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ORIGINAL PAPER

Diabetic Neuropathy Prevalence and Its Associated Risk Factors in Two Representative Groups of Type 1 and Type 2 Diabetes Mellitus Patients from Bihor County

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ABSTRACT

Background. *Diabetic neuropathy has an important impact on the quality of life of affected individuals due to the presence of chronic symptoms like distal neuropathic pain, but it also influences the survival of diabetic patients, given that the clinical forms of diabetic neuropathy produce complications such as diabetic foot syndrome in distal peripheral neuropathy or life threatening arrhythmias in autonomic cardiac neuropathy. The prevalence of diabetic neuropathy in representative cohorts is very discordant in numerous studies, and our purpose was to evaluate the frequency of this microvascular complication in Bihor County and to determine some risk factors for its development in order to perform a more rigorous screening in certain risk groups.*

Material and method. *We formed two representative cohorts for type 1 and type 2 diabetes mellitus population in our county and applied a questionnaire with three subsets of questions for sensitive, motor and autonomic symptoms. Every patient was evaluated by using semi quantitative tests for distal neuropathy and two tests for determination of cardiac autonomic neuropathy.*

Results. *The prevalence of diabetic neuropathy was 28.70% in patients with type 1 diabetes mellitus and 50.70% in those with type 2 diabetes mellitus. Distal neuropathy was the most frequent clinical form, autonomic neuropathy having a low prevalence. The same risk factors were associated ($p<0.01$) with an increased risk of diabetic neuropathy in both type 1 and type 2 diabetes mellitus: age, diabetes duration, HbA_1c, hypertension, dyslipidaemia, and other microvascular complications.*

Conclusion. *Screening for distal symmetric polyneuropathy can be easily done by using a symptom questionnaire and semi quantitative tests, and it is important to consider the fact that over 50% of type 2*

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diabetes patients in the representative cohort were affected by the complication. Control of modifiable risk factors can reduce the risk of neuropathy development considering the lower frequency of neuropathy in the groups with good glycaemic control, normal blood pressure and absence of dyslipidaemia.

Keywords: diabetic neuropathy prevalence, risk factors for diabetes microcomplications.

INTRODUCTION

Diabetic neuropathy represents the presence of signs or symptoms specific for peripheral nerve damage in a patient diagnosed with diabetes mellitus (DM) after exclusion of other causes that can lead to similar manifestations (1). Diabetic neuropathy is the most frequent complication of DM. Its presence represents an important cause of morbidity and mortality because of the complications that can appear: diabetic foot ulcers, leading often to limb amputations or balance maintaining difficulties leading to fall related traumatisms (2). It is estimated that after a history of DM of over 20 years, the frequency of diabetic neuropathy is more than 50% (3). The most frequent clinical type of diabetic neuropathy is distal symmetric polyneuropathy (DSPN), that accounts for over 75% of diabetic neuropathies, explaining the increased prevalence of lower limb amputations in diabetic patients as a consequence of diminished perception of plantar micro traumatisms. American Diabetes Association recommends the screening of diabetic neuropathy at five years from diagnosis in patients with type 1 DM (T1DM) and in the moment of diagnosis in patients with type 2 diabetes mellitus (T2DM) (4).

The most important complication of diabetic neuropathy is the diabetic foot syndrome. Of all the complications of DM, diabetic foot syndrome is the leading cause of hospitalisation. The presences of diabetic neuropathy rises the risk of limb amputation by 1.7 fold compared with DM patients without neuropathy; the presence of a foot deformity, as a consequence of muscle wasting also a result of motor neuropathy, rises the risk of amputations 12 fold, and if the patient is diagnosed with a diabetic foot ulcer the risk is 36 fold higher (5). Lower limb amputations in DM patients account for 70% of the amputations of non-traumatic cause made worldwide (6). Because diabetic neuropathy causes peripheral nerve damage of small peripheral nerve fibres, with an important role in pain perception, and large nervous fibres, with an important role in vibration perception, the local traumas at the foot level are not properly perceived by the patients, and skin ulcerations that can appear are prone to infection and further destruction of underlying tissues (7).

Autonomic neuropathy is another clinical form of diabetic neuropathy; the damaged nervous fibres are the unmyelinated fibres that control the sympathetic and parasympathetic nervous system. A particular importance is given to the cardiac autonomic neuropathy because it is correlated with an increased cardiovascular morbidity and mortality, as a result of pathogenic mechanisms that determine a predominance of sympathetic nervous system over the parasympathetic nervous system; therefore, there is an increased frequency of hypertension and malignant arrhythmias (8).

