ORIGINAL ARTICLE

Impact of polymorphism of selected genes on the diagnosis of type 2 diabetes in patients with obstructive sleep apnea

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KEY WORDS

apolipoprotein A-V, diabetes, epidemiology, gene polymorphism, obstructive sleep apnea

ABSTRACT

INTRODUCTION Although the coexistence of type 2 diabetes mellitus (T2DM) and obstructive sleep apnea (OSA) may be attributed to environmental risk factors common for both diseases, a genetic background should also be considered. Data on the role of genetic factors in the development of T2DM in patients with OSA are lacking.

OBJECTIVES The study was aimed to evaluate the prevalence of polymorphisms of selected genes that are known to be associated with diabetes or obesity in patients with OSA and concomitant T2DM and to assess these polymorphisms in the context of OSA severity.

PATIENTS AND METHODS Consecutive patients with newly diagnosed OSA confirmed by polysomnography underwent genotyping for the following single nucleotide polymorphisms (SNPs): *SREBF1* rs11868035, *HIF1A* rs11549465, *APOA5* rs3135506, *TCF7L2* rs7903146, and *FTO* rs16945088. The frequency of genotypes was compared between patients with and without concomitant T2DM and was analyzed with regard to OSA severity.

RESULTS A total of 600 patients with newly diagnosed OSA were enrolled to the study. Of these, 121 patients (20.2%) were diagnosed with T2DM (97 men and 24 women; median age, 58 years; range, 52–64 years). The prevalence of T2DM was significantly lower in *APOA5* rs3135506 GG homozygotes than in CG heterozygotes (18.8% vs 33.3%, $P = 0.02$). *APOA5* rs3135506 CG heterozygotes were at higher risk for developing T2DM (adjusted odds ratio, 2.64; 95% confidence interval,1.38–5.04; $P = 0.003$). No significant differences were found for the genotype distribution of the other investigated SNPs.

CONCLUSIONS Our study shows a possible link between the polymorphism of the gene encoding *APOA5* and T2DM in patients with OSA.

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INTRODUCTION Obstructive sleep apnea (OSA) is the most frequent breathing disorder during sleep. It is characterized by recurrent nocturnal airflow limitation in the upper airways, resulting in blood oxygenation decrease and subsequent arousals. Since the classic study by Young et al,[1] in which the prevalence of OSA had been estimated as 4% in men and 2% in women, many studies report increasing OSA prevalence rates.[2] A recent systematic analysis showed that the OSA prevalence ranged from 13% to 33% in men and from 6% to 17% in women.[3] This trend may probably be attributed to the increasing worldwide prevalence of obesity,[4,5] which has been identified as one of the most important factors predisposing to OSA.[3]

The disease burden of OSA is significantly affected by its increased daytime sleepiness[6] and

TABLE 1 Brief description of the genes selected for evaluation

Gene acronym	Location	Full name	Potential relationship with risk of type 2 diabetes mellitus
SREBF1	17p11.2	Sterol regulatory element--binding transcription factor 1	Transcription factor involved in the regulation of lipid and cholesterol production.[20] Genetic variants of this gene are associated with type 2 diabetes, insulin resistance, and blood lipid levels as well as sleep disorders during nonrapid eye movement sleep.[44-46]
HIF1A	14q23.2	Hypoxia-inducible factor 1α	Regulates response to hypoxia, lower expression may be involved in the development of diabetic microangiopathy.[21] Genetic variants are associated with type 2 diabetes.[47]
APOA5	11q23.3	Apolipoprotein A-V	Component of high-density lipoprotein. Plays an important role in regulating plasma triglyceride levels. Genetic variants are associated with obesity and higher triglyceride levels.[23,48]
TCF7L2	10q25.2--q25.3	Transcription factor 7 like 2	Transcription factor that plays an important role in the Wnt signaling pathway. Genetic variants are associated with impaired insulin secretion and increased risk of type 2 diabetes.[22]
FTO	16q12.2	α-ketoglutarate–dependent dioxygenase	FTO gene codes α-ketoglutarate dependent dioxygenase which physiological function is unclear. Genetic variants are associated with body mass index, risk of obesity and type 2 diabetes[24,49,50]

comorbidities, mainly cardiovascular diseases and diabetes.[7-9] OSA significantly increases cardiovascular risk (including cardiovascular death), the risk of stroke, and is one of the most frequent causes of arterial hypertension (particularly treatment resistant).[10] Analogically, the prevalence of type 2 diabetes mellitus (T2DM) in patients with OSA is higher than that in the general population and ranges from 15% to 30%.[11-13] Abnormal sleep architecture, intermittent nocturnal hypoxia, and recurrent arousals along with increased sympathetic activity are listed among the predisposing factors for glucose intolerance and T2DM in these patients.[13,14] The likelihood of T2DM has also been demonstrated to increase with OSA severity.[15]

