

Osteoprotegerin gene rs2073617 and rs3134069 polymorphisms in type 2 diabetes patients and sex-specific rs2073618 polymorphism as a risk factor for diabetic foot

Piotr Nehring¹, Beata Mrozikiewicz-Rakowska¹, Agnieszka Sobczyk-Kopcioł², Adam Makowski¹, Przemysław Krasnodębski¹, Rafał Płoski³, Grażyna Broda⁴, Waldemar Karnafel¹

1 Gastroenterology and Metabolic Diseases Department, Medical University of Warsaw, Warszawa, Poland

2 Department of General Biology and Parasitology, Medical University of Warsaw, Warszawa, Poland

3 Department of Medical Genetic, Medical University of Warsaw, Warszawa, Poland

4 Department of Epidemiology, Cardiovascular Disease Prevention and Health Promotion, Institute of Cardiology in Warsaw, Warszawa, Poland

KEY WORDS

diabetes, foot, neuroarthropathy, osteoprotegerin, polymorphism

ABSTRACT

INTRODUCTION Diabetic foot is a severe diabetic complication, which may result in ulcerations that are unresponsive to treatment and in lower limb amputation. Osteoprotegerin is a protein that is involved in the pathogenesis of diabetic foot.

OBJECTIVES The aim of the study was to evaluate the frequency of alleles in the *TNFRSF11B* gene rs2073617, rs2073618, and rs3134069 polymorphisms in patients with diabetic foot, diabetes, and healthy controls.

PATIENTS AND METHODS The study comprised 877 patients, including 122 with diabetic foot, 293 with type 2 diabetes without diabetic foot, and 462 healthy controls.

RESULTS In the rs2073618 polymorphism, the C allele was a risk factor for diabetic foot in patients with diabetes in the allelic variants [CC] vs. [CG + GG] (odds ratio [OR], 1.72; 95% confidence interval [CI], 1.03–2.86; $P = 0.035$), and in men in the following allelic variants: CC vs. GG (OR, 3.16; 95% CI, 1.27–7.87; $P = 0.011$), CC vs. CG (OR, 3.33; 95% CI, 1.47–7.54; $P = 0.002$), and [CC] vs. [CG + GG] (OR, 3.28; 95% CI, 1.48–7.24; $P = 0.002$). A similar association was observed between men with diabetic foot and those only with diabetes in the following allelic variants: CC vs. GG (OR, 2.30; 95% CI, 0.91–5.85; $P = 0.076$), CC vs. CG (OR, 2.69; 95% CI, 1.16–6.22; $P = 0.018$) and [CC] vs. [CG + GG] (OR, 2.56; 95% CI, 1.13–5.77; $P = 0.02$). For patients with neuropathic diabetic foot, the association was demonstrated in variant CC vs. CG (OR, 2.5; 95% CI, 1.00–6.23; $P = 0.044$) and only for men in the following allelic variants: [CC] vs. [CG + GG] (OR, 3.17; 95% CI, 1.07–9.38; $P = 0.029$) and CC vs. CG (OR, 3.49; 95% CI, 1.15–10.58; $P = 0.02$). The A allele of the rs2073617 polymorphism protected women in variant AA vs. AG against diabetic foot compared with controls (OR, 0.45; 95% CI, 1.00–4.92; $P = 0.045$). The rs3134069 polymorphism was not observed to be a risk factor for diabetic foot.

CONCLUSIONS The analysis of the *TNFRSF11B* gene may be used to assess the risk of diabetic foot and neuropathic diabetic foot in patients with type 2 diabetes.

Correspondence to:

Piotr Nehring, MD, Katedra i Klinika Gastroenterologii i Chorób Przemiany Materii, Warszawski Uniwersytet Medyczny, ul. Banacha 1a, 02-097 Warszawa, Poland, phone: +48-22-599-28-38, fax: +48-22-599-18-38, e-mail: piotr.nehring@gmail.com