The goal of the present study was to evaluate the frequency of clinical forms of diabetic neuropathy in a cohort of T1DM patients and in one of T2DM which were representative for the population with DM from Bihor County, a county in Nord-Western Romania. Also, we aimed to determine risk factors for the presence of diabetic neuropathy testing the influence of age, DM duration, sex, glycaemic control, height, hypertension, dyslipidaemia and other microvascular complications of DM on the frequency of diabetic neuropathy. ❑

MATERIAL AND METHOD

We included 126 patients with T1DM and 142 with T2DM using a systematic procedure designed to ensure the representativeness of the included patients for the population of T1DM and T2DM patients from our county. The method of selection was non-proportional strati-

fied sampling because it is well known that the prevalence of T1DM is 5-10% and that of T2DM 90-95%. Every Monday in the period July-December of 2017, we included the first patient (obviously diagnosed with T1DM) who presented for his/her diabetes prescription in the ambulatory in the T1DM cohort (if that patient met the inclusion criteria; if not, the next one was included), and every tenth patient in the T2DM cohort.

Inclusion criteria were: giving the written consent for participation in the study, patients with confirmed T1DM or T2DM, age over 18 and a value of glycated haemoglobin <10%. *Exclusion criteria* were: presence of other causes of neuropathy (advanced chronic kidney disease, malnutrition, hepatic cirrhosis, chronic alcohol consumption and autoimmune diseases), presence of conditions characterized by symptoms like chronic pain: trigeminal neuralgia, lumbar spondylosis, zoster zone, post stroke conditions, glycated haemoglobin>10% at the last determination.

Patients completed a questionnaire for the determination of symptoms of diabetic neuropathy and were submitted to different clinical tests.

I. The *questionnaire* had the following parts with assessment of:

1. Sensitive symptoms – adapted after *Diabetic Neuropathy Symptom Score*: presence of numbness or lack of sensibility in the foot, tingling sensation, instable walking, pain or burning sensation in the lower limbs.

2. Motor symptoms – difficulties while walking, handling small objects, climbing the stairs, or lifting small objects.

3. Autonomic symptoms – adapted after *Survey of Autonomic Symptoms*: dizziness after getting up from lying position, low tolerance to physical effort, palpitations, previous episodes of syncope (cardiac autonomic neuropathy); nausea, vomiting or bloating, persistent diarrhea in the past two weeks, persistent constipation in the past two weeks (digestive neuropathy); involuntary urine loss, difficulty of getting or maintaining erection (genitourinary neuropathy).

II. *Performance of semi quantitative tests* for evaluation of peripheral sensitivity: testing of tactile sensibility with the 10 g Semmens–Weinstein monofilament, thermic sensibility testing using Tip-Therm device, painful stimuli sensitivity testing using neurotips, vibratory sensitivity evaluation using Rydel-Seiffer tuning fork, evaluation of knee reflex and Achilles reflex.

III. *Clinical exam of lower limbs* for evaluating the presence of foot ulcers or scars appeared as a result of trauma.

IV. *Performance of tests for determination of the presence of cardiac autonomic neuropathy*: determination of reduced heart rate variability during deep breathing, the patient was asked to perform six deep inspirations and expirations during a minute under EKG control, a positive test was a difference between the highest heart rate and the lowest heart rate ≤10 beats; determination of the presence of orthostatic hypotension.

Criteria for diagnosis of the following clinical forms of diabetic neuropathy:

• *Sensitive distal symmetric polyneuropathy (DSPN-S)*: at least one positive answer at the sensitive symptoms questions and two modified semi quantitative tests for peripheral sensitivity evaluation (according to the recommendation of American Diabetes Associations for performance of at least two semi quantitative tests).

• *Sensitive and motor distal symmetric polyneuropathy (DSPN-SM)*: the same criteria as for DSPN-S and presence of at least three motor symptoms and/or trophic lesions at the level of lower limbs like ulcerations or scars produced by ulceration healing.

• *Cardiac autonomic neuropathy (CAN)*: at least one modified test (heart rate variability or orthostatic hypotension) with or without symptoms suggestive for CAN.

• *Digestive autonomic neuropathy (DAN)*: at least two positive answers at the questionnaire for digestive symptoms in the absence of other conditions that can be responsible for those manifestations.

• *Genitourinary autonomic neuropathy (GNAU)*: at least one positive answer at the questions for urinary or genital symptoms in the absence of other conditions that can be responsible for those manifestations.

