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Adiponectin gene variants and the risk of coronary artery disease in patients with type 2 diabetes

Nasser M. Al-Daghri · Omar S. Al-Attas · Majed S. Alokail · Khalid M. Alkharfy · Tajamul Hussain

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Abstract Patients with type 2 diabetes (T2D) are more susceptible to develop cardiovascular complications than non-diabetic subjects. Several studies have indicated a role of adiponectin gene in the increased coronary artery disease (CAD) risk in T2D patients. The data however is limited and have been inconsistent. In this study we examined the association of SNP45T>G and SNP276G>T of adiponectin gene with CAD risk in T2D patients in a Saudi population. A total of 418 type 2 diabetic patients were randomly recruited in this study from the RIYADH COHORT. Of the total diabetes patients, 123 were also diagnosed to have CAD, while the rest were control subjects. Anthropometric, clinical and biochemical parameters were measured by standard procedures. Genotyping of polymorphisms was carried out by PCR–RFLP analysis. Genotype distribution of SNP45T>G was significantly ($P = 0.005$) different between control and CAD subjects, while the distribution of SNP276G>T genotypes was comparable between the subjects. The SNP45T>G was significantly associated with risk of CAD [OR (95% CI), 4.7 (1.6–13.5), $P < 0.003$] but not SNP276G>T [OR (95% CI), 1.02 (0.53–1.9), $P > 0.05$]. The association of SNP45T>G with CAD risk remained significant even after adjusting for potential confounding factors [OR (95% CI), 7.2 (1.1–45.9), $P < 0.05$]. The SNP45T>G of adiponectin gene is an independent risk factor for CAD in T2D patients in a Saudi population. These findings support a role for adiponectin gene in the increased CAD risk in diabetes patients and are consistent with genetic heterogeneity in the association between adiponectin gene and coronary artery disease.

Keywords Adiponectin · Polymorphisms · Coronary artery disease · Type 2 diabetes

N. M. Al-Daghri (✉) · O. S. Al-Attas · M. S. Alokail · T. Hussain
Department of Biochemistry, College of Science, King Saud University, PO Box 2455, Riyadh 11451, Saudi Arabia
e-mail: nasseraldaghri@hotmail.com

K. M. Alkharfy
Department of Clinical Pharmacy, College of Pharmacy, King Saud University, Riyadh, Saudi Arabia

Introduction

Adiponectin, the most abundant adipose tissue derived protein is linked to the incidence of cardiovascular diseases (CVD) in patients with type 2 diabetes (T2D). The protective effect of adiponectin has been attributed mainly to its anti atherogenic, anti-inflammatory and insulin sensitizing properties [1–5]. Adiponectin is encoded by adiponectin gene, ADIPOQ, located on chromosome region 3q27 [6], where a susceptibility locus for T2D [7, 8] and the cardiovascular risk factors [9, 10] has been mapped. Moreover, serum adiponectin concentrations are highly heritable and are linked to adiponectin gene [11, 12], underlining the importance of studying adiponectin gene as a candidate in understanding the genetic basis of cardiovascular risk in type 2 diabetes patients. Accordingly, several single nucleotide polymorphisms (SNPs) in the adiponectin gene have been examined for their associations with CVD risk in diabetes patients [13]. Of all, SNPs at 45T>G in exon 2 and 276G>T in intron 2 of adiponectin gene are commonly studied and are linked to CVD risk in T2D patients [14–17]. However, the data is limited and have been inconsistent. The SNP276G>T is shown to be associated with decreased coronary artery disease (CAD)

risk in T2D men and women in Italian population [14]. Similarly, T2D patients carrying the SNP276G>T are at a lower risk to develop CVD in an American men [15]. However, this effect was seen only in men [15] but not in women [18]. In contrast, the SNP276G>T is reported to be associated with an increased CAD risk in the same Italian population [19]. In both Italian and American studies, the SNP45T>G is not a significant determinant of CVD risk in T2D subjects. Unlike above reports, SNP45T>G is a risk factor for increased CAD risk in T2D patients in French and Swiss T2D populations [16] and for carotid artery plaques in Korean T2D patients [17]. Collectively, above data indicate an ambiguity in the associations between adiponectin gene and CAD risk in patients with preexisting diabetes. Among the several confounding factors, ethnicity can significantly modulate the genetic heterogeneity and thus can contribute to discrepancies in the association studies. Thus, in this study our aim is to examine whether 45T>G and 276T>G SNPs of adiponectin gene have any role in the CAD risk either independently or through gene-environmental interactions in T2D patients in a Saudi ethnic population and whether this information can be of help to identify the subjects genetically predisposed to develop CAD.

