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Original Article

Association of Adiponectin and Resistin Gene Polymorphisms with Undernutrition Risk among Type 2 Diabetes Patients in Bosnia and Herzegovina

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Abstract

Background: Undernutrition disorder is a prevalent comorbidity (up to 25%) in type 2 diabetes (T2D) patients which significantly compromises their health. We aimed to assess the association between single nucleotide polymorphysms (SNPs) adiponectin (*ADIPOQ*) +276 (G/T) and resistin (*RETN*) -420 (C/G) with the risk of developing T2D and undernutrition in patients with T2D.

Methods: The research was conducted as prospective case-control study among 106 patients with T2D and 106 healthy control individuals in the territory of the Bosnia and Herzegovina from Sep 1st 2022 to May 1st 2023. For assessing the nutritional status, the mini nutritional assessment (MNA) was used. DNA analysis was carried out by restriction fragment length polymorphism-polymerase chain reaction (RFLP-PCR) method. The data were analyzed using chi-square test, t-test for independent samples and binary multivariate logistic regression.

Results: The research included 212 subjects of which 124 (58.5%) were male. The mean age of the subjects was 68.48±4,67 yr. Almost 20% of subjects were undernourished, significantly more T2D patients when compared to controls (33% vs. 6.6%; $P<0.001$). *ADIPOQ* +276 GT genotype was identified as significant predictor of T2D (OR: 3.454; 95% CI: 1.400-8.521; $P=0.007$) and undernutrition disorder (OR: 3.453; 95% CI: 1.331-8.961; $P=0.011$) in T2D population, while the presence of *RETN* -420 CG genotype had protective effect against occurrence of T2D (OR: 0.353; 95% CI: 0.144-0.867; $P=0.023$). However, *RETN* genotypes were not associated with undernutrition disorder.

Conclusion: *ADIPOQ* +276 gene polymorphism represent a significant predictor for development of T2D and undernutrition disorder in T2D population, while *RETN* -420 gene polymorphism was identified as a significant factor associated with a reduced risk for T2D, but was not associated with undernutrition.

Keywords: Adiponectin; Resistin; Polymorphism; Type 2 diabetes; Undernutrition

Introduction

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Diabetes mellitus is on the rise, with 2017 estimates projecting around 640 million cases by 2040, 90% of which will be type 2 diabetes (T2D) (1). Malnutrition, affecting 925 million people worldwide, is a major health concern that includes a spectrum of imbalances, from undernutrition to obesity. While obesity is one of the most common comorbidities of T2D, the prevalence of undernutrition in T2D is also significant, ranging from 12% to 58.8% (2, 3).

Undernutrition is defined by low blood albumin levels and a low body mass index (BMI) (4); however, the Mini Nutritional Assessment (MNA) is currently the most effective tool for evaluating nutritional status (5). Undernourished T2D patients experience increased risks, including higher infection and complication rates, reduced bone mass and muscle function, immune dysfunction, delayed healing, prolonged hospital stays, higher treatment costs, and overall functional decline (6).

Adipose tissue acts as a key endocrine organ, producing adipokines adiponectin and resistin that regulate appetite, lipid, and carbohydrate metabolism. Adiponectin levels are reduced in T2D and obesity but elevated in undernourished patients, while resistin levels are generally higher in obese individuals and T2D patients (7). Single nucleotide polymorphisms (SNPs) of the *ADIPOQ* and *RETN* genes have been especially investigated in obese patients and patients with T2D. Japanese subjects with the *ADIPOQ* +276 GG genotype have been found to have a notably higher risk of T2D (8). *ADIPOQ*+276 SNP is not only associated with the T2D but also with metabolic syndrome (9). In a Polish study involving undernourished girls with anorexia nervosa, the distribution of the *ADIPOQ*+276 TT, GG and TG genotypes was associated with adiponectin serum levels (10). Yoshida et al (11) showed association between *RETN*-420 GG genotype and risk for developing T2D in adulthood of individuals with low birth weight (<2.500 g). However, recent study (12) found no significant evidence that *RETN*-420 polymorphism was linked to T2D.

