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Original scientific paper

THE ASSOCIATION BETWEEN ADIPONECTIN AND ADIPOQ GENE POLYMORPHISMS WITH OBESITY AMONG YOUNG JORDANIAN WOMEN

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Obesity is a risk for multiple diseases and an independent cause of morbidity and mortality with staggering global rates. Adiponectin is an adipocyte-derived peptide associated with reduced obesity. In this study, the effect of *ADIPOQ* gene single nucleotide polymorphisms (SNPs) on obesity and adiponectin relationship was examined. The study was conducted on 389 adult females. Obesity was measured using body weight, BMI, percent body fat, and waist and hip ratio. *ADIPOQ* G276T and I164T SNPs were genotyped using RFLP procedure. Adiponectin plasma levels were quantified using ELISA technique. Adiponectin correlated with all obesity measures ($p<0.05$). However, when divided according to genotypes, adiponectin remained correlating ($p<0.05$) with obesity measures in the participants with GT of the G276T SNP but not ($p>0.05$) with GG and TT of the G276T SNP. With respect to‘ I164T SNP, the correlations between adiponectin and obesity measures remained in all genotypes except with W/H ratio and %Bf remained in the participants with CC genotype and with W/H ratio in CT/TT genotypes. Further analyses reveled that adiponectin was lower ($p<0.05$) in the participants with GT versus the GG and TT genotypes of G276T SNP. The data confirms the effect of adiponectin for obesity. It also shows the importance of *ADIPOQ* SNPs in the relationship between adiponectin and obesity in young adult females.

Key words: Women obesity; ADIPOQ; G276T and I164T SNPs; BMI; Waist/Hip

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INTRODUCTION

Obesity is an independent cause of morbidity and mortality (LEE, 2015) and associated with increased risk of cardiovascular, metabolic, immune, and orthopedic diseases (ASHRAF and BAWEJA, 2013; KELSEY *et al.*, 2014; WALTER *et al.*, 2009). According to estimates, since 1980 to 2013, the global obesity prevalence has increased from 857 million to 2.1 billion, respectively, whereas it is expected to reach ~3.3 billion in 2030 (KELLY *et al.*, 2008; NG *et al.*, 2014). Obesity is attributed mainly to the positive energy balance, resulting from high caloric/fat intake and physical inactivity (MALIK *et al.*, 2013). However, the etiology is multifactorial, and involves the interplay of many causes. Therefore, the WHO has called for a global surveillance system to identify risk factors, thus strategies, to restrain obesity proliferation by 2025 (GORTMAKER *et al.*, 2011).

Obesity trends are different in some subgroups (COSSROW and FALKNER, 2004; FRIEDMAN, 2003; GOLDEN *et al.*, 2012). For example, Pima Indians, Pacific Islanders (FRIEDMAN, 2003; GOLDEN *et al.*, 2012) and African- and Hispanic-Americans (COSSROW and FALKNER, 2004) have experienced disproportionate increase in obesity. Since these subgroups are exposed to similar living standards, differences cannot be explained by lifestyle, economic, or environmental factors alone, indicating a genetic contribution.

Adiponectin is an adipocyte-derived peptide with several health-protective characteristics including anti-inflammatory, -atherogenic, and -diabetic (DIEZ and IGLESIAS, 2003; LIU and LIU, 2014). Obesity is associated with reduced circulatory adiponectin, which in turn, increases the risk of diabetes mellitus, metabolic syndrome, and cardiovascular diseases (DIEZ and IGLESIAS, 2003; MATSUDA and SHIMOMURA, 2014). The adiponectin gene (*ADIPOQ*) has been located on chromosome 3q27 with two identified polymorphisms, SNP G276T and I164T. These polymorphisms seem to modulate adiponectin level and activity with diabetes and metabolic syndrome susceptibility locus (LEE *et al.*, 2013; RAMYA *et al.*, 2013). The SNP G276T is associated with type 2 diabetes (VENDRAMINI *et al.*, 2010), insulin resistance, and obesity (HARA *et al.*, 2002; RAMYA et al., 2013; YU *et al.*, 2012), whereas I164T is associated with the metabolic syndrome and coronary artery disease (OHASHI *et al.*, 2004). The effect of these polymorphisms on the relationships of adiponectin with obesity is yet to be clarified.

