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Short Communication

Adiponectin gene polymorphisms (T45G and G276T), adiponectin levels and risk for metabolic diseases in an Arab population

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ABSTRACT

In this study we examined the association of adiponectin gene variants with circulating adiponectin, and known metabolic diseases in 298 healthy controls and 297 Saudi subjects with type 2 diabetes mellitus (T2DM). Anthropometric and biochemical parameters were measured by standard procedures. Genotyping of T45G and G276T single nucleotide polymorphisms of adiponectin gene was carried out by PCR-RFLP analysis. No significant differences in the genotype distribution of T45G and G276T polymorphism were found between control and diabetic subjects. Neither SNP conferred an association with T2DM, obesity, hypertension or dyslipidemia. Despite a marked decrease in patients as opposed to controls, adiponectin levels were not different according to genotypes of T45G and G276T polymorphisms in control and patients. Thus, neither adiponectin SNPs independently conferred increased T2DM risk nor in other metabolic conditions considered such as obesity, hypertension or dyslipidemia. These findings support the existence of population based differences in the association of adiponectin gene variants with metabolic phenotypes and emphasize the importance of studying multiple polymorphisms, sufficient enough to identify the adiponectin gene as a genetic marker for several non-chronic communicable diseases.

1. Introduction

Adiponectin is a collagen-like protein hormone produced in adipose tissue and is believed to have anti-inflammatory and insulin sensitizing properties (Maeda et al., 1996; Kadowaki et al., 2006). Accordingly, reduced plasma levels of adiponectin are reported to be associated with an increased risk in developing insulin resistance, type 2 diabetes mellitus (T2DM), obesity, metabolic syndrome, and even osteoarthritis (Kadowaki et al., 2006; Matsuzawa et al., 2004; Weyer et al., 2001; Daimon et al., 2003; Hu et al., 2011). The protective effect of adiponectin against these metabolic phenotypes may involve the suppression of hepatic gluconeogenesis, stimulation of fatty acid oxidation in the liver, stimulation of fatty acid oxidation and glucose uptake in the muscle and the stimulation of insulin secretion (Rabe et al., 2008). These effects are suggested to be mediated by the activation of signaling pathways of adenosine monophosphate activated protein kinase and the peroxisome proliferator activated receptor-alpha (PPAR-α) (Rabe et al., 2008). Adiponectin expression is affected by weight loss, PPAR-γ receptors, inflammatory and angiogenic factors (Yang et al., 2001; Maeda et al., 2001; Hajer et al., 2008; Bruun et al., 2003). Consistent with the association at protein levels, genetic studies have also demonstrated a link between adiponectin gene and the metabolic phenotypes. Several single nucleotide polymorphisms (SNPs) are described in the adiponectin gene and were found to be associated with obesity (Stumvoll et al., 2002; Bouatia-Naji et al., 2006), type 2 diabetes mellitus (Hara et al., 2002; Hivert et al., 2008; Tso et al., 2006; Schwarz et al., 2006; Szopa et al., 2009) and insulin resistance (Stumvoll et al., 2002; Jang et al., 2008; Pérez-Martínez et al., 2008; Rasmussen-Torvik et al., 2009; Melistas et al., 2009). Although it should be noted that other studies have reported a lack of such an association; with conflicting reports observed, at times, within the same ethnicity (Lee et al., 2005; Vasseur et al., 2002; Populaire et al., 2003; Gu et al., 2004; Vozarova de Courten et al., 2005). Moreover these discrepancies were also found within the same population (Jang et al., 2008; Lee et al., 2005; Hwang et al., 2010; Li et al., 2011).

There is a high incidence of T2DM within the Saudi population as well as other metabolic diseases; attributed mainly to a considerable

Abbrevation: BMI, body mass index; DNA, deoxyribonucleic acid; HDL-Cholesterol, high density lipoprotein cholesterol; HOMA-IR, homeostasis model assessment for insulin resistance; PCR, polymerase chain reaction; PPAR, peroxisome proliferator activated receptor; RFLP, restriction fragment length polymorphism; SNP, single nucleotide polymorphism; SPSS, statistical Package for the Social Sciences; T2DM, type 2 Diabetes Mellitus.