Patients were also examined clinically by measuring their height, weight, BMI, blood pressure; laboratory analysis – venous blood glycaemia, glycated haemoglobin (if the patients did not have any determination in the past three months, or used the value of the last HbA_1c done in the past year, or the average of two values done in the past year back from the moment of inclusion), total cholesterol, LDL-cholesterol, tri-

glycerides, HDL-cholesterol, creatinine – were performed too. The presence of diabetic retinopathy was determined by ophthalmological examination and the presence of chronic kidney disease by calculation of GFR using the MDRD-Study formula, with the presence of renal impairment at a value <90 mL/min/1.73 m^2. ❑

RESULTS

The prevalence of diabetic neuropathy in T1DM was 28.57% (36 cases) and in T2DM 50.70% (72 cases). Diabetic neuropathy had a statistically significant ($p<0.01$) higher prevalence in T2DM than in T1DM.

Out of 126 patients with T1DM, 14 were diagnosed with DSPN-SM (11.11%, or 38.89% out of 36 patients with T1DM and diabetic neuropathy), 11 with DSPN-S (8.73%, or 30.56% out of 36 patients with T1DM and diabetic neuropathy), four with AN only (3.17%, or 11.11% out of 36 patients with T1DM and diabetic neuropathy), four with both DSPN-SM and AN (3.17%, or 11.11% out of 36 patients with T1DM and diabetic neuropathy) and three with DSPN-S and AN (2.38%, or 8.33% out of 36 patients) (Table 1).

Neuropathy –clinical diagnosis	Percentage of patients reported to the total number of T1DM included in the study (n=126)	Percentage of patients reported to the number of T1DM patients with diabetic neuroapthy (n=36)	Number of cases
DSPN – SM	11.11%	38.89%	14
DSPN – S	8.73%	30.56%	11
AN	3.17%	11.11%	4
DSPN-SM + AN	3.17%	11.11%	4
DSPN-S +AN	2.38%	8.33%	3
Total	28.57%	100%	36

TABLE 1. Frequency of diabetic neuropathy clinical forms in T1DM patients

Neuropathy –clinical diagnosis	Percentage of patients reported to the total number of T2DM included in the study (n=142)	Percentage of patients reported to the number of T2DM patients with diabetic neuropathy (n=72)	Number of cases
DSPN – SM	16.20%	31.94%	23
DSPN – S	23.94%	47.22%	34
AN	2.82%	5.56%	4
DSPN-SM + AN	4.23%	8.33%	6
DSPN-S +AN	3.52%	6.94%	5
Total	50.70%	100%	72

TABLE 2. Frequency of diabetic neuropathy clinical forms in T2DM patients

In T1DM patients with diabetic neuropathy (36 cases), the frequency of clinical types of diabetic neuropathy was: DSPN-SM with a frequency of 50% of cases (18 cases), DSPN-S with a frequency of 38.89% of cases (14 cases) and AN with a frequency of 30.56% of cases (11 cases).

Out of 142 patients with T2DM, 23 were diagnosed with DSPN-SM (16.20%, or 31.94% out of 72 patients with T2DM and diabetic neuropathy), 34 with DSPN-S (23.94%, or 47.22% out of 72 patients with T2DM and diabetic neuropathy), four with AN only (2.82%, or 5.56% out of 72 patients with T2DM and diabetic neuropathy), six with both DSPN-SM and AN (4.23%, or 8.33% out of 72 patients with T2DM and diabetic neuropathy) and five with DSPN-S and AN (3.52%, or 6.94% out of 72 patients T2DM and diabetic neuropathy) (Table 2).

In T2DM patients with diabetic neuropathy (72 cases), the frequency of clinical types of diabetic neuropathy was: DSPN-SM with a frequency of 40.28% of cases (29 cases), DSPN-S with a frequency of 54.17% of cases (39 cases) and AN with a frequency of 20.83% of cases (15 cases).

In T1DM out of 11 patients with AN, eight were diagnosed with CAN (72.73%), five with GUAN (45.45%) and two with DAN (18.18%). In patients with CAN, five presented reduced heart rate variability (62.50% out of eight patients) and three orthostatic hypotension (37.50% out of eight patients).

In T2DM out of 15 patients with AN, 12 were diagnosed with CAN (80%), seven with GUAN (46.67%) and two with DAN (13.33%). In patients with CAN, nine presented reduced heart rate variability (75% out of 12 patients) and five orthostatic hypotension (41.67% out of 12 patients).