Materials and methods

Subjects

A total of 418 randomly selected Saudi T2D patients that are part of the Biomarker Screening in Riyadh Project (RIYADH COHORT), a capital-wide epidemiologic study taken from over 10,000 consenting Saudis coming from different Primary Health Care Centers (PHCCs) were included. Of the total diabetic patients, 123 were diagnosed to have CAD by angiography, which was defined as having at least one major coronary artery showing more than 50% of stenosis. Those without CAD were considered as control subjects, defined as those who were asymptomatic and had no signs of myocardial ischemia as determined by electrocardiogram (ECG), negative cardiovascular history and normal exercise treadmill test. Subclinical CAD in the diabetic patients was ruled out by the structured questionnaire and ECG. A standard questionnaire was obtained from all patients, collecting the information on ethnicity, medical history, smoking habits, presence or absence of hypertension, dyslipidemia and current medications. Ex-smokers who stopped smoking within 1 year of the commencement of the study were excluded. Study was conducted in accordance with the guidelines set by the Ethics Committee of the Research Center, College of Science, King Saud University, Riyadh, Saudi Arabia.

Clinical and biochemical measurements

Fasting blood samples were collected at their respective PHCCs and were delivered immediately in iced (0–4°C) non-heparinized tubes to the Biomarkers Research Program (BRP) in King Saud University, Riyadh, Saudi Arabia. Clinical and biochemical parameters were measured by the standard laboratory procedures. Body mass index (BMI) was calculated as weight in kilograms divided by the square of height in meters. Subjects with systolic blood pressure above 140 mmHg and/or diastolic blood pressure above 90 mmHg, measured at different time intervals and currently taking anti-hypertensive medication were considered to be hypertensive. Fasting plasma glucose, triglycerides, total and HDL-cholesterol were measured by clinical chemistry auto analyzer (KoneLab, UK). Insulin was analyzed by a solid phase enzyme amplified sensitivity immunoassay (Medgenix INS-ELISA, Biosource, Belgium). Smoking indicates the current smokers. Individuals were defined as dyslipidemic if their total cholesterol concentration was more than 220 mg/dl and/or their triglyceride concentration was more than 200 mg/dl. Homeostasis model assessment for insulin resistance (HOMA-IR) was utilized to evaluate insulin resistance and was calculated as the product of glucose (mmol/l) and insulin (uμl/ml)/22.5.

Genotyping

The two SNPs, a T>G substitution at +45 in exon 2 (45T>G) and a G>T substitution at +276 in intron 2 (276G>T) of adiponectin gene were genotyped by PCR amplification of peripheral blood genomic DNA extracted using Blood genomic prep mini spin kit (GE Health Care, Buckinghamshire, UK) followed by restriction enzyme digestion. Briefly, for 45T>G polymorphism analysis, DNA was amplified using the forward primer, 5′-GAAGTAGACTCTGCT GAGATGG-3′ and the reverse primer, 5′-TATCAGTGT AGGAGGTCTGTGATG-3′. The amplified products were digested with restriction enzyme, *Sma*I (Fermentas, Germany) and the genotypes were ascertained by agarose gel electrophoresis. For 276G>T polymorphism, DNA was PCR amplified using the forward primer, 5′-GGCCTCTTTC ATCACAGACC-3′ and the reverse primer, 5′-AGATGC AGCAAAGCCAAAGT-3′. The amplified products were digested with restriction enzyme, *Mva*1269I (Fermentas, Germany).

Statistical analysis

Variables among the groups were compared by Student's independent *t*-test with log and square root transformation

where applicable. Frequency distribution of genotypes between the groups was done by χ^2 test. Multinomial logistic regression analysis using the presence of CAD as dependent variable and other risk factors as independent variables was used to determine odd ratios. Significance was set at $P < 0.05$, and data was analyzed using SPSS version 11.5 (SPSS Inc., Chicago, IL, USA).

Results

Basic parameters in control and coronary artery disease patients

Anthropometric, clinical and biochemical parameters in CAD and control subjects are presented in Table 1. CAD subjects were significantly older and had higher systolic blood pressure, hypertension, HDL-cholesterol and waist circumference than control. On the other hand, total cholesterol and diastolic blood pressure were decreased in CAD subjects compared to control. No significant differences were found in fasting glucose, insulin, HOMA-IR, triglycerides, BMI, and LDL-cholesterol, between CAD and control subjects. Also non-smokers and smokers were comparable between the groups.

