Short communication

Adiponectin gene 45T>G polymorphism is not associated to plasma adiponectin in a cohort of patients with type 2 diabetes from Romania

Polimorfismul 45T>G al genei adiponectinei nu este asociat cu adiponectina plasmatica la pacienti diabetici de tip 2 din Romania

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Abstract

Background: We aimed to evaluate the prevalence of 45T>G polymorphism of the ADIPOQ gene in a cohort of type 2 diabetes patients from Romania. The influence of the polymorphism on adiponectinemia and its relationship to presence of albuminuria were also assessed. Materials and methods: 115 type 2 diabetic patients were genotyped for the ADIPOQ 45T>G polymorphism. Medical history, laboratory evaluation and total plasma adiponectin were obtained. Results: TT genotype occurred in 101 (87.82%) patients, TG genotype in 12 (10.43%) and GG genotype in 2(1.73%) subjects. Genotypes for the 45T>G polymorphism were not significantly associated to plasma adiponectin. Patients were divided according to the presence of albuminuria in albuminuric patients (albumin/creatinine ratio> 30 mg/g creatinine) and normoalbuminuric (albumin/creatinine ratio< 30 mg/g creatinine). Albuminuric patients had significantly higher adiponectin levels (14.58±2.07 versus 6.91±0.84 μg/ml); however there was no difference in genotype distribution between normoalbuminuric and albuminuric patients (p=0.61). Logistic regression showed that systolic blood pressure p=0.044 (OR 1.04; CI 1.01/1.08), adiponectin p=0.03 (OR 1.07; CI 1.00/1.14) and age p=0.07 (OR 1.05; CI 0.99/1.12), but not genotype are predictors of albuminuria. Conclusion: The ADIPOQ 45T>G polymorphism did not influence plasma adiponectin levels in a cohort of patients with type 2 diabetes from Romania.

Keywords: *adiponectin, gene polymorphism, type 2 diabetes*

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Rezumat

Introducere. Scopul studiului a fost de a evalua polimorfismul 45T>G al genei adiponectinei într-o populație de pacienți diabetici de tip 2 din România; influența sa asupra adiponectinemiei şi asupra prezenței albuminuriei la acesti pacienți a fost deasemenea studiată. Material şi metodă: 115 pacienți diabetici de tip 2 au fost genotipați pentru polimorfismul ADIPOQ 45T>G. Anamneza, evaluarea paraclinică şi adiponectina plasmatică totală au fost efectuate la fiecare pacient. Rezultate. Genotipul tip TT a fost prezent la 101 (87.82%) dintre pacienți, genotipul TG la 12 (10.43%) iar GG la 2 (1.73%) pacienți. Genotipurile pentru polimorfismul 45T>G nu au fost semnificativ asociate cu adiponectina plasmatică. Pacienții au fost împărțiți, în funcție de prezența albuminuriei, în pacienți albuminurici (raport albumină/creatinină urinară > 30 mg/g creatinină) şi normoalbuminurici (raport albumină/creatinină urinară < 30 mg/g creatinină). Pacienții albuminurici au avut adiponectina semnificativ mai mare (14.58±2.07 față de 6.91±0.84 μg/ml); însă nu s-a observat nici o diferență de distribuție a genotipurilor între pacienți normoalbuminurici şi albuminurici (p=0.61). Regresia logistică a arătat ca predictori semnificativi ai albuminuriei tensiunea arterială sistolică p=0.044 (OR 1.04; CI 1.01/1.08), adiponectina p=0.03 (OR 1.07; CI 1.00/1.14) şi vârsta p=0.07 (OR 1.05; CI 0.99/1.12), dar nu şi genotipul. Concluzie. Polimorfismul ADIPOQ 45T>G nu influențează adiponectina plasmatică la cohorta noastră de pacienți diabetici de tip 2.

Cuvinte cheie: *adiponectina, polimorfism genetic, diabet tip 2*

Background

Adiponectin is an anti-inflammatory, insulin-sensitizing and antiatherogenic cytokine produced by mature adipocytes. Plasma adiponectin levels are influenced by various factors and their relative influence is still a matter of debate, but genetic determinism might play a decisive role. Numerous polymorphisms in the gene coding for adiponectin (*ADIPOQ*), laying in the 3q27 region, have been described. Some of them seem to influence adiponectin levels or have been associated to insulin resistance, type 2 diabetes or its microvascular complications (1,2). One of the most frequent polymorphisms in the *ADIPOQ* gene is the 45T>G substitution. Studies regarding its association to plasma adiponectin, insulin resistance, metabolic syndrome, prevalence of diabetes and diabetic nephropathy report inconsistent results. Some of the differences may be due to ethnic background.

