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Risk factors of diabetic foot of neuropathic origin in patients with type 2 diabetes

Czynniki ryzyka neuropatycznego zespołu stopy cukrzycowej u chorych z cukrzycą typu 2

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Abstract

Introduction: Diabetic foot is a diabetes mellitus complication leading to recurrent ulcerations, risk of osteomyelitis and tissue necrosis which may finally result in amputation. Diabetic foot of neuropathic origin manifesting as autonomic and sensory motor neuropathy is the most common type of this complication. The aim of this study was to identify risk factors of diabetic foot of neuropathic origin occurrence in patients with type 2 diabetes.

Material and methods: The study included 240 patients, 74 with diabetic foot of neuropathic origin and 166 with diabetes. Cases and controls were matched in terms of age structure. Patients with peripheral arterial disease were excluded from the study. The study was conducted in the Gastroenterology and Metabolic Diseases Department, Medical University of Warsaw, Poland. We used logistic regression models, χ^2, *U* Mann-Whitney's and *t*-Student tests.

Results: Logistic regression analysis showed that diabetic foot of neuropathic origin risk factors were: male gender (OR = 6.63; 95% CI: 3.31–13.27; p = 0.00001), duration of diabetes (OR = 1.10; 95% CI: 1.06–1.14; p = 0.00001), height (OR = 1.09; 95% CI: 1.06–1.13; p = 0.00001), weight (OR = 1.04; 95% CI: 1.04–1.06; p = 0.00001) and waist circumference (OR = 1.05; 95% CI: 1.02–1.08; p = 0.001). Although there was a correlation between diabetic foot of neuropathic origin and BMI value, it had no impact on DF occurrence risk.

Conclusion: It is possible to identify patients at risk of diabetic foot development by evaluating anthropometric features. The existence of specific factors increasing the odds of diabetic foot of neuropathic origin occurring may lead to the identification of patients at risk of its development. **(Endokrynol Pol 2015; 66 (1): 10–14)**

Key words: *diabetic foot of neuropathic; diabetes; risk*

Streszczenie

Wstęp: Zespół stopy cukrzycowej jest powikłaniem cukrzycy prowadzącym do powstania nawracających owrzodzeń, ryzyka zapalenia kości i szpiku kostnego, a ostatecznie martwicy tkanek wymagającej amputacji kończyny dolnej. Zespół stopy cukrzycowej o etiologii neuropatycznej jest najczęstszym rodzajem tego powikłania, w którym dominują objawy neuropatii autonomicznej i czuciowo-ruchowej. Celem pracy była ocena czynników ryzyka neuropatycznego zespołu stopy cukrzycowej u chorych z cukrzycą typu 2.

Materiał i metody: Do badania włączono 240 osób, 74 chorych z zespołem stopy cukrzycowej typu neuropatycznego oraz 166 chorych z cukrzycą typu 2 bez zespołu stopy cukrzycowej. Grupę badaną i kontrolną dobrano pod względem struktury wieku. Chorych z chorobą naczyń obwodowych wyłączono z badania. Badanie przeprowadzono w Katedrze i Klinice Gastroenterologii i Chorób Przemiany Materii Warszawskiego Uniwersytetu Medycznego. Użyto modelu regresji logistycznej oraz testów: χ^2, *U* Mann-Whitneya i *t*-Studenta.

Wyniki: Analiza regresji logistycznej wykazała, że czynnikami ryzyka neuropatycznego zespołu stopy cukrzycowej były płeć męska (OR = 6,63; 95% CI: 3,31–13,27; p = 0,00001), czas trwania cukrzycy (OR = 1,10; 95% CI: 1,06–1,14; p = 0,00001), wzrost (OR = 1,09; 95% CI: 1,06–1,13; p = 0,00001), masa ciała (OR = 1,04; 95% CI: 1,04–1,06; p = 0,00001) i obwód talii (OR = 1,05; 95% CI: 1,02–1,08; p = 0,001). Zaobserwowano również korelację między neuropatycznym zespołem stopy cukrzycowej a wartością BMI, która nie miała wpływu na ryzyko wystąpienia zespołu stopy cukrzycowej (p = 0,01).