Table 1 Basic characteristics of control and CAD subjects

Parameters	Control	CAD	*P*-value
N	297	123	
Age	60.7 ± 11.6	69.4 ± 9.8	<0.001
Gender (male)	207 (70.0)	74 (60)	0.07
Smoking, *n* (%)	120 (60.0)	70 (57)	0.08
Hypertension, *n* (%)	70 (23.5)	44 (35.7)	0.01
Dyslipidemia, *n* (%)	138 (46.4)	53 (43.0)	0.60
BMI (kg/m^2)	30.3 ± 6.2	32.2 ± 8.0	0.22
WC (cm)	96.7 ± 22.5	105.2 ± 17.7	0.002
Hips (cm)	100.0 ± 25.8	105.4 ± 17.6	0.067
Systolic (mmHg)	127.7 ± 16.6	137.2 ± 17.7	<0.0001
Diastolic (mmHg)	80.7 ± 9.4	78.0 ± 105	0.038
Glucose (mmol/l)	9.4 ± 1.5	8.9 ± 1.4	0.062
Insulin (μU/ml)	12.4 ± 2.2	11.6 ± 2.9	0.083
HOMA-IR	4.3 ± 2.3	4.16 ± 1.8	0.091
Cholesterol (mmol/l)	5.2 ± 1.1	4.4 ± 0.93	<0.001
LDL-cholesterol (mmol/l)	3.5 ± 1.0	3.3 ± 1.13	0.07
HDL-cholesterol (mmol/l)	0.76 ± 0.03	0.96 ± 0.02	<0.001
Triglyceride (mmol/l)	1.8 ± 0.14	1.3 ± 0.11	0.101

Data represent mean ± SD, Groups were compared by *t*-test

WC waist circumference, *BMI* body mass index, *HOMA-IR* homeostasis model assessment-insulin resistance

Table 2 Genotype distribution of 45T>G and 276G>T SNPs of adiponectin gene in control and CAD subjects

SNPs	Genotype	Control	Frequency	CAD	Frequency	*P*
45T>G	TT	220 (73.8%)		77 (63.1%)		
	TG	72 (24.1%)	0.14[a]	35 (28.7)	0.22[a]	0.005
	GG	6 (2.1%)		10 (8.2%)		
276G>T	GG	111 (37.4%)		47 (38.2%)		
	GT	142 (47.8%)	0.39[a]	57 (46.4%)	0.39[a]	0.96
	TT	44 (14.8%)		19 (15.4%)		

Comparison of genotypes was done by χ^2 test

[a] Minor allele frequency

Genotype distribution of 45T>G and 276G>T SNPs of adiponectin gene

We compared the genotype distribution of SNPs 45T>G and 276G>T of ADIPOQ in CAD and control subjects to examine if they are significantly related to CAD in T2D patients. Distribution frequencies of 45T>G and 276G>T polymorphisms among the CAD and control subjects are shown in Table 2. Genotype frequencies of both the polymorphisms satisfied the Hardy–Weinberg equilibrium. Frequency of TT, TG and GG genotypes of 45T>G SNP was significantly different between CAD and control subjects with GG genotype being significantly associated with CAD as opposed to control (8.2 vs. 2.1%, $P < 0.005$), while the genotype frequencies of SNP276G>T between CAD and control groups were comparable with TT frequencies to be 15.4 and 14.8% ($P = 0.96$) in CAD and control subjects respectively.

Coronary artery disease risk in patients with diabetes

We also assessed the association of SNPs 45T>G and 276G>T of ADIPOQ gene with the risk of developing CAD in T2D patients. The odds ratios indicating the association of SNPs with CAD are presented in Table 3. Significant association was found between 45T>G polymorphism and the incidence of CAD with the odds ratios (OR) of 4.7 for TT vs. GG (95% CI 1.6–13.5, $P < 0.003$), and 1.64 for TT vs. TG + GG (95% CI 1.05–2.5, $P < 0.029$), while no significant association was found between TT vs. TG genotypes with OR of 1.38 (95% CI 0.85–2.2, $P = 0.18$). Association between 276G>T polymorphism and CAD risk in the diabetes patients was not statistically significant with OR of 1.02 for GG vs.TT (95% CI 0.5–1.9, $P = 0.95$), 0.96 for GG vs. GT + TT (95% CI 0.62–1.4, $P < 0.87$) and 0.94 for GG vs. GT (95% CI 0.6–1.5, $P = 0.87$). We further evaluated the association of 45T>G SNP with the CAD risk after adjusting for potential risk factors including the male gender, age, smoking status,

