The Relationship of adiponectin level and ADIPOQ gene variants with BMI among young adult women

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\textbf{ABSTRACT}

The current study examined the effect of single nucleotide (SNPs) polymorphisms in the \textit{ADIPOQ} gene (I146T and G276T) on body mass index (BMI) of young adult women. The women were divided into underweight, normal, overweight and obese according to BMI. The circulating levels of adiponectin were measured using commercially available ELISA kits. Genetic polymorphisms were genotyped using the PCR-RFLP method. G276T and I164T SNPs are common in the examined population as the frequency of G allele of 276 SNP was 54.8\% and for the T allele of 164 SNP it was 41.7\%. Circulating adiponectin levels were related to BMI and were lowest in the obese versus overweight, normal weight and underweight groups (p<0.01). However, \textit{ADIPOQ} gene SNPs (I146T and G276T) showed no association with BMI groups. In conclusion, the results may suggest that adiponectin level, but not \textit{ADIPOQ} gene SNPs, is a good indicator to BMI in young adult women.

\textbf{ARTICLE HISTORY}

Received 8 March 2018
Accepted 15 May 2018

\textbf{KEYWORDS}

Adiponectin; ADIPOQ gene; BMI; G276T and I164T SNPs; Jordan; Obesity; Women

\textbf{Introduction}

Obesity is an independent risk factor for early morbidity and mortality and has been implicated in cardiovascular, metabolic, musculoskeletal, immune, and nervous disorders. It has become a global epidemic, especially in developing countries including Jordan. The etiology is multifactorial, with genetic, environmental, socioeconomic, behavioral, and psychological contributions.\textsuperscript{1,2}

Opposites to originally believe, adipose tissue is a dynamic organ that might contribute to whole-body metabolism.\textsuperscript{3} These actions are mediated by cytokines secreted from the adipocytes.\textsuperscript{4,5} Adiponectin is a cytokine that appears to play an important metabolic role, as it has been implicated in controlling insulin sensitivity and lipid metabolism.\textsuperscript{6,7} It is a protein circulating abundantly in the plasma\textsuperscript{8,9} yet it is lowered in patients with obesity,\textsuperscript{10} insulin resistance,\textsuperscript{6} and type 2 diabetes.\textsuperscript{11,12}

The adiponectin gene (\textit{ADIPOQ}) has been located on chromosome 3q27, with polymorphisms that influence the level and activity of adiponectin, SNP 276 (G>T) and I164T. The first is associated with type 2 diabetes,\textsuperscript{13,14} insulin resistance, and obesity,\textsuperscript{15} while the latter is a missense mutation associated with the metabolic syndrome and coronary artery disease (CAD).\textsuperscript{16,17} However, the exact underlying mechanism for these actions are still unclear. Therefore, this study verified the relationship of body mass index (BMI), a measure of obesity, with adiponectin level. Subsequently, the contribution of \textit{ADIPOQ} gene variants (I146T and G276T) to the prevalence of obesity was examined.

\textbf{Materials and methods}

\textbf{Subjects}

Young adult females were invited to participate in the study. Exclusion criteria included known pregnancy, diabetes, and thyroid abnormalities. Written informed consent form was obtained from all participants in accordance with the requirements of the Institutional Review Boards in the university. The subjects were divided into four groups, underweight, normal weight, overweight, and obese according to BMI.
**Sample Collection and Handelling**

Venous blood samples were obtained from participants after fasting overnight. Each sample was distributed in 2 evacuated EDTA tube (4.5 ml) and 1 plain tube (4 ml). Part of the EDTA blood sample was stored at -4 and used for DNA extraction. The remaining EDTA samples and plain blood were centrifuged at 3500xg for 5 minutes and the resulting plasma and serum were isolated and stored at -80 °C until used except for 500 µl of serum were sent to the Health Center of Jordan University of Science and Technology for lipid profile analysis. Lipid profiles were analyzed using the Roche Chemistry Analyzer and Roche kits (Roche Diagnostics, Germany).

**Body mass index**

Body mass index (BMI) of the participants were calculated from their respective height and weight using the following equation: BMI = weight in kg/ (height in meters). Subsequently, the participants were stratified to underweight; ≤ 18.49, normal weight; 18.5-24.9, overweight; 25–29.9, and obese; ≥ 30.19

**Adiponectin plasma Level**

Human Adiponectin ELISA based on sandwich enzyme immunoassay was used for quantitative measurement of human adiponectin. The Human Adiponectin ELISA kit was purchased from R&D systems for research purposes (DuoSet; Minneapolis, MN, USA). Plasma samples were diluted at 1/800 (concentration of reagent diluent solution: plasma) followed by the addition of 100 µl of the diluted plasma into mouse anti-human adiponectin antibody microtiter wells. Streptavidin conjugated to horseradish peroxidase (HRP) was used for detection (R&D; Minneapolis, MN, USA). Reaction steps, incubation times and number of washes after each step were as described the kit instructions. The absorbance was measured spectrophotometrically at 450 nm using an ELx800 microplate reader (BioTek Instruments, Winooski, VT, USA). The concentration of adiponectin was directly proportional to color intensity of the test sample. Finally, the concentration of samples was determined using the standard curve.18

**Molecular analysis**

The polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) technique was used for genotyping18,20,3 DNA was extracted from whole blood using a DNA extraction kit purchased from Promega as described in the protocol. Then the DNA fragments of the SNPs (G276T and I164T) were amplified by using Go Taq Green Master Mix purchased from Promega (Madison, WI, USA) with primers and PCR conditions described in Table 1.

