

## Gender-Specific Differences in the Association of Adiponectin Gene Polymorphisms with Body Mass Index

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### ■ Abstract

**OBJECTIVE:** Adiponectin gene polymorphisms are associated with obesity, metabolic syndrome and type 2 diabetes (T2D). The study evaluated possible associations of +45T/G and -11391G/A adiponectin gene polymorphisms with body mass index (BMI), waist circumferences (WC), and blood pressure in diabetic and non-diabetic Iranians. **METHODS:** This cross-sectional study involved two groups of subjects: 243 diabetic patients and 173 non-diabetic subjects recruited from Rafsanjan city in the south-east of Iran. **RESULTS:** No significant association was found between +45T/G and -11391G/A adiponectin gene polymorphisms and systolic or diastolic blood pressure. However, male carriers of the TT genotype of +45T/G had a significantly higher mean BMI

than male GG homozygotes ( $p = 0.018$ ). Also, male carriers of the GG genotype of -11391G/A had significantly higher mean BMI than male GA or AA homozygotes ( $p = 0.041$ ). Female carriers of the GG genotype of -11391G/A had significantly higher mean WC than female GA or AA homozygotes ( $p = 0.038$ ). **CONCLUSIONS:** We observed a significantly higher BMI in women, and GA or AA carriers of -11391G/A polymorphism. Also, there was a significantly lower WC in females and GG carriers of +45T/G. These results point to a gender-specific impact of the studied genotypes on BMI and WC.

**Keywords:** type 2 diabetes · adiponectin · polymorphism · body mass index · BMI · blood pressure · waist · gender · metabolic syndrome · polymerase chain reaction

### Introduction

 diponectin is an adipocyte-derived hormone with metabolic effects on glucose and lipid metabolism by improving the insulin action [1, 2]. The normal circulating adiponectin level is between 3 and 30  $\mu\text{g/ml}$  dependent on age and gender [3]. Its concentration is higher in women than men [4], and increases with age [5]. It seems that this gender effect is due to a direct effect of

androgens on the synthesis of adiponectin [6]. Serum adiponectin levels are negatively associated with body mass index (BMI) [7-9], waist circumferences (WC) [10], type 2 diabetes (T2D) [11], adverse features of metabolic syndrome [7, 8, 10, 12-15], and weight reduction [16].

The adiponectin gene has several variants. The prevalence of these variants has been studied in several populations including European, North American, and Japanese [17, 18]. The most com-

monly studied variants are -11391 G/A, -11377 C/G, +45 T/G and +276 G/T [17, 18]. Although these variants have shown associations with markers of metabolic syndrome, T2D, and cardiovascular disease, studies have shown different results due to sample discrepancies. For example in one French sample, -11391G represented a risk haplotype for diabetes [19, 20], but in another French sample, the G haplotype was the protective allele [21]. In yet another study, Hu *et al.* did not find an association between variants of adiponectin genes such as +45T/G and +276 G/T with T2D [22]. However, they found an association between +276 G/T and T2D, after adjustment for diabetes risk factors. In a study of diabetic Pima Indians, no association could be detected between adiponectin gene polymorphisms and T2D [23].

In an earlier study by our group (unpublished data), we did not find an association between +45T/G and -11391G/A polymorphisms of the adiponectin gene with T2D in an Iranian population. Similar results were found in a Korean population study by Lee *et al.* who examined the distribution of single nucleotide polymorphism (SNP) +45 T/G and SNP +76 G/T frequencies [24]. However, in another study, it was found that some of the adiponectin gene polymorphisms were associated with diabetes, in a gender-dependent manner [25]. Therefore, in present study of an Iranian population, we aimed to evaluate the association between +45T/G and -11391G/A polymorphisms of the adiponectin gene, with BMI, WC, and blood pressure in consideration of gender.

## Patients and methods

### Study population

The present study involved two cross sections: firstly, 243 T2D patients randomly recruited from a diabetes clinic in Rafsanjan (in south-east of Iran), and secondly, 173 non-diabetic subjects from the same area. T2D was diagnosed according to American Diabetes Association criteria [26]. All included patients had Fars origin.

After obtaining informed consent, we filled a personal and demographic questionnaire. Then, height, weight, WC, and blood pressure were recorded. Height and weight were used to calculate BMI in units of kg/m<sup>2</sup>. WC measurement was carried out in standing position, taking the greatest value obtained between the margin of lower limb and iliac crest. All measurements were carried out in metric (cm), by the same investigator. Systolic

and diastolic blood pressures were measured at the right arm in sitting position after 5-10 minutes rest. Venous blood samples (3-5 ml) were collected in EDTA tubes, stored at -20°C for DNA extraction.