Table 3 Unadjusted odds ratios for CAD among carriers of 45T>G and 276G>T polymorphisms of ADIPOQ

45T>G	Reference category	Odds ratio (95% CI)	*P*-value
TG	TT	1.38 (0.85,2.2)	0.180
GG	TT	4.7 (1.6,13.5)	0.003
TG + GG	TT	1.64 (1.05,2.5)	0.029
276G>T			
GT	GG	0.94 (0.6,1.5)	0.82
TT	GG	1.02 (0.5,1.9)	0.95
GT + TT	GG	0.96 (0.62,1.4)	0.87

Odds ratios (95% confidence intervals)

dyslipidemia, hypertension and the combinations therein (Table 4). We found that SNP45T>G was significantly linked to CAD risk even after adjusting for the potential risk factors for TT vs. GG ($P < 0.05$) or TT vs. TG + GG genotypes combined ($P < 0.05$). Contrarily, SNP 276G>T was not associated with CAD risk before or after adjusting for risk factors (Table 5).

Discussion

Adiponectin is a major modulator of insulin sensitivity and possesses antiatherogenic and anti-inflammatory properties [4]. This has corroborated with the reports identifying the role of adiponectin in the development of metabolic syndrome, T2D, CVD and of metabolic comorbidities [3, 13, 20]. Patients with T2D are suggested to be more prone to develop CAD than non diabetic subjects. Several genetic studies have linked this increased CAD risk to adiponectin gene variants and found this association to be either independent or dependent of gene-environmental interactions. However, the data have been inconsistent in relation to the association of genotypes and/or the type of allele per se that is associated with the CAD risk in diabetes patients. Among the several possible confounding factors, ethnicity can be a major determinant of genetic variability affecting the outcome of the disease. Thus, in this study we examined whether 45T>G and 276G>T SNPs of adiponectin gene contribute to CAD risk in T2D patients in a Saudi ethnic population. In the present study, we found that distribution of GG genotype of SNP45T>G was significantly

Table 4 Odds ratios for cardiovascular risk factors by genotypes of 45T>G SNP of ADIPOQ gene in control and CAD subjects

	TG	GG	TG + GG
Crude OR	1.38 (0.85,2.2)	4.7 (1.6,13.5)*	1.64 (1.05,2.5)*
Age, years (A)	1.3 (0.83,2.2)	5.4 (1.7,16.3)*	1.6 (1.04,2.6)*
Males (G)	1.38 (0.83,2.2)	5.4 (1.7,16.3)*	1.6 (1.07,2.6)*
Hypertension (H)	1.54 (0.87,2.7)	6.3 (1.07,36.8)*	1.69 (0.98,2.9)
Dyslipidemia (D)	1.35 (0.83,2.2)	4.3 (1.5,12.4)*	1.6 (1.0,2.5)*
Smoking (S)	1.03 (0.84,1.9)	3.76 (1.1,12.8)*	1.7 (1.01, 2.14)[b]
A + G + H	1.5 (0.8,2.8)	7.8 (1.2,49.6)*	1.7 (1.0,3.14)*
A + G + D	1.37 (0.81,2.3)	5.03 (1.6,15.3)*	1.6 (1.02,2.7)*
A + G + S	1.43 (0.88,2.1)	4.51 (1.8,19.4)*	1.59 (1.11,2.1)[c]
A + G + H + D	1.5 (0.84,2.8)	7.2 (1.1,45.9)*	1.72 (0.96,3.08)

Data expressed as OR (95% CI)

*$P < 0.05$

[b] $P = 0.057$

[c] $P = 0.06$

Table 5 Odds ratios for cardiovascular risk factors by genotypes of 276G>T SNP of ADIPOQ gene in control and CAD subjects

	GT	TT	GT + TT
Crude OR	0.94 (0.59,1.5)	1.02 (0.53,1.9)	0.96 (0.62,1.48)
Age, years (A)	0.93 (0.58,1.5)	0.90 (0.46,1.7)	0.92 (0.59,1.46)
Males (G)	0.94 (0.59,1.5)	0.98 (0.51,1.8)	0.95 (0.61,1.47)
Hypertension (H)	0.66 (0.38,1.1)	0.58 (0.24,1.3)	0.64 (0.38,1.09)
Dyslipidemia (D)	1.0 (0.54,1.96)	1.03 (0.54,1.9)	1.01 (0.65,1.56)
Smoking (S)	0.89 (0.51, 1.62)	1.12 (0.88,2.2)	1.36 (0.81,2.2)
A + G+ H	0.65 (0.36,1.17)	0.49 (0.20,1.18)	0.61 (0.35,1.06)
A + G + D	0.96 (0.58,1.58)	0.82 (0.41,1.6)	0.92 (0.58,1.47)
A + G + S	1.07 (0.65,1.2)	1.05 (0.86,8.7)	1.18 (0.94,2.3)
A + G + H + D	0.71 (0.39,1.2)	0.49 (0.20,1.19)	0.65 (0.37,1.14)