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change in the dietary habits and sedentary life style (Al-Daghri et al., 2011a; Al-Daghri et al., 2010; Al-Daghri, 2010). Studies on circulating adiponectin in this population was also observed to be highly heritable (Al-Daghri et al., 2011b), and is associated with telomere length, a biomarker for aging (Al-Daghri et al., 2011c). However, no genetic studies to date have examined whether any of the reported adiponectin gene variants noted in other studies are associated with diabetic risk in a Saudi population. Thus, here we study the distribution of two common and widely studied adiponectin SNPs, T45G and G276T, their association with T2DM risk, circulating adiponectin, insulin resistance and anthropometric parameters in a Saudi population with and without T2DM.

2. Materials and methods

2.1. Subjects

This cross sectional study included 297 T2DM patients and 298 control subjects of Saudi Arabian descent. Studies were conducted in accordance with the guidelines set by the ethics committee of the Research Center, College of Science, King Saud University, Riyadh. Informed consents were obtained from all the subjects prior to their inclusion into the study. A standard questionnaire was obtained from all the subjects collecting the information on medical history, use of past and current medications, and demography. T2DM was defined as fasting plasma glucose levels in excess of 126 mg/dl (7.0 mmol/l) and a history of using anti-diabetic medication. Patients with any medical condition or patients on medication known to interfere with glucose metabolism, or suffering from chronic kidney disease were excluded from the study. Control subjects were apparently healthy, non-T2DM individuals free of any medical complications and were attending the primary care centers for routine health check-ups. Control subjects with history of T2DM, fasting plasma glucose levels measuring ≥126 mg/dL (≥7.0 mmol/l) or HbA1C > 5.8%, parental history of T2DM or history of using anti diabetic medication were excluded from the study.

2.2. Anthropometric and clinical measurements

Anthropometric measurements were obtained by trained personnel of health care centers. Height and body weight were measured without shoes and the study subjects wearing light clothes. Height was measured to the nearest 0.5 cm and weight to the nearest 0.1 kg. Waist circumference was measured to the nearest 0.5 cm at the levels between the midpoint of the lowest rib and iliac crest parallel to the floor in a standing position, while the hip circumference was measured to the nearest 0.5 cm at maximum extension of the buttocks. Body mass index (BMI) was calculated as weight/height^2 (kg/m^2). Subjects with BMI 30 kg/m^2 were categorized as obese group. Blood pressure of the subjects in a sitting position was measured taking the mean of the two reading collected at an interval of 30 min. Hypertension was defined as mean systolic blood pressure of 140 mm Hg and/or a diastolic blood pressure of 90 mm Hg.

2.3. Biochemical parameters

Biochemical parameters including, HDL-cholesterol, triglycerides, total cholesterol, and fasting plasma glucose were measured by automated clinical chemistry analyzer (KoneLab) using the commercially available kits. Insulin was assayed by a solid phase enzyme amplified sensitivity immunoassay (Medgenix INS-ELISA, Biosource, Belgium). Plasma adiponectin levels were measured by radioimmunoassay following the manufacturer's instructions (Millipore, Billerica, MA, USA), with an intra- and inter-assay variation of 5.6–15.0% and a minimum detectable concentration of 145.5 pg/ml. Insulin resistance was measured by homeostasis model assessment (HOMA-IR), calculated using the formula; insulin (μU/ml) × glucose (mmol/l) / 22.5. Dyslipidemia (low levels of HDL-cholesterol) was defined as HDL-cholesterol levels <1.03 mmol/l for men and <1.29 mmol/l for women.

2.4. Genotyping

Two SNPs, a T > G substitution at +45 in exon 2 (T45G) and a G > T substitution at +276 in intron 2 (G276T) of adiponectin gene were arbitrarily chosen for genotyping on the bases of literature review and a higher allele frequency in the SNP data base. Genotyping was carried out 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 as was used in previous study (Al-Daghri et al., 2011b). For T45G polymorphism analysis, DNA was amplified using the forward primer, 5′- GAA GTA GAC TCT GCT GAG ATG G -3′ and the reverse primer, 5′- TAT CAG TGT AGG AGG TCT GTG ATG -3′. The amplified products were digested with restriction enzyme, *Sma I* (Fermentas, Germany) and the genotypes were ascertained by agarose gel electrophoresis. For G276T polymorphism, DNA was PCR amplified using the forward primer, 5′- GGC CTC TTT CAT CAC AGA CC -3′ and the reverse primer, 5′- AGA TGC AGC AAA GCC AAA GT -3′. The amplified products were digested with restriction enzyme, *Mva 1269I* (Fermentas, Germany). PCR product size for 45T/G (wild type allele) was 372 bp [Fragment size: 219 and 153 bp for homozygous mutant allele; 372, 219 and 153 bp for heterozygote allele] and 196 bp (homozygous mutant allele) for 276G/T [Fragment size: 148 and 48 bp for wild type allele; 196, 148 and 48 bp for heterozygote allele].