Recent investigations reported gender differences in the relationship between adiponectin levels and obesity with strong association between low adiponectin plasma levels and obesity among women (EGLIT *et al.*, 2013; PERVANIDOU *et al.*, 2009; URBINA *et al.*, 2009). Therefore, the current study will examine the relationship of obesity measures with adiponectin in different polymorphism genotypes among young adult women.

MATERIAL AND METHODS

Design and participants

The study was retrospective, observational, and cross-sectional. Apparently healthy women 18-60 years were invited to participate in the study. Females with known pregnancy, or cardiovascular, metabolic, immune, and orthopedic diseases were excluded from the study. All participants signed an informed consent approved by the Institutional Ethical Committee after a detailed orientation of the study requirements, possible risk, and benefits.

Obesity measurements

Obesity was measured using body mass index (BMI), percent body fat (%Bf), waist and hip ratio (W/H). Standard weight scale and tab measure were used to obtain the women participants' weight and height, respectively. Additionally, the participants' %Bf was measured using bioelectrical impedance (Microlife WS 100, Microlife AG, Heerbrugg, Switzerland). The W/H was calculated after determining the waist and hip circumferences at the umbilicus height and at the greatest circumference in the pelvic bone, respectively (ADAMS and BEAM, 2008; ALOMARI *et al.*, 2011; ALOMARI *et al.*, 2012).

Isolation of genomic DNA

Blood samples obtained in EDTA tubes were used for genomic DNA isolation. DNA was extracted from samples using kit obtained from Promega (Wizard DNA extraction kit, Madison, WI, USA) as previously described (KHABOUR *et al.*, 2010). After extraction, the concentration of the isolated DNA was quantified using Bio-Rad SmartSpect_3000 device (Hertfordshire, UK). Isolated DNA was stored at 20° C until used.

Genotyping of ADIPOQ SNP G276T and I164T SNPs

Genotyping of *ADIPOQ* SNP G276T and I164T was performed using restriction fragment length polymorphism (RFLP) as previously described (KHABOUR *et al.*, 2010; KHABOUR *et al.*, 2013). The primer sequences used for 276 SNP were: forward (5' TCT AGG CCT TAG TTA ATA ATG AAT G 3'); reverse (5' GAG AAA GGA GAT CCA GGT AAG A 3') and for I164T SNP: forward (5' CCC ATT CGC TTT ACC AAG ATC 3'); reverse (5' GAA GAA AGC CTG TGA AGG TG 3'). Ready to use PCR master mix (Promega, USA) was used for DNA amplification. Cycling conditions for both SNPs were 94°C for 5 minutes, then 35 cycles at 94°C for 1 minute, 60°C for 30 seconds, and 72°C for 1 minute, followed by final extension at 72°C for 7 minutes. Amplified PCR fragments were digested with Bsm1 and Bcc1 (Fermentas, Glen Burnie, MD, USA) for genotyping of 276 and I164T SNPs respectively. Restricted products were visualized on a 2% agarose gel stained with ethidium bromide (KHABOUR *et al.*, 2010; KHABOUR *et al.*, 2013).

Plasma adiponectin levels

Blood samples obtained from subjects in EDTA tubes were readily centrifuged at 3000 xg for 5 minutes. Levels of plasma adiponectin were measured as previously described (KHABOUR *et al.*, 2014) using ELISA technique and commercially kit purchased from R&D Systems (DuoSet; Minneapolis, MN, USA). Samples were diluted 1:800 with the reagent diluent solution supplied by the kit prior to loading into the microplate wells. Plates were read using ELx800 ELISA reader (BioTek Instruments, Inc., Winooski, VT, USA) at 450 nm. A standard curve was constructed using known concentrations of adiponectin supplied by the kit. Levels of adiponectin in the samples were deducted from the standard curve.