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INTRODUCTION A better accessibility to new research methods now allows to include molecular testing in the differential diagnosis of metabolic diseases. New molecular testing methods provide an opportunity to understand the pathogenesis of the most common conditions including osteoporosis and coronary heart disease. Recently, numerous researchers have focused on proteins regulating the metabolic pathways in the human body. An increase in the knowledge about the role of the OPG/RANKL/RANK system fosters the search for new applications of the discovered associations, especially for osteoprotegerin (OPG). OPG is a protein that belongs to the tumor necrosis factor (TNF) superfamily. It plays an important role in the regulation of bone resorption.¹ It protects the receptor activator of nuclear factor κ B (RANK) from the interactions with the RANKL ligand (RANKL).² In the absence of OPG, the RANKL cytokine connects to RANK localized on the entire osteoclast cell line, leading to bone tissue resorption.³ OPG is an antagonist of RANKL, and as such it protects the bone tissue against resorption. OPG gene (*TNFRSF11B*) polymorphisms are involved in the pathogenesis of numerous diseases. The T245G polymorphism in *TNFRSF11B* has been found to be associated with osteoporosis, Paget's disease, idiopathic hyperphosphatemia, and an increased risk of ischemic heart disease.⁴⁻⁹ Recent studies have proved a link between the *TNFRSF11B* gene T245G and C1181G polymorphisms and the prevalence of Charcot neuroarthropathy.¹⁰

Diabetic foot is a diabetic complication of varied etiology leading to delayed wound healing and even amputation of the lower limb.¹¹ Based on etiology, we differentiated between neuropathic diabetic foot (with dominating sensorimotor neuropathy), diabetic foot related to angiopathy (characterized predominantly by atherosclerotic lesions in the lower limb vessels), and mixed diabetic foot (in which both sensorimotor neuropathy and atherosclerotic changes are present). The most common type is neuropathic diabetic foot. If autonomic neuropathy is present, neuroarthropathy may develop as a consequence of blood flow dysregulation in the small arteries. Due to loss of vessel innervation, there is an increased flow that passes through the distal tissues supplied by small arterioles. The blood reaches the venous system by avoiding shunts. An increased blood flow leads to severe bone tissue resorption in the foot. Only an early medical intervention during the acute phase of Charcot neuroarthropathy may help decrease bone tissue resorption. In many patients, changes in resorption lead to foot curve alignment and tissue ulceration. Therefore, Charcot neuroarthropathy diagnosed during the chronic stage usually leads to lower limb amputation.

The biomarkers of bone mineral density in obese perimenopausal women have recently been evaluated in a 5-year follow-up by Holecki et al.¹² The results showed that obese

postmenopausal women were characterized by higher bone mineral density and lower serum OPG concentrations compared with nonobese subjects. Therefore, OPG seems to be a significant factor in Charcot joint disease and, generally, in the pathogenesis of diabetic foot.

Based on the HapMap database and the available literature, we chose 3 single nucleotide polymorphisms (SNPs): rs2073617 (C950T), rs2073618 (C1181G), and rs3134069 (T245G). SNP rs3134069 is localized in the promoter region, rs2073617 in the 5' untranslated region (5'UTR), and rs2073618 in the first exon of the *TNFRSF11B* gene. The G allele from rs2073618 (C1181G) results with aspartic acid substitution to lysine (N3K) in the 3' amino terminus in the *TNFRSF11B* signal region, which may lead to alterations in protein activity.^{13,14}

The aim of the study was to investigate whether the rs2073617 (C950T), rs2073618 (C1181G), and rs3134069 (T245G) polymorphisms in the *TNFRSF11B* gene are risk factors for diabetic foot, irrespective of its type. The rationale for the study was the role of the OPG/RANKL/RANK system in common pathogenetic pathways leading to diabetic foot of the ischemic and neuropathic origin. It seems that genetic variability in the *TNFRSF11B* gene may explain the presence of diabetic foot in some patients with diabetes.

PATIENTS AND METHODS The study was conducted in the Department of Gastroenterology and Metabolic Diseases and the Department of Medical Genetics, Medical University of Warsaw, Poland, between October 2010 and September 2011. It included 877 individuals: 415 patients (122 with type 2 diabetes and diabetic foot and 293 with type 2 diabetes without diabetic foot) treated in the Department of Gastroenterology and Metabolic Diseases, and 462 individuals without diabetes who served as controls. Control subjects were selected from the WOBASZ (Polish National Multi Center Health Survey) study database.¹⁵ The characteristics of the study groups are presented in **TABLE 1**.