This study was approved by the Ethics Committee of Tehran University of Medical Sciences of Iran.

### Abbreviations:

A	- adenine
ADIPOQ	- G/T intron 2 adiponectin gene
ANOVA	- analysis of variance
Arg	- arginine
BMI	- body mass index
C	- cytosine
DNA	- deoxyribonucleic acid
EDTA	- ethylenediaminetetraacetic acid
F3	- coagulation factor III
G	- guanine
Gly	- glycine
MspI	- <i>Moraxella</i> species isoschizomer (restriction enzyme)
PCR	- polymerase chain reaction
PON1	- A/G Arg 160Gly paroxonase 1 gene
RFLP	- restriction fragment length polymorphism
SD	- standard deviation
SNP	- single nucleotide polymorphism
SPSS	- statistical package for the social sciences
T2D	- type 2 diabetes
THBS2	- 3'UTR T/G thrombospondin 2 gene
T	- thymine
WC	- waist circumferences

### DNA extraction and genotyping

DNA was extracted from anticoagulated blood collected in EDTA using the salting out method. Molecular analysis of +45T/G adiponectin gene polymorphism was performed based on standard assay, as described by Schaffler *et al.* [27]. We have developed a polymerase chain reaction (PCR) restriction fragment length polymorphism (RFLP) assay for genotyping the -11391 polymorphism. The following primers were designed: forward: CATC AGAA TGTG TGGC TTGC. Reverse: AGAA GCAG CCTG GAGA ACTG.

MspI restriction endonuclease was used to digest the PCR product, yielding DNA fragments of 137 and 26 base pairs when the G allele was present. It made 163 bps of undigested PCR product when the A allele was present. The products of the digest were then visualized on a 3.5% agarose gel stained with ethidium bromide.

### Statistical analysis

We used *t*-test, one-way ANOVA with Bonferroni post-hoc tests, and chi-squared test for analysis. Also, we used univariate and multivariate

**Table 1.** Genotype frequencies of +45 T/G and -11391 G/A in diabetic and non-diabetic Iranians

Genotype	Diabetes	Non-diabetes	p-value
<b>+45TT/TG/GG</b>			
Total	171/63/7	117/47/9	NS
Men	48/20/2	88/35/7	NS
Women	123/43/5	29/11/2	NS
<b>-11391GG/GA/AA</b>			
Total	227/15/1	92/7/0	NS
Men	66/4/0	54/4/0	NS
Women	161/11/1	38/3/0	NS

**Legend:** Data are numbers of subjects with either +45TT/TG/GG or -11391GG/GA/AA genotype.  $p \leq 0.05$  in chi-square test is considered as significant. NS: not significant.

ate linear regression models to adjust for gender, T2D, and different carriers of +45T/G and -11391 G/A polymorphisms of the adiponectin gene. Outcome variables included: BMI, WC, systolic or diastolic blood pressure. All independent variables which had  $p < 0.1$  in the univariate model, were selected for the multivariate model. The analysis was performed by SPSS version 16 and STATA version 10.  $p \leq 0.05$  was considered a statistically significant difference.

## Results

### *Baseline characteristics of diabetic and non-diabetic subjects*

Mean  $\pm$  standard deviation (SD) of age in the participants was  $53 \pm 10.5$  years and  $51 \pm 14$  years, in diabetic patients and non-diabetic subjects, respectively. BMI was  $27 \pm 4$  kg/m<sup>2</sup> in diabetics, and  $26 \pm 4$  kg/m<sup>2</sup> in non-diabetics. For (systolic/diastolic) blood pressure, we observed ( $135 \pm 21/84 \pm 10$  mmHg) in the diabetes group and ( $126 \pm 16/81 \pm 15$  mmHg) in the non-diabetic group. WC in diabetic subjects was  $91 \pm 9$  cm, and in non-diabetic subjects  $97 \pm 11$  cm. All values had significant p-values.

### *Genotype frequencies of adiponectin +45T/G and -11391G/A in the different groups*

We found that adiponectin genotype frequencies were similar in diabetic, and non-diabetic, subjects (Table 1). Next, we examined allele and genotype frequencies of the adiponectin gene, by pooling all subjects ( $n = 416$ ) in a single group with a cross-sectional study design. By this method, we found that some carriers of these polymorphisms (men and women) had significantly high mean BMI and WC (Tables 2 and 3). Male carriers of the TT genotype of +45T/G polymorphisms had significantly higher mean BMI than male GG homozygotes ( $p = 0.018$ ), Table 2). Also, male carriers of the GG genotype of -11391G/A polymorphisms had significantly higher mean BMI than male GA or AA homozygotes ( $p = 0.041$ ). Finally, female carriers of the GG genotype of -11391G/A had significantly higher mean WC than female GA, or AA, homozygotes ( $p = 0.038$ ), Table 3).