The data on *ADIPOQ* and *RETN* gene polymorphisms as risk factors for T2D remains inconsistent. Although these polymorphisms may be linked to undernutrition and obesity in non-T2D patients, there is limited research on their association with T2D risk or undernutrition in T2D patients. Identifying these associations could enhance understanding of predisposition to undernutrition and assist clinicians in preventing complications by monitoring at-risk patients. While *ADIPOQ* and *RETN* genes are known to influence the metabolic phenotype of undernourished patients (13), more research is needed for T2D cases. Therefore, we aimed to examine the association of *ADIPOQ* and *RETN* SNPs with T2D occurrence and undernutrition in T2D patients within the Bosnian population.

Materials and Methods

Study Design

The research was conducted as a prospective case-control study in the territory of the Bosnia and Herzegovina.

The study was carried out after taking informed written consent from all individuals and after approval of the Ethics Committee of Faculty of Medicine Foča, University of East Sarajevo (reg. number 01-2-56, from May 17, 2022). The research was conducted from Sep 1st 2022 to May 1st 2023.

The first group (case group) consisted of randomly chosen patients previously diagnosed with T2D who were being on regular checkup on outpatient basis (n=56, 52.8%) or hospitalized (n=50,47.2%) at the Endocrinology Department of the University Hospital Foča because of appearance of acute or chronic complication of T2D. T2D subjects were diagnosed by an endocrinologists using American Diabetes Association (ADA) criteria (14), with fasting blood glucose (FBG) levels at diagnosis ≥7.0 mmol/L or glycated hemoglobin (HbA1c) levels ≥6.5%. The diagnosis was confirmed by an oral glucose tolerance test (OGTT). The patients with severe liver

and kidney disease, and other endocrine diseases, as well as history of malignant diseases were excluded from the study.

Subjects with FBG less than 6.1 mmol/L were taken as control group, who came for normal routine checkup in Occupational Medicine Service of the Health Center Foča on the same day, and they were matched with T2D group based on gender and age (± 3 yr).

Socio-demographic data, were collected using a specially designed questionnaire. Clinical parameters included data obtained from the physical examination of patients and BMI was measured for every subject. Routine laboratory analyses such as white blood cells (WBC), red blood cells (RBC) and platelets (PLT) count was measured and general biochemical findings: FBG, HbA1C, sodium (Na), potassium (K), free tyroxine (FT4), free triiodothyronine (FT3), thyroid stimulating hormone (TSH), cholesterol, triglycerides, low-density lipoprotein (LDL) and high-density lipoprotein (HDL), were performed for all subjects, using the enzyme chemiluminescence method on the "DXI-600, Beckman Coulter" analyzer.

Assessing the Nutritional Status of the Subjects

For assessing the nutritional status of the group of patients and the control group, the MNA test, was used. The complete version of the MNA (15) consists of 18 items classified into four groups. Individuals with a total score ≥24 are considered well-nourished, those scoring from 17-23.5 are at a risk of undernutrition, and those scoring <17 are in a state of undernutrition (5). For the purpose of the study respondents were divided into two groups, first group was named well nourished and was comprised of well nourished and subjects with the risk for undernutrition (total score ≥17) and second group was comprised of undernourished subjects (total score less than <17).

Genotyping of the ADIPOQ and RETN Genes

In all participants, after an overnight fast of eight hours, 5 ml of whole blood was collected into a Vacutainer tube containing ethylenediaminetetraacetic acid (EDTA) and frozen in a freezer at a temperature of -80 ˚C until further analysis. Genomic deoxyribonucleic acid (DNA) was isolated from 200 µl of whole blood using a commercial DNA isolation kit (GeneJET Genomic DNA Purification Kit, thermo Scientific, Waltham, MA, USA). The DNA concentration was determined using a commercial kit (Qubit dsDNA BR Assay Kit, Thermo Fisher Scientific, Waltham, MA, USA) using the Qubit 4 fluoremeter (Thermo Fisher Scientific, Waltham, MA, USA). Alleles of the SNP +276 G/T of *ADIPOQ* (rs1501299) and the SNP -420 C/G *RETN* (rs1862513) genes were amplified using the polymerase chain reaction (PCR). DNA-fragments were amplified from genomic DNA using following specific and enzymes primers (Table 1). The final reaction volume concentration was 0.5mM. The reaction was conducted using a thermocycler (Eppendorf Mastercycler Personal) in a final volume of 25 µl. PCR conditions were as followed: initial denaturation (95 ˚C, 5 min), followed by 30 amplification cycles consisting of denaturation (90 ˚C, 30 seconds), primers annealing (72˚, 20 sec), extension (72 ˚C, 20 sec), and one cycle of final elongation (72 ˚C, 10 min). Amplification was confirmed by 1% agarose gel electrophoresis stained with ethidium bromide and visualized under UV light (Vilber FUSION Solo X). After confirming amplification, 10 µl of each amplified DNA sample was digested at 37 ˚C for 1 hour using restriction endonuclease enzymes (BsmI and BbsI, New England, Biolabs Inc., Ipswich, MA, USA) (Table 1) and then inactivated at 65˚ for 20 min. The digested products were then visualized by staining with 4% ethidium bromide agarose gel. Genetic analyses using the PCR were performed at the Faculty of Medicine Foča.