Wnioski: Istnienie specyficznych czynników zwiększających ryzyko wystąpienia neuropatycznego zespołu stopy cukrzycowej może się przyczynić do wyłonienie grupy chorych, którzy mogliby odnieść największą korzyść z objęcia długoterminową opieką w warunkach specjalistycznej opieki zdrowotnej. Wczesna identyfikacja takich chorych może zmniejszyć ryzyko wielomiesięcznego gojenia owrzodzeń, a także amputacji kończyn dolnych. **(Endokrynol Pol 2015; 66 (1): 10–14)**

Słowa kluczowe: *neuropatyczny zespół stopy cukrzycowej; cukrzyca; ryzyko*

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Introduction

A diabetic foot is the most common complication of long-lasting diabetes mellitus (DM) [1–3]. Diabetic foot (DF) occurs in approximately 12–25% of patients with DM type 2 [4]. According to the International Consensus on the DF and Practical Guidelines, DF may occur in the form of ulceration, inflammation and/or deep foot tissues lesions located below the ankle in patients with DM [5]. The presence of sensory deficiency and angiopathy may result in foot ulcerations and delayed wound healing.

Neuropathy is one of the most important factors in the aetiopathogenesis of DF that increases its risk by 1.7 fold [6]. Neuropathy is a cause of 50–75% of non-traumatic amputations in developed countries [7]. Neuropathy often coexists with foot deformation and recurrent ulcerations that increase the risk of death by 12- and 36-fold respectively [8]. Patients who undergo a lower limb amputation (LLA) due to the complications of long-lasting DM are at 50% risk of a second amputation within 3–5 years [9]. The five-year death risk in this group is 50% [9]. Neuropathy is also the most important factor affecting DF recurrence. The recurrence is much more frequent in the first three years after LLA and reaches up to 50% [1]. Neuropathy in diabetic patients is often asymptomatic and may affect as many as 80–90% of patients at different stages of diabetes [10]. In patients diagnosed with DM type 2, neuropathy is often present at the moment of diagnosis, whereas in patients with DM type 1, it may appear as much as five years after diagnosis [11].

Patients diagnosed with DF of neuropathic origin have a much better prognosis of complete wound healing compared to DF of ischaemic or mixed origin [12]. They have also a lower risk of recurrence, shorter duration of treatment, lower risk of toe or foot amputation, and a likely lower death ratio [12]. Usually, patients are diagnosed with DF at a very advanced stage of inflammation [13]. This results in a high amputation rate in this group. To prevent amputation in DF patients, it is critical to assess the risk of its occurrence.

The identification of factors that increase the risk of DF of neuropathic origin in patients with type 2 DM may result in the improved care of patients prone to its development. Improved care may result in a decrease in the frequency of DM complications, decrease in pace of complications advance, or lower patient and/or budget costs spend on their treatment. The Elbert et al. study conducted in the United States showed that in the coming 25 years, the number of patients with DM will double and the total costs of DM treatment will increase [14]. Without modifications in individual and global approaches to DM and its complications management, the healthcare budget burden will increase dramatically. It is estimated that the total cost of DM and its complications treatment in the United States ranges between 4.6 and 13.7 billion dollars [15]. As much as 27% of such costs may be spent on the management of neuropathy and DF.

The aim of this study was to identify factors increasing the risk of DF of neuropathic origin in patients with type 2 DM. The rationale for the study was clinically observed differences between patients with DF of neuropathic origin and patients with DF of ischaemic or mixed aetiology. There have been a few studies comparing groups of patients with DF of neuropathic origin to patients with type 2 DM with no clinical history of ulcerations or neuropathy. The available studies are either based on small study groups or focused only on risk factors of neuropathy [12, 13, 16–24].

