg for several measurements

or from anamnestic data. Fasting morning blood samples were collected for glycosylated hemoglobin (HbA1c), creatinine, and blood lipid analysis. The estimated glomerular filtration rate (eGFR) was calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation. Dyslipidemia was diagnosed according to the European Society of Cardiology Guidelines [19] or in case of statin use.

2.3. Diabetic Polyneuropathy Assessment

DPN was evaluated using three diagnostic techniques: clinical neurological examination, CPT measurement, and NCSs.

2.3.1. Clinical Neurological Examination

A clinical neurological examination was performed using the neuropathy symptom score (NSS) and neuropathy disability score (NDS) as described previously [20]. NDS was derived from vibration, temperature, and pain sensation at the great toe and examination of the ankle reflex. Vibration sense was measured by a 128 Hz tuning fork, temperature sensation by a Tip Therm stick, and pain sensation by pin-prick (Ortopodomed, Riga, Latvia) [20]. In the case of painful neuropathy, the Symptom Assessment Scale (SAS) score from 0 to 10 was used to self-evaluate pain intensity, with 0 being no symptoms and 10 being the worst possible. The assessment was based on the standardized SAS questionnaire [21].

2.3.2. Current Perception Threshold Measurement

CPT was measured by the trained endocrinologist using the Neurometer NervScan™ LLC device (Neurotron, Incorporated, Baltimore, MD, USA). Both lower extremities were tested in the toe area, using three distinct electrical impulse frequencies. Each frequency stimulates a different type of nerve fiber: 2000 Hz—large myelinated (A-beta) fibers, 250 Hz—small myelinated (A-delta) fibers, and 5 Hz—small unmyelinated fibers [22,23]. During the examination, the intensity of the electric stimulus was gradually increased until the patient sensed prickling, buzzing, or tingling. According to manufacturer specifications, CPT values for each fiber type ranged from 1 to 25. Sensation from 6 to 13 was normal, whereas 1–5 was hyperesthesia, and 14–25 was hypoesthesia. Both bilateral hyperesthesia and hypoesthesia were considered pathological results.

2.3.3. Nerve Conduction Studies

NCSs were performed with Neuropack X1 device (Nihon Kohden, Tokyo, Japan). All patients had the conventional orthodromic motor and antidromic sensory nerve conduction studies on the common peroneal motor, tibial, and sural nerves. Peroneal motor and tibial nerves were tested unilaterally, and sural nerves were tested bilaterally. Results of nerve conduction velocity (NCV), distal latency (DL), compound muscle action potential (CMAP) amplitudes, and sensory nerve action potential (SNAP) amplitudes were compared to age- and gender-correlated normal values established in our laboratory before this study, based on nerve conduction data from a cohort of healthy subjects. The diagnosis of polyneuropathy was based on the diagnostic criteria for distal symmetric polyneuropathy proposed by the American Academy of Neurology [24]. The minimal electrophysiological criteria for polyneuropathy were changes in at least two nerve responses (at least one of the nerves—the sural nerve). Responses were considered abnormal if their value was below or above the mean and the two standard deviations. Specifically, motor nerve responses were considered abnormal if the CMAP amplitude was below 2.7 mV for the peroneal nerve or 3.8 mV for the tibial nerve; if the distal latency exceeded 4.6 ms for the peroneal nerve or 4.3 ms for the tibial nerve; or if the nerve conduction velocity (NCV) was below 40.4 m/s (peroneal) or 40.0 m/s (tibial). For the sural sensory nerve, SNAP amplitude was classified as abnormal if it was below 5.4 μ V, and NCV if it was below 39.7 m/s.

To evaluate how positive results of DPN assessment methods overlap for the same patient, we calculated how many times the positive outcome of one method matched a positive result of at least one other method.

