The Impact of Adiponectin Gene Polymorphisms on the Insulin Resistance Index in Patients with Diabetes and Newly Diagnosed Type 2 Diabetes

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Keywords

Adiponectin · Insulin resistance · Anthropometric and metabolic characteristics · Diabetes

Abstract

Background: Some adipokine hormones can affect both human and animal models of insulin resistance. **Aims:** This study was conducted to assess the association between rs17300539 and rs266729 of the adiponectin gene and insulin resistance and anthropometric and metabolic characteristics in impaired fasting glucose (IFG)/type 2 diabetes mellitus (T2DM) and nondiabetic participants. **Methods:** DNA was extracted from 80 participants with fasting blood sugar (FBS) <100 mg/dL in nondiabetics and 80 participants with FBS ≥100 mg/dL in the IFG/T2DM group. Genotyping was performed using a polymerase chain reaction-restriction fragment length polymorphism assay. Statistical analysis was performed using SPSS software version 20. Insulin and adiponectin hormone were measured using enzyme-linked

immunosorbent assay and other biochemical variables were determined using the standard methods. **Results:** The levels of homeostatic model assessment of insulin resistance (HOMA-IR) between the IFG/T2DM and the nondiabetic group were significantly different (IFG/T2DM = 3.27, nondiabetic = 1.71; $p < 0.001$). The frequency of the GA genotype of rs17300539 was higher in the insulin-resistant (HOMA-IR ≥2.6, 29.7%) than in the insulin-sensitive group (HOMA-IR <2.6, 18.4%) and the GG genotype were more frequent in the insulin-sensitive group (81.6%); however, it had a marginal association ($p = 0.07$). This association was not statistically significant for rs266729. HOMA-IR had a positive correlation with triglyceride (TG) and total cholesterol (TC) and was negatively correlated with adiponectin level. **Conclusion:** IFG/T2DM patients have a higher level of HOMA-IR in comparison with nondiabetics. The genotype of GA in rs17300539 increases the risk of HOMA-IR. HOMA-IR has a positive correlation with TC and TG. Moreover, HOMA-IR increases the risk of T2DM.

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Introduction

Diabetes mellitus accounts for 8.4% of all mortalities worldwide [1]. Type 2 diabetes mellitus (T2DM), the predominant type of diabetes mellitus, is caused by decreased physical activity and genetic factors [2]. The International Diabetes Federation stated that 415 million people had diabetes in 2015, with the largest adult diabetic population living across the Middle East and North Africa region [3]. In this regard, it was estimated that 8% of the Iranian population had diabetes in 2010 [4]. The prediabetes rate increases in parallel with diabetes and coincides with the presence of impaired fasting glucose (IFG). IFG contributes to the condition where plasma glucose level is above normal, but still lower than in people categorized to be diabetic [5]. Glucose intolerance, hypertension, dyslipidemia, and central obesity with insulin resistance are the components of metabolic syndrome and the risk factors of T2DM [6]. Insulin resistance is referred to as a condition where peripheral tissue show a lower response to the presence of insulin. This hormone, which is secreted by pancreatic beta cells, keeps the glucose level in a normal range. Lack of proper circulation of insulin in the body leads to some metabolic disorders, such as T2DM [7].

In recent studies, it has been proved that the levels of some adipokine hormones can modulate insulin sensitivity and influence insulin resistance [8]. Adiponectin (also known as AdipoQ or apM1) is a 244-amino-acid protein that is mostly secreted by adipose tissue and encoded by the APM1 gene. The adiponectin gene spans 17 kb on chromosome locus 3q27, which is a susceptible locus for T2DM and metabolic syndrome [9]. According to genome-wide association studies, T2DM has strong genetic roots. Recently, rs266729 and rs17300539 in the promoter of the ADIPOQ gene on T2DM have been widely studied [10–13].

