

## Original Article

# Early Diagnosis of Peripheral Diabetic Neuropathy – Something Old that Should Always Be Considered Something New

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Received: March 16<sup>th</sup>, 2020 / Accepted: April 30<sup>th</sup>, 2020

### Abstract

**Introduction:** Diabetic peripheral neuropathy is a frequent complication and disability of diabetes mellitus that requires complex management. The importance of an early diagnosis is emphasized by the high risk of subsequent foot ulceration or amputation and an increase in the mortality rate. The aim of the study was to evaluate the utility of quantitative sensory testing in monitoring peripheral diabetic neuropathy and its correlation with micro- and macrovascular complications of diabetes mellitus. **Material and Methods:** We included 136 patients admitted to N. C. Paulescu National Institute for Diabetes, Nutrition and Metabolic Diseases over six months, and analyzed their clinical and paraclinical data using Excel and PSP software. Each patient had quantitative sensory testing performed. **Results:** The group consisted of 61.03% males and 38.97% females, with a mean age of 55.97±15.2 years. Of them, 22.79% presented type 1 diabetes mellitus, 30.88% had type 2 diabetes mellitus, and 46.32% had insulin-treated type 2 diabetes mellitus, with a mean glycosylated hemoglobin of 9.64%±2.49% and a mean duration of diabetes mellitus of 11.94 years. Diabetes complications were diabetic peripheral neuropathy (68.38%), diabetic retinopathy (27.94%), chronic kidney disease (25.74%), atherosclerotic disease (38.24%). Diabetic peripheral neuropathy diagnosis positively correlated with age (p=0.031), body mass index (p<0.0001), albumin to creatinine ratio (p=0.049), presence of chronic kidney disease (p=0.01) and diabetic retinopathy (p=0.001), and diabetes duration (p<0.001). **Conclusions:** Diabetic peripheral neuropathy accounts for considerable morbidity and mortality and reduced quality of life. Clinical recognition is required for allowing early symptomatic management in order to reduce the morbidity associated with this condition. Quantitative sensory testing is used for screening and diagnosing diabetic peripheral neuropathy. Given the significant association with other microvascular complications, such as chronic kidney disease and diabetic retinopathy, neuropathy's diagnosis should immediately lead to screening for other complications of diabetes and certain risk factors and consequent measures.

**Keywords:** Quantitative sensory testing, diabetes mellitus, diabetic peripheral neuropathy, HbA1c.

### Introductory Remarks

Diabetes mellitus (DM) is one of the modern chronic non-transmittable disorders with a prevalence that reached epidemic proportions [1]. The impact of DM on the patient's quality of life resides in both chronic microvascular – such as diabetic peripheral neuropathy (DPN), diabetic retinopathy, diabetic chronic kidney disease and macrovascular complications – such as atherosclerotic cardiovascular disease

(myocardial infarction, ischemic stroke) or limb amputations, thus generating considerable morbidity and mortality, translated into a significant financial burden for the healthcare systems [2].

DPN is the most frequent cause of neuropathy worldwide, and it affects roundly half of the patients with DM [3]. It requires complex management once diagnosed, but beforehand, it should be stressed on the importance of early screening for DPN, given the severity of the debilitating complications that could arise –



limb ulcerations or lower limb amputations. The latter mentioned complications are substantial factors that alter the patient’s quality of life [4].

The American Diabetes Association (ADA) recommends quantitative sensory testing (QST) - such as 10-g monofilament and tuning fork as a complementary assessment to the clinical examination, aiming to evaluate the small and large fiber function and the protective sensation, in order to screen for the existing neuropathy and to predict the risk of developing further complications such as foot ulceration and amputation [5].

Despite the unmodifiable risk factors such as age or diabetes duration, a close look, and prompt intervention is required on the modifiable risk factors such as smoking, metabolic parameters, or high blood pressure [6].

Diabetic polyneuropathy prevalence is heterogeneous, as depicted in the epidemiological studies, depending on the different patient populations, definitions of neuropathy used, and assessment methods [1, 7]. A reported fact is that prevalence of diabetic peripheral neuropathy is increasing with age [4].