2.4. Cardiac Autonomic Neuropathy Assessment

CARTs detected CAN using the Cardiosys Extra diagnostic device (MDE GmbH, Munich, Germany). The examination was performed under standard conditions according to guidelines [25]. Antihypertensive drugs, such as beta-blockers, calcium-channel blockers, angiotensin-converting enzyme inhibitors, and diuretics, were discontinued 14 h before the tests. Four diagnostic tests were performed: heart rate response to deep breathing, Valsalva maneuver, and standing and arterial pressure response to standing (orthostatic hypotension). The results of Heart Rate Variability tests were evaluated using technique-specific normative data as previously described [26]. Postural hypotension was defined as a drop of more than 30 mmHg in systolic blood pressure. Cardiac autonomic neuropathy was diagnosed if at least one test was abnormal.

2.5. Statistical Analyses

Data were analyzed with IBM SPSS Statistics v. 26.0. Categorical variables were characterized using frequencies, presented as the number of patients and corresponding percentages. Fisher's exact test was used to compare the frequencies of categorical variables. Quantitative variables were expressed as mean $\pm$ standard deviation (SD), and a comparison between groups was made using the Mann–Whitney U-test.

The sufficiency of the sample size was evaluated using statistical power calculations with the online tool StatsKingdom [27]. For comparisons between T1DM and T2DM groups, statistical power exceeded 0.80 for categorical (effect size $h = 0.5$) and continuous variables (effect size $d = 0.5$). For within-group analyses, the power exceeded 0.50 for medium (0.5) and 0.90 for large (0.8) effect sizes.

To evaluate the risk factors for diabetic peripheral neuropathy (DPN) and cardiovascular autonomic neuropathy (CAN), multivariate analysis using logistic regression was performed on variables that showed statistically significant differences in univariate comparisons. This approach allowed us to control for potential confounding factors and reduce the likelihood of spurious associations.

The level of statistical significance was set at $p < 0.05$.

3. Results

The patient's basic characteristics are presented in Table 1. There was no difference in gender distribution, disease duration, glycemic control, and prevalence of diabetic nephropathy and retinopathy between T1DM and T2DM patients. The proportion of patients with HbA1c of more than 7% in at least two recent measurements did not differ between the groups and was 58.5 and 71.8% in T1DM and T2DM, respectively ($p = 0.162$). The percentage of current smokers was 32.2% in the T1DM group and 17.7% in the T2DM group ($p = 0.054$). However, T1DM patients were significantly younger, had lower BMI, and a lower incidence of comorbidities ($p < 0.05$).

Table 1. Basic characteristics of study patients.

	T1DM (n-66)	T2DM (n-79)	<i>p</i> Value
Demographic and Disease Characteristics			
Male/female, n (%)	34/32 (51.5/48.5)	32/47 (40.5/59.5)	0.241 [△]
Age (years)	40.8 ± 15.2	59.8 ± 11.6	<0.001 [*]
Diabetes duration (years)	14.1 ± 13.4	11.9 ± 8.1	0.927 [*]
BMI (kg/m ²)	23.7 ± 3.5	35.1 ± 6.2	<0.001 [*]
HbA1c (%)	9.4	10.3	0.091 [*]
eGFR, (mL/min/1.73 m ²)	90.6 ± 24.8	86.9 ± 17.1	0.131 [*]
DM Complications and Concomitant Diseases			
Dyslipidemia, n (%)	27 (40.9)	63 (79.7)	<0.001 [△]
Obesity, n (%)	3 (4.5)	60 (75.9)	<0.001 [△]
Hypertension, n (%)	23 (34.8)	69 (87.3)	<0.001 [△]
Retinopathy, n (%)	25 (37.9)	27 (34.2)	0.729 [△]
Nephropathy, n (%)	15 (22.7)	10 (12.7)	0.126 [△]

Data were expressed as mean ± SD, and a proportion of positive patients in number and percentage (n, %);

^{*} Mann–Whitney test; [△] Fisher’s exact test. BMI—body mass index; HbA1c—glycated hemoglobin; T1DM—type 1 diabetes mellitus; T2DM—type 2 diabetes mellitus.

The prevalence of DPN did not differ between T1DM and T2DM groups; however, the proportion of DPN depended on the method used and was the most diagnosed with CPT (53.0% vs. 46.8%), followed by NCSs (44.1% vs. 41.2%) and clinical examination (25.8% vs. 31.6%), $p > 0.05$ for all.

Clinical evaluation revealed that vibration perception was the only test significantly worse in patients with T2DM compared to those with T1DM (Table 2).