Patients were examined using a specially designed survey. Diabetic foot was diagnosed based on the International Consensus on the Diabetic Foot and Practical Guidelines criteria as ulceration, infection, or destruction of deep tissues located in the lower limbs below the ankles in patients with diabetes and neuropathy and/or peripheral arterial disease.¹⁶ All patients underwent physical examination and their medical history was taken. The physical examination included the assessment of foot ulceration and deformation, knee and Achilles tendon reflexes, and the pulse on the tibial posterior and dorsal arteries. The stage of neuropathy was assessed with Thermo-tip (temperature discrimination), Monofilament (sense of touch), Neurotips (discrimination of pain), Semmes-Weinstein tunnel fork (discrimination of vibration). Neuropathic diabetic foot was diagnosed if the ulceration was painless. Each patient had

TABLE 1 Characteristics of the study groups

	Diabetic foot (n = 122)	Type 2 diabetes without diabetic foot (n = 293)	Control group (n = 462)
women/men, %	41/59	59/41	52/48
age, y	men	66.28 ± 11.64	72.42 ± 10.46
	women	63.06 ± 10.96	69.65 ± 11.53
diabetes duration, y	15.83 ± 10.35	12.28 ± 8.95	–
weight, kg	91.55 ± 16.96	80.72 ± 16.82	73.08 ± 13.44
height, cm	171.37 ± 8.62	165.48 ± 9.32	165.69 ± 8.62
body mass index, kg/m ²	32.27 ± 5.18	29.93 ± 5.83	26.58 ± 4.20
waist circumference, cm	110.14 ± 14.37	104.55 ± 17.25	91.62 ± 11.81
hip circumference, cm	110.57 ± 12.50	108.47 ± 12.74	105.00 ± 9.72

Data are presented as mean ± standard deviation.

the ankle-brachial index measured and, if below the norm, a Doppler ultrasound was performed. Patients also underwent computed tomography angiography as recommended by a vascular surgeon. Neuropathy was identified according to the Toronto Clinical Neuropathy Score.¹⁷

The genetic material was isolated from the whole blood samples collected in an EDTA tube using the salting-out method.¹⁸ The inclusion criteria for the control group from the WOBASZ study were as follows: age over 50 years, absence of diabetes, fasting glucose below 100 mg/dl (<5.6 mmol/l), no heart defects, myocardial infarction, or a history of thrombotic events. The above criteria were applied to comply with the age of the study group and to avoid the effect of cardiac conditions.

The SNPs rs2073618 and rs3134069 were genotyped using the predesigned TaqMan SNP Genotyping Assays (Applied Biosystems, United States), C__1971047_1_ and C__27464534_20 respectively. The rs2073618 polymorphism was typed with the Custom TaqMan SNP Genotyping Assay using a forward primer: GAC CAA ACT TTG CAC CTT TCT TTT TTA G; reverse primer: CGC CCC AGC CCT GAA A; reporter sequence 1: AAG CTC CAG GAT TAA C; and reporter sequence 2: AAG CTC CAG GGT TAA C. The reactions were performed on the ABI PRISM 9700 platform (Applied Biosystems). The results were analyzed using the 7500 System SDS Software (Applied Biosystems) v. 1.2.3. All genetic tests were performed with negative control. Statistical calculations were performed using the STATISTICA 9.1 software (StatSoft, Inc. 2008). The frequencies of rs2073617, rs2073618, and rs3134069 alleles in cases and controls were compared using the χ^2 test. The obtained distribution of the rs2073617, rs2073618, and rs3134069 genotypes were statistically analyzed with an online test (<http://ihg.gsf.de/cgi-bin/hw/hwa1.pl>).