2.5. Statistical analysis

Statistical analysis was performed by Statistical Package for Social Sciences (SPSS 11.5 SPSS Inc., Chicago and USA.) and SAS 9.1 for Windows. All non-Gaussian variables were either log or square root transformed. Differences between variables were computed using *t* test and ANOVA. Post-Hoc tests, such as Bonferroni or Dunnett's *T* test were used to compare multiple groups. Allele frequency difference between controls and T2DM subjects was determined by Chi-square test, where $p < 0.05$ was considered to be statistically significant.

3. Results

The general characteristics of control and T2DM subjects are presented in Table 1. T2DM subjects were significantly older than controls. Anthropometric measures including BMI, waist circumference, and sagittal abdominal diameter were also significantly higher in T2DM patients compared with control subjects. Among the insulin resistance parameters, T2DM subjects had increased levels of fasting glucose, insulin and HOMA-IR. Additionally, triglycerides, LDL-cholesterol, systolic and diastolic blood pressures were markedly elevated in diabetic patients, while HDL-cholesterol is decreased in comparison with control subjects.

3.1. Association of adiponectin gene SNPs with T2DM and other metabolic abnormalities

The distribution of T45G and G276T polymorphisms of adiponectin gene are provided in Table 1. The genotype distribution of both T45G and G276T SNPs were in agreement with the Hardy–Weinberg equilibrium. We observed that the frequency of TT, TG and GG genotypes of T45G SNP was not statistically different between control and patients (minor allele frequency; 0.16 vs. 0.14 respectively, $p = 0.5$). Similarly, the frequency of GG, GT and TT genotypes of G276T SNP was comparable among the control and diabetic subjects (minor

Table 1
General characteristics of T2DM and control subjects.

Parameters		Control	T2DM	p-Value
N		298	297	
Age (years)		38.7 ± 11.9	50.7 ± 11.6	<0.001
Weight (kg)		76.0 ± 16.3	79.7 ± 15.3	0.006
Height (cm)		161.1 ± 9.6	162.0 ± 11.3	0.3
BMI (kg/m²)		29.1 ± 5.7	30.3 ± 6.2	0.02
Waist circumference (cm)		91.9 ± 20.5	96.7 ± 22.5	0.01
Hips (cm)		101.3 ± 18.9	100.0 ± 25.8	0.5
SAD(cm)		21.7 ± 5.5	25.0 ± 8.2	<0.001
Systolic(mm Hg)		117.4 ± 13.2	127.7 ± 16.6	<0.001
Diastolic(mm Hg)		77.0 ± 10.1	80.7 ± 9.4	<0.001
Glucose (mmol/l)		5.7 ± 1.2	9.4 ± 1.5	<0.001
Insulin(μU/ml)		12.5 ± 1.8	16.2 ± 2.2	<0.001
HOMA-IR		3.15 ± 1.9	6.8 ± 2.4	<0.01
Total Cholesterol (mmol/l)		5.1 ± 1.02	5.2 ± 1.1	0.2
LDL-Cholesterol (mmol/l)		3.6 ± 0.9	3.5 ± 1.0	0.049
HDL-Cholesterol (mmol/l)		0.68 ± 0.04	0.76 ± 0.03	0.005
Triglycerides (mmol/l)		1.4 ± 0.1	1.8 ± 0.14	<0.001
Adiponectin (μg/ml)		9.7 ± 1.9	7.0 ± 2.1	<0.001
T45G	TT	209 (70.1)	220 (73.8)	0.50
	TG	80 (26.8) (0.16)[a]	72 (24.1) (0.14)[a]	
	GG	9 (3.1)	6 (2.1)	
G276T	GG	122 (41.1)	111 (37.4)	0.60
	GT	133 (44.8) (0.36)[a]	142 (47.8) (0.38)[a]	
	TT	42 (14.1)	44 (14.8)	
Haplotype	TG/TG	75 (25)	74 (25)	0.90
	TG/X	40 (13)	38 (13)	
	X/X	183 (62)	185 (62)	

Note: Data represented as mean ± SD for continuous variables, N (%) for frequencies; p Values for independent T-test are given. Values of glucose were Log transformed, while triglyceride and HDL-cholesterol were square root transformed. p-Value significant at <0.05.