No difference in sensation was observed during CPT measurement between the groups. However, a significantly larger proportion of patients with T1DM showed axonal lesion of peroneal motor fibers on NCSs compared to those with T2DM (Table 2).

Painful DPN (SAS 1–9) was more often diagnosed in T2DM, compared to T1DM patients—41 (51.9%) vs. 18 (27.3%), respectively ($p = 0.004$), but the severity of pain did not differ between the groups with an equal average SAS score of 4.5 points in both T1DM and T2DM.

DPN overlap evaluation showed the best repeatability for NCSs ($n = 77$), followed by clinical neurological evaluation ($n = 68$) and CPT ($n = 62$). As NCS was used only for a particular sample of patients, clinical neurological evaluation was considered to assess DPN risk factors.

CAN was significantly more common in T2DM compared to T1DM patients—59.5% vs. 32.3%, respectively ($p < 0.05$), primarily due to the higher frequency of pathological deep breathing test (Table 2).

Within the group, T1DM patients with DPN were older, had longer diabetes duration, higher SBP, lower eGFR, and worse long-term glycemic control, and were more often diagnosed with other comorbidities and microvascular complications in comparison with those without DPN ($p < 0.05$ for all) (Table 3). However, T1DM patients with and without DPN did not differ significantly in terms of sex, smoking status, BMI, and HbA1c levels.

Table 2. The proportion of patients with impaired test results.

Abnormal Test	T1DM, n (%)	T2DM, n (%)	<i>p</i> Value
NDS, n = 145 *	66 (100)	79 (100)	
Vibration perception	32 (48.5)	57 (72.2)	0.006
Temperature perception	17 (25.8)	25 (31.6)	0.589
Pin-prick perception	12 (18.2)	13 (16.5)	0.828
Ankle reflexes	11 (16.7)	13 (16.5)	0.549
CPT, n = 145 *	66 (100)	79 (100)	
Lesion of large myelinated fibers	23 (34.8)	21 (26.6)	0.365
Lesion of small myelinated fibers	29 (43.9)	28 (35.4)	0.311
Lesion of small unmyelinated fibers, n (%)	24 (36.4)	20 (25.3)	0.202
NCS, n = 85 *	34 (51.5)	51 (64.6)	
Reduced peroneal motor amplitude	14 (41.2)	10 (19.6)	0.048
Prolonged peroneal motor distal latency	8 (23.5)	3 (5.9)	0.023
Reduced peroneal motor conduction velocity	11 (32.4)	6 (11.8)	0.027
Reduced tibial motor amplitude	5 (14.7)	9 (17.6)	0.775
Prolonged tibial motor distal latency	3 (8.8)	4 (7.8)	1.000
Reduced tibial motor conduction velocity	6 (17.6)	7 (13.7)	0.761
Reduced sural sensory amplitude	15 (44.1)	19 (37.3)	0.647
Reduced sural sensory conduction velocity	13 (38.2)	17 (33.3)	0.813
CARTs, n = 136 *	62 (93.9)	74 (93.7)	
HR response to the deep breathing test	12 (19.4)	34 (45.9)	0.001
HR response to Valsalva maneuver	5 (8.1)	10 (13.5)	0.413
HR response to standing	20 (32.3)	31 (41.9)	0.288
BP's response to standing	13 (21.0)	14 (18.9)	0.831

* Rows represent the proportion of tested patients. BP—blood pressure; CARTs—cardiovascular autonomic reflex tests; CPT—current perception threshold; HR—heart rate; NCSs—nerve conduction studies; NDS—neuropathy disability score; T1DM—type 1 diabetes mellitus; T2DM—type 2 diabetes mellitus.

Table 3. Comparison of clinical variables showing statistically significant differences in patients with and without diabetic polyneuropathy (DPN−/+) based on clinical neurological examination.