RESULTS We observed that irrespective of the patients' age, the duration of diabetes was associated with an increased risk of diabetic foot and with longer diabetes duration in patients with diabetic foot (mean, 15.85 vs. 12.34 years;

$P = 0.001$; odds ratio [OR], 1.039; 95% confidence interval [CI], 1.015–1.063). In diabetic patients, the risk of diabetic foot increases by almost 4% with each year. The study showed that the C allele of the rs2073618 polymorphism is a risk factor for diabetic foot in subjects in the allelic variant [CC] vs. [CG + GG] (OR, 1.72; $P = 0.035$) as compared with healthy controls. This association was also sex-specific and observed only in men. It was demonstrated in the following allele variants: CC vs. GG (OR, 3.16; $P = 0.011$), CC vs. CG (OR, 3.33; $P = 0.002$) and [CC] vs. [CG + GG] (OR, 3.28; $P = 0.002$). A similar association was observed between male patients with diabetic foot and those with diabetes but without diabetic foot in the following allele variants: CC vs. CG (OR, 2.69; $P = 0.018$), CC vs. GG (OR, 2.30; $P = 0.076$), and [CC] vs. [CG + GG] (OR, 2.56; $P = 0.020$). Moreover, the statistically significant association was observed for neuropathic diabetic foot and demonstrated in subjects in the CC vs. CG variant (OR, 2.50; $P = 0.044$). A strong association between the C allele and male sex was present in patients with neuropathic diabetic foot with the following allele variants: [CC] vs. [CG + GG] (OR, 3.17; $P = 0.029$) and CC vs. CG (OR, 3.49; $P = 0.02$) (TABLE 2).

In the rs2073617 polymorphism, the A allele protected against diabetic foot in women in variant AA vs. AG (OR, 0.45; $P = 0.045$). The statistical analysis did not show any correlations with diabetic foot in any of the following groups: men and women with diabetic foot, men with diabetic foot, or patients with neuropathic diabetic foot. There was no correlation between the prevalence of the SNP alleles in the population of diabetic patients. No associations were observed between patients with diabetic foot and those only with diabetes. Because of the small group size, it was not possible to assess the associations with Charcot joint disease (TABLE 3).

Our study did not show any correlation between SNP rs3134069 and diabetic foot, neuropathic diabetic foot, and Charcot joint compared with the control group. We observed a rare homozygote in the occurrence of the C allele; therefore, we did not assess the Hardy-Weinberg equilibrium and allele associations (TABLE 4).

TABLE 2 Associations of SNP rs2073618 (C1181G) (G/C) in patients with diabetic foot, neuropathic diabetic foot, diabetes without diabetic foot, and controls

Study groups	Genotypes					
	GG	GC	CC	heterozygous	homozygous	G allele carriers
	%	%	%	CC vs. CG	CC vs. GG	[CC] vs. [CG + GG]
	n/N	n/N	n/N	OR (95% CI)	OR (95% CI)	OR (95% CI)
			<i>P</i>	<i>P</i>	<i>P</i>	
diabetic foot	18.80 22/117	54.70 64/117	26.50 31/117	1.68 (0.98–2.85) 0.056	1.81 (0.99–3.33) 0.052	1.72 (1.03–2.86) 0.035
diabetic foot (men)	11.76 8/68	61.77 42/68	26.47 18/68	3.33 (1.47–7.54) 0.002	3.16 (1.27–7.87) 0.011	3.28 (1.48–7.24) 0.002
diabetic foot (women)	28.57 14/49	54.90 22/49	26.53 13/49	0.82 (0.39–1.72) 0.6	1.096 (0.47–2.55) 0.83	0.91 (0.46–1.80) 0.78
neuropathic diabetic foot	15.00 6/40	65.00 26/40	20.00 8/40	2.50 (1.00–6.23) 0.04	1.72 (0.58–5.12) 0.33	2.26 (0.92–5.51) 0.07
neuropathic diabetic foot (men)	12.12 4/33	66.67 22/33	21.21 7/33	3.49 (1.15–10.58) 0.02	2.46 (0.68–8.88) 0.16	3.17 (1.07–9.38) 0.03
diabetes	26.03 76/292	47.60 139/292	26.37 77/292	1.05 (0.74–1.50) 0.77	1.31 (0.86–1.97) 0.21	1.13 (0.81–1.58) 0.47
control group	27.06 125/462	46.97 217/462	21.00 97/462	–	–	–
diabetic foot vs. diabetes	–	–	–	1.59 (0.91–2.78) 0.10	1.39 (0.74–2.62) 0.31	1.52 (0.89–2.59) 0.12
diabetic foot vs. diabetes (men)	–	–	–	2.69 (1.16–6.22) 0.018	2.30 (0.91–5.85) 0.076	2.56 (1.13–5.77) 0.020
diabetic foot vs. diabetes (women)	–	–	–	0.95 (0.43–2.11) 0.9	0.87 (0.36–2.14) 0.77	0.92 (0.44–1.93) 0.82
Charcot vs. diabetes	–	–	–	10.45 (0.60–181.48) 0.03	2.96 (0.12–73.83) 0.32	7.42 (0.43–128.15) 0.06