The amplified PCR fragments of G276T and I164T SNPs were restricted with BsmI (3 units/reaction, Fermentas, Germany) and BccI (10 units, Fermentas, Germany) respectively. Restriction conditions were 4 hours at 65 °C for G276T SNP and Overnight at 37 °C for I164T SNP. Reaction

| SNP | PCR conditions | Primers | Fragment length |
|-----|----------------|---------|----------------|
| G276T | Denaturation at 94°C for 5 min 35 cycles of: Denaturation at 94°C for 35 sec Annealing at 58°C for 35 sec Extention at 72 °C for 35 sec | F: 5’-GTCCTAGCCCTTAGTTAATAATGAATG-3’ R: 5’-GAGAAAGGAGATCCAGGTAAGA-3’ | 104 bp |
| I164T | Denaturation at 94°C for 5 min 35 cycles of: Denaturation at 94°C for 1 min Annealing at 60°C for 1 min Extention at 72°C for 1 min | F: 5’-CCC ATT CGC TTT ACC AAG ATC-3’ R: 5’-GAA GAC CTG TGA AGG TG-3’ | 339 bp |
products were subsequently detected on a 3% agarose gel stained with ethidium bromide.

**Statistical analysis**

The genotype distributions of *AQIPOQ* gene SNPs were examined for Hardy–Weinberg equilibrium using Chi square analysis. Statistical procedures (ANOVA and frequency distributions) were performed using SPSS software (Version 19, SPSS Inc Company, USA). P < 0.05 was considered significant.

**Results**

**Participant Characteristics**

Four hundred young women from Northern Jordan agreed to participate in the study. They were divided into underweight (n = 78), normal weight (n = 116), overweight (n = 103), and obese (n = 103), according to BMI. Age, waist circumference, waist to hip ratio, and percent body fat were shown in Table 2.

**Relationship of adiponectin with BMI**

Plasma adiponectin range in the participants was 1.6-3.3 µg/ml. Adiponectin concentration in the plasma correlated with BMI (r = -0.23; p<0.0001). Additionally, as shown in Figure 1, the ANOVA revealed that adiponectin was lowest in the obese versus overweight, normal weight and underweight groups (p<0.01), without differences between the other groups (p>0.05).

**Effect of ADIPOQ polymorphisms on BMI and adiponectin concentration**

Tables 3 and 4, show the distribution of genotypes and alleles of *ADIPOQ* gene SNPs, G276T and I164T. The frequency of G allele of G276T SNP was 54.8%, while it was 45.2% for the A allele. Also the frequency of the C allele of I164T SNP was 58.3% while it was 41.7% for T allele. The distribution of alleles is in Hardy-Weinberg equilibrium.

No differences (p<0.05) in the distribution of *ADIPOQ* gene SNPs G276T (G versus A allele) and I164T genotypes (C versus T allele), according to BMI groups. The ANOVA in Table 5 shows no

![Figure 1](image_url). Plasma adiponectin levels among participants. Plasma adiponectin levels were measured using ELISA procedure. Adiponectin plasma level was lower in obese participants compared to other groups. Data are expressed as mean ± SEM. P < 0.05 was considered significant.

### Table 2. Clinical and biochemical characteristics of the study population.

|                | Underweight (n = 78) | Normal weight (n = 116) | Overweight (n = 103) | Obese (n = 103) | P-value* |
|----------------|----------------------|-------------------------|----------------------|----------------|---------|
| Age (years)    | 21.15±3.134 †        | 21.85±5.334 †           | 24.77±9.07 ‡         | 30.82±12.1 ‡‡  | <0.0001*|
| BMI (kg/m²)    | 17.62±0.858 †        | 22.04±1.657 †           | 26.9±1.305 ‡         | 34.2±4.09 ‡‡  | <0.001* |
| WC             | 65.4±3.231 †         | 72.69±5.316 †           | 82.73±5.65 ‡         | 96.4±9.21 ‡‡  | <0.0001*|
| Waist/hip ratio| 0.74±0.04-            | 0.74±0.046 -            | 0.77±0.054 †         | 0.8±0.067 ‡‡  | <0.0001*|
| % BF           | 23.81±5.5 †          | 27.31±5.316 †           | 33.87±5.60 ‡         | 44.85±7.71 ‡‡ | <0.0001 |
| TC             | 4.17±0.883           | 4.14±0.777              | 4.41±1.021           | 4.65±1.129 ‡  | 0.0001  |
| HDL            | 1.46±0.284           | 1.39±0.28               | 1.39±0.307           | 1.35±0.31 ‡‡  | 0.129   |
| LDL            | 2.33±0.769           | 2.38±0.745              | 2.62±0.887           | 2.74±0.808 ‡‡ | 0.0001  |
| Triglycerides  | 0.81±0.424           | 0.76±0.312              | 0.9±0.347            | 1.29±0.692 ‡‡ | <0.0001 |