The aim of our research was to assess the prevalence of this polymorphism in an Eastern European Caucasian population of type 2 diabetic patients from Romania and to determine whether there is an association between the *ADIPOQ* 45T>G polymorphism and adiponectin levels or presence of diabetes associated kidney disease.

Subjects and methods

Subjects. The size of the cohort was estimated to a minimum of 100 patients, according to previously reported data in the literature on differences in adiponectinemia according to 45T>G polymorphism in diabetic patients (3,4). One hundred and fifteen consecutive type 2 diabetes patients presenting in the outpatient unit of the "Mihai Manasia" Clinic of Nephrology and Dialysis Cluj were genotyped for the *ADIPOQ* 45T>G polymorphism. Inclusion criteria were presence of type 2 diabetes as well as willing to participate. Exclusion criteria were presence of acute inflammation, infection or other acute clinical condition. The study was approved by the Ethical Committee of "Iuliu Hatieganu" University of Medicine and Pharmacy Cluj Napoca , informed and written consent was obtained from each participant in accordance to the World Medical Association Declaration of Helsinki, revised in 2000, Edinburgh.

Evaluation at baseline consisted of medical history, physical exam, anthropometric measurements, standard laboratory evaluation (including lipid profile), glycated hemoglobin and urinary albumin/creatinine ratio, C-reactive

protein (CRP), total plasma adiponectin (Cyber ELISA). Presence of metabolic syndrome was established according to ATPIII criteria.

Material and methods. The *ADIPOQ* 45T>G polymorphism was genoptyped by a PCR-RFLP (Polymerase Chain Reaction – Restriction Fragments Length Polymorphism) assay. One 367 base pair fragment of the ADIPOQ gene was amplified by using polymerase chain reaction with the following amplification protocol: a denaturising step for 10 min at 95ºC, followed by 35 cycles of denaturising 30s at 95 ºC, annealing 30s at 57 ºC and elongation 30s at 72 ºC, and final elongation 7 min at 72 ºC. The primers used were: Fw_5'-GCA GCT CCT AGA AGT AGA CTC TG-3'; Rev_ 5'-TCT GTG ATG AAAGAG GCCAG-3'.

The obtained amplicon was digested overnight at 30ºC with 5U restriction enzyme SmaI (Fermentas MBI, Vilnius, Lituania). Genotypes were separated by electrophoretic migration in 3% high resolution MetaPhor agarose gel, coloured with ethidium bromide. In the presence of the T alelle the 367 pb amplicon resists to SmaI digestion but the G allele creates an restriction site for this restriction enzyme. Thus, after digestion, homozygotes for the wild-type (T) allele present a 367 pb fragment, homozygotes for the G allele have 2 fragments of 204 and 163 base respectively and heterozygotes present all 3 fragments. Electrophoresis was documented by the use of a photo plate coupled to a transiluminator (Vilber Lourmat, France).

Statistical analysis was performed using SPSS 13.0, StatView 7.0 and Microsoft EXCEL programs. For identifying correlation between two normally distributed continuous variables, Pearson's correlation coefficient (r) was used; for non- normally distributed continuous variables Spearman's (r) coefficient was employed. This was followed by linear univariate and multivariate logistic regression (enter method), to estimate correlation between two or more quantitative variables and to estimate a dichotomial dependent variable. Assumptions were verified, including multicollinearity (VIF<10). Coefficients or odds ratio (OR), confidence intervals (CI) and statistical significance of each parameter were presented. $\chi 2$ test was used to compare the distribution of nonparametric variables. For comparison of three or more means of normally distributed continuous variables ANOVA test was used, followed by a Scheffe post-hoc analysis. If distribution of variables was not normal, Kruskall-Wallis followed by Mann-Whitney test was used. For testing normal distribution Kolmogorov-Smirnov test was applied. Statistic significance threshold was considered $\alpha = 0.05$. Values are expressed as mean ±standard error of the mean.