Table 1: Primers and enzymes used for polymerase chain reaction

Genes	Primers	REE
SNP +276 (G/T) of *ADIPOQ* gene	Forward 5'-CTCCTACACTGATATAAACTATATGAAT-3' Reverse 5'-AATGTACTGGGAATAGGGATGA-3'	BsmI
SNP -420 (C/G) of *RETN* gene	Forward 5'-TGTCATTCTCACCCAGAGACA-3' Reverse 5'-TGGGCTCAGCTAACCAAATC-3'	BbsI

REE – restriction endonuclease enzymes, SNP – single nucleotide polymorphism, ADIPOQ – adiponectin gene, RETN – resistin gene

Statistical Analysis

To detect a statistically significant difference among subject groups at a $P<0.05$ significance level with 80% study power, the study included 212 patients, or 106 per group. The sample size was calculated using the G*Power program with a chi-square ($\chi 2$) test. Groups were compared according to their difference in their genotype and alleles frequencies using $\chi 2$ test. The independent t-test was used to test the differences in mean values. An association between various SNPs with T2D and undernutrition risks were assessed using odds ratio (OR) with 95% confidence intervals (95% CI) using binary multivariate logistic regression analysis, and regression models were adjusted by univariately significant variables (BMI and laboratory parameters). The data were analyzed using the statistical software SPSS ver. 24 (Chicago, IL, USA). The results were expressed as mean value ± standard deviation (SD) and p-value less than 0.05 was considered statistically significant.

Results

The research included 212 subjects with mean age of 68.48±4,67 yr, of which 124 (58.5%) were male, equally distributed in T2D and control group. T2D patients were more often obese (BMI) and undernourished (MNA) when compared to the control group. The differences in mean values of laboratory analyses are presented in Table 2.

The frequency of the *ADIPOQ* GG genotype was higher in the controls (67.9%) compared to the T2D group (50%) ($P=0.008$), while *ADIPOQ* GT was more frequent in the T2D group (45.3% vs. 28.3%; $P=0.010$). *RETN* GT was more frequent in the undernourished (60%) in comparison to the well-nourished T2D patients (38%) ($P=0.033$). Presence of *ADIPOQ* GT genotype (OR=3.454, $P=0.007$) was associated with occurrence of T2D when compared to referent *ADIPOQ* GG genotype. Presence of *RETN* CG genotype (OR=0.353, $P=0.023$) had protective effect against occurrence of T2D. Presence of *ADIPOQ* GT genotype (OR=3.454, $P=0.011$) was associated with occurrence of undernutrition in T2D patients. *RETN* SNP was not identified as significant risk factor associated with undernutrition (Table 3).