[a] Minor allele frequency of each site.

allele frequency; 0.36 vs. 0.38, p = 0.6). We also examined the haplotype distribution among control and T2DM subjects and observed no significant association of any of the haplotypes (TG/TG, TG/X or X/X) with disease status. The odds ratios for TG and GG genotypes in reference to TT genotype of T45G SNP and GT and TT genotypes in reference to GG genotype of G276T SNP were not significantly related with the risk of developing T2DM, obesity, hypertension and dyslipidemia in this studied population (Fig. 1).

3.2. Effect of adiponectin gene SNPs on adiponectin levels

We also examined the relationship between Adiponectin T45G and G276T SNPs with circulating adiponectin. Adiponectin levels were significantly reduced in T2DM patients than in controls (7.0 ± 2.1 μg/ml vs. 9.7 ± 1.9 μg/ml respectively, p<0.001) in both men (7.3 ± 2.0 μg/ml vs. 10.0 ± 2.07 μg/ml respectively, p<0.001) and women (9.5 ± 1.8 μg/ml vs. 6.2 ± 2.3 respectively, p<0.001). No significant differences were found in adiponectin levels between men and women in either control (10.0 ± 2.07 μg/ml vs. 9.5 ± 1.8 μg/ml respectively, p<0.5) and T2DM subjects (7.3 ± 2.0 μg/ml vs. 6.2 ± 2.3 μg/ml respectively, p<0.08). Although adiponectin levels were significantly decreased in T2DM patients regardless of SNP, no significant differences in the adiponectin levels were found among TT, TG and GG genotypes of T45G and among GG, GT and TT genotypes of G276T polymorphisms in both control and T2DM groups (data not shown). Moreover, for a given genotype of T45G and G276T SNPs, circulating adiponectin was markedly reduced in T2DM subjects than controls.

3.3. Effect of adiponectin gene SNPs on anthropometric and insulin resistance parameters

Considering the lack of associations between adiponectin T45G and G276T polymorphisms with T2DM and adiponectin levels, we tested whether these gene variants were linked to metabolic parameters in control and T2DM subjects. We showed no significant association between SNPs with any anthropometric parameters and insulin resistance features including glucose, insulin and HOMA-IR in control and T2DM subjects (Table 2).

4. Discussion

In the present study we examined the association of two common and widely studied polymorphisms, T45G and G276T SNPs, of adiponectin gene with metabolic disease risk and adiponectin protein levels among in T2DM and non-T2DM Saudi population. We found that none of the genotypes were associated with either, disease status, circulating adiponectin or other anthropometric and biochemical factors analyzed.

It is understood that the etiology of T2DM is multi-factorial with genetic and environmental factors affecting the disease onset and progression. The adiponectin gene resides within the susceptibility loci for T2DM and insulin resistance syndrome on chromosome 3q27 (Kissebah et al., 2000; Vionnet et al., 2000). Accordingly, several SNPs have been described in the adiponectin gene and are associated with metabolic phenotypes including obesity, T2DM and insulin resistance (Stumvoll et al., 2002; Bouatia-Naji et al., 2006; Hara et al., 2002; Hivert et al., 2008; Tso et al., 2006; Schwarz et al., 2006; Szopa et al., 2009; Jang et al., 2008; Pérez-Martínez et al., 2008; Rasmussen-Torvik et al., 2009; Melistas et al., 2009). Among all, T45G and G276T SNPs of adiponectin gene are widely studied in relation to their associations with the metabolic phenotypes. However, data from the literature has been inconsistent, with several studies demonstrating significant associations between T45G and G276T SNPs and the metabolic phenotypes (Stumvoll et al., 2002; Bouatia-Naji et al., 2006; Hara et al., 2002; Hivert et al., 2008; Tso et al., 2006; Szopa et al., 2009; Jang et al., 2008; Melistas et al., 2009; Menzaghi et al., 2002; Yang et al., 2007) whist in contrast, other studies have also reported the lack of such associations (Lee et al., 2005; Vasseur et al., 2002; Populaire et al., 2003; Gu et al., 2004; Vozarova de Courten et al., 2005). In this present study we did not find significant differences in the distribution of genotypes of T45G and G276T SNPs among control and T2DM subjects. Additionally, no significant association was found between the genotypes and the T2DM status, as well as examining obesity, dyslipidemia and hypertension, indicating that these SNPs may not be important determinants of cardiometabolic disease risk in the Saudi population. Furthermore, our data suggest that these SNPs do not contribute to the variation in the adiponectin gene expression as we could not detect any change in the adiponectin levels according to the genotypes of T45G and G276T SNPs in subjects with and without T2DM, despite a marked decrease in circulating adiponectin. In addition, no associations were noted between genotypes and anthropometric parameters, including glucose, insulin in any cohort, indicating that these SNPs may not independently contribute to obesity and insulin resistance states in the studied population.

