Effect of Genetic Variations in the ADIPOQ Gene on Susceptibility to Type 2 Diabetes Mellitus

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Background: ADIPOQ (adiponectin) affects fatty acid oxidation, glucose uptake, and glycogen synthesis, all of which are involved in the development of diabetes. As a result, ADIPOQ is being studied as a potential gene for type 2 diabetes mellitus (T2DM), which is a polygenic disease with genetic inheritance. This study aims to investigate the genetic variants (rs17846866 and rs1501299) in the ADIPOQ gene with T2DM in the Saudi population.

Methods: In this study, T2DM patients (n=96) and healthy controls (n=96) were recruited for molecular analysis for rs17846866 and rs1501299 single nucleotide polymorphisms (SNPs). Clinical data were analyzed using t-tests, HWE analysis, and genotype and allele frequencies were calculated for the rs17846866 and rs1501299 SNPs between T2DM cases and controls. ANOVA analysis was also used to investigate the relationship between the SNPs rs17846866 and rs1501299 and T2DM characteristics.

Results: The current study results confirmed a positive association between clinical characteristics, HWE analysis, genotype, and allele frequencies in both rs17846866 and rs1501299 SNPs (p<0.05). In T2DM patients, ANOVA analysis with rs17846866 and rs1501299 SNPs in the ADIPOQ gene has no effect on any of the involved parameters (p>0.05).

Conclusion: This study concludes as rs17846866 and rs1501299 SNPs were strongly associated in the Saudi population with T2DM patients.

Keywords: type 2 diabetes mellitus, T2DM, adiponectin (ADIPOQ) gene, rs17846866 and rs1501299 SNPs

Introduction

Diabetes Mellitus (DM) is a group of metabolic disorders characterized by elevated serum glucose levels or persistent hyperglycemia, as well as abnormalities in insulin secretion and/or action. Diabetes is estimated to affect 439 million people by 2030, representing a 7.7% increase in the number of adults aged between 20–79 years. Type 2 diabetes mellitus (T2DM) has now become a common disease in the entire globe. Around 382 million people were diagnosed with T2DM in 2013, and that number is expected to increase to 592 million in 130 countries by 2035. According to the World Health Organization (WHO), the Kingdom of Saudi Arabia has the second highest prevalence of diabetes in the Middle East and the seventh highest in the world population. T2DM was shown to be extremely common in the Gulf region, with prevalence rates of 25.7% in Bahrain, 16.1% in Oman, 21.2% in Kuwait, and 31.6% in Saudi Arabia. Diabetes was diagnosed in roughly 0.9 million Saudis in 1992, but, by 2010, the figure had climbed to 2.5 million, implying a 2.7-fold increase in incidence rates in just two decades. Diabetes is becoming more common for many reasons, including an aging population and an increase in the obesity rate. Obesity is associated with hypertension, diabetes, cardiovascular diseases (CVD), dyslipidemia, and cancers. T2DM is defined as a chronic heterogeneous group of metabolic and multifactorial disorders with elevated blood glucose levels due to insulin deficiency and impaired insulin secretion from pancreatic β-cells. Diabetes complications can be classified into microscopic (Retinopathy, neuropathy, and nephropathy) and macroscopic (CVD, peripheral artery disease, and stroke) complications. Genetic risk factors are important contributors for the development of human diseases and, in T2DM, both genetic and environmental factors play a major role in disease prognosis. Understanding disease pathogenesis and developing better diagnostic, preventative, and therapeutic methods necessitate the identification of genes. Single nucleotide polymorphisms (SNPs) are the most common type of genetic polymorphisms and are actively applied in genetic mapping and
genome-wide association studies (GWAS). There have been previous GWA studies in other populations that have identified a number of T2DM-related genes. Genes associated to T2DM have been shown in previous studies to increase the likelihood of developing the disease by a moderate amount.\textsuperscript{11} Obesity has been identified as a risk factor for diabetes and it can contribute to insulin resistance. A wide range of biochemical markers (adiponectin (\textit{ADIPOQ}) and leptin) have been associated with obesity and insulin resistance.\textsuperscript{12} Multiple GWAS in European and Asian populations established the \textit{ADIPOQ} locus as the key genetic factor determining blood adiponectin levels.\textsuperscript{13,14} The \textit{ADIPOQ} gene, which is derived from adipose tissue, spans \textasciitilde16 kb on chromosome 3q27 and has been implicated to metabolic syndrome (MetS), T2DM, and CVD. Adiponectin levels are substantially impacted by heredity, with heritability ranging from 30–50%. T2DM, obesity, and coronary heart disease patients have reduced adiponectin levels. \textit{ADIPOQ} is a diabetes susceptibility gene with three exons and two introns.\textsuperscript{15,16} This study used a couple of intronic SNPs (ie, intron 1 and 2). Previously, these SNPs (+10211T>G rs17846866; +276G>T rs1501299) were studied in T2DM, obesity, MetS, and other human diseases.\textsuperscript{12,16–20} T2DM patients in Saudi Arabia have not been examined with the \textit{ADIPOQ} gene. Diabetes is growing more common in Saudi Arabia as a result of obesity and poor nutrition.\textsuperscript{21} This study aimed to investigate \textit{ADIPOQ} intronic SNPs in T2DM patients from Saudi Arabia.