Results

The distribution of the genotypes for the 45T>G polymorphism in our cohort was in accordance with the Hardy-Weinberg equilibrium. The power of the study for detecting differences in plasma adiponectin levels was 1.00. TT genotype occurred in 101 (87.82%), TG genotype in 12 (10.43%) whereas GG genotype in 2 (1.73%) subjects. Characteristics of subgroups according to genotype are shown in *Table 1*. There were not significant differences in adiponectinemia between patients with various genotypes. Carriers of the three genotypes had also similar anthropometric characteristics, blood pressure, history and control of diabetes, prevalence in retinopathy, lipid profile and CRP. Data regarding albuminuria were collected. Albuminuria was defined as presence of microalbuminuria or proteinuria: urinary albumin/creatinine ratio > 30 mg albumin/g creatinine. Comparison of albuminuric to normoalbuminuric patients is shown in *Table 2*. As expected, albuminuric patients had lower estimated glomerular filtration rate (GFR) (65.16±24.17 vs. 81.85±28.73 ml/min/1.73m^2, p: 0.01), lower hemoglobin levels (12.37±0.28 vs. 13.68±0.20 g/dl, p: <0.001) and had a tendency towards higher CRP and lower BMI. Albuminuric patients had higher adiponectin levels than normoalbuminuric subjects (14.58±2.07 vs. 6.91±0.84 μg/ml,

Table 1. Comparison of patients according to genotype

Parameter	Genotype			p
	TT n=101 (87.82%)	TG n=12 (10.43%)	GG n=2 (1.73%)	
Age (years)	64.05±0.91	58.09±4.19	60.50±9.50	0.16
Sex, n (%male)	60 (59.40)	5 (41.66)	0 (0.00)	0.09
Metabolic syndrome, n (%)	80 (80.20)	10 (83.30)	1 (50)	1.00
BMI (kg/m^2)	30.96±0.67	31.08±1.87	43.38±10.18	0.47
Waist circumference (cm)	108.39±1.46	108.85±4.54	125.00±5.21	0.67
SBP (mmHg)	141.41±1.96	140.83±4.99	117.50±27.50	0.82
DBP (mmHg)	82.01±1.12	80.42±2.08	65.00±15.00	0.37
Adiponectin (μg/ml)	11.22±1.29	6.07±1.23	7.81±1.23	0.41
LDL cholesterol (mg/dl)	190.16±13.02	148.97±15.02	167.15±12.65	0.74
HDL cholesterol (mg/dl)	42.66±1.30	45.06±3.68	31.75±11.25	0.89
Triglycerides (mg/dl)	204.48±14.74	162.91±20.82	481.50±301.50	0.89
HbA1c (%)	7.42±0.14	7.56±0.50	8.10±1.40	0.73
Diabetes length(years)	10.01±0.81	7.95±2.29	17.00±3.12	0.43
CRP(mg/dl)	0.99±0.20	0.92±0.26	2.28±2.18	0.57
Hemoglobin (g/dl)	13.07±0.19	12.24±0.73	11.00±1.00	0.15
Diabetic retinopathy (%)	41.50	50.00	50.00	0.73

BMI – body mass index, SBP- systolic blood pressure, DBP – diastolic blood pressure, HDL- high density lipoprotein, LDL – Low density lipoprotein, CRP – C reactive protein

p = 0.003), but no significant differences in genotype distribution were found between these subgroups. However, the power of the study for detecting differences in gene distribution between albuminuric and normoalbuminuric patients was 0.47. There were no other significant differences in clinical and biochemical characteristics between albuminuric and normoalbuminuric patients. Logistic regression showed that factors that systolic blood pressure p=0.044 (OR 1.04; CI 1.01/1.08); adiponectin p=0.03 (OR 1.07; CI 1.00/1.14) and age p=0.07 (OR 1.05; CI 0.99/1.12) are factors that predict the presence of albuminuria.

Discussion

Some studies have reported that 45T>G polymorphism is determinant of plasma adiponectin levels (3-5), the variant allele being responsible for higher plasma adiponectin levels (5, 6). However this finding is not generally accepted, several well powered studies failed to find such an association (8-11). Some studies detected difference in plasma adiponectin levels but this was considered a secondary finding due to linkage disequilibrium with other polymorphisms (12). Some authors instead associated presence of G allele with lower plasma adiponectin levels (13,14). Ethnic differences might also play a role. To our knowledge the only report of 45T>G polymorphism in our geographical area was that of Szopa et al, in a Czech cohort (15). In our study, patients with GT and GG genotype had somewhat lower values of plasma adiponectin as compared to TT patients, but the difference did not reach statistical significance.