Table 2: Socio-demographic and laboratory characteristics among T2D and control group of subjects, as well as among well nourished and undernourished T2D patients

Variables	T2D group (n=106, 50%)		Control group (n=106, 50%)		P*	Well nourished (n=71, 67%)		Undernourished (n=35, 33%)		P*
	n	%	n	%		n	%	n	%	
Male gender	63	59.4	61	57.5	0.780*	43	60.6	20	57.1	0.736*
Age (M±SD)	68.83±5.25		68.13±3.99		0.278**	69.36±5.67		67.74±4.14		0.136**
Age groups										
61 to 70 yr	72	67.9	70	66.0	0.770*	48	67.6	24	68.6	0.920*
71 to 82 yr	34	32.1	36	34.0		23	32.4	11	31.4	
BMI (kg/m^2) (M±SD)	28.06±4.44		26.72±4.26		0.026**	27.84±4.61		28.52±4.10		0.463**
BMI categories (kg/m^2)										
Underweight (<18.5)	11	10.4	1	0.9	0.003*	3	4.2	8	22.9	0.014*
Healthy weight (18.6-24.9)	12	11.3	30	28.3		8	11.3	4	11.4	
Overweight (25-29.9)	46	43.4	49	46.2		36	50.7	10	28.6	
Obesity (≥30)	37	34.9	26	24.6		24	33.8	13	37.1	
Education					0.097*					
Primary school	24	22.6	38	35.8		13	18.3	11	31.4	0.122*
High school	72	67.9	58	54.7		49	69.0	23	65.7	
University degree	10	9.4	10	9.4		9	12.7	1	2.9	
Undernutrition	35	33.0	7	6.6	<0.001	/	/	/	/	/
Laboratory analyses (M±SD)										
WBC (3.71-10.67 x 10^9/L)	6.92±1.72		6.15±1.09		<0.001**	6.81±1.66		7.15±1.85		0.338**
RBC (3.87-5.68 x 10^{12}/L)	4.72±0.43		4.61±0.33		0.051**	4.65±0.38		4.86±0.49		0.052**
Haemoglobin (120-175g/L)	138.47±15.77		133.56±9.49		0.054**	138.15±14.68		139.11±18.01		0.770**
Haematocrit (0.35-0.50 L /L)	40.45±3.74		40.39±2.86		0.898**	40.53±3.67		40.27±3.93		0.731**
PLT (150-450 x 10^9/L)	240.52±74.19		262.05±65.64		0.026**	238.76±70.39		244.11±82.34		0.729**
FBG (4.1-6.1 mmol/L)	8.48±3.85		5.48±0.99		<0.001**	8.87±3.95		7.70±3.56		0.140**
HbA1c (under 6.5%)	6.76±1.58		5.15±1.41		<0.001**	7.05±1.64		6.16±1.26		0.006**
Urea (2.8-7.2 mmol/L)	6.69±2.65		5.41±1.47		<0.001**	6.85±2.82		6.38±2.24		0.392**
Creatinine (58-110 mmol/L)	88.60±28.04		87.45±16.02		0.714**	88.02±25.59		89.79±32.82		0.761**
Na (135-147 mmol/L)	139.90±2.07		140.64±1.08		0.001**	139.66±2.19		140.40±1.75		0.085**
K (4.5-5.4 mmol/L)	4.15±0.36		4.27±0.17		0.005**	4.23±0.37		4.34±0.34		0.132**
FT4 (0,70-1,48 ng/dL)	1.21±0.12		1.24±0.10		0.025**	1.22±0.11		1.18±0.14		0.147**
FT3 (1,71-3,71 pg/mL)	2.52±0.47		2.45±0.46		0.299**	2.53±0.49		2.51±0.44		0.892**
TSH (0,35-4,94 mIU/ml)	2.71±0.76		2.92±0.51		0.020**	2.88±0.62		2.36±0.92		0.005**
Cholesterol (< 5.2 mmol/L)	3.93±1.05		4.16±0.94		0.096**	4.03±1.09		3.72±0.95		0.175**
LDL (< 3.4 mmol/L)	2.86±0.91		2.65±0.71		0.836**	2.50±0.91		3.03±1.01		0.536**
HDL (≥1.55 mmol/L)	0.93±0.38		0.85±0.10		0.383**	0.97±0.46		0.86±0.22		0.513**
Triglycerides (< 1.70 mmol/L)	1.52±0.83		1.62±0.94		0.427**	1.44±0.88		1.69±0.94		0.156**
Duration of T2D (years) (M±SD)	10.29±4.60		/		/	10.11±4.90		10.65±3.96		0.224**