Our study aimed to evaluate the utility of QST, a simple and easily accessible tool, in monitoring the peripheral diabetic neuropathy and its correlation with the presence of other micro- and macrovascular complications of DM.

## Material and Methods

A retrospective, observational study was conducted at N. C. Paulescu National Institute for Diabetes, Nutrition and Metabolic Diseases, Bucharest, Romania, over six months. The study included 136 inpatients after signed informed consent was obtained who had a positive diagnosis of type 1 DM (T1DM) or type 2 DM (T2DM) and underwent QST, which included a 10-g monofilament and a tuning fork evaluation, and thermal sensory testing. Patients under eighteen years old, patients with neuropathies secondary to other causes or patients with secondary forms of diabetes were not included in the study. We collected and analyzed their clinical data (age, gender, body mass index, DM type, DM duration, presence of DM complications, presence of DPN risk factors - high blood pressure, smoking, obesity, dyslipidemia) and paraclinical data (A1c hemoglobin, albumin to creatinine ratio, QST results) using Microsoft Excel and PSPP software. Linear correlations and t-tests were performed as well.

## Results

The group characteristics were as follows: 61.03% (n=83) were males and 38.97% (n=53) were females; the group mean age was of 55.97±15.2 years - 54.38±14.7 years for males, 64.31±10.93 years for females and 39.03±14.26 years for T1DM and 60.97±11.43 years for T2DM. Regarding the DM distribution in the study group, 22.79% (n=31) had type 1 DM, 30.88% (n=42) had type 2 DM, and 46.32% (n=63) had insulin-treated T2DM. The mean value for HbA1c was 9.64%±2.49%. The mean duration of DM was 11.94 years. The most frequent DM complications were: DPN in 68.38% of patients (84% with T2DM), diabetic retinopathy in 27.94% of patients, chronic kidney disease (CKD) in 25.74% of patients and atherosclerotic disease in 38.24% of patients (Table 1).

Table 1: Distribution of Chronic Complications of Diabetes Mellitus (DM).

DM Complication	Type 1 DM		Type 2 DM	
	N	%	n	%
<b>Diabetic Peripheral Neuropathy</b>	15	48.38%	78	74.28
<b>Diabetic Retinopathy</b>	9	29.03%	29	27.61%
<b>Chronic Kidney Disease (CKD)*</b>	5	16.12%	30	28.57%
<b>Atherosclerotic Cardiovascular Disease (ASCVD)**</b>	1	3.22%	51	48.57%

\*CKD is represented by eGFR<60 ml/min/1.73m<sup>2</sup> and ACR>200 mg/g Creatinine  
 \*\*ASCVD is represented by Angina Pectoris, Ischemic Coronary Disease, Myocardial Infarction

The risk factors for DPN (Table 2) can be categorized into modifiable and unmodifiable, and according to their contribution to DPN, these factors can be further described as major, others and additional, as detailed in Table 3. In the study group, the risk factors were: poor glycemic control (as defined by HbA1c > 7%) - 81.61%, high blood pressure in 65.44% of patients, dyslipidemia in 82.35%, obesity in 36.76%, and smoking in 27.2% of patients. DM mean duration was 11.94 years, patients’ mean age was 55.97 years, and 8.08% of patients had prediabetes.

Table 2: Distribution of Modifiable Diabetic Peripheral Neuropathy (DPN) Risk Factors.

DPN risk factors	Type 1 DM	Type 2 DM
	%	%
Hyperglycaemia/poor metabolic control	90.32%	79.04%
High Blood Pressure	19.35%	79.04%
Dyslipidaemia (Ct > 130 mg/dL)	93.54%	79%
Obesity (BMI > 29.9 kg/m <sup>2</sup> )	6.45%	45.71%
Smoking	38.71%	16.19%

Table 3: Risk factors for diabetic peripheral neuropathy, as cited in the literature [9].