Data were represented as mean±SD. *ANOVA test used. Post hoc tests: † = p<0.05 versus underweight, ‡ = p<0.05 versus normal weight, * = p<0.05 versus overweight. WC: waist circumference; BMI: body mass index; WHR: waist to hip ratio; %BF: percent body fat; TC: total cholesterol; HDL: high-density lipoprotein; LDL: low-density lipoprotein.
differences (p>0.05) the participants’ BMI or adiponectin between the G276T or I164T SNP genotypes.

**Discussion**

The current study examined the association of obesity with adiponectin level and genetic variations in young Jordanian women. The results showed correlations of BMI with plasma adiponectin but not with the examined ADIPOQ SNPs, the G276T and I164T.

The incidence of obesity has dramatically increased, reaching global epidemics. Obesity is associated with several adverse effects as it increases the likelihood of various diseases, particularly heart disease, type 2 diabetes, obstructive sleep apnea, cancer, osteoarthritis and asthma. The etiology is multifactorial; most commonly caused by a combination of excessive food energy intake, and lack of physical activity. However, in some cases it is caused by a genetic susceptibility, endocrine disorders, medications, or psychiatric illnesses.

The relationship of adiponectin with BMI, found herein, is consistent with the majority of previous reports, suggesting that adiponectin can positively modify obesity. Studies have shown that elevated circulatory adiponectin is associated with reduced obesity. For example, overexpression of adiponectin by the transgene offsets the development of diet-induced obesity in rats. In addition, administration of adiponectin decreases insulin resistance and circulatory glucose in animal models.

The mechanisms through which adiponectin exerts these metabolic actions are largely unknown. It is believed, however, that adiponectin exerts insulin-mimetic and -sensitizing actions, including...
stimulation of glucose uptake in skeletal muscle and suppression of glucose production in the liver.\textsuperscript{30} In addition, adiponectin has been shown to decrease the influx of fatty acids in the liver and to increase fatty acid oxidation via PPAR activation, which lead to decreased body triglycerides.\textsuperscript{31} In contrast, few studies presented lack of association between adiponectin level and BMI.\textsuperscript{32,33}

The genotype frequencies of G276T SNPs of \textit{ADIPOQ} gene were investigated and no interaction was found between the four BMI groups and genotypic distribution or differences in BMI and adiponectin between the genotypes of G276T and I164T SNPs. Several studies showed no differences in G276T SNP according to BMI groups in various populations. These populations include healthy Japanese,\textsuperscript{34} type 2 diabetics,\textsuperscript{35} black and white women,\textsuperscript{23,26} none-diabetic Koreans,\textsuperscript{36} Chinese with obstructive sleep apnea,\textsuperscript{37} and Framingham offspring type 2 diabetics.\textsuperscript{38}

On the other hand, different studies detected variation according to BMI. For example G/G genotype in women,\textsuperscript{39} a G/T genotype in Italian none-diabetics and Taiwan elderly individuals\textsuperscript{40,41} and G/G or G/T had higher BMI.\textsuperscript{42} Meanwhile, T/T genotype was more frequent in lean individuals than nondiabetic obese Italians.\textsuperscript{43} It appears that G276T polymorphism may not affect BMI in healthy individuals and may be related to BMI only in specific populations. Similarly, I164T polymorphism of adiponectin gene has shown the same trend. No significant association between genotype frequencies of I164T SNP and BMI categories which is in contrast with two studies among Japanese.\textsuperscript{6,17}

It is noteworthy that BMI might be controlled by several environmental and genetic factors. For example, lifestyle plays a crucial role in gaining weight; such as physical activity and exercises, the amount and type of food intake, glycemic load and high-caloric diet.\textsuperscript{44,45} Also, some acquired conditions like hypothyroidism or medications are known to cause weight gain or changes in body composition such as insulin, antidepressants, steroids, certain anticonvulsants (phenytoin and valproate), and hormonal contraception.\textsuperscript{46} Moreover, genetic factors as polymorphisms in various genes controlling appetite and metabolism have been shown to predispose to obesity (e.g. fat mass and obesity associated gene FTO gene), as well as several rare genetic syndromes (e.g. Prader-Willi syndrome).\textsuperscript{47} Therefore, the absence of association does not necessarily indicate a lack of effect because body composition changes may be conferred by a collection of variants rather than a single one.

**Conclusions**

The current study found that plasma adiponectin and BMI correlated negatively, with obese participants showed least adiponectin. However, BMI or adiponectin were not related to G276T and I164T SNPs of \textit{ADIPOQ} gene in young adult women.

**Conflict of interest**

The authors have nothing to declare.

**Acknowledgement**

The current research was fully funded by the Deanship of Research in Jordan University of Science and Technology with grant number OK-MA 111–2014.

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