Data expressed as OR (95% CI)

different in T2D subjects with CAD as compared to those without CAD. Moreover, SNP45T>G was significantly associated with the incidence of CAD in T2D patients. Importantly this association remained significant even after adjusting for several classical CAD risk factors, suggesting that SNP45T>G can independently alter the CAD risk in diabetic patients. However, the possibility of risk factors other than those accounted in this study to affect the CAD risk can not be ruled out. On the other hand, distribution of SNP276G>T genotypes was not different between the T2D patients with CAD and those without CAD in our study. Further, no association was found between SNP276G>T and CAD risk among T2D patients irrespective of the adjustment of risk factors, implying that this genetic variant is unlikely to play a role in the CAD etiology in the studied T2D patients. Our findings are consistent with several studies. The SNP45T>G is associated with CAD risk in T2D patients in Swiss and French populations [16] and with carotid artery plaques in T2D patients in a Korean population [17]. Moreover, in these studies the correlation between the 45T>G SNP and CAD risk was independent of several risk factors. Matching with our data, both these reports have indicated the lack of an association of SNP276G>T with CAD risk in T2D patients. Our study, however, contrasts with several other studies. In an Italian study, the T allele of SNP276G>T of ADIPOQ was found to be associated with the reduced CAD risk in diabetic men and women, while no association was observed in the case of SNP45T>G [14]. Similarly, the same allele of SNP276G>T had a protective role for CVD in diabetic men but not women in an American population [15]. However, in this population, a common haplotype encompassing SNP276G>T is linked to lower CAD risk in diabetic women [18]. In contrast to above studies, SNP276G>T is reported to be a major risk factor for CAD in an Italian population [19]. Taken together, above data clearly indicate the ambiguity in the association studies involving 45T>G and 276G>T SNPs and CAD risk in T2D patients. The inconsistency in these studies can possibly be explained by differences in sample size, environmental exposure or genetic heterogeneity because of different ethnic backgrounds.

Studies examining the effect of 45T>G SNP on adiponectin gene expression have been inconsistent [17, 21–26]. Since we did not measure the adiponectin levels in the studied subjects, it is not clear whether 45T>G variant resulted in a variable adiponectin gene expression. The 45T>G SNP is a silent substitution (Gly15Gly) within exon 2 of the adiponectin gene, which does not lead to amino acid change, [27] and thus unlikely contribute to variable adiponectin gene expression or modify the biological properties of adiponectin protein. The SNP 45T>G is also suggested to be in linkage disequilibrium with other functional variants as the effect of this SNP on adiponectin protein is seen when it is in linkage disequilibrium with −11377 and −11391 SNPs of the 5′ promoter region [28]. Importantly, it is reported that linkage disequilibrium structures may vary between the populations [11, 29], possibly explaining the inconsistency associated with SNP 45T>G and adiponectin levels. Alternatively, SNP45T>G might be a marker for variant in 3′ UTR region through linkage disequilibrium, which can lead to accelerated degradation of mRNA resulting in decreased adiponectin levels [30]. However, several attributes can make SNP45T>G to independently influence the adiponectin expression. It is possible for this exonic SNP to affect the mRNA splicing and alter the protein levels [31]. Additionally, decreased adiponectin transcripts are reported owing to allele specific differential expression related to 45T>G SNP in human omental adipose tissue [26] indicating the participation of this variant in deciding the adiponectin levels.

Taken together our data demonstrate that 45T>G SNP is significantly associated with the increased CAD risk in T2D patients independent of potential confounding factors and suggest that preexisting diabetes state may confer the increased CAD risk in individuals harboring the 45T>G polymorphism of adiponectin gene. Further, no association was found between 276G>T SNP and CAD risk among the diabetic patients. To our knowledge this is the first study to show the association of adiponectin gene polymorphisms with CAD risk in T2D patients in a Saudi ethnic population. Our findings are consistent with the existence of population based genetic variability with respect to adiponectin gene and CAD risk in T2D.

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