It is estimated that 40% of the risk of OSA may be attributed to genetic factors.[16] Genetic associations between metabolic disorders and respiratory disease have already been documented.[17] Nevertheless, studies on candidate genes for OSA development, including genes encoding apolipoprotein E4, tumor necrosis factor, and angiotensin-converting enzyme, have not yielded encouraging results. In contrast, a number of candidate genes for increased T2DM risk in the general population have been identified.[18,19] Despite a large body of literature on the mutual relationships between OSA and T2DM, data on the role of genetic factors in the development of T2DM in patients with OSA are lacking. We therefore undertook a study aimed to evaluate the prevalence of the polymorphism of selected genes known to be associated with diabetes or obesity in patients with OSA and concomitant T2DM and to assess these polymorphisms in the context of OSA severity.

PATIENTS AND METHODS

Study design This observational study was performed in 2 reference pulmonary centers in Warsaw. Participants were recruited from institutional outpatient clinics and comprised patients with a new OSA diagnosis based on the results of polysomnography (PSG).

Patient evaluation included detailed medical history, anthropometric measurements (weight, height, neck, abdominal and hip circumference), PSG, and blood sampling for routine biochemical testing (cholesterol, triglycerides, creatinine, fasting glucose, glycated hemoglobin A_{1c} [HbA_{1c}]).

On the basis of literature data,[20-24] 5 genes related to T2DM and obesity were selected (*SREBF1*, *HIF1A*, *APOA5*, *TCF7L2*, *FTO*; TABLE 1). After genotyping, the frequency of genotypes for selected SNPs were analyzed and compared in OSA patients with regard to OSA severity, obesity, and age.

The study protocol was approved by the Institutional Review Board (KB/2/2010). All patients signed an informed consent to participate in the study.

Study participants Study participants were recruited from the outpatient clinics of the Central Teaching Hospital of the Medical University of Warsaw and the Institute for Tuberculosis and Lung Diseases in Warsaw between 2010 and 2012. The major inclusion criteria were: 1) age >30 years; 2) newly established diagnosis of OSA confirmed in PSG; and 3) signed informed consent to participate in the study (and, in particular, to undergo genetic testing).

Diagnosis of obstructive sleep apnea In all patients, the diagnosis of OSA was based on at least 6-hour PSG (Alice 4 camera, RESPIRONICS, Murrysville, Pennsylvania, United States; Embla S4000, Reykjavik, Iceland), which included an electroencephalogram, electrooculogram, electromyogram, and electrocardiogram recording. Body position was recorded with a gravity sensor, and chest and abdominal motion were monitored by inductive plethysmography. Airflow was registered with a nasal cannula and thermistor. Arterial oxygen saturation was measured with pulse oximetry at the fingertip. Sleep structure was assessed according to the guidelines of Rechtschaffen and Kales and the American Academy of Sleep Medicine (AASM).[25,26]

TABLE 2 Basic characteristics of patients with obstructive sleep apnea with and without type 2 diabetes mellitus

Variable	All patients (n = 600)	OSA		*P* value (with vs without T2DM)
		Without T2DM (n = 479)	With T2DM (n = 121)	
Age, y	58.0 (52–64)	58.0 (51–64)	59.0 (53–63)	0.18
BMI, kg/m^2	31.8 (28–36)	30.7 (27.5–34.9)	36.2 (32.1–41.5)	<0.001
Hip circumference, cm	110.0 (102–120)	108.0 (100–117)	119.5 (110–130)	<0.001
Waist circumference, cm	108 (98–120)	105.0 (97–115)	120.0 (110–130)	<0.001
Neck circumference, cm	43.0 (40–45)	42.0 (40–44)	45.0 (42–47)	<0.001
Fasting glucose, mg/dl	96.0 (87.0–108.0)	95 (87–105)	103.0 (90–126)	<0.001
HbA_{1c}, %	6.0 (5.7–6.5)	6.0 (5.6–6.3)	6.8 (6.1–8.3)	<0.001
Total cholesterol, mg/dl	188.0 (160–215)	191.0 (166–215)	171.0 (146–205)	<0.001
Triglycerides, mg/dl	138.0 (92–190)	130.0 (87–181)	154.0 (113–216)	<0.001
Creatinine, mg/dl	0.9 (0.8–1.0)	0.9 (0.8–1.0)	0.9 (0.8–1.1)	0.22
Polysomnography				
AHI, n/h	38.4 (24–59)	38.0 (23–57)	45.0 (26–66)	0.01
ODI, n/h	31.1 (16–55)	28.0 (15–51)	43.0 (25–68)	<0.001
Mean SpO_2 during sleep, %	92.0 (89–94)	92.0 (90–94)	90.0 (86–93)	<0.001
Minimal SpO_2 during sleep, %	77.0 (68–83)	78.0 (71–83)	71.0 (60–78)	<0.001