Material and methods

This study was conducted in the Gastroenterology and Metabolic Diseases Department and Department of Medical Genetics, Medical University of Warsaw, Poland. The study involved 240 individuals. The study group consisted of 74 patients with type 2 DM and DF of neuropathic origin, and 166 patients with type 2 DM without a history of foot ulcerations as a control group. The control group was matched to cases in terms of age structure. Patients with peripheral arterial disease were excluded from the study. A questionnaire was used in the assessment of DF presence according to the criteria of the International Consensus on the Diabetic Foot and Practical Guidelines [5].

DF was defined as ulceration, infection or damage of deep tissues in the foot below the ankle in a patient with DM and the presence of neuropathy and/or peripheral arterial disease according to the International Consensus on the DF and Practical Guidelines [2]. Neuropathy was diagnosed in patients who achieved more than six points in examination according to the Toronto Clinical Neuropathy Scale [25]. When a painless ulceration was present, a DF of neuropathic origin was diagnosed. Foot tissue wounds were assessed in the University of Texas Classification [26]. Neuropathy was assessed using standard tests confirming the presence of neuropathy if the sense of touch with a 10-g monofilament of Semmes-Weinstein was absent in at least two of the three places identified by the International DF Consensus [27]. Other tests were used to assess neuropathy (sense of temperature due to Thermo-Tip, vibration due to Rydel-Seiffer tuning fork, and neurothesiometer). Assessment of arterial blood flow was performed in clinical examination (the presence of pulse on dorsal pedis and tibial posterior arteries) confirmed due to routinely assessed Ankle Brachial Index and Ultrasound Doppler of lower limbs arteries. Patients with previously performed revascularisation had angiography

Table I. *Characteristics of studied groups*
Tabela I. *Charakterystyka badanych grup*

Group	Diabetic foot of neuropathic origin	Diabetes mellitus type 2	p value
Total number	74	166	–
Women/men (%)	17/83	58/42	0.00001
Mean age (years)	61 ± 10	63 ± 8	0.1
Mean diabetes duration (years)	17 ± 8	10 ± 8	0.00001
Mean height [cm]	174 ± 8	166 ± 10	0.00001
Mean weight [kg]	96 ± 17	83 ± 18	0.00001
Mean body mass index [kg/m^2]	32 ± 5.4	30.4 ± 5.6	0.06
Waist circumference [cm]	114 ± 14	104 ± 15	0.001
Hip circumference [cm]	112 ± 12	108 ± 13	0.1

Table II. *Characteristics of clinical complications present in studied groups*
Tabela II. *Charakterystyka powikłań obecnych w badanych grupach*

	Diabetic foot of neuropathic origin n = 74	Type 2 diabetes mellitus n = 166	p value
Overweight, BMI > 24.9 kg/m^2	59/66	139/162	0.5
Hyperlipidaemia	29/67	93/158	0.03
Hypertension	49/62	100/124	0.8
Ischaemic heart disease	27/69	43/153	0.1
Myocardial infarction	22/68	35/151	0.1
Thromboembolic events	12/64	12/154	0.02
Retinopathy	43/69	29/165	0.00001
Nephropathy	20/70	9/155	0.00001

of arteries of lower limbs. Patients included into the study were in the acute or chronic stages of DF, and it was their first or recurrent ulceration.

The statistical calculations were performed using STATISTICA 10PL (StatSoft Inc. 2011) software. In assessment of qualitative variables, a χ^2 test was used. In assessment of quantitative predictors for normal and not normal distribution of variables, a *t*-Student and *U* Mann-Whitney's tests were used respectively. A univariate logistic regression was performed for quantitative predictors and grouping variables when a statistical significance was present. The univariate logistic regression analysis was performed with an online 'Logistic Regression by John C. Pezzullo, Version 05.07.20' (http://statpages.org/logistic.html) program. The statistical significance level was $\alpha = 0.05$. In statistical analysis, missing data was removed in pairs.

Results

There were no differences in age of the individuals between groups (61 ± 10 years *v* 63 ± 8 years; p = 0.1). In the study group, the mean time between type 2 DM diagnosis and first occurring DF of neuropathic origin was eight years; SD = 8. There was no significant difference between the mean time from DM diagnosis to DF occurrence in cases and the mean duration of type 2 DM in controls (mean 8 ± 8 years *vs.* 10 ± 8 years; p = 0.06). Characteristics of studied groups are presented in Table I. Characteristics of clinical complications are presented in Table II.