The aim of the current study was to investigate the association of rs266729 and rs17300539 with insulin resistance in diabetic and prediabetic patients with no history of metabolic drug usage such as metformin, which changes the level of homeostatic model assessment of insulin resistance (HOMA-IR).

Materials and Methods

A case-control study was conducted on 160 participants with an age range of 20–70 years. The subjects were categorized into two groups: (1) the nondiabetic group (fasting blood sug-

ar [FBS] <100 mg/dL) with 80 participants and (2) the IFG/T2DM (IFG or newly diagnosed T2DM) group (FBS ≥100 mg/dL) with 80 participants referred to Bu Ali Hospital, Tehran, Iran. The diagnostic criteria were based on the diabetes guidelines published in 2003 [14]. The exclusion criteria in both groups were the following: diabetic drug consumption, pregnancy, suffering from chronic kidney disease, any type of liver problem, any type of cancer, acute illness, autoimmune disease, and infection. Additionally, participants with missing data were excluded from statistical analysis. Subsequently, the participants were questioned concerning their demographic information. Weight (in kg) was measured in the standing position using a calibrated balance (without shoes,) while height was measured using a rigid tape. Body mass index (BMI) was measured using the standard equation of the World Health Organization [15].

DNA was extracted from blood samples using a standard salting-out method [16]. Polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) was done in order to discover single nucleotide polymorphisms of the adiponectin gene. PCR was carried out in 25 µL of PCR master mix (Amplicon Co., Denmark) and 0.9 µL forward (5'-AGG CTC TGT GTG GAC TGT GGA-3') and reverse (5'-CCT GGA GAA CTG GAA GCT GC-3') primers. Both targeted single nucleotide polymorphisms (rs266729 and rs17300539) can be amplified by one pair of primers. The PCR reaction was performed in 30 cycles as follows: initial denaturation at 94 °C for 5 min, denaturation at 94 °C for 45 s, annealing at 65 °C for 45 s, extension at 72 °C for another 60 s, and a final extension at 72 °C for 10 min. The validity of PCR was approved using 8% acrylamide gel electrophoresis. Then, the PCR products were digested by MSPI and HhaI, which were detected to be rs17300539 and rs266729, respectively. Both enzymes were purchased from Cinnagen Co. The RFLP-produced patterns of rs17300539 have been described before [17].

Adiponectin and insulin levels were measured using a commercially available human enzyme-linked immunosorbent assay kit (Mercodia, Sweden). Triglyceride (TG), high-density lipoprotein (HDL), total cholesterol (TC), and FBS levels were measured by an enzyme colorimetric method. Low-density lipoprotein was measured by the Friedewald formula [18]. HOMA-IR was determined using the following equation: $\text{HOMA-IR} = \text{fasting insulin (mU/L)} \times \text{FBS (mmol/L)} / 22.5$. To define IR, a threshold of 2.6 was used based on previous studies [19]. Continuous variables with normal distribution and skewed variables were illustrated as mean $\pm$ standard deviation and median (interquartile range), respectively. Categorical variables were illustrated as percentage. Genotype distributions of the nondiabetics were calculated using Hardy-Weinberg equilibrium. Linear regression analyses were performed for the association of HOMA-IR and anthropometric or metabolic characteristics. Associations between HOMA-IR with skewed distribution and anthropometric or metabolic characteristics were evaluated by the Spearman correlation coefficient. Continuous variables with normal distribution were analyzed using the independent-sample *t* test. Continuous variables with skewed distribution were analyzed using the Mann-Whitney U test. Finally, categorical variables were analyzed using the χ^2 test. Statistical evaluation was carried out using the SPSS software version 20 (SPSS, Chicago, IL, USA). The significance level was considered as $p < 0.05$.