Data are presented as median (first and third quartiles).

SI conversion factors: to convert triglycerides to mmol/l, multiply by 0.0113; total cholesterol to mmol/l, by 0.02586; and creatinine to µmol/l, by 88.4.

Abbreviations: AHI, apnea–hypopnea index; BMI, body mass index; HbA_{1c}, glycated hemoglobin A_{1c}; ODI, oxygen desaturation index; OSA, obstructive sleep apnea; SpO_2, blood oxygen saturation measured by pulse oximetry; T2DM, type 2 diabetes mellitus

The diagnosis of OSA and OSA severity were established in accordance with the recommendations of the AASM,[27] using the following diagnostic criteria: apnea–hypopnea index (AHI) of 5/h or higher in the presence of typical OSA symptoms or AHI of 15/h or higher regardless of the presence of symptoms. Daytime sleepiness was assessed with the Epworth Sleepiness Scale (ESS),[28] with excessive daytime sleepiness defined as a score of more than 10 points.

Diagnosis of diabetes Patients with self-reported T2DM and those with newly diagnosed T2DM diagnosis were allocated to the group of patients with OSA with concomitant T2DM. Newly diagnosed diabetes was recognized in any patient included to the study with at least one of the following: 1) HbA_{1c} ≥6.5% or 2) fasting plasma glucose ≥126 mg/dl or 3) plasma glucose ≥200 mg/dl 2 hours after a 75-g oral glucose tolerance test or 4) random plasma glucose ≥200 mg/dl in a symptomatic patient.[29]

DNA isolation and genotyping Genomic DNA was isolated from the whole blood using QIAamp DNA Blood Mini Kit (Qiagen, Hilden, Germany). Gene polymorphisms were assessed using TaqMan® SNP Genotyping Assays (Life Technologies, Carlsbad, California, United States) and TaqMan® Universal Master Mix II, no UNG (Life Technologies). Assay IDs with corresponding polymorphisms are given in Supplementary material, *Table S1*. Real-time polymerase chain reaction (PCR) was conducted on the 7500 Real-Time PCR System (Life Technologies), using 100-ng genomic DNA as a template. The results were analyzed using SDS 2.4 software (Life Technologies).

Statistical analysis Statistical analysis was performed with Statistica for Windows (STATISTICA version 9; Statsoft Inc.). Data were presented as a median followed by the first and third quartile. The Shapiro–Wilk test was used to verify the hypothesis of normal distribution of analyzed continuous data. The Mann–Whitney test was used for comparisons between 2 groups. Categorical data were presented as a number with percentage and compared with the χ^2 test. A logistic regression model was used to assess the impact of SNP on T2DM development after adjustment for potential confounding factors. All tests were 2-tailed and statistical significance was set at a *P* value of less than 0.05.

RESULTS **Patient characteristics** Of the 600 patients with OSA confirmed by PSG, 121 (20.2%) were diagnosed with T2DM (97 men and 24 women; median age, 58 years; range, 52–64 years). Of these, 106 patients (17.7%) had a previous T2DM diagnosis, whereas 15 (2.5%) were newly diagnosed with T2DM.

Patients with OSA and T2DM were characterized by a higher degree of obesity and a higher OSA severity when compared with patients with

TABLE 3 Distribution of frequency of individual genotypes and alleles in patients with obstructive sleep apnea with and without coexisting type 2 diabetes mellitus