Abbreviations: CI – confidence interval, n – number of alleles, N – total number of alleles, OR – odds ratio, SNP – single nucleotide polymorphism

The analysis showed that rs2073617 | rs2073618 haplotype AG alleles protect against diabetic foot compared with the control group ($P = 0.05$; TABLE 5).

DISCUSSION Our study confirmed the correlation between rs2073618 in the *TNFRSF11B* gene and diabetic foot in patients with diabetes irrespective of the type of diabetic foot. Moreover, it showed that the genetic predisposition for diabetic foot in patients with diabetes may result from *TNFRSF11B* gene variability. The study showed that the rs2073618 polymorphism in the *TNFRSF11B* gene does not increase the risk of diabetes itself, which makes the genetic analysis in patients with diabetic foot more significant. The presence of this correlation only in men provides important data and increases the sensitivity of the potential genetic panel by narrowing the target group. Moreover, we proved the role of the A allele of the rs2073617 polymorphism in the prevention of diabetic foot in women. The above association concerns only the rs2073617 polymorphism.

An Italian study conducted in 2009 showed a significant correlation between rs2073618 and rs3134069 *TNFRSF11B* gene polymorphisms and Charcot neuroarthropathy.¹⁰ It included

59 patients with Charcot joint, 41 individuals with neuropathic diabetic foot, and 103 healthy controls. The results proved the association between the genetic background and clinical presentation of diabetic foot. The significance of the OPG/RANKL/RANK system was also demonstrated in studies showing the correlation between the prevalence of diabetic foot and the serum OPG concentration in patients with diabetes.^{19,20} Our study did not confirm the above associations with the frequency of the rs3134069 polymorphism.

A recent study by Korzon-Burakowska et al.,²¹ which included 54 individuals with Charcot joint, 35 patients with neuropathy without Charcot joint, and 95 healthy controls, showed that OPG 950T>C (rs2073617) and 245T>G (rs3134069) polymorphisms were more common in patients with Charcot joint compared with the control group.²¹ Moreover, in patients with neuropathy, there was a difference in the occurrence of 1217C>T, 950T>C, and 245T>G OPG polymorphisms.²¹ Our study did not confirm those results.

Adamczyk et al.²² studied 88 individuals with aortic stenosis and demonstrated a correlation between the increased serum OPG concentration and the presence of coronary artery disease in patients with moderate aortic sclerosis.²² The study

TABLE 3 Association of SNP rs2073617 (C950T) (G/C) in patients with diabetic foot, neuropathic diabetic foot, diabetes without diabetic foot, and controls group.

Study groups	Genotypes					
	GG	AG	AA	heterozygous AA vs. AG	homozygous AA vs. GG	G allele carriers [AA] vs. [AG + GG]
	% n/N	% n/N	% n/N	OR (95% CI) P	OR (95% CI) P	OR (95% CI) P
diabetic foot	29.41 30/102	42.16 43/102	28.43 29/102	0.74 (0.44–1.25) 0.26	0.90 (0.51–1.60) 0.72	0.80 (0.49–1.29) 0.36
diabetic foot (women)	40.00 16/40	32.50 13/40	27.50 11/40	0.45 (0.20–1.00) 0.045	0.80 (0.34–1.85) 0.59	0.56 (0.28–1.12) 0.10
neuropathic diabetic foot	32.35 11/34	47.06 16/34	20.59 7/34	1.20 (0.54–2.66) 0.66	0.73 (0.27–1.95) 0.53	1.25 (0.59–2.64) 0.57
diabetes	26.07 73/280	47.14 132/280	26.79 75/280	1.14 (0.82–1.58) 0.44	1.18 (0.78–1.79) 0.43	1.09 (0.89–1.33) 0.39
control group	26.62 123/462	46.32 214/462	23.16 107/462	–	–	–