Statistical analysis

Statistical analysis was performed using SPSS software (Version 19, SPSS Inc Company, USA). $p<0.05$ was considered significant. Pearson product-moment correlations were used to examine the relationship of adiponectin with obesity. Additionally, 1-way ANOVA and Student's t-tests were used, when appropriate, to examine the differences between genotypes. The genotype distributions of the studied polymorphisms were tested in accordance with Hardy–Weinberg

equilibrium using the chi-squared test. Power calculation was computed using an online sample size calculator (OSSE). For a sample size of 389 at a level of significance of 0.05, the power exceeded 70%.

RESULTS AND DISCUSSION

A total of 389 females agreed to participate in the study. As in Table 1, the average age, wight, and height were 24.8±9.10 years, 66.0±16.7 kg and 1.6±0.06 m, respectivly. Table 2 shows the participants' adiponectin level correlated ($p<0.05$) with all obesity measures obtained in the study including weight, BMI, waist, and hip circumferences, W/H, and %Bf. After dividing the participants according G276T SNP, as in Table 2, correlations ($p<0.05$) of adiponectin with obesity measures were maintained in the GT but not ($p<0.05$) in the GG or TT genotypes. Furthermore, Table 3 shows that obesity measures were similar in the three genotypes of G276T SNP, however adiponectin was less in the GT versus GG or TT genotypes.

Table 1. Participant Charactrariticss

Characterstic	**Mean±SD**
Age (years)	24.8±9.10
Weight (kg)	66.0±16.7
Height (m)	1.6±0.06
Waist & hip ratio (W/H)	0.76±0.05
Body mass index (k/m^2)	25.5±6.40
Body fat (%)	32.8±10.0
Adiponectine (ng/ml)	1133.0±1082.96

Values are in Mean±SD.

Table 2 shows relationships of adiponectin with obesity measures in the participants with CC and CT/TT genotypes of the I164T SNP. Due to low number of subjects with TT genotype and to increase statistical power, TT group was combined with CT group. The correlations between adiponectin and obesity measures remained in all genotypes except with W/H ratio and %Bf remained in the participants with CC genotype and with W/H ratio in CT/TT genotypes. Furthermore, Table 3 shows that obesity measures were similar in the genotypes of I164T polymorphisms.

The current study showed that the participants' adiponectin level correlated negatively with the obesity measures including weight, BMI, waist, and hip circumferences, W/H, and %Bf. After dividing the participants according to G276T and I164T SNPs, analyses revealed that adiponectin remained correlated with obesity measures in the participants with GT but not in the GG or TT genotypes of the G276T SNP and with the CC and CT/TT genotypes of the I164T SNP. Comparison analyses also showed that adiponectin was less in the GT versus the GG and TT genotypes of the G276T SNP and was the same in the CC versus the CT/TT genotypes of the I164T SNP. The data show a regulatory role of *ADIPOQ* genotypes to the relationship of

adiponectin with obesity. The results advocate the importance of accounting for the *ADIPOQ* genotypes, when considering relationships between adiponectin and obesity.