T45G SNP is a silent substitution (Gly15Gly) within exon 2 of the adiponectin gene, which does not result in the amino acid change, while G276T is in intron 2, distant from the consensus splice site (Takahashi et al., 2000), thus these SNPs, by themselves, are unlikely to contribute to variable adiponectin gene expression or modify the biological properties of the protein. Additionally, in vitro data does not necessarily support a functional role for G276T SNP in adiponectin gene expression (Bouatia-Naji et al., 2006). Conflicting studies have been reported for the association of T allele of SNP276 with

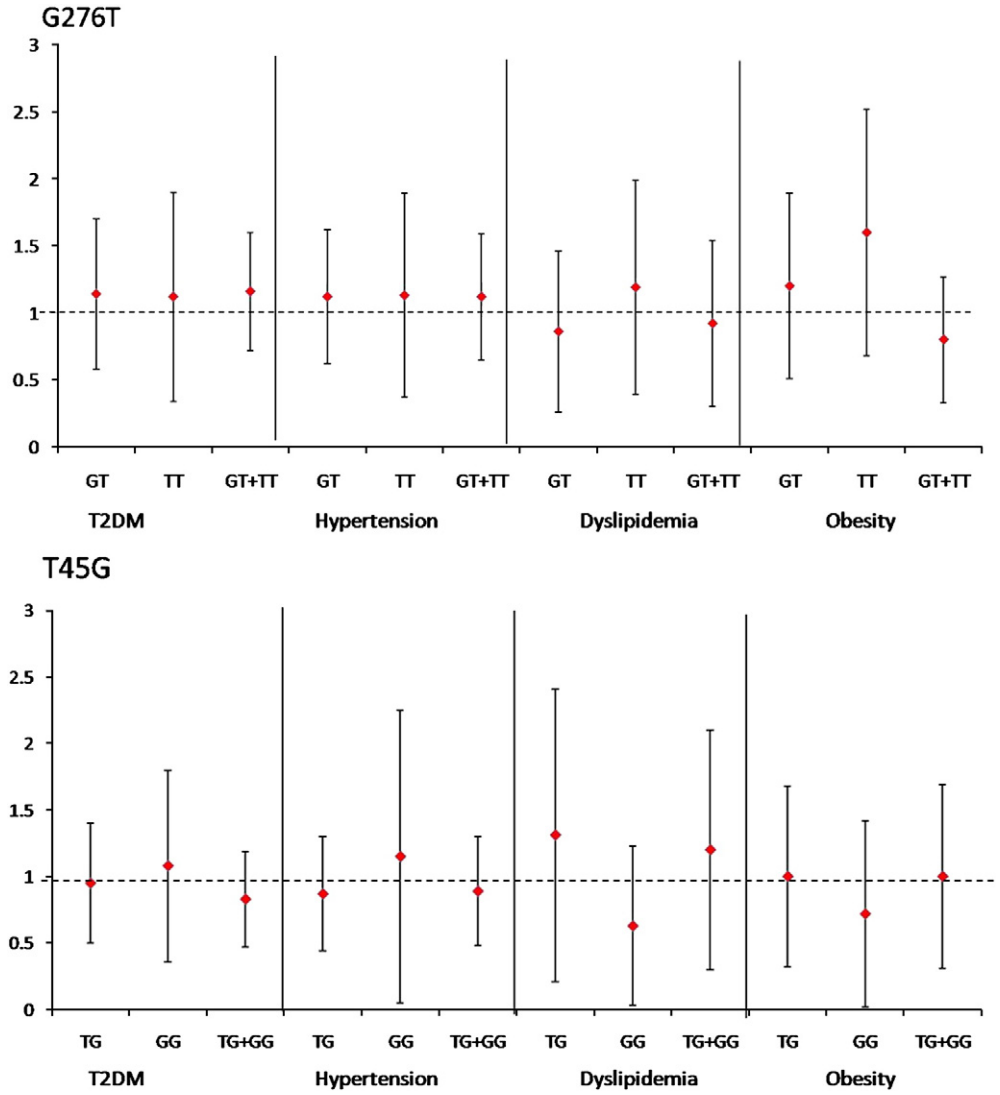

Fig. 1. Odds ratios (OR) with confidence intervals for selected metabolic diseases for G276T and T45G polymorphisms of adiponectin gene; no significance elicited.

reduced circulating adiponectin (Hara et al., 2002; Jang et al., 2008; Filippi et al., 2004). Additionally however current data indicates that both T and G alleles of SNP T45G are associated with obesity, insulin resistance and T2DM (Stumvoll et al., 2002; Hara et al., 2002; Menzaghi et al., 2002). On balance taking into account data from this present and previous studies, current analysis may suggest that

Table 2
Characteristics of subjects according to SNPs T45G and G276T.

Parameters	SNP T45G				SNP G276T			
	TT	TG	GG	p-Value	GG	GT	TT	p-Value
N	209	80	9		122	134	41	
Age	39.8 ± 11.5	36.3 ± 1 + 2.3	34.2 ± 13.0	0.05	38.1 ± 13.1	39.1 ± 11.1	39.1 ± 10.8	0.76
Weight (kg)	76.6 ± 16.3	74.8 ± 15.9	70.2 ± 21.3	0.39	74.6 ± 17.2	77.4 ± 16.9	75.5 ± 11.1	0.40