	T1DM (n = 66)			T2DM (n = 79)		
	DPN (−)	DPN (+)	<i>p</i> Value	DPN (−)	DPN (+)	<i>p</i> Value
N, (%)	49 (74.2)	17 (25.8)		54 (68.4)	25 (31.6)	
Age (years)	36.2 ± 12.9	53.9 ± 14.0	<0.001 *	58.1 ± 11.9	63.4 ± 10.1	0.059 *
Diabetes duration (years)	9.7 ± 11.1	25.4 ± 12.9	<0.001 *	10.7 ± 8.6	14.8 ± 5.7	0.008 *
eGFR, (mL/min/1.73 m ²)	93.9 ± 25.8	80.9 ± 18.8	0.002 *	89.3 ± 15.2	82.0 ± 19.6	0.079 *
Dyslipidemia, n (%)	13 (26.5)	14 (82.4)	<0.001 †	42 (77.8)	21 (84.0)	0.764 †
Hypertension, n (%)	9 (18.4)	14 (82.4)	<0.001 †	45 (83.3)	24 (96.0)	0.157 †
Retinopathy, n (%)	11 (22.4)	14 (82.4)	<0.001 †	16 (29.6)	11 (44.0)	0.308 †

Table 3. *Cont.*

	T1DM (n = 66)			T2DM (n = 79)		
	DPN (–)	DPN (+)	p Value	DPN (–)	DPN (+)	p Value
Nephropathy, n (%)	6 (12.2)	9 (52.9)	0.001 [‡]	6 (11.1)	4 (16.0)	0.717 [‡]
CAN	11 (22.9)	9 (64.3)	0.008 [‡]	27 (54.0)	17 (70.8)	0.210 [‡]

Continuous data were expressed as mean $\pm$ SD, and the proportion of positive patients in number and percentage (n, %). ^{*} Mann–Whitney test; [‡] Fisher’s exact test. CAN—cardiac autonomic neuropathy, BMI—body mass index; HbA1c—glycated hemoglobin; eGFR—estimated glomerular filtration; DPN (–)—patients without polyneuropathy; DPN (+) patients with polyneuropathy; T1DM—type 1 diabetes mellitus; T2DM—type 2 diabetes mellitus.

Within the T2DM group, those with DPN had longer diabetes duration compared to those without DPN ($p < 0.05$) (Table 3). Nevertheless, no significant differences were observed in terms of sex, age, smoking status, BMI, HbA1c, eGFR, comorbidities, or other microvascular complications.

T1DM patients with CAN had longer diabetes duration and lower eGFR and were more often diagnosed with arterial hypertension, diabetic retinopathy, and diabetic nephropathy than those without CAN ($p < 0.05$) (Table 4). However, the groups did not differ significantly in terms of sex, smoking status, BMI, and HbA1c. T2DM patients with CAN were older and more often diagnosed with diabetic retinopathy compared to those without CAN (Table 4). Nevertheless, no significant differences were observed in terms of sex, age, smoking status, BMI, HbA1c, eGFR, comorbidities, or other microvascular complications.

Table 4. Comparison of clinical variables showing statistically significant differences in patients with and without cardiac autonomic neuropathy (CAN–/+).

	T1DM (n = 62)			T2DM (n = 74)		
	CAN (–)	CAN (+)	p Value	CAN (–)	CAN (+)	p Value
N, (%)	42 (67.7)	20 (32.3)		30 (40.5)	44 (59.5)	
Age (years)	37.7 $\pm$ 13.3	43.8 $\pm$ 15.4	0.104 [*]	56.1 $\pm$ 12.9	62.0 $\pm$ 10.2	0.04 [*]
Diabetes duration (years)	9.0 $\pm$ 10.6	22.0 $\pm$ 14.5	0.001 [*]	10.3 $\pm$ 9.4	12.8 $\pm$ 6.7	0.091 [*]
eGFR (mL/min/1.73 m ²)	98.1 $\pm$ 22.4	76.2 $\pm$ 25.9	<0.001 [*]	85.6 $\pm$ 19.2	87.8 $\pm$ 16.5	0.582 [*]
Hypertension, n (%)	7 (16.7)	12 (60)	0.001 [‡]	25 (83.3)	39 (88.6)	0.514 [‡]
Retinopathy, n (%)	9 (21.4)	13 (65.0)	0.001 [‡]	4 (13.3)	20 (45.5)	0.005 [‡]
Nephropathy, n (%)	4 (9.5)	11 (55.0)	<0.001 [‡]	3 (10)	6 (13.6)	0.731 [‡]

Continuous data were expressed as mean $\pm$ SD, and the proportion of positive patients in number and percentage (%); ^{*} Mann–Whitney test; [‡] Fisher’s exact test. CAN (–)—patients without cardiac autonomic neuropathy; CAN (+)—patients with cardiac autonomic neuropathy; BMI—body mass index; HbA1c—glycated hemoglobin; eGFR—estimated glomerular filtration; T1DM—type 1 diabetes mellitus; T2DM—type 2 diabetes mellitus.