T2D – type 2 diabetes; WBC - white blood cells; RBC - red blood cells; PLT – platelets; FBG – fasting blood glucose; HbA1C – glycated haemoglobin; Na - sodium; K - potassium; FT4 – free thyroxine; FT3 - free triiodothyronine; TSH - thyroid-stimulating hormone; LDL - low-density lipoprotein; HDL - high-density lipoprotein; M - mean ± SD - standard deviation; p – statistical significance was measured by *χ^2 – chi square test and **independent t test, significant values are bolded

Table 3: Frequency of *ADIPOQ* +276 (G/T) and *RETN* -420 (C/G) genotypes and alleles and association of genotipes with T2D risk and undernutrition in the Bosnian T2D population

Distribution of genotypes and alleles	**Univariate**			**Multivariate**			
SNP +276 (G/T) of *ADIPOQ* gene	T2D group (%) (n=106)	Control group (%) (n=106)	*P*	B	OR	95% CI	*P*
GG (%)	53 (50.0)	72 (67.9)	0.008	/	/	/	referent
GT (%)	48 (45.3)	30 (28.3)	0.010	1.240	3.454	1.400-8.521	0.007
TT (%)	5 (4.7)	4 (3.8)	0.733	1.265	3.543	0.638-19.663	0.148
G	154 (72.65)	174 (82.07)	0.289				
T	58 (27.35)	38 (17.93)	0.154				
SNP -420 (C/G) of *RETN* gene							
CC	54 (50.9)	42 (39.6)	0.098	/	/	/	referent
CG	44 (41.5)	53 (50.0)	0.215	-1.041	0.353	0.144-0.867	0.023
GG	8 (7.5)	11 (10.4)	0.471	-0.264	0.768	0.180-3.282	0.722
C	152 (71.7)	137 (64.62)	0.388				
G	60 (28.3)	75 (35.38)	0.103				
SNP +276 (G/T) of *ADIPOQ* gene	Well nourished (%) (n=71)	Undernourished (%) (n=35)	*P*	B	OR	95% CI	*P*
GG (%)	39 (54.9)	14 (40.0)	0.148		/	/	referent
GT (%)	27 (38.0)	21 (60.0)	0.033	1.239	3.453	1.331-8.961	0.011
TT (%)	5 (7.0)	0 (0.0)	0.108	-6.548	0.491	0.108-0.793	0.671
G	105 (74.0)	49 (70.0)	0.809				
T	37 (26.0)	21(30.0)	0.672				
SNP -420 (C/G) of *RETN* gene							
CC	39 (54.9)	15 (42.9)	0.242		/	/	referent
CG	28 (39.4)	16 (45.7)	0.537	0.201	1.222	0.489-3.054	0.668
GG	4 (5.6)	4 (11.4)	0.288	1.259	3.520	0.736-16.841	0.115
C	106 (74.6)	46 (65.7)	0.328				
G	36 (25.35)	24 (34.3)	0.196				

T2D – type 2 diabetes; B - unstandardized regression coefficient; OR – odds ratio; 95% CI – confidence interval, p – statistical significance; significant values are bolded, multivariate analysis adjusted for body mass index and univariately significant laboratory parameters.

Discussion

Our prospective case-control study included 106 patients diagnosed with T2D and 106 healthy control subjects. This is, to our knowledge the first study to analyze an association in two loci, the *ADIPOQ*+276 (G/T) and *RETN*-420 (C/G) gene polymorphisms with the risk of developing T2D and risk for undernutrition in T2D patients in Bosnian population.

The rate of undernutrition among elderly diabetic patients was found to be 21.2%, irrespective of BMI (16). Our results have shown that in a control group prevalence of undernutrition measured by MNA was 6.6%, while in the group of T2D was 33%, however 0.9% of healthy subjects and 10.4% of T2D patients were underweight measured by BMI. This difference between BMI and MNA results are in line with other studies (17) where the MNA can identify undernutrition even in obese patients, making it a major complication of T2D and a significant challenge in diabetes management, leading to possible misdiagnosis and mismanagement with restrictive diets (3).