Height (cm)	161.4 ± 8.6	160.5 ± 5.5	159.2 ± 16.1	0.66	159.7 ± 10.3	162.9 ± 9.6	159.4 ± 5.8	0.018
BMI (kg/m^2)	29.3 ± 5.8	28.9 ± 5.5	26.8 ± 6.4	0.41	29.0 ± 6.0	29.1 ± 6.0	29.7 ± 4.1	0.84
Waist circumference (cm)	92.7 ± 20.5	90.2 ± 21.0	86.7 ± 18.2	0.51	91.8 ± 19.1	92.8 ± 21.3	89.2 ± 22.5	0.69
Hip circumference (cm)	103.0 ± 18.2	98.2 ± 20.0	94.0 ± 22.3	0.09	101.1 ± 18.8	102.2 ± 18.0	99.3 ± 22.3	0.67
Sagittal abdominal diameter (cm)	21.9 ± 5.7	21.0 ± 5.0	22.1 ± 6.05	0.4	21.7 ± 5.9	22.0 ± 4.9	20.15 ± 6.02	0.21
Systolic blood pressure (mm Hg)	117.0 ± 13.7	117.6 ± 11.6	126.1 ± 13.9	0.16	116.9 ± 13.7	118.5 ± 13.01	115.5 ± 12.6	0.50
Diastolic blood pressure (mm Hg)	77.4 ± 10.7	75.6 ± 8.9	78.5 ± 2.8	0.38	76.5 ± 10.9	77.4 ± 9.4	76.9 ± 10.02	0.82
Glucose (mmol/l)	5.4 ± 1.3	5.7 ± 1.2	6.04 ± 1.15	0.76	5.8 ± 1.2	5.7 ± 1.24	5.52 ± 1.2	0.59
Insulin (μU/ml)	12.4 ± 1.8	13.7 ± 1.6	7.3 ± 1.2	0.33	12.0 ± 1.7	14.2 ± 1.8	9.7 ± 1.6	0.06
HOMA-IR	3.1 ± 1.9	3.3 ± 1.7	2.0 ± 1.1	0.55	3.0 ± 1.7	3.5 ± 2.0	2.4 ± 1.6	0.07
Triglycerides (mmol/l)	1.4 ± 0.1	1.4 ± 0.08	1.3 ± 0.04	0.90	1.53 ± 0.08	1.4 ± 0.09	1.2 ± 0.06	0.37
Total cholesterol (mmol/l)	5.1 ± 1.0	5.1 ± 1.06	4.8 ± 0.9	0.57	5.1 ± 1.02	5.0 ± 0.9	4.9 ± 1.1	0.60
LDL-cholesterol (mmol/l)	3.6 ± 0.93	3.7 ± 0.9	3.5 ± 0.8	0.43	3.7 ± 0.9	3.6 ± 0.93	3.5 ± 1.0	0.79
HDL-cholesterol (mmol/l)	0.69 ± 0.03	0.6 ± 0.03	0.65 ± 0.01	0.87	0.68 ± 0.03	0.67 ± 0.04	0.72 ± 0.03	0.98

Note: Data represented by mean ± standard deviation; p-values for ANOVA; Multiple groups were compared by Bonferroni Post-Hoc test, p-value significant at <0.05.