In logistic regression model, male gender was an important factor increasing the risk of DF of neuropathic origin development in patients with type 2 DM (OR = 6.63; 95% CI: 3.31–13.27; p = 0.00001) (Fig. 1., Table III).

Factors that increase the risk of DF of neuropathic origin occurrence were: duration of DM (mean 17 ± 8 years *vs.* 10 ± 8 years; OR = 1.10; 95% CI: 1.06–1.14; p = 0.00001) increasing odds of DF by 10% per each year of DM duration; height (mean 174 ± 8 cm *vs.* 166 ± 10 cm; OR = 1.09; 95% CI: 1.06–1.13; p = 0.00001) increasing this risk by 9% per each cm of patient's height; weight (mean 96 ± 17 kg *vs.* 83 ± 18 kg; OR = 1.04; 95% CI: 1.04–1.06; p = 0.00001) that has an impact of 4% increase in the risk of DF per each additional kg; and waist circumference (mean 114 ± 14 cm *vs.* 104 ± 15 cm; OR = 1.05;

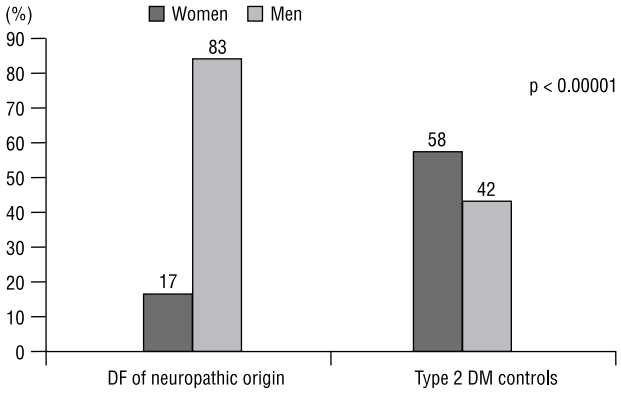

Figure 1. *Gender structure in study and control groups (percentage)*

Rycina 1. *Struktura płci w grupach badanej i kontrolnej (odsetek)*

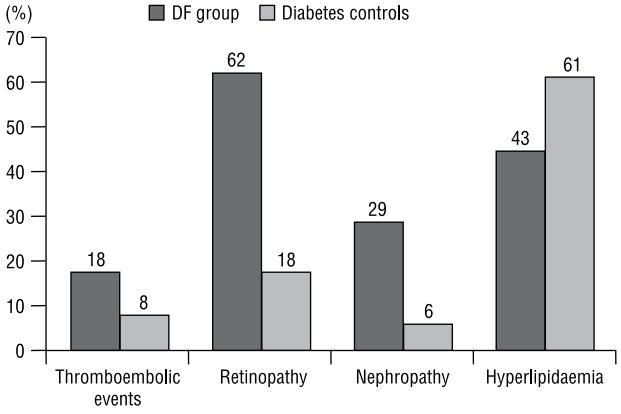

Figure 2. *Percentage of complications in studied groups for variables presenting statistically significant difference*

Rycina 2. *Odsetek powikłań w badanych grupach dla zmiennych istotnych statystycznie*

95% CI: 1.02–1.08; p = 0.001) increasing odds by 5% for each extra cm in waist. Similarly, the presented study showed a positive correlation between BMI value and DF of neuropathic origin frequency; however, it had no impact on its occurrence risk. There was no difference in hips circumference value between the groups. In the study group, thromboembolic events (18% *vs.* 8%; p = 0.02), retinopathy (62% *vs.* 18%; p = 0.00001) and nephropathy (29% *vs.* 6%; p = 0.00001) were more often present. Hyperlipidaemia was less often present in the study group (43% *vs.* 61%; p = 0.03) (Fig. 2). Retinopathy, nephropathy and hyperlipidaemia were assessed only as qualitative variables. There were no differences in the frequency of overweight, hypertension, ischaemic heart disease and myocardial infarction between the groups.