Risk Factors for Diabetic Peripheral Neuropathy	
Modifiable	Unmodifiable
<b>Major:</b> Hyperglycemia	<b>Major:</b> Diabetes duration, Age
<b>Others:</b> High Blood Pressure, Dyslipidemia, Obesity.	<b>Others:</b> Prediabetes
<b>Additional:</b> Smoking	<b>Additional:</b> Height, Insulin resistance, Hypoinsulinemia

When QST was performed, the following values were obtained:

- altered 10-g monofilament test in 68.38% of patients (54.83% of the patients with type 1 DM and 72.38% of the patients with type 2 DM);
- a modified thermal threshold in 77.2% of patients (67.74% of the patients with type 1 DM and 80% of the patients with type 2 DM);
- altered level of vibration perception in 86.02% of patients (83.87% of the patients with type 1 DM and 86% of the patients with type 2 DM).

Furthermore, the QST results were used in a linear correlation with clinical and paraclinical parameters. We obtained a significant correlation of the mean score of quantitative sensory tests with age ( $p=0.003$ ,  $r=0.211$ ), body mass index ( $p<0.001$ ,  $r=0.272$ ), albumin to creatinine ratio ( $p=0.049$ ,  $r=-0.105$ ) and, also, with DM duration ( $p<0.001$ ,  $r=0.431$ ).

As shown before, the prevalence of DPN increases with age and DM duration, regardless of the

DM type. Nonetheless, DPN was more frequent in T2DM patients at any stage of age or DM duration, and it can be present at the moment of diagnosis (Figure 1).

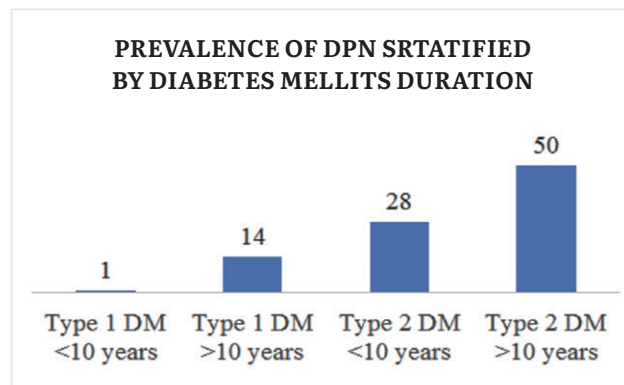


Figure 1: Prevalence of diabetic peripheral neuropathy stratified by diabetes mellitus duration.

## Discussion

DPN refers to a heterogeneous group of disorders affecting the nervous system, with various clinical manifestations, from asymptomatic (up to 50% of cases) [6] to debilitating pain. Alternative etiologies of neuropathy should be considered, diagnosed, and treated. The most common form of DPN is distal symmetric sensorimotor neuropathy [8], even though autonomic nerves, cranial, thoracoabdominal, and limb nerves can be involved as well [6].

Underlying mechanisms consist of glucotoxicity and microangiopathy [1]. Despite the considerable, healthcare-related economic burden and effect on the quality of life, specific nerve damage treatment options are limited in DPN (improved glycaemic control is recommended), and prevention remains the key goal [1, 6]. ADA's Standards of Medical Care in Diabetes (2019) issues that the early recognition of neuropathy and appropriate management are essential to managing patients with DM [6]. Glycemic control can prevent DPN and cardiac autonomic neuropathy in T1DM and may modestly slow their progression in T2DM, although not reversing neuronal damage.

The risk factors for the development of neuropathy identified in the EURODIAB IDDM complications study included age, duration of DM, poor glycemic control, elevated low-density lipoprotein cholesterol and triglycerides, high blood pressure, obesity, and smoking. Furthermore, the study reported a 23.5% increase in diabetic neuropathy over 7 years of follow-up. [1].