Table 2. Relationships of Adiponectin with Obesity Measures

	Weight (kg)	**BMI** (kg/m^2)	**WC** (cm)	**HC** (cm)	**W/H** (ratio)	**Bf** (%)
All Participants (n=389)	r=-0.20; p=0.000	r=-0.2; p=0.000	r=-0.2; p<0.000	r=-0.2; p=0.000	r=-0.1; p=0.062	r=-0.2; p=0.000
G276T SNP						
GG (n=86)	r=-0.08; *p*<0.450	r=-0.08; *p*<0.425	r=-0.04; *p*<0.730	r=-0.09; *p*<0.430	r=-0.08; *p*<0.500	r=-0.05; *p*<0.682
GT(n=250)	r=-0.30; *p*<0.000	r=-0.30; *p*<0.000	r=-0.30; *p*<0.000	r=-0.25; *p*<0.000	r=-0.20; *p*<0.005	r=-0.25; *p*<0.000
TT (n=53)	r=-0.16; *p*<0.255	r=-0.14; *p*<0.313	r=-0.17; *p*<0.230	r=-0.25; *p*<0.072	r=-0.04; *p*<0.805	r=-0.01; *p*<0.900
I164T SNP						
CC (n=72)	r=-0.25; *p*=0.030	r=-0.21; *p*=0.075	r=-0.26; *p*=0.026	r=-0.24; *p*=0.040	r=-0.12; *p*=0.306	r=-0.11; *p*=0.362
CT/TT (n=317)	r=-0.22; *p*=0.000	r=-0.22; *p*=0.000	r=-0.20; *p*=0.001	r=-0.20; *p*=0.000	r=-0.09; *p*=0.118	r=-0.20; *p*=0.001

BMI=body mass index; WC=waist circumference; HC= hip circumference; W/H=waist and hip ratio; %Bf=percent body fat

The current results further confirm the importance of adiponectin for obesity, as we found that adiponectin correlated negatively with obesity measures. Though adiponectin involvement in diseases is not precisely known, it's anti-inflammatory, -atherogenic, and -diabetic roles have been identified (DIEZ and IGLESIAS, 2003). It stimulates the expression of molecules involved in enhancing muscle and liver consumption of triglyceride (HE *et al.*, 2003; YAMAUCHI *et al.*, 2003; YAMAUCHI *et al.*, 2001), fatty acid oxidation, inhibition of cholesterol synthesis, lipogenesis, triglyceride synthesis, and tissue glucose uptake (WOLF, 2003). These processes lead to reduced glucose production and insulin resistance subsequently up-regulates muscle insulin signaling and sensitivity (KADOWAKI and YAMAUCHI, 2005; YAMAUCHI *et al.*, 2002). Furthermore, adiponectin inhibits expression of adhesion molecules (OUCHI *et al.*, 1999), inflammatory factors (OUCHI *et al.*, 2000), foam cells (OUCHI, 2001), and smooth muscle cell proliferation and migration (ARITA *et al.*, 2002; FUERST *et al.*, 2012), and uptakes of oxidized LDL (OUCHI, 2001). These roles inhibit inflammatory and adhesion activities suggesting anti-atherosclerotic effects.

Table 3. Obesity Measures According to G276T and I164T SNPs

	Adiponectin (µg/ml)	**Weight** (kg)	**BMI** (kg/m^2)	**WC** (cm)	**HC** (cm)	**W/H** (ratio)	**Bf** (%)
G276T SNP							
GG (n=86)	2442.6±848.5	63.9±18.1	24.9±7.1	78.9±14.2	101.9±14.6	0.77±0.06	33.0±11.0
GT(n=250)	2289.4±990.4*	65.9±16.2	25.5±6.2	79.4±12.3	104.4±12.3	0.76±0.05	32.2±9.3
TT (n=53)	2575.9±809.1	67.2±16.7	25.6±6.2	79.9±11.7	104.7±12.2	0.76±0.05	32.5±9.5
I164T SNP							
CC (n=72)	2540.2±904.5	65.2±17.6	25.1±6.3	78.6±12.1	103.2±13.4	0.76±0.05	30.9±9.7
CT/TT (n=317)	2321.9±946.2	65.7±16.5	25.4±6.4	79.5±12.7	104.0±12.7	0.76±0.05	32.7±9.7

Values are in Mean±SD. BMI=body mass index; WC=waist circumference; HC= hip circumference; W/H=waist and hip ratio; %Bf=percent body fat.