Table 1. Clinical characteristics of the study participants

Variable	IFG/T2DM (<i>n</i> = 80)	Nondiabetic (<i>n</i> = 80)	<i>p</i> value
Age, years	52.9±13.1	36.9±11.7	<0.001*
BMI, kg/m ²	28.29±6.14	25.09±4.70	<0.001*
WC, cm	96.3±12.6	103.1±13.1	0.006*
HC, cm	105.2±14.6	96.9±15.7	0.004*
HDL, mg/dL	46 (34–54)	47 (40.2–57)	0.232
LDL, mg/dL	115.3±42.0	104.3±23.2	0.143
TC, mg/dL	185±49	166.8±40.1	0.055
TG, mg/dL	138 (98.7–202)	95.5 (83.2–161.2)	0.012*
FBS, mg/dL	165.5±59.8	87.8±8.7	<0.001*
Insulin, mU/L	9.5 (6.1–15.3)	8.4 (5.5–13.9)	0.219
HOMA-IR, mol × μU/I ²	3.27 (2.42–5.82)	1.71 (1.17–2.97)	<0.001*
Adiponectin, μg/mL	6.6 (5.2–9.4)	7.4 (5.4–11.3)	0.115
Female sex	44 (55%)	55 (68.8%)	0.073

Values are presented as mean ± standard deviation, median (interquartile range), or *n* (%). BMI, body mass index; FBS, fasting blood sugar; HC, hip circumference; HDL, high-density lipoprotein; HOMA-IR, homeostatic model assessment of insulin resistance; IFG, impaired fasting glucose; LDL, low-density lipoprotein; T2DM, type 2 diabetes mellitus; TC, total cholesterol; TG, triglyceride; WC, waist circumference. * Significant at *p* < 0.05.

Results

The clinical characteristics of the IFG/T2DM group and the nondiabetic group of the study population are shown in Table 1. HOMA-IR was higher in the IFG/T2DM (3.27 mol × μU/I²) compared to the nondiabetic group (1.71 mol × μU/I²), suggesting a statistically significant difference between them (*p* < 0.001). The mean FBS was significantly higher in the T2DM/IFG compared to the nondiabetic group (nondiabetic = 88.5 mg/dL, IFG/T2DM = 146 mg/dL; *p* < 0.001). Also, the variables TG (mg/dL), age (years), BMI (kg/m²), waist circumference (WC, cm), and hip circumference (HC) (cm) were significantly different between IFG/T2DM and nondiabetic subjects.

Genetic Association with HOMA-IR

The ADIPOQ gene polymorphisms (rs17300539 and rs266729) were genotyped in all subjects. There was no significant difference concerning the genotype distribution or allelic frequencies between the insulin-resistant and non-insulin-resistant groups (*p* > 0.05), suggesting no association of genotype distribution or allelic frequencies with insulin resistance. The distribution of ADIPOQ gene polymorphisms among insulin-resistant (HOMA-IR <2.6) and non-insulin-resistant subjects (HOMA-IR ≥2.6) is presented in Table 2. The frequency of GG genotype in rs17300539 was higher in

insulin-sensitive participants (HOMA-IR <2.6) (81.6%) compared to the insulin-resistant group (HOMA-IR ≥2.6) (68.9%). Also, the frequency of GA genotype was higher (29.7%) in insulin-resistant subjects compared to insulin-sensitive subjects (18.4%), suggesting that the GA genotype is more frequent in the insulin-resistant group.

Correlations of HOMA-IR with Anthropometric and Metabolic Characteristics

HOMA-IR had a significant positive correlation with HC, age, and TG (*p* < 0.001, *p* = 0.007, and *p* < 0.001, respectively) and a significant negative correlation with adiponectin (*p* = 0.002). Data before adjustment for sex and age are not shown. Next, a linear regression analysis was done to assess the predictive factors of HOMA-IR in the participants. The parameters adiponectin, TC, and TG were significant predictors of HOMA-IR even after adjustment for sex and age (*p* = 0.025, *p* = 0.032, and *p* < 0.001, respectively) (Table 3).