After multivariate adjustment for significant covariates in T1DM patients, the odds [OR (95% confidence intervals)] for DPN increased with age [1.198 (1.034–1.389)], $p = 0.016$, and the odds of CAN were higher in patients with diabetic nephropathy, $p = 0.031$, and lower with better renal function (higher eGFR) [0.971 (0.941–1.002)] (near-significant $p = 0.066$) (Table 5). No reliable logistic regression model could be established for patients with T2DM, probably because of only minor differences between groups with and without neuropathy and a relatively small sample size.

Table 5. Association of diabetic polyneuropathy and cardiac autonomic neuropathy with clinical indicators in a cohort of type 1 diabetes patients, calculated using logistic regression analysis.

	Variables	β Coefficient	Standard Error	p Value	Odds Ratio	95% Confidence Interval
Polyneuropathy	Constant	−20.274	8.113	0.012		
	Age	0.181	0.075	0.016	1.198	(1.034, 1.389)
	Diabetes duration	−0.018	0.050	0.720	0.982	(0.891, 1.083)
	eGFR	0.073	0.040	0.063	1.076	(0.996, 1.163)
	Dyslipidemia	−0.508	1.526	0.739	0.602	(0.030, 11.980)
	Hypertension	5.225	2.856	0.067	185.947	(0.690, 50,122, 761)
	Retinopathy	0.864	1.614	0.592	2.374	(0.100, 56.145)
	Nephropathy	4.836	2.567	0.060	125.952	(0.822, 19,303.899)
	Cardiac autonomic neuropathy	−0.323	1.380	0.815	0.724	(0.048, 10.829)
	Chi-square	43.625, df=8, $p < 0.001$				
Cardiac autonomic neuropathy	Constant	0.578	1547	0.708		
	Diabetes duration	0.046	0.034	0.174	1.047	(0.980, 1.118)
	eGFR	−0.029	0.016	0.066	0.971	(0.941, 1.002)
	Hypertension	0.479	0.856	0.576	1.614	(0.301, 8.641)
	Retinopathy	−0.276	0.928	0.766	0.759	(0.123, 4.678)
	Nephropathy	1.831	0.851	0.031	6.241	(1.178, 33.065)
	Chi-square	22.572, df=5, $p < 0.001$				

4. Discussion

Most epidemiological studies reveal that DPN is more common and manifests at earlier stages (even in prediabetes) in T2DM patients compared to T1DM [4,28]. In our study, we did not observe any difference in the prevalence of DPN between T1DM and T2DM, most probably due to the specific study population with severe and advanced disease.

4.1. Diagnostic Method Comparison

There was a significant difference in the prevalence of DPN depending on the method used in both types of diabetes. This might be explained by the different methods' sensitivity and specificity. Clinical evaluation, performed by NSS and NDS, is one of the most widely used clinical diagnostic tools that shows the damage of both small and large nerve fibers [29]. However, due to relatively low sensitivity (NDS reaching 68%), only advanced nerve damage can be detected with this method [30], and the prevalence of DPN was the lowest in our study [30]. An NCS is an objective, highly sensitive method for diagnosing DNP, and it is used as a gold standard in clinical studies, but it only reveals large nerve fiber damage. Therefore, our study's prevalence of DNP diagnosed using NCS was moderate [30]. CPT shows early signs of both large and small nerve fiber damage. However, like all subjective sensory tests, it significantly varies depending on patient cooperation, examiner experience, and confounding factors [31,32]. In our study, Neurometer showed the highest prevalence of DPN, which is consistent with the results of other studies [33,34]. Therefore, as a highly sensitive quantitative test, it may serve in suspecting early DPN or monitoring DPN progression [22].

