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ORIGINAL ARTICLE

THE PREDISPOSITION FOR TYPE 2 DIABETES MELLITUS AND METABOLIC SYNDROME

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ABSTRACT

Type 2 diabetes mellitus (T2DM) and metabolic syndrome (MetS) are diseases caused by the interaction of genetic and non-genetic factors. Therefore, the aim of our study was to investigate the association between six common genetic polymorphisms and T2DM and MetS in males. A total of 120 T2DM, 75 MetS, and 120 healthy controls (HC) were included in the study. *ACE* ID, *eNOS* 4a/b, *ATR1* A1166C, *OXTR* (A>G), *SOD1* +35A/C, *CAT*-21A/T gene polymorphisms were genotyped by PCR or PCR-RFLP techniques. T2DM was diagnosed at an earlier age compared to MetS (54 vs 55 years old, p=0.0003) and the difference was greater in carriers of the *OXTR* G allele (54 vs 56 years old, p=0.0002) or both *OXTR* G and *eNOS* b alleles (54 vs 56, p=0.00016). The *SOD1* AA genotype (O.R.=0.11, p=0.0006) and the presence of both *ACE* I and *OXTR1* A (O.R.=0.39, p=0.0005) alleles revealed to be protective for T2DM. *SOD1* AA and AC genotypes were protective factors for triglyceride (p=0.0002 and p=0.0005, respectively) and HDL cholesterol (p=0.0002 and p=0.0004, respectively) levels in T2DM patients. *ACE* DD was identified more frequently in hypertensive T2DM patients (O.R.=3.77, p=0.0005) and in those who reported drinking alcohol (p=0.0001) comparing to HC and T2DM patients who did not drink alcohol, respectively. We observed that T2DM patients who reported drinking alcohol had an increased frequency of *ACE* DD and *eNOS* bb (p<0.0001), or *ACE* DD and *OXTR* G (p<0.0001) compared to non-drinkers. No gene polymorphisms were associated with MetS.

Keywords: *ACE* ID, *eNOS* VNTR 4a/b, metabolic syndrome, *OXTR* (A>G), *SOD1* +35A/C, type 2 diabetes mellitus

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INTRODUCTION

It has been estimated that the worldwide prevalence of diabetes mellitus and metabolic syndrome (MetS) are 10.5% and 12.5 – 31.4%, respectively, and the values are predicted to increase during the following years (1,2) .

Type 2 diabetes mellitus (T2DM) is a complex metabolic disorder mainly characterized by insulin resistance and β-cell dysfunction (3). Besides insulin resistance, MetS is described by a cluster of conditions, namely high blood pressure, abdominal obesity, high triglyceride levels, low HDL cholesterol level, and impaired fasting glucose. Several risk factors have been identified for T2DM and MetS, such as high adiposity, abnormal blood biomarkers levels, medical history, regional and psychosocial factors. In addi-

tion, lifestyle factors such as daily caloric intake, smoking and alcohol consumption are considered to be related to the prevalence of T2DM and MetS (4,5).

Dysfunction of many biological pathways may be involved in the pathophysiology of the diseases. Mutations in protein-coding genes involved in oxidative stress (OS) reduction (*SOD1* and *CAT*) (6,7), endothelial functions (*eNOS*) (8) and hemodynamics (*ACE, ATR1)* (9–12) or in the carbohydrate metabolism (*OXTR*) (13,14) may to be involved in predisposition for T2DM or MetS. There are gender-related differences regarding the relative contribution of risk factors for these diseases (15,16). Therefore, we evaluated the susceptibility in men of the association of common polymorphisms in six genes with T2DM and MetS.

MATERIAL AND METHODS

Clinical data

The case-control study included Caucasian men considered healthy (n=120) or diagnosed with T2DM (n=120) or MetS (n=75). The American Diabetes Association 2016 and NCEP ATP III criteria were used for the diagnosis of these diseases (17). Healthy individuals were selected based on a standard clinical evaluation and on paraclinical data. Patients with a diagnosis of chronic kidney diseases, retinopathy, diabetic peripheral neuropathy or with an addiction to drugs were not included in the study. We collected clinical, paraclinical, and lifestyle data from all patients. Subjects were considered smokers if they smoked between 2 and 25 cigarettes per day for at least a year. Alcohol consumers were considered those who drunk at most 50 g alcohol per day for at least a year, but were not heavy drinkers (56g alcohol/day). The research was approved by the ethics committee of the National Research and Development Institute for Food Bioresources (966/27.08.2019).