Our results indicated that T2D patients had higher WBC, FBG, HbA1c, and urea levels and lower PLT, Na, K, FT4, and TSH levels compared to healthy controls. Additionally, undernourished T2D patients showed higher HbA1c and TSH levels than well-nourished patients. Although T2D patients in our study had higher mean HbA1c levels compared to controls, their HbA1c values were only slightly above the normal range (6.76±1.58%), likely due to many patients being evaluated during their six-month follow-up with an endocrinologist, where therapy adjustments could be made for better glycemic control. These findings align with the pathophysiology and expected laboratory profiles reported in other studies on T2D patients (18, 19).

The present case control study observed a significant association of *ADIPOQ*+276 and *RETN*-420 SNPs with T2D, and *ADIPOQ* +276 SNP with undernutrition of T2D patients, however, significant association of *RETN*-420 genotypes with undernutrition among Bosnian population was not found. Studies conducted among Taiwanese, North Indians, Caucasians, Egyptians and Kashmiri population showed significant association between *ADIPOQ*+276 genotypes and T2D (20-23). Additionally, in Japanese population, the *ADIPOQ*+276 GT genotype was linked to T2D (24) and our study confirmed these results. However, *ADIPOQ*+276 was not determined to be associated with T2D in the Chinese (8) and Iranian (22) populations and these disparities could be caused by variations in race, sample size, complex disorders etc.

Initially, Osawa et al (25) proposed that *RETN*-420 (C/G) gene may significantly increase the chance of developing T2D in the Japanese population, and this result was later verified by Nadeem et al (26). Tan et al (27) investigated the *RETN*+62 G/A SNP and found a lower frequency of the A allele in patients with T2D compared to healthy subjects. In contrast, Rathwa et al (28) even suggested that *RETN*-420 GG genotype or G allele has been associated to a reduced risk of T2D, which is in line with our results. However, *RETN*-420 SNPs were not associated to the T2D risk (29, 30). These inconsistent results forced us to elucidate the possible association between the *RETN*-420 SNPs and T2D risk, and we observed its protective effect against occurrence of T2D (CG genotype). However, *RETN*-420 was not associated with undernutrition in our T2D patients. Based on previously mentioned results we can draw a conclusion that there are ethnic differences in the distributions of the *RETN*-420 gene. The study by Křížová et al (13) which investigated the frequency of the SNP +45T/G and +276G/T of the *ADIPOQ* gene and +62G/A and -180C/G of the *RETN* gene in obese patients, undernourished because of anorexia nervosa, and in healthy subjects concluded that polymorphisms in *ADIPOQ* and *RETN* genes can contribute to metabolic phenotype of patients with undernutrition (13). Furthermore, serum cholesterol levels in undernourished individuals were greater in those who carried the mi-

nor T allele in position 276 of the *ADIPOQ* gene compared to those with the G/G genotype (13). Our results once again confirmed low frequency of T allele, and T/T genotype in locus + 276 of *ADIPOQ* gene in undernourished T2D patients.
Our study has several limitations. Firstly, only Bosnian subjects were included, which may have introduced selection bias, so similar studies in other ethnicities are needed. Second, even though the study was done on previously calculated sample size, larger sample size would reduce possibility of random variation, so larger studies are required to confirm our findings. Third, factors like adiponectin and resistin levels, which could affect polymorphism analysis, were not considered. Fourth, we didn't account for other comorbidities or their association with *ADIPOQ* and *RETN* polymorphisms. Lastly, undernutrition is influenced by both biological and socio-economic factors, and related gene polymorphisms may also affect our findings.

Conclusion

Carriers of the heterozygous *ADIPOQ*+276 GT genotype is susceptible to develop T2D, and undernutrition disorder if they develop T2D. Heterozygous *RETN*-420 CG genotype was identified as a significant factor associated with a reduced risk for T2D, but was not associated with undernutrition. Homozygous state of *ADIPOQ* and *RETN* SNPs did not show any association, so the general decision about this association should be made with caution. Further functional studies are needed to identify the actual biological roles of *ADIPOQ* and *RETN* gene polymorphisms in T2D population and their risk for undernutrition disorder.

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Journalism Ethics considerations

Ethical issues (Including plagiarism, informed consent, misconduct, data fabrication and/or falsification, double publication and/or submission, redundancy, etc.) have been completely observed by the authors.

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Conflict of interest

The authors declare that there is no conflict of interests.

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