The frequency of diabetic neuropathy in both T1DM and T2DM patients was statistically significant higher in the following categories: patients with a longer duration of DM ($p<0.01$), patients with poor glycemic control, the average of at least two HbA_1c values determined in the

Risk factor for diabetic neuropathy	Correlation with the frequency of diabetic neuropathy (DN) in T1DM patients (n=126) *positive correlation (p<0.01)			Correlation with the frequency of diabetic neuropathy (DN) in T2DM patients (n=142) *positive correlation (p<0.01)		
	Correlation	Mean values without and with DN		Correlation	Mean values without and with DN	
Age (years)	+	22.36	38.57	+	40.23	58.86
Diabetes Duration(years)	+	5.43	10.25	+	3.42	9.76
Sex (M/F) (%)	-	73.44%/69.35%	25.56%/30.65%	-	50%/48.65%	50%/51.35%
Height (m)	-	1.68m	1.71m	-	1.72m	1.71m
Mean HbA_1C in the past year	+	6.3%	7.8%	+	6.5%	8.2%
Smoking (%)	-	29.52%	23.81%	-	30.21%	35.82%
Hypertension (mm Hg)	+	19.79%	56.67%	+	34.09%	58.16%
Dyslipidemia (%)	+	20.62%	55.17%	+	23.53%	65.93%
Presence of diabetic retinopathy	+	11.58%	60.98%	+	34.18%	71.43%
Presence of chronic kidney disease	+	19.05%	51.61%	+	36.05%	73.21%

TABLE 3. Risk factors for diabetic neuropathy in the two cohorts

past year >7% (if the patient had two determinations, and if not, the presence of one value) ($p<0.01$), patients with more advanced age ($p<0.01$), patients with dyslipidemia ($p<0.01$), patients with hypertension ($p<0.01$), patients with diabetic retinopathy ($p<0.01$) or chronic kidney disease ($p<0.01$) (Table 3). The frequency of diabetic neuropathy was not influenced by sex, height or smoking status. ❑

DISCUSSION

In the EURODIAB IDDM Complications Study that analysed the prevalence of T1DM complications in 16 European countries, the prevalence of diabetic neuropathy was on average 28% (9), which is close to the frequency of diabetic neuropathy identified in our study in patients with T1DM of 28.57%. Regarding the prevalence of diabetic neuropathy in T2DM, this was 32.1% in a study performed in the UK, and in the patients over 60 the prevalence was over 50% (10). In our study, patients with T2DM had an average age of 56.8 years and the prevalence of diabetic neuropathy was 50.70%, these results being very close to those from the UK study.

Other studies confirm the statistical significant higher prevalence of diabetic neuropathy in T2DM patients compared to T1DM patients regarding the duration of the disease. In a study from Belgium, the prevalence of diabetic neuropathy was 50.8% in T2DM patients and 25.6% in T1DM patients (11). The possible explication is that, in T2DM, other factors besides hyperglycaemia are implicated in the development and progression of diabetic neuropathy. It appears that metabolic syndrome and its components, obesity, hypertriglyceridemia, low HDL-cholesterol and arterial hypertension are independent factors of diabetic neuropathy (12).

In our study DSPN was the most frequent form of diabetic neuropathy, 88.89% out of the 36 patients with T1DM and diabetic neuropathy were diagnosed with DSPN, of which 50% had both a motor and sensitive component and 38.89% only a sensitive component. Data from the literature report that DSPN accounts for more than 75% of all cases of diabetic neuropathy (1), which is also in accordance with the findings obtained in our study, where 94.43% of the 72 T2DM patients with diabetic neuropathy were diagnosed with DSPN.

The data concerning the prevalence of autonomic diabetic neuropathy is very discordant in the literature, ranging from 1% to 90% (13), and the data refers mostly to cardiac autonomic neuropathy. In DCCT study, at the closure of investigations, patients had a prevalence of cardiac autonomic neuropathy of 7.1% in the intensive treatment of hyperglycaemia group and 9.9% in the conservative treatment of hyperglycaemia

group. In our study, the prevalence of CAN was low (6.35% in the 126 T1DM patients and 8.45% in the 142 T2DM patients), which could be explained by the fact that only two tests from Ewing battery of tests were performed for CAN diagnosis.

Numerous studies in the literature investigated the impact of different risk factors on diabetic neuropathy prevalence. The factors that presented the most powerful impact on diabetic neuropathy prevalence were: diabetes duration, hyperglycaemia and patient age (14). Both in case of T1DM and T2DM, diabetes duration correlated with diabetic neuropathy frequency regarding the patients' age (9).