Some of studies (10,16) also found an association between 45T>G polymorphism and plasma lipids. However a recent meta-analysis of

Table 2. Comparison of diabetic patients according to presence or absence of kidney disease

Parameter		Albuminuria – n=56	Albuminuria + n=57	p	
Age (years)		62.02±1.43	64.82±1.16	0.13	
Sex, n (%male)		32 (57.14)	33 (57.89)	0.93	
BMI		32.05±0.83	30.53±0.99	0.09	
Waist circumference (cm)		109.16±2.39	107.87±2.34	0.49	
Metabolic syndrome n (%)		46 (82.14)	45 (78.94)	0.67	
SBP (mm Hg)		137.16±2.39	144.71±1.86	0.08	
DBP (mm Hg)		81.08±1.57	81.76±1.41	0.92	
Adiponectin (μg/ml)		6.91±0.84	14.58±2.07	0.003	
GFR (ml/min)		81.85±28.73	65.16±24.17	0.01	
LDL cholesterol (mg/dl)		196.75±18.39	167.33±11.49	0.48	
HDL cholesterol (mg/dl)		42.52±1.91	42.84±1.86	0.87	
Triglycerides (mg/dl)		296.91±18.39	205.89±20.22	0.88	
CRP (mg/dl)		0.66±0.11	1.41±0.35	0.07	
Hemoglobin (g/dl)		13.68±0.20	12.37±0.28	<0.001	
HbA1C (%)		7.70±0.19	7.14±0.18	0.04	
Length of diabetes (years)		8.87±0.85	11.50±1.51	0.18	
Genotype n(%)	TT	48 (85.70)	52 (91.20)	TT/GT	0.61
	GT	7 (12.50)	4 (7.00)	GT/GG	
	GG	1 (1.80)	1 (1.80)	TT/GG	
Diabetic retinopathy, n (%)		23 (41.07)	24 (42.10)	0.81	

Albuminuria – = normoalbuminuric patients, Albuminuria + = micro or macroalbuminuric patients, BMI – body mass index, SBP- systolic blood pressure, DBP – diastolic blood pressure, GFR – glomerular filtration rate estimated according to the abbreviated Modification of Diet in Renal Disease Formula, HDL- high density lipoprotein, LDL – Low density lipoprotein, CRP – C reactive protein

available studies concluded that this SNP is not significantly associated to lipid profile (17). In line with these findings we did not detect any association of this polymorphism to lipid profile.

An association of variation within the *ADIPOQ* gene to diabetic complications is also an ongoing subject for debate. In type 1 diabetes, an association of SNP of the ADIPOQ gene to diabetic kidney disease was found for a series of single nucleotide polymorphisms, mainly those located in the promoter region (18-22). The effect of 45T>G polymorphism was studied by some authors with conflicting results: 45T>G polymorphism was associated to the presence of type 1 diabetes but not diabetic nephropathy in a Swedish Caucasian population (22). However Jaziri et al (23) found that in French subjects G allele at position 45 might be associated to risk of incident renal events. In our cohort we found, as expected, higher adiponectin levels in albuminuric patients, in concordance with many previous reports. These patients also had lower GFR and, as a consequence of chronic kidney disease, a tendency towards anemia and inflammation and have lower BMI, suggesting incipient malnutrition-inflammation syndrome of renal failure.

We did not find different genotype distribution between albuminuric or normoalbuminuric subjects, but the power of the study to detect such dif-

ferences was only 0.47. However, we might speculate that the detected difference in plasma adiponectin might also be attributed to other factors. First, albuminuric patients have significantly lower GFR. Adiponectin is excreted and catabolized in the kidney and its level is known to increase with decreasing renal function (24-27). Secondly, there might be a reactive increase in adiponectin synthesis secondary to the inflammation associated to diabetic kidney disease, in an effort to restore renal physiology (26), as adiponectin has been shown to have antiproteinuric and nephroprotective effects (29, 30). This is in line with the results of the logistic regression that designate plasma adiponectin but not genotype as predictor for the presence of albuminuria, along with systolic blood pressure and age.

We recognize the limitation of the study due to the relatively low number of patients, especially in the homozygous mutant group. However, to our knowledge this is the first report of 45 G>T polymorphism in Romania and further studies are needed.

Conclusion

The 45T>G adiponectin polymorphism did not influence plasma adiponectin levels in our cohort of type 2 diabetic patients.

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Conflict of interest: none declared

Abbreviations

ADIPOQ - Adiponectin Gene
BMI - Body mass index
CI - Confidence Intervals
CRP - C-reactive protein
DBP - Diastolic blood pressure
GFR - Glomerular filtration rate estimated according to the Modification of Diet in Renal Disease Formula
HDL - High density lipoprotein
LDL - Low density lipoprotein
OR - Odds Ratio
PCR-RFLP - Polymerase Chain Reaction – Restriction Fragments Length Polymorphism
SBP - Systolic blood pressure

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