Polymorphism		OSA			
		With T2DM (n = 121)		Without T2DM (n = 479)	
		Number	Frequency	Number	Frequency
SREBF1 rs11868035 (A/G)	AA	12	0.10	54	0.11
	AG	48	0.40	210	0.44
	GG	61	0.50	215	0.45
	Minor allele	72	0.30	318	0.33
	$P = 0.55$, χ^2 for HWE = 0.31, P for HWE = 0.58				
APOA5 rs3135506 (C/G)	CC	0	0.0	3	0.01
	CG	20	0.17	40	0.08
	GG	101	0.83	436	0.91
	Minor allele	20	0.08	46	0.05
	$P = 0.02$, χ^2 for HWE = 3.59, P for HWE = 0.06				
FTO rs16945088 (A/G)	AA	114	0.94	423	0.88
	AG	7	0.06	53	0.11
	GG	0	0.0	3	0.01
	Minor allele	7	0.03	59	0.06
	$P = 0.15$, χ^2 for HWE = 0.11, P for HWE = 0.74				
TCF7L2 rs7903146 (C/T)	CC	69	0.57	285	0.59
	CT	45	0.37	172	0.36
	TT	7	0.06	22	0.05
	Minor allele	59	0.24	216	0.23
	$P = 0.81$, χ^2 for HWE = 0.38, P for HWE = 0.54				
HIF1A rs11549465 (C/T)	CC	108	0.89	401	0.84
	CT	12	0.1	77	0.16
	TT	1	0.01	1	0.0
	Minor allele	14	0.06	79	0.08
	$P = 0.14$, χ^2 for HWE = 1.86, P for HWE = 0.17				

A P value was computed for comparison between groups.

Abbreviations: HWE, Hardy–Weinberg equilibrium; others, see TABLE 2

OSA without T2DM. The comparison of the 2 subgroups is shown in TABLE 2.

Type 2 diabetes mellitus prevalence and gene polymorphism Data on the distribution of the genotypes of studied SNPs are shown in TABLE 3. In the whole group, the least frequent genotypes were *APOA5* rs3135506 CC, *FTO* rs16945088 GG, *HIF1A* rs11549465 TT, and *TCF7L2* rs7903146 TT homozygotes. None of the patients with OSA and T2DM were *APOA5* rs3135506 CC and *FTO* rs16945088 GG homozygotes. The analysis of T2DM prevalence in the whole group showed a significant difference only for *APOA5* rs3135506.

In the group of people with T2DM, the genotype CG APOA5 rs3135506 was more frequent than among nondiabetic patients: 17% vs 8%, respectively, $P = 0.02$. There were no differences in the frequency of polymorphisms for the genes: *SREBF1* rs11868035, *FTO* rs16945088, *TCF7L2* rs7903146, *HIF1A* rs11549465 between these groups. A detailed summary is presented in TABLE 3.

In the logistic regression model after adjustement for age, body mass index, sex, and other parameters, an increased risk of T2DM in patients with SNP *APOA5* rs3135506 (CG vs GG, adjusted OR, 2.64; 95% CI, 1.38–5.04; $P = 0.003$) was demonstrated. The logistic regression model is presented in TABLE 4.

Gene polymorphisms and selected patient characteristics The comparison of genotype distribution among the investigated OSA patients stratified according to sex, OSA severity, BMI, and age is presented in Supplementary material, *Tables S2-S5*. With the exception of a lower prevalence of *APOA5* rs3135506 GG homozygotes in patients older than 65 years, no significant differences were found.

DISCUSSION To our knowledge, this is one of the first studies to present a genetic polymorphism associated with the prevalence of T2DM in patients with OSA. We found that the *APOA5* gene polymorphism may affect T2DM prevalence and that *APOA5* rs3135506 GG homozygotes are characterized by a lower prevalence of T2DM, particularly in patients with mild OSA, overweight (but not obese) individuals, and in elderly patients. We also found some sex-dependent differences in the genotype distribution of the SNPs in the study groups. Our findings confirm the hypothesis that the genetic polymorphism may contribute to the development of T2DM in patients with OSA.

The results of our study may be helpful in further studies on the molecular mechanisms connecting carbohydrate metabolism disorders and OSA. Identification of patients with the gene polymorphisms that increase the risk of T2DM in patients with OSA may allow an early prevention and a reduction of risk through intensive education about lifestyle changes, discontinuation of exposure to harmful factors (eg, tobacco smoke, alcohol), as well as warrant early and more radical interventions in terms of OSA treatment.