Table III. *Results of univariate logistic regression analysis*

Tabela III. *Wyniki jednoczynnikowej analizy regresji logistycznej*

Predictors	Odds ratio	95% confidence interval	p value
Male gender	6.63	3.31–13.27	0.00001
Type 2 diabetes duration	1.10	1.06–1.14	0.00001
Height	1.09	1.06–1.13	0.00001
Weight	1.04	1.04–1.06	0.00001
Waist circumference	1.05	1.02–1.08	0.001

Discussion

The strengths of the presented study are relatively large study and control groups, no differences in age structure of studied groups, detailed anthropometric and clinical features descriptions, and a neuropathy classification based on clear criteria according to the Toronto Clinical Neuropathy Scale.

The limitations of the presented study are studied groups restricted to the Polish population, lack of assessment of DM metabolic control, not fully collected patient data, and the omission of patient educational level. Data on the percentage of foot ulcers recurrences and small amputations were not collected.

The presented study proved the existence of specific risk factors for DF of neuropathic origin occurrence in patients with type 2 DM. The explanation of men's predisposition to DF of neuropathic origin development is their susceptibility to develop neuropathy. This fact has been proved in other studies and observed in clinical practice. The impact of male gender as a risk factor of neuropathy in patients with DM was demonstrated in other studies [12, 20, 28]. The presented study showed that male gender was also a factor increasing the risk of DF of neuropathic origin in type 2 DM population. This may result from poorer hygiene in men than in women. The impact of patients' height may be interpreted with the positive correlation between peripheral nerves length and the neuropathy occurrence. The influence of weight may be the effect of higher pressure on the foot area in overweight patients. Patients with higher BMI have increased load for foot tissue.

The most similar study was performed by Fargol et al. [12]. That study included 55 patients with DF of neuropathic origin and 55 with type 2 DM without DF. Fargol et al. showed the following factors increased the risk of DF development: patient's age, female gender, total cholesterol concentration, DM duration and three or more (per eight possible) points in the Michigan Neuropathic Diabetic Scoring.

In the presented study, there is no confirmation of the influence of higher age and female gender on DF frequency. Moreover, in the presented study, female gender decreased the odds of DF of neuropathic origin development. However, the presented study confirms the impact of DM duration on DF prevalence. All patients were assessed on the Toronto Clinical Neuropathy Scale as six or more points, and that itself was a factor increasing the risk of complications of neuropathy [25].

Another similar study was performed by Bennett et al. on 77 individuals (27 with DF of neuropathic origin and 50 with type 2 DM without DF and/or neuropathy) [17]. In that study, cases and controls were matched with sex structure and age. The following risk factors of DF of neuropathic origin were demonstrated: increased blood pressure in foot arteries and decreased ankle joints mobility. There were also a positive correlation between HbA_{1C} value and DF frequency observed in the study group. The impact of DM duration or BMI value was not demonstrated.

There have been several studies on the risk factors of neuropathy development in patients with DM. The multicentre Tesfaye et al. study conducted in 1996 on 3,250 patients demonstrated that the risk factors of neuropathy development in diabetic population were: age, DM duration, metabolic control, height, proliferative retinopathy presence, tobacco use, HDL concentration and coronary heart failure presence [16]. In the presented study, some of the abovementioned factors were identified as important in DF of neuropathic origin development.

The Barbosa et al. study showed that a history of thrombotic episodes increased the risk of neuropathy occurrence in patients with DM [21]. The presented study did not confirm the impact of the history of thrombotic episodes on the odds of DF of neuropathic origin frequency.

Conclusion

The identification of specific factors increasing the risk of DF of neuropathic origin in patients with type 2 DM is important due to the implications for a clinician who classifies patients to risk groups. A patient's classification to the high risk group of DF development may be performed using simple anthropometric measurements without additional tests. The aim of high risk group identification is to increase clinician awareness and care, and in consequence avoid not only DF of neuropathic origin occurrence, but also protect against other complications, especially lower limb amputation.

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