Linear regression analysis was performed to assess the association of genotypes and alleles with HOMA-IR in the study population. The genotypes and alleles holding rs266729 had no significant association with HOMA-IR, while rs17300539 was marginally associated with HOMA-IR. Thus, it is inferred that in rs17300539, presence of allele A and genotype GG is associated with HOMA-IR (*p* = 0.06) (Table 4).

Table 2. Distribution of the ADIPOQ gene polymorphisms

Group	N	SNP	Genotypes			<i>p</i> value	Alleles		<i>p</i> value
		rs266729	CC	CG	GG		C	G	
IFG/T2DM	80		44 (56.4)	32 (41)	2 (2.6)	0.657	120 (76.9)	36 (23.1)	0.421
Control	80		50 (62.5)	29 (36.3)	1 (1.3)		129 (80.6)	31 (19.4)	
		SNP	Genotypes				Alleles		
		rs17300539	GG	GA	AA		G	A	
IFG/T2DM	80		49 (62.8)	27 (35.5)	2 (2.6)	0.001*	125 (80.1)	31 (19.9)	<0.001*
Control	80		71 (88.8)	9 (11.3)	0 (0)		151 (94.4)	9 (5.6)	
		SNP	Genotypes				Alleles		
		rs266729	CC	CG	GG		C	G	
HOMA-IR <2.6			48 (63.2)	28 (36.8)	0 (0)	0.192	124 (81.6)	28 (18.4)	0.212
HOMA-IR ≥2.6			41 (55.4)	30 (40.5)	3 (4.1)		112 (75.7)	36 (24.3)	
		SNP	Genotypes				Alleles		
		rs17300539	GG	GA	AA		G	A	
HOMA-IR <2.6			62 (81.6)	14 (18.4)	0 (0)	0.105	138 (90.8)	14 (9.2)	0.068
HOMA-IR ≥2.6			51 (68.9)	22 (29.7)	1 (1.1)		124 (83.8)	24 (16.2)	

Values are presented as *n* (%). HOMA-IR, homeostatic model assessment of insulin resistance; IFG, impaired fasting glucose; SNP, single nucleotide polymorphism; T2DM, type 2 diabetes mellitus. * Significant at *p* < 0.05.

Table 3. Regression coefficients for the relationship between anthropometric and metabolic characteristics and log insulin resistance index (HOMA-IR)

Variable	Univariate		Multivariate	
	standardized coefficient	<i>p</i> value	standardized coefficient	<i>p</i> value
Log adiponectin	-0.215	0.008*	-0.219	0.025*
BMI, kg/m ²	0.179	0.033*	0.147	0.130
WC	-0.027	0.775	-0.027	–
HC	0.196	0.039*	0.178	0.069
HDL	0.119	0.289	0.209	–
LDL	0.212	0.076	0.233	–
TC	0.242	0.023*	0.234	0.032*
Log TG	0.403	<0.001*	0.421	<0.001*

Multivariable linear regression models adjusted for age and sex. BMI, body mass index; HC, hip circumference; HDL, high-density lipoprotein; HOMA-IR, homeostatic model assessment of insulin resistance; LDL, low-density lipoprotein; TC, total cholesterol; WC, waist circumference. * Significant at *p* < 0.05.

Table 4. Regression coefficients for the relationship between adiponectin genotype and log insulin resistance index (HOMA-IR)

Genotype	Coefficient	Standard error	<i>p</i> value
rs266729			
G	0.052	0.058	0.376
CC	-0.052	0.058	0.376
CG	0.028	0.059	0.635
GG	0.298	0.203	0.145
rs17300539			
GG	-0.122	0.064	0.060
GA	0.113	0.065	0.085
AA	0.312	0.345	0.367
A	0.122	0.064	0.060

HOMA-IR, homeostatic model assessment of insulin resistance.