Research methods

Genomic DNA was extracted from peripheral venous blood using the Promega Wizard Genomic DNA purification kit (Promega Corporation, Madison, WI), followed by a Polymerase Chain Reaction (PCR) to genotype the rs4646994 (*ACE* I/D) (18), rs1799983 (*eNOS* VNTR 4a/b) (18), and rs53576 (*OXTR* A>G) (19) polymorphisms. A PCR-restriction fragment length polymorphism was used to genotype the *ATR1* rs5186 (A1166C) (18), *CAT* rs7943316 (-21A/T) (20), and *SOD1* rs2234694 (+35A/C) polymorphismes (20).

Statistical analysis

Statistical analysis was performed with the MedCalc software (version 20.111, Ostend, Belgium). After Bonferroni correction for multiple hypotheses (n=33) a p value at $p<0.0015$ was considered statistically significant.

RESULTS

The clinical data of subjects enrolled in the study are shown in Table 1. MetS patients have 3 (64%), 4 (32%) or 5 (4%) NCEP ATP III criteria for diagnosis.

We found that T2DM was diagnosed at an earlier age compared to MetS (p=0.0003). The statistical significance of difference was greater when comparing patients who are carriers of *OXTR* G (54.04 vs 56.05 years old, p=0.0002) or both *OXTR* G and *eNOS* b alleles (54.00 vs 56.05, p=0.00016).

Our results showed that the *SOD1* AA genotype (p=0.0006) and the presence of both *ACE* I and *OXTR* A alleles (p=0.0005) are protective factors for T2DM. T2DM patients with lower triglyceride levels (<150 mg/dl) were more frequent carriers of *SOD1* AA and AC genotypes when compared to HC subjects (p=0.0002 and p=0.0005, respectively). Similarly, *SOD1* AA and AC genotypes were more frequent in T2DM patients with HDL levels over 40 mg/dl when comparing to HC (p=0.0002 and p=0.0004, respectively). Hypertensive T2DM patients were more frequent carriers of *ACE* DD genotype than HC (56.76% vs 25.83%, p=0.0005) (Table 3). In addition, this genotype, in association with *eNOS* bb or *OXTR* G, was found more frequently in alcohol consumers compared to those without this habit (p<0.0001) (Table 3). No other statistically significant associations were found between the investigated groups or subgroups of subjects.

DISCUSSION

In this study, we evaluated the association between six common polymorphisms in the *ACE*, *eNOS*, *OXTR*, *ATR1*, *CAT*, and *SOD1* genes with characteristics of T2DM and MetS in Romanian Caucasian men. Thus, we tried to avoid the impact of gender on these associations. Patients with acute or chronic hyperglycemia have increased OS levels can be predisposed to long term complications of diabetes (21). *SOD1* gene codes for an antioxidant enzyme and therefore, it is a functional candidate for obesity (22), T2DM, and its long-term complications (23). In our study, *SOD1* AA was a protective factor for T2DM (p<0.0006). Concordant results were reported in the study by Flekac et al., where both Czech males and females were included. The authors reported that *SOD1* +35A/C had potential effect on enzyme activity and genotype AA was protective for T2DM (p<0.05) (24). Additionally, in our study *SOD1* AA and AC genotypes were associated with triglycerides (p=0.0002 and p=0.0005, respectively) and HDL cho-

Table 1. Characteristics of the study participants

Parameters	T2DM	MetS	HC
Number of subjects	120	75	120
Age[d]	54.00 (51–56) [a]	55.00 (54–58)	NA
Age[i]	58 (54.5–59) [a, b]	59 (57–61) [b]	55 (53–59)
BMI[d]	32.99 (29.41–35.22)	33.66 (29.74–35.29)	NA
BMI[i]	30.95 (27.97-33.07)[a,b]	32.83 (28.8–33.74) [b]	24.55 (23.71–27.74)
Glycemia[i] (mg/dl)	113.5 (102.5–123) [a,b]	109 (98–116)	98 (93–104.5)
Obesity[d]	68	54	0
Hypertension	37	50	0
Hyperglycemia[d](≥110 mg/dl)	120	33	0
HDL cholesterol[d](<40 mg/dl)	39	55	12
Triglycerides[d](≥150 mg/dl)	48	63	8
Stroke[i]	10	9	0
Coronary heart diseases[i]	9	6	0
Sexual dysfunctions[i] (yes/ no/ refused to respond)	17/80/23	10/47/18	12/91/17
Subjects with offspring	45	25	100
Smokers[i]	19	42	57
Alcohol consumers[i]	43	28	27

Values are presented as number of subjects (n), median (range), or ratio as specified; [i] at study inclusion; [d] at disease diagnosis; a $p<0.0015$ compared to MetS group, b $p<0.0015$ compared to HC group.

Sample genotyping was performed for all patients included in the study. The distribution of the studied genotypes was in accordance with Hardy-Weinberg Equilibrium (Table 2).