Impairment of vibration perception is a sign of large nerve fiber dysfunction and was more common in T2DM in comparison with T1DM in our study. This aligns with other research, which also revealed reduced vibration perception in T2DM compared to T1DM, evaluated by a biothesiometer [35] or Vibratory Sensor Analyzer [36]. Although vibration perception decreases with age [37], previous diabetes studies revealed higher vibration perception impairment in T2DM than in T1DM across various age groups; however, not all authors specified whether age-related norms were applied [35,36,38]. Interestingly, CPT testing, which also allows assessment of large fiber dysfunction at the 2000 Hz frequency, did not reveal significant differences between diabetes types in our study. It is possible that a ceiling effect in CPT testing limited its ability to differentiate between T1DM and T2DM

patients with more advanced neuropathy. Similar plateau effects have been documented in vibration perception testing using biothesiometer devices [39]. In CPT assessments, clustering of high threshold values among severely neuropathic individuals has been reported to reduce their discriminatory power [40].

Other clinical evaluation tests, showing either small (temperature or pin-prick perception) or large (ankle reflexes) fiber damage, did not show any differences between diabetes types in our study. In contrast, the results of previous studies are controversial [16,36,41].

There was no difference in sensory sural nerve and motor tibial nerve dysfunction between T1DM and T2DM, consistent with previous data [16,35]. In contrast, peroneal motor nerve function was significantly more often impaired in T1DM. It is considered that motor manifestations follow sensory loss and indicate a progressive nerve dysfunction. Thus, we speculate that patients with T1DM more often had severe nerve damage compared to those with T2DM. However, other authors report no difference in motor nerve dysfunction between diabetes types [35] or reveal opposite results when motor nerve dysfunction was more pronounced in T2DM than in T1DM [16]. Thus, further investigation is needed in this area.

CPT perception of large or small nerve fibers did not differ between T1DM and T2DM, which is inconsistent with the objective evaluation results, where large nerve fiber dysfunction, evaluated by a 128 Hz tuning fork, was more prevalent in T2DM. According to previous studies, the sensitivity of the 128 Hz tuning fork ranges between 62.5% and 84.6% [42–44], generally lower than CPT, where sensitivity reaches 94% [22]. Therefore, we might hypothesize that T2DM patients more often had advanced, but not initial, large nerve fiber damage. In our study, painful neuropathy was significantly more common in T2DM patients than in T1DM, consistent with previous studies [20,45]. It is not precisely known why T2DM patients are prone to develop painful DPN. Comorbidities more common in T2DM might be responsible for additive damage to small nerve fibers, which are responsible for pain perception [31,46]. However, our results show that, despite a higher prevalence of neuropathic pain in T2DM patients, pain intensity did not differ between types of diabetes.

Prevalence of CAN varies from 2% to 91% in T1DM and from 25% to 75% in T2DM [47,48], and those studies that compared CAN prevalence in T1DM vs. T2DM report mixed results: in one study, CAN was more prevalent in T2DM [49], while in the other, in T1DM [50], there was no significant difference between diabetes types [51,52]. In our study, the prevalence of CAN was almost twice as common in T2DM patients as in T1DM patients. This was due to the higher impairment of the three tests, showing parasympathetic dysfunction—heart rate response to deep breathing, Valsalva maneuver, and standing. However, a significant difference was reached only in the deep breathing test. The deep breathing test was the most common pathological test in T2DM, which is in line with the data of Pan et al., who reported the highest sensitivity of the deep breathing test for CAN detection in T2DM [53]. There are data that obesity may impair the results of the deep breathing test due to the attenuation of chest reflexes in T2DM patients [25]; however, even though most T2DM patients were obese in our study, we did not observe any significant association between obesity and impairment of the deep breathing test.

The blood pressure response to standing, which shows sympathetic dysfunction and advanced disease, was slightly more impaired in T1DM, but the difference was not statistically significant. We might presume that T1DM patients are more prone to severe CAN, but this finding needs further evaluation with a larger sample size.