Table 5. Frequency of insulin resistance (HOMA-IR ≥ 2.6) and insulin sensitivity (HOMA-IR < 2.6) in the IFG/T2DM and the non-diabetic group

Group	Nondiabetic	IFG/T2DM	<i>p</i> value
HOMA-IR < 2.6	55 (68.8%)	22 (30.6%)	< 0.001
HOMA-IR ≥ 2.6	25 (31.2%)	50 (69.4%)	

Values are presented as *n* (%). HOMA-IR, homeostatic model assessment of insulin resistance; IFG, impaired fasting glucose; T2DM, type 2 diabetes mellitus.

Frequency of Insulin-Resistant and Insulin-Sensitive Participants in the Groups

The results in Table 5 indicate that the frequency of insulin-resistant participants (HOMA-IR ≥ 2.6) was higher in the IFG/T2DM (69.4%) compared to the non-diabetic group (31.2%), indicating a statistically significant difference ($p < 0.001$).

Discussion

This study was conducted to assess the possible association between rs17300539 and rs266729 of adiponectin gene with insulin resistance in a nondiabetic and an IFG/T2DM group.

HOMA-IR was higher in the IFG/T2DM compared to the nondiabetic group, indicating a statistically significant difference between them. HOMA-IR was significantly higher in diabetic and gestational diabetes mellitus patients compared to nondiabetic subjects in an Iranian population [20, 21]. Higher levels of BMI and WC were also seen in the IFG/T2DM compared to the nondiabetic group in our study; this difference was statistically significant as well. This association was similarly seen in Karachi (Pakistan), where the IFG group had higher BMI and WC compared to normal subjects [22].

In the current study, GG genotype and allele A (rs17300539) were marginally associated with HOMA-IR, and the frequency of GA genotype was higher in insulin-resistant participants. In contrast to our results, a study in Spain revealed that GG genotype (rs17300539) was also associated with higher HOMA-IR and increased the risk of insulin resistance in obese subjects [23]. In line with our study, GA and AA carriers in the Netherlands [24] and of European origin [25] had higher HOMA-IR. However, we found no association between rs266729

and HOMA-IR in our study. In the SHARE/SHARE-AP studies, rs266729 was not associated with HOMA-IR, but it was associated with HOMA-IR to an extent that exceeded its effect on adiponectin level [26]. Consistent with our findings, this result confirms the adiponectin level and may be associated with HOMA-IR in Arab families [27].

In our study, a significant positive correlation was found between insulin resistance and TG level. It seems that higher insulin resistance could increase the risk of TG in patients. This result is in accordance with the findings of Pourfarzam et al. [28] and Ren et al. [29]. Both TC/HDL and TG/HDL ratios were significantly correlated with insulin resistance [30] and TC [31, 32]. Our result confirmed that insulin resistance is negatively associated with adiponectin level. Consistent with our results, some studies showed that HOMA-IR is significantly inversely associated with adiponectin in an Iranian gestational diabetic population [20] and also in 107 Caucasian subjects with IFG/T2DM [31, 33], which is also consistent with our results.

We found that the frequency of HOMA-IR was higher in the IFG/T2DM group compared to nondiabetics, and this was statistically significant. HOMA-IR increases the risk of T2DM in American Indians [34]. In addition, consistent with our results, the frequency of prediabetic and diabetic subjects was lower in the insulin-sensitive and higher in the insulin-resistant group in African and European Americans [35].

In conclusion, it seems that nucleotide change in rs17300539 could play an important role in insulin resistance; however, rs266729 had no direct association with HOMA-IR. Furthermore, HOMA-IR increases the risk of T2DM.

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Statement of Ethics

The study protocol was in accordance with the Helsinki declaration and was approved by the research ethics committee of Islamic Azad University, Tehran Medical Branch. Written consent was obtained from all participants and is available upon request. No animal samples were used in this study.

Disclosure Statement

The authors declare that they have no conflict of interest.

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Author Contributions

All authors participated in preparation of the study. The manuscript was read and approved by all of the authors.

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