No significant difference for systolic, or diastolic, blood pressure was found in male, or female, carriers of different genotypes of +45T/G and -11391G/A adiponectin gene polymorphisms (Tables 2 and 3). After adjusting for presence of diabetes, we observed significant gender-related changes only in mean BMI, or WC, in different carriers of the studied polymorphisms. The effect of T2D presence on increased systolic, or diastolic, blood pressure was significant. This effect was independent of carriers. These results are shown in Table 4.

## Discussion

We did not find an association between +45T/G and -11391 G/A adiponectin gene polymorphisms

**Table 2.** Baseline characteristics in carriers of different genotypes of +45T/G according to gender

Variable	Men			Women		
	TT	TG	GG	TT	TG	GG
BMI (kg/m <sup>2</sup> )	26 $\pm$ 4	25 $\pm$ 4	23 $\pm$ 3*	27 $\pm$ 4	27 $\pm$ 4	24 $\pm$ 6
WC (cm)	97 $\pm$ 10	96 $\pm$ 12	91 $\pm$ 8	91 $\pm$ 9	91 $\pm$ 10	84 $\pm$ 12
SBP (mmHg)	128 $\pm$ 15	127 $\pm$ 18	126 $\pm$ 14	134 $\pm$ 22	136 $\pm$ 21	123 $\pm$ 31
DBP (mmHg)	82 $\pm$ 10	81 $\pm$ 8	80 $\pm$ 16	83 $\pm$ 15	84 $\pm$ 12	77 $\pm$ 19

**Legend:** Values are mean  $\pm$  SD. BMI: body mass index. WC: waist circumference. SBP: systolic blood pressure. DBP: diastolic blood pressure. \* TT versus GG in male significant ( $p \leq 0.05$ ) by one-way ANOVA with Bonferroni post-hoc test.

in diabetic, and non-diabetic, subjects. Also, we did not find any gender differences for association between these polymorphisms and T2D. These results were not in line with previous results reported in Japanese [28], or French (Caucasian [19]), populations. However, it might be speculated that these differences were related to a variation in inclusion criteria for sample recruitment (diabetic, non-diabetic groups), and also due to differences in populations [20, 21, 25]. It is well-known that drugs such as rosiglitazone affect adiponectin plasma levels and gene variants [29]. Other drugs can affect the rennin-angiotensin-aldosterone system, and can change adiponectin physiology [30]. Whilst our patients were not using rosiglitazone at the time of the study, we did not have information about past usage of anti-hypertensive drugs. Also, it is possible that there were lifestyle differences, or other environmental factors, which we did not set out to identify [25].

**Table 3.** Baseline characteristics in -11391G/A genotype carriers according to gender

Variable	Men		Women	
	GG	GA+AA	GG	GA+AA
BMI (kg/m <sup>2</sup> )	24 ± 4	21 ± 3 <sup>*</sup>	27 ± 4	25 ± 5
WC (cm)	93 ± 10	91 ± 11	91 ± 9	86 ± 6 <sup>*</sup>
SBP (mmHg)	129 ± 18	120 ± 11	134 ± 23	132 ± 17
DBP (mmHg)	81 ± 10	78 ± 9	83 ± 15	79 ± 13

**Legend:** Values are mean ± SD. BMI: body mass index. WC: waist circumference. SBP: systolic blood pressure. DBP: diastolic blood pressure. <sup>\*</sup> p ≤ 0.05 by *t*-test.

We did not find a significant change in mean systolic, or diastolic, blood pressure among men, or women, carriers of different genotypes of the +45G/T, or -11391 G/A, adiponectin gene polymorphism. But the effect of T2D presence was significant with respect to increased systolic, or diastolic, blood pressure. This effect was independent of carriers. The association between adiponectin gene polymorphisms and diabetes was evaluated according to gender [25]. This association was reported for the 3'UTR T/G thrombospondin 2 gene (THBS2) polymorphism, the -603A/G coagulation factor III gene (F3) polymorphism, the G/T intron 2 adiponectin gene (ADIPOQ) polymorphism in men, and the A/G Arg 160Gly paroxonase 1 gene (PON1) polymorphism in women. Mousavinasab *et*

*al.* examined the association of SNP+276, and SNP+45, with adiponectin plasma level and blood pressure in Finnish men. They found an association between SNP+276 with adiponectin blood concentration, and blood pressure [31]. Also, they found a weak association between SNP+45 and adiponectin plasma levels. They did not find an association between SNP+45 and blood pressure [31].