Uniquely, the relationship of adiponectin with obesity measures did not holdup in all participants, rather varied according *ADIPOQ* gene SNPs. After dividing the participants according to *ADIPOQ* variants, the relationships with obesity measures were adjusted for each SNP, G276T and I164T. Adiponectin remained associated with obesity in the participants with GT of the G276T SNP as well as CC and CT/TT of the I164T SNP, while "dissociated" with obesity in the participants with GG and TT of the G276T SNP. This is the first study to show this difference in the relationship according to *ADIPOQ*, gene variants makes difficult to compare the results with previous studies. However, it certainly suggests a regulatory role of this gene variants in this relationship. It seems that the GT of the G276T SNP as well as CC and CT/TT of the I164T SNP are pivotal in the relationship of adiponectin with obesity but not GG and TT of the G276T SNP. Therefore, the data point to the importance of accounting for the *ADIPOQ* genotypes, when considering relationships between adiponectin and obesity measures. These findings are valid in young healthy Jordanian females. Therefore, future studies should verify, confirm, and explain these findings in other genders, age groups, race, and geographical locations. Additionally, the effect of various stimuli including diseases, medications, diet, exercise, and heat exposure on these relationships should also be examined.

Obesity is rapidly spreading throughout the world and associated with detrimental consequences. Therefore, the WHO has called for global surveillance to identify causes and treatment planes to combat obesity. According to the current study, obesity is associated with lower serum adiponectin levels in the participants with *ADIPOQ* genotype GT of the G276T.

Therefore, obese individuals with this genotype should be the target of future treatment planes that include adiponectin.

CONCLUSIONS

The study confirms the value of adiponectin to obesity. However, points to the importance of accounting for different genotypes of *ADIPOQ* gene when examining the relationship between adiponectin and obesity measures in young adult women. Therefore, future studies are still needed to further confirm and explain these results. Additionally, future obesity treatment planes that include adiponectin should take into account *ADIPOQ* SNPs genotypes of individuals.

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ASOCIJACIJA IZMEĐU POLIMORFIZMA PULA GENA ZA ADIPONEKTIN ADIPO-Q GENA SA DEBLJINOM MLADIH ŽENA U JORDANU

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Izvod

Debljina pretstavlja rizik za mnoge bolesti i nezavisan uzrok bolesti i umiranja koji je u porastu na globalnom nivou. Vršena su ispitivanja efekta SNP (Single Nucleotide polymorphisms) *ADIPOQ* gena na debljinu i odnos sa adinopektinom. Ispitivanja su obuhvatila 389 odraslih žena. Genotiping *ADIPOQ* G276T i I164T SNPs su utvrđeni metodom RFLP (Restriction Fragment Length Polymorphysm). Nivo plazme adinopektina je utvrđen ELISA testom. Adinopektin je u korelaciji sa svim merama debljine (p< 0,05%). Kada su podeljene prema genotipu, adinopektin je ostao u korelaciji (<0,05%) sa merama debljine u ispitanika sa GT SNp markera ali ne sa CG i TT polimorfizmom (<0,05%) G276T SNP markera. U odnosu na I164T SNP, korelacija između adiponektina i merama debljine ostaje kod svih genotipova izuzev sa W/H odnosom (težina/visina) i %Bf je ostao je ostao kod CC genotipa and with W/H ratio in CT/TT genotypes. u ispitanika sa CC genotipom i sa odnosom težina/visina kod participanata CC genotype I sa W/H (težina/visina odnos) kod CT/TT genotipova. Dalje analize su pokazala da je adiponektin bio niži (<0,05%) kod ispitanika sa GT odnosno GG i TT genotipova G276T SNP markera. Podac dokazuju efekat adiponectina na gojaznost. Takođe su pokazali značaj *ADIPOQ* SNPs u odnosu između adiponektina i gojaznosti kod mladih odraslih žena.

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