Glycaemic control is a very important risk factor for diabetic neuropathy, and it was demonstrated that, with an increase of 1% of glycated haemoglobin, the prevalence of diabetic neuropathy increased with 10-15% (15). Other factors found to have a moderate impact on diabetic neuropathy risk included hypertension, height, obesity, oxidative stress, vitamin D deficiency and subclinical inflammation (14). In our study, the prevalence of diabetic neuropathy correlated with diabetes duration, glycated haemoglobin, age, dyslipidaemia and presence of microvascular complications of diabetes mellitus. ❑

CONCLUSION

In patients with T1DM from Bihor County, the prevalence of diabetic neuropathy (28.57%) was significantly lower (28.57%) than in those with T2DM (50.70%). In both cohorts, distal symmetric polyneuropathy was the most frequent clinical form of diabetic neuropathy. The prevalence of cardiac autonomic neuropathy was low in both groups. Interestingly, the same risk factors were associated with an increased frequency of diabetic neuropathy: age, diabetes duration, glycated hemoglobin, hypertension, dyslipidemia and presence of diabetic retinopathy or chronic kidney disease. The study shows the particular importance of screening for diabetic neuropathy in T2DM, given the high prevalence of this complication and the high risk of diabetic foot syndrome in these patients. ❑

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References

1. **Bansal V, Kalita J, Misra UK.** Diabetic neuropathy. *Postgraduate Medical Journal* 2006;964:95-100.
2. **Juster-Switlyk K, Smith AG.** Updates in diabetic peripheral neuropathy. *F1000Research.* 2016;5:F1000 Faculty Rev-738.
3. **Kaur S, Pandhi P, Dutta P.** Painful diabetic neuropathy: an update. *Annals of Neurosciences* 2011;4:168-175.
4. **Pop-Busui R, Boulton AJ, Feldman EL, Bril V, Freeman R, Malik RA, Sosenko JM, Ziegler D.** Diabetic Neuropathy: A Position Statement by the American Diabetes Association. *Diabetes Care* 2017;1:136-154.
5. **Vinik AI.** Advances in Diabetes for the Millennium: New Treatments for Diabetic Neuropathies. *Medscape General Medicine* 2004;6(3 Suppl):13.
6. **Yazdanpanah L, Nasiri M, Adarvishi S.** Literature review on the management of diabetic foot ulcer. *World Journal of Diabetes* 2015;1:37-53.
7. **Singh S, Pai DR, Yuhhui C.** Diabetic Foot Ulcer - Diagnosis and Management. *Clin Res Foot Ankle* 2013;1:120.
8. **Serhiyenko VA, Serhiyenko AA.** Cardiac autonomic neuropathy: Risk factors, diagnosis and treatment. *World Journal of Diabetes* 2018;1:1-24.
9. **Tesfaye S, Stevens LK, Stephenson JM, Fuller JH, Plater M, Ionescu-Tirgoviste C, et al.** Prevalence of diabetic peripheral neuropathy and its relation to glycaemic control and potential risk factors: the EURODIAB IDDM Complications Study. *Diabetologia* 1996;11:1377-1384.
10. **Young MJ, Boulton AJ, MacLeod AF, Williams DR, Sonksen PH.** A multicentre study of the prevalence of diabetic peripheral neuropathy in the United Kingdom hospital clinic population. *Diabetologia* 1993;2:150-154.
11. **Van Acker K, Bouhassira D, De Bacquer D, Weiss S, Matthys K, Raemen H, et al.** Prevalence and impact on quality of life of peripheral neuropathy with or without neuropathic pain in type 1 and type 2 diabetic patients attending hospital outpatients clinics. *Diabetes Metab* 2009;3:206-213.
12. **Tesfaye S, Chaturvedi N, Eaton SE, Ward JD, Manes C, Ionescu-Tirgoviste C, et al.** EURODIAB Prospective Complications Study Group. Vascular risk factors and diabetic neuropathy. *N Engl J Med* 2005;4:341-350.
13. **Vinik AI, Erbas T.** Diabetic autonomic neuropathy. *Handb Clin Neurol* 2013;117:279-294.
14. **Papanas N, Ziegler D.** Risk Factors and Comorbidities in Diabetic Neuropathy: An Update 2015. *Rev Diabet Stud* 2015;1-2:48-62
15. **Ziegler D, Papanas N, Vinik AI, Shaw JE.** Epidemiology of polyneuropathy in diabetes and prediabetes. *Handb Clin Neurol* 2014;126:3-1222.