DPN affects up to 50% of older T2DM patients

[9]. On the contrary, the prevalence of DPN is considered to be low in patients with early T1DM, although as seen in the Diabetes Control and Complications Trial, the prevalence of modified neurologic tests ranged from 10% in those receiving intensive treatment to 20% in those receiving conventional treatment [10]. Furthermore, the prevalence of DPN in youth (<20 years) with a shorter duration of DM has been re-evaluated in the Search for Diabetes in Youth, suggesting an increased burden of DPN in adolescents, with a prevalence rate higher in T2DM vs. T1DM (22% and 7%, respectively) [11].

QST is reproducible, reliable and assesses both large and small fibers. Although nerve conduction study represents the gold standard technique in diagnosing DPN, it only detects the large fiber damage and is not recommended by ADA for the diagnosis of typical DPN [1, 6]. In contrast, QST, which includes a thermal threshold assessment for cold and warm sensation, thus addressing small fiber dysfunction, can detect early neuropathy, but the process may be highly subjective [1]. A study conducted by Scherens *et al.* in order to determine the prevalence and type of neuropathy in patients presenting dysesthesias of the lower limbs using QST, nerve conduction study and skin biopsy of the dorsum of the foot, found that nearly all patients with pathological QST had a reduced intraepidermal nerve fiber density, indicating a high positive predictive value (93%) of QST in screening for this parameter, correlating with neuropathy [12].

In the study population that we analyzed, DPN was the most frequent DM microvascular complication, both in T1DM and T2DM patients, followed by diabetic retinopathy in T1DM and CKD in T2DM. While screening for the microvascular complications, we found that QST mean values correlated to the albumin to creatinine ratio (as a marker of diabetic kidney disease) for values lower than 200 mg/g of creatinine; therefore we could presume that microvascular complications such as diabetic kidney disease are present alongside DPN and can be identified at early stages. Therefore, QST used to screen and diagnose DPN can further lead to screening for other microvascular complications.

A significant percentage of patients in our study presented modifiable risk factors for DPN, such as poor metabolic control, high blood pressure, obesity, dyslipidemia. Therefore, glycaemic control is the central component of treatment, but it is difficult to achieve for many patients. Secondary, cardiovascular

risk factors play a significant role in the pathogenesis of DPN and should be intensively controlled [1], thus suggesting the complexity of the required approach in DPN.

While running the statistical analysis, we found that QST mean values correlated with age - a peak value at around 55 years of age, thus emphasizing the increasing prevalence of DPN proportionally with DM duration; taken separately, DM duration - an evolution of DM longer than 10 years had a stronger correlation with the mean value of QST, indifferent of the DM type, reconfirming the strong implication of DM duration in DPN development [4]. Moreover, DPN was more frequent in T2DM patients, regardless of the DM duration.

Abnormalities in QST were also associated with the degree of weight excess. Highly significant results were obtained for a BMI over the obesity threshold (30 kg/m<sup>2</sup>).

## Conclusions

DPN accounts for considerable morbidity and mortality and reduced quality of life. Clinical recognition is required for allowing early symptomatic management in order to reduce the morbidity associated with this condition. Present guidelines recommend that the screening for DPN should begin from the DM diagnosis and be continued yearly, except for T1DM, where the yearly screening begins after five years from the diagnosis.

QST should be used more frequently as it can detect diabetic neuropathy in its early stages, thus allowing timely management and treatment, a fact proved by the presence of DPN in patients regardless of age or duration of DM. Furthermore, it is not to be forgotten that neuropathy is not a solitary microvascular complication of DM; therefore, the diagnosis of neuropathy should immediately lead to screening for other DM complications. The positive correlation between QST and microvascular complications, such as microalbuminuria, should emphasize their utility and importance.

QST is easily available, even in outpatient clinics. A DPN-suggestive test-result should lead to screening for certain risk factors and consequent measures, thus preventing the development of other DM complications, such as foot ulcers, or lower limb amputation. We should remember that the small things make the

biggest differences - an inexpensive test performed at the proper time could save further significant financial expenditures and, more importantly, provide a better quality of life for patients.

## Conflict of Interest

The authors declare that there is no conflict of interest.

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