SNPs T45G and G276T are unlikely to exert a direct biological effect and may not be independently associated with the metabolic phenotypes. The SNPs T45G and G276T are also suggested to be in linkage disequilibrium with other functional variants as the effect of these SNPs on adiponectin protein are seen when they are in linkage disequilibrium with −11377 and −11391 SNPs of the 5′ promoter region (Vasseur et al., 2002). Similarly, SNP G276T has been proposed to be a marker for functional variant in 3′ UTR region through linkage disequilibrium (Menzaghi et al., 2007). It has also been reported that linkage disequilibrium structures may vary between the populations (Comuzzie et al., 2001; Lindsay et al., 2003). Hence, the possible differences in the linkage disequilibrium structures among the populations may explain the inconsistency in the association of SNP T45G and G276T with metabolic phenotypes in different populations. It is possible therefore that in our study, SNPs T45G and G276T might not be in linkage disequilibrium with other functional variants and this could have led to the lack of associations with the diabetes risk in the studied population. The lack of associations of SNPs T45G and G276T with circulating adiponectin in the present study as well as in others (Lee et al., 2005; Vasseur et al., 2002) could also be explained by the possibly different linkage disequilibrium structures that do not result in a change in circulating adiponectin (Lee et al., 2005; Comuzzie et al., 2001; Lindsay et al., 2003). It is also possible that within the adiponectin gene locus different SNPs may participate in different phenotypes as variants in the 5′ and 3′ regulatory regions which have resulted in the altered adiponectin expression, while a non synonymous variant is linked to diabetes risk without affecting the adiponectin levels (Hivert et al., 2008). Gene–gene interaction involving adiponectin gene and tumor necrosis alpha gene is also identified to influence the circulating adiponectin (González-Sánchez et al., 2006). Alternatively, adiponectin levels that are commonly measured in plasma may not reflect the levels in the subendothelial space where adiponectin presumably exerts its effects (Matsuda et al., 2002). Altered adiponectin mRNA stability resulting due to 3′ UTR SNPs in the gene may also contribute to altered adiponectin levels (Conne et al., 2000). It is worthy to note however that despite the negative findings on T2DM itself, the SNPs used in this study specifically 45T > G has been identified previously to confer increased risk for coronary artery disease (CAD) in the T2DM population (Al-Daghri et al., 2011a, 2011b, 2011c). Additionally the gene polymorphism rs 266729 has also been documented to increase the risk of ischemic stroke in the Chinese Han population (Liu et al., 2011). Taken together these studies highlight that adiponectin variants appear more closely linked to vascular diseases rather than insulin resistance itself.

In conclusion, we observed no significant differences in the genotype distribution of SNPs, T45G and G276T of adiponectin gene in subjects with and without T2DM within a Saudi population. Moreover, no associations were found between the studied SNPs on circulating adiponectin, insulin resistance or obesity in this population. Screening for additional SNPs in the adiponectin gene may potentially reveal the existence of other such associations within the adiponectin gene and metabolic disease risk in a Saudi population. Other such SNPs linked to T2DM in different ethnic groups might include paraoxonase (PON)3 for dyslipidemia and T2DM (Labrecque et al., 2009); PEA15 gene for diabetes (Wolford et al., 2000), and Npr3 for hypertension (Gilmore, et al., 2001), to name a few. Although we did not find associations with studied SNPs, the findings emphasize that "ethnicity" based differences exist in the associations between adiponectin SNPs and the risk of developing metabolic phenotypes. Our data also underscore the importance of analyzing multiple variants of adiponectin gene as studying fewer variants is not likely to be sufficient to identify potential functional effects of this gene on diabetes risk. To our knowledge this is the first study to examine the association of adiponectin gene polymorphisms with T2DM in a Saudi ethnic population.

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