4.2. Risk Factors and Comorbidities Associations

Poor glycemic control was a significant risk factor for DPN and CAN in T1DM but not in T2DM in our study. This aligns with the current knowledge that hyperglycemia

is the primary driver of nerve injury in T1DM, whereas modest or no effect is observed in T2DM [54]. Diabetes duration, which, along with hyperglycemia, reflects cumulative glycemic exposure, was also more associated with DN in T1DM than in T2DM. Importantly, HbA1c results, which represent blood glucose control over the last three months, did not show any associations with DN in either T1DM or T2DM, reflecting the shortcomings of this test in cross-sectional studies.

Other traditional risk factors, such as older age, other microvascular complications, and comorbidities, were more common in patients with CAN and DPN in both T1DM and T2DM. However, the significant association was more common in T1DM. The association of the above-mentioned risk factors with DPN and CAN in T1DM was also observed in the European Insulin Dependent Diabetes Mellitus Prospective Complications Study (EURODIAB IDDM) [55] and solely with DPN in the T1D Exchange and the Scottish Register studies [56]. The association of DN with other microvascular complications was not surprising due to common pathogenetic pathways in both types of diabetes. However, contrary to our results, a stronger association of CAN with other microvascular complications was observed in T2DM compared to T1DM in another similar study [50]. Diabetic nephropathy and lower eGFR were significantly associated with CAN and DPN in T1DM but not T2DM in our study. The presence of CAN is associated with increased glomerular filtration pressure, glomerular endothelial cell damage, and erythropoietin secretion [53], and the positive association between CAN and reduced kidney function was proved in both T1DM [57,58] and T2DM [59] studies. Uremic neuropathy, describing more progressive DPN in patients with impaired renal function due to damage to large nerve fibers, was also described by previous authors [60].

A stronger association of comorbidities with DPN and CAN in T1DM than in T2DM was unexpected. For the prevention of DN, many previous studies stress the importance of glycemic control in T1DM and a more holistic approach in T2DM, comprising correction of arterial hypertension and dyslipidemia together with hyperglycemia [14,54]. However, such results in epidemiological studies might be due to the lower prevalence of comorbidities in T1DM compared to T2DM [61,62]. In our study, severely ill, hospitalized patients with T1DM had a high prevalence of dyslipidemia and hypertension, which might result in a strong association with DPN and CAN. This might suggest that, in T1DM patients, comorbidities are associated not with a lower risk but with a higher risk of DPN. Overall, there were similar risk factors in T1DM and T2DM, but a relatively small sample size most probably limited the power to identify significantly associated risk factors of diabetic neuropathy with T2DM.

4.3. Limitations of the Study

Some limitations of this study should be considered. This single-center study was performed at a tertiary center, not in a community. Thus, most patients had a poorly controlled and progressive disease. Therefore, the results cannot be generalized to all patients with diabetes. The cross-sectional study design precludes the assessment of the correlation between risk factors and DN, and a relatively small sample size not only limits the detection of statistically significant associations but also may cause statistical instability and overfitting. For example, exceptionally large odds ratios for polyneuropathy and variables such as hypertension and nephropathy were found in the T1DM group. Nonetheless, these have very wide confidence intervals and should be considered with caution and not overinterpreted.

5. Conclusions

In this confirmatory study based on established diagnostic methods, we did not find a significant difference in the overall prevalence of DPN between T1DM and T2DM groups; however, the proportion of detected cases varied by method, being highest with CPT, followed by NCSs and clinical examination.

In T2DM patients, vibration perception was more often impaired, painful neuropathy was more frequently diagnosed, and CAN was more prevalent. In contrast, motor dysfunction was more common in T1DM patients. Cardiovascular risk factors showed a stronger association with nerve damage in T1DM.

Importantly, our findings indicate specific differences in the presentation of diabetic neuropathies between T1DM and T2DM, underscoring potential differences in their pathophysiology and clinical manifestations. These differences may have critical implications for refining diagnostic and treatment strategies. The observed associations, particularly in the T1DM subgroup, highlight areas that warrant further investigation. Future studies should include larger cohorts, adopt longitudinal designs to clarify causal relationships, and evaluate targeted interventions based on neuropathy subtypes.

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