Genome-wide association studies (GWASs) have identified more than 40 T2DM susceptibility variants in the general population.[18] As previously mentioned, T2DM is more prevalent in OSA patients compared with the general population.[11-13] The prevalence of T2DM in our investigated cohort was 20.2%. This value is within the range of the reported T2DM prevalence in OSA[13] and approximately 3- to 4.5-fold higher than that reported for the general Polish population.[11,30,31] The gap between T2DM prevalence in the general population and OSA patients indicates that the latter have specific risk factors for T2DM. Some predisposing factors related to the consequences of OSA have been identified[32-35]; however, studies on the genetic susceptibility of patients with OSA to T2DM are lacking. Our results indicate a possible association between T2DM in patients with OSA and the polymorphism of the gene encoding apolipoprotein

TABLE 4 Logistic regression model for an increased risk of type 2 diabetes mellitus in subjects with single nucleotide polymorphism *APOA5* rs3135506 after adjustment for age, body mass index, sex, hypertension, and apnea–hypopnea index

Parameter	Crude OR (95% CI)	Adjusted OR (95% CI)	*P* value (Wald test)
Age, y	1.01 (0.99–1.03)	1.04 (1.02–1.07)	0.001
BMI, kg/m^2	1.14 (1.1–1.18)	1.15 (1.11–1.2)	<0.001
Sex	1.46 (0.89–2.38)	1.74 (0.99–3.05)	0.053
Hypertension	4.14 (2.26–7.59)	2.55 (1.33–4.89)	0.005
AHI, n/h	1.011 (1.0028–1.0192)	0.9999 (0.9999–1.0097)	0.99
APOA5 rs3135506 (CG vs GG)	2.15 (1.21–3.84)	2.64 (1.38–5.04)	0.003

Abbreviations: OR, odds ratio; others, see TABLE 3

A-V (*APOA5*), a key protein in the regulation of triglyceride metabolism,[36] particularly in overweight subjects. This observation is in line with the GWAS study showing that CC homozygotes for *APOA5* rs3135506 are predisposed to hypertriglyceridemia.[37] Variants of the *APOA5* gene are related to the increased risk of cardiovascular diseases and diabetes.[38] Although, to our knowledge, there have been no studies on the *APOA5* gene in OSA, a negative correlation between the serum concentration of apolipoprotein A-V and OSA severity has been reported.[39]

The analysis of the polymorphisms of other investigated genes showed no evident trend in their respective frequencies in patients with OSA and T2DM, with the exception of a significant difference in the prevalence of *HIF1A* variants in women with OSA and T2DM. Hypoxia-inducible factor 1α (*HIF1A*) is involved in the response to hypoxic injury. Its polymorphism has been found to be involved in the development of diabetic microangiopathy.[21,40] Sex differences in the *HIF1A* polymorphism have also been demonstrated by Gu et al,[40] who studied patients with diabetic nephropathy. These authors showed that a particular genetic variant of *HIF1A* decreases the risk of diabetic nephropathy in men, but not in women. In our study, sex-dependent differences in the distribution of genotypes were also demonstrated for *APOA5*, with a significant trend in men and no difference in women. Although, to our knowledge, the issue of sex-dependent differences in the gene polymorphism has not been previously addressed in patients with OSA or T2DM (or both), results of studies on the frequency of *APOA5* polymorphisms in coronary heart disease indicate that some specific *APOA5* polymorphisms associated with the disease differ in prevalence between men and women.[41,42]

Our study has some limitations. First, a number of patients in the investigated cohort was relatively small. Nonetheless, the group was well defined, with the diagnosis of OSA confirmed with PSG. Furthermore, the male predominance and the proportion of patients with T2DM in our group was in line with the epidemiologic data from other studies in this population. The use of the American Diabetes Association recommendations, and not the Polish national guidelines, for the diagnosis of diabetes may also be considered a limitation. This, on one hand, may decrease the reliability of the comparison of our results with those of other studies in the Polish population, but, on the other, it enables a comparative analysis with studies in the non–Polish setting. Furthermore, this was an observational study and no correction for multiple testing was performed, because we analyzed the already established associations but in a smaller and more uniform population.[43]

To conclude, the prevalence of T2DM in patients with OSA in the Polish population is similar to that reported in other epidemiological studies. The *APOA5* gene polymorphism may be involved in the susceptibility to T2DM in patients with OSA. Patients with OSA and T2DM show sex-dependent differences in the distribution of *HIF1A* and *APOA5* genotypes.

SUPPLEMENTARY MATERIAL Supplementary material is available with the main article at www.pamw.pl.

CONTRIBUTION STATEMENT RCh, MKr, PŚ, and PB conceived the study design. MB, MK, RP, LJ, and AP recruited patients and collected data. KB, RP, and PB performed the statistical analysis. KB and TS conducted the genetic examination. PB and AP interpreted data and prepared the manuscript draft. RCh, MKr, and PŚ critically reviewed the final version of the manuscript. All authors approved the final version of the manuscript.

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