We found that mean BMI was significantly increased in females and diabetics, but significantly decreased in GG carriers of +45T/G. Also, mean WC was significantly lower in females, and GG carriers of +45T/G. In our study, TT was associated with higher, and GG with lower, BMI in females. The effect of T2D presence was significant on BMI, but not on WC.

Our data on +45T/G polymorphism are similar to those of Menzaghi *et al.* [32]. These authors studied 413 non-diabetic subjects and 310 Caucasians diabetic patients. They found the T allele to be a risk factor for increased body weight (p = 0.03), but not for T2D. Also, they observed that +45T/G and +276T/G polymorphisms was associated with obesity and insulin resistance. In patients carrying the homozygote T allele, there was a susceptibility towards increasing body weight, WC, systolic and diastolic blood pressure, fasting blood sugar and insulin [32].

For -11391G/A polymorphism, we found significantly higher BMI in females, diabetics, and, GA, or AA, carriers. However, we found a significantly lower WC in females than in males, and a significantly higher WC in GA or AA carriers of the -11391G/A polymorphism. Consequently, we received a gender-dependent result where higher BMI and lower WC in females was associated with GA, or AA, carriers of the -11391G/A adiponectin gene polymorphism. These results confirm studies carried out on a French Caucasian population [21]. In that study, the subjects were normoglycemic at baseline, but after 3 years of follow-up the risk for becoming hyperglycemic was significantly increased in GA carriers of the -11391G/A polymorphism and in GG carriers of the +45T/G polymorphism [21]. In contrast to our results, another study found that the G allele of -11391G/A had protective effect against diabetes [33].

This study should be repeated with a larger sample size to confirm the results. Also, determination of adiponectin plasma levels would be useful. More detailed information on lifestyle and habits together with other risk factors of metabolic syndrome should be co-examined.

**Table 4.** Coefficients of univariate and multivariate regression models

Variable	BMI (kg/m <sup>2</sup> )		WC (cm)		SBP (mmHg)		DBP (mmHg)	
	Univariate	Multivariate	Univariate	Multivariate	Univariate	Multivariate	Univariate	Multivariate
Gender (male/female)	0.75 <sup>*</sup>	0.9 <sup>**</sup>	-6.1 <sup>*</sup>	-4.0 <sup>**</sup>	6.5 <sup>*</sup>	NS	1.44	NS
Diabetes	0.85 <sup>*</sup>	1.5 <sup>**</sup>	-5.4 <sup>*</sup>	NS	8.9 <sup>*</sup>	7.7 <sup>**</sup>	3.10 <sup>*</sup>	3.6 <sup>**</sup>
-11391G/A (GA + AA/GG)	1.80 <sup>*</sup>	2.9 <sup>**</sup>	7.4 <sup>*</sup>	4.4 <sup>**</sup>	-4.8 <sup>*</sup>	NS	0.50	NS
+45T/G (TG/TT)	-0.68 <sup>*</sup>	NS	-0.4	NS	1.0	NS	-0.12	NS
+45T/G (GG/TT)	-3.10 <sup>*</sup>	-2.2 <sup>**</sup>	-6.1 <sup>*</sup>	-5.6 <sup>**</sup>	-7.1	NS	-4.30	NS

**Legend:** Regression calculated between independent variables and body mass index, waist circumference, systolic or diastolic blood pressure. BMI: body mass index. WC: waist circumference. SBP: systolic blood pressure. DBP: diastolic blood pressure. NS: not significant. <sup>\*</sup> p < 0.1 in linear regression with univariate model. <sup>\*\*</sup> p ≤ 0.05 in linear regression with multivariate model.

## Conclusions

In the present study, we found no significant changes in mean systolic or diastolic blood pressure among male, or female, carriers of different genotypes of the +45G/T and -11391 G/A adiponectin gene polymorphisms. However, the effect of diabetes on increasing systolic or diastolic blood pressure was significant. This effect was independent of genotype carriers.

Mean BMI was significantly higher in females and diabetics, but lower in GG carriers of +45T/G. Whereas, mean WC was significantly lower in females and GG carriers of +45T/G. This points to a gender-dependent effect.

BMI was significantly increased in females, diabetics, and GA, or AA, carriers of the -11391G/A adiponectin gene polymorphism. We observed a significantly smaller WC in females, whilst GA or AA carriers of -11391G/A polymorphism showed a significantly higher WC. These results point to a gender-specific effects on BMI and WC in different carriers of +45T/G and -11391G/A polymorphisms independent of diabetes in our population.

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