Abbreviations: see TABLE 2

TABLE 4 Association of SNP rs3134069 (T245G) (A/T) in patients with diabetic foot, neuropathic diabetic foot, diabetes without diabetic foot and controls

Study groups	Genotypes					
	AA	AC	CC	heterozygous AA vs. AC	homozygous AA vs. CC	C allele carriers [AA] vs. [AC + CC]
	% n/N	% n/N	% n/N	OR (95% CI) P	OR (95% CI) P	OR (95% CI) P
diabetic foot	84.48 98/116	15.52 18/116	0.0 0/116	1.12 (0.04–28.77) 0.55	0.79 (0.03–19.52) 0.61	0.83 (0.03–20.39) 0.60
diabetic foot of neuropathic origin	82.93 34/41	17.07 7/41	0.0 0/41	0.46 (0.02–12.22) 0.71	0.28 (0.01–6.91) 0.76	0.29 (0.01–7.33) 0.76
diabetes	86.64 253/292	13.36 39/292	0.0 0/292	2.39 (0.10–60.39) 0.37	2.03 (0.08–50.05) 0.41	2.07 (0.08–51.04) 0.41
control group	80.95 374/462	10.60 49/462	0.22 1/462	–	–	–

Abbreviations: see TABLE 2

did not show a significant correlation between the aortic valve calcium score and serum OPG concentration.²² The above results confirm the role of the OPG/RANK/RANKL system in the pathogenesis of atherosclerosis and cardiovascular diseases.

The strength of our study is the inclusion of groups with type 2 diabetes and healthy controls that were irrespectively compared with patients with diabetes and diabetic foot. The limitation is the lack of the representative group of patients with Charcot neuroarthropathy and lack of individuals with type 1 diabetes to make comparisons with type 2 diabetic patients.

Our study confirmed the association of neuropathic diabetic foot only for the rs2073618 polymorphism in the *TNFRSF11B* gene. It also showed an association between the C allele of the rs2073618 polymorphism and diabetic foot. Diabetic foot, including the neuropathic type, showed

to be associated with male sex. This association was observed also when comparing the prevalence of the C allele of the rs2073618 polymorphism between patients with diabetic foot and those only with diabetes. We proved that the rs2073618 polymorphism did not occur more frequently in patients with diabetes without diabetic foot, which is in line with the cited studies. Thus, it may be assumed that the presence of diabetic foot, including that of neuropathic origin, in patients with diabetes has a genetic background. Although, the OPG/RANKL/RANK system is involved in the pathogenesis of diabetic complications, including diabetic foot, not every polymorphism in the *TNFRSF11B* gene shows frequency variations in the population of patients with all types of diabetic foot. We believe that further research into the genetic markers of the risk of diabetic foot may be helpful in the prognosis of

TABLE 5 Haplotype analysis for diabetic foot, diabetes, and control groups

SNPs	Haplotype	Study group	Control	χ^2	Degree of freedom	<i>P</i>
rs2073617 rs2073618	AC	0.421	0.367	1.91	1	0.17
rs2073617 rs2073618	GC	0.127	0.095	1.77	1	0.18
rs2073617 rs2073618	AG	0.069	0.118	3.85	1	0.05
rs2073617 rs2073618	GG	0.384	0.420	0.86	1	0.35
rs2073618 rs3134069	CC	0.083	0.060	1.44	1	0.23
rs2073618 rs3134069	CA	0.451	0.405	1.44	1	0.23
rs2073618 rs3134069	GA	0.466	0.535	3.15	1	0.08

Abbreviations: see [TABLE 2](#)

diabetic complications. However, until new data become available, the only useful tools that may help identify diabetic patients at a high risk of diabetic foot are a patient's history, interpretation of anthropometric features, and the experience of a clinician. In the meantime, a good metabolic control and the patient's awareness of diabetic foot disease remain the key factors in the prevention of diabetic complications.²³

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Polimorfizmy rs2073617 i rs3134069 genu osteoprotegeryny u pacjentów z cukrzycą typu 2 oraz związany z płcią polimorfizm rs2073617 jako czynnik ryzyka zespołu stopy cukrzycowej