Table 2. Distribution of the genotypes in the studied groups

Polymorphisms	Genotypes	T2DM	MetS	HC
***ACE* I/D (rs4646994)**	DD	44	25	31
	ID	49	35	61
	II	27	15	28
***ATR1* A1166C (rs5186)**	AA	70	43	65
	AC	38	31	44
	CC	12	1	11
***eNOS* VNTR 4a/b (rs1799983)**	bb	90	52	82
	ba	26	23	36
	aa	4	0	2
***OXTR* A>G (rs53576)**	GG	59	31	42
	GA	47	34	49
	AA	14	10	29
***SOD1* +35A/C (rs2234694)**	AA	27	13	33
	AC	62	44	51
	CC	31	18	36
***CAT*-21A/T (rs7943316)**	AA	104	71	118
	AT	15	4	2
	TT	1	0	0

lesterol ($p=0.0002$ and $p=0.0004$, respectively) levels in T2DM patients. Our results are supported by previous publications in which *SOD1* concentration was negatively correlated with HDL cholesterol concentration. However, unlike previously published data, we found no statistically significant association between *SOD1* polymorphism and obesity ($p<0.05$) (25).

Ethnicity and gender may explain, at last partially, previous conflicting results regarding the impact of *ACE* I/D in predisposition for T2DM (26). The *ACE* DD genotype was found to increased risk of hypertension and/ or diabetes in Egyptian (27), Malaysian (28), Chinese (29) populations, but not in Turkish (30) or Emirati (31). Meta-analyses have also described a positive association with subjects from Middle East, North Africa (26) or Asia (32), whereas, among Europeans, the results are more heterogenous (33,34). The number of *ACE* D variants was correlated with an increase in ACE activity (35) and angiotensin II signal transduction influences secretion of oxytocin (36,37). Long-term ACE hyperactivity may predispose to insulin hypersecretion and impairment of vessel walls compliance which increase the risk for T2DM and hypertension development (38). Although the distribution

Table 3. Statistically significant results in the studied groups

Groups compared	Genetic variants	Distribution	O.R., 95% CI, p value
T2DM vs HC	*SOD1* AA	104/16 vs 118/2	0.11, 0.03 – 0.49, 0.0006
T2DM vs HC	*ACE* I and *OXTR* A	32/88 vs 58/62	0.39, 0.23 – 0.67, 0.0005
T2DM with triglycerides level <150 mg/dl vs HC	*SOD1* AA	60/12 vs 110/2	0.09, 0.02 – 0.42, 0.0002
	SOD1 AC	11/61 vs 2/110	9.92, 2.13 – 46.21, 0.0005
T2DM with HDL level > 40 mg/dl vs HC	*SOD1* AA	67/14 vs 106/2	0.09, 0.02 – 0.41, 0.0002
	SOD1 AC	13/68 vs 2/106	10.13, 2.22 – 46.31, 0.0004
T2DM with hypertension vs HC	*ACE* DD	21/16 vs 31/89	3.77, 1.75 – 8.12, 0.0005
T2DM alcohol drinkers vs T2DM non-drinkers	*ACE* DD	30/13 vs 14/63	10.38, 4.35 – 24.82, <0.0001
	ACE DD and *eNOS* bb	25/18 vs 10/67	9.31, 3.79 – 22.87, <0.0001
	ACE DD and *OXTR*1 G	26/17 vs 12/65	8.28, 3.48 – 19.73, <0.0001

of polymorphisms in *ACE* or *OXTR* did not differ between our groups, the presence of both *ACE* I and *OXTR* A alleles could be a protective factor for T2DM (OR=0.39, p<0.0005).

OXTR mediates the impact of stressful experience and influences social support seeking during distress (39). *OXTR* polymorphisms may influence the response to stress, via hypothalamic–pituitary–adrenal axis, and the risk for stress-related disorders, including T2DM (13,39,40). Carriers of the rs53576 G allele were more sensitive to both favorable or negative surroundings and individuals with GG genotype had altered cortisol levels and blood pressure after rejection (39).

Predisposition to T2DM involves the interaction between different genetic and non-genetic factors. It was considered that moderate alcohol consumption (24 g/day) is protective for T2DM development, while higher quantities (60 g/day alcohol) represents a risk factor (41). In our T2DM group, patients carrying the *ACE* DD genotype were more often alcohol consumers. The association of *ACE* DD with *eNOS* bb or with *OXTR* G were found more frequently in drinking compared to non-drinking T2DM patients. We found no association regarding the *OXTR* gene polymorphisms and smoking habits in T2DM patients.

No association was identified concerning gene polymorphisms in the MetS patients who reported being smokers or drinking alcohol.

Our study indicated no significant association between MetS and tested polymorphisms or between T2DM and *ATR1* A1166C or *CAT*-21A/T.

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Ethics approval: All procedures performed in this study involving human participants were in accordance with the ethical standards of the institutional research committee and with the 1964 Helsinki Declaration and its later amendments of comparable ethical standards.

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