Piotr Nehring¹, Beata Mrozikiewicz-Rakowska¹, Agnieszka Sobczyk-Kopcioł², Adam Makowski¹, Przemysław Krasnodębski¹, Rafał Płoski³, Grażyna Broda⁴, Waldemar Karnafel¹

1 Katedra i Klinika Gastroenterologii i Chorób Przemiany Materii, Warszawski Uniwersytet Medyczny, Warszawa

2 Katedra i Zakład Biologii Ogólnej i Parazytologii, Warszawski Uniwersytet Medyczny, Warszawa

3 Zakład Genetyki Medycznej, Warszawski Uniwersytet Medyczny, Warszawa

4 Zakład Epidemiologii, Prewencji Chorób Układu Krążenia i Promocji Zdrowia, Instytut Kardiologii w Warszawie, Warszawa

SŁOWA KLUCZOWE

cukrzyca,
neuroartropatia,
osteoprotegeryna,
polimorfizm, stopa

STRESZCZENIE

WPROWADZENIE Zespół stopy cukrzycowej (ZSC) to poważne powikłanie cukrzycy, które może skutkować powstaniem niegojących się owrzodzeń oraz amputacją kończyn dolnych. Osteoprotegeryna jest białkiem biorącym udział w patogenezie ZSC.

CELE Celem badania była ocena częstości alleli polimorfizmów rs2073617, rs2073618 i rs3134069 genu *TNFRSF11B* w grupach chorych z ZSC i cukrzycą oraz osób zdrowych.

PACJENCI I METODY Do badania włączono 877 chorych, w tym 122 z ZSC, 293 z cukrzycą typu 2 bez ZSC i 462 osoby zdrowe.

WYNIKI Allel C polimorfizmu rs2073618 był czynnikiem ryzyka wystąpienia ZSC u pacjentów z cukrzycą w wariacie allelicznym [CC] vs [CG + GG] (iloraz szans [odds ratio – OR] 1,72; 95% przedział ufności [confidence interval – CI]: 1,03–2,86; p = 0,035) oraz ZSC u mężczyzn w następujących wariantach allelicznych: CC vs GG (OR 3,16; 95% CI: 1,27–7,87; p = 0,011), CC vs CG (OR 3,33; 95% CI: 1,47–7,54; p = 0,002) oraz [CC] vs [CG + GG] (OR 3,28; 95% CI: 1,48–7,24; p = 0,002). Zależność dla mężczyzn występuje również między grupą z ZSC a grupą chorych na cukrzycę w następujących wariantach allelicznych: CC vs GG (OR 2,30; 95% CI: 0,91–5,85; p = 0,076), CC vs CG (OR 2,69; 95% CI: 1,16–6,22; p = 0,018) oraz [CC] vs [CG + GG] (OR 2,56; 95% CI: 1,13–5,77; p = 0,02). Wśród pacjentów z neuropatycznym ZSC stwierdzono zależność dla wariantu CC vs CG (OR 2,5; 95% CI: 1,00–6,23; p = 0,044) oraz tylko wśród mężczyzn w następujących wariantach allelicznych [CC] vs [CG + GG] (OR 3,17; 95% CI: 1,07–9,38; p = 0,029) i CC vs CG (OR 3,49; 95% CI: 1,15–10,58; p = 0,02). Allel A rs2073617 w grupie kobiet chroni przed wystąpieniem ZSC względem grupy kontrolnej u osób w wariacie AA vs AG (OR 0,45; 95% CI: 1,00–4,92; p = 0,045). Jak się okazało, polimorfizm rs3134069 nie jest czynnikiem ryzyka ZSC.

WNIOSKI Ocena polimorfizmów genu *TNFRSF11B* może być przydatna do oceny ryzyka rozwoju ZSC i neuropatycznego ZSC u pacjentów z cukrzycą typu 2.

Adres do korespondencji:

lek. Piotr Nehring, Katedra i Klinika Gastroenterologii i Chorób Przemiany Materii Warszawskiego Uniwersytetu Medycznego, ul. Banacha 1a, 02-097 Warszawa, tel.: 22-599-28-38, fax: 22-599-18-38, e-mail: piotr.nehring@gmail.com

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