### Materials and Methods

#### IRB Specifics

Ethical grant was approved from Institutional Review Board, college of medicine at King Saud University (KSU). The informed consent form was signed by all patients who participated in this study. The current study was carried out in accordance with the Declaration of Helsinki of 1975 (revised in 2013).\textsuperscript{22}

#### Distribution of Sample Size

The sample size was calculated based on the given formula from Charan and Biswas.\textsuperscript{23} In this case-control study, T2DM was categorized as disease subjects and controls as non-diseased subjects.

\[
\text{Sample size} = \frac{Z_{1-\alpha/2}^2\text{SD}^2}{d^2}
\]

\[
\text{Sample size} = \frac{1.96^2(25)^2}{5^2} = 96
\]

With a confidence level of 95% and a margin of error of 6%, the sample size was determined to be 25 units. Each group had a sample size of 96 participants. Finally, 96 T2DM cases and 96 healthy controls were involved in this study.

#### Clutching of Studied Population

This study has been designed as a single center case-control in KSU hospital in the capital city of the Kingdom. In this study, 192 Saudi participants were enrolled. The main purpose of recruiting the Riyadh city residents is due to the 7.5 million population, which is the highest in the Kingdom of Saudi Arabia. The 192 Saudi participants were bifurcated into 96 subjects diagnosed with T2DM and 96 healthy controls. The inclusion criteria of T2DM cases was recruited based on American Diabetes Association Criteria.\textsuperscript{24} The norms of inclusion criteria should be exceeding the following values for biochemical parameters: Fasting Blood Glucose (FBG) levels should be \textasciitilde7.2 mmol/L, postprandial blood glucose (PPBG) should be \textasciitilde10 mmol/L, and hemoglobin A1c (HbA1c) should cross 7%. T2DM subjects who had low levels of FBG, PPBG, and HbA1c were excluded from this study. The control subjects were recruited based on normal serum levels (FBG, PPBG, and HbA1c), without any complications and normal body mass index (BMI). The exclusion criteria of control subjects were based on elevated serum levels.\textsuperscript{25}

#### Anthropometric Measurements

In this study, age was measured in years, BMI (kg/m\textsuperscript{2}) was calculated using weight in kilograms (kg) and height in centimeters (cm). Normal BMI was 24.9 kg/m\textsuperscript{2}, overweight was between 25.0–29.9 kg/m\textsuperscript{2}, and obesity was classified as
Waist circumference was measured in cm. Diagnostic criteria for hypertension (HTN) were measured based on the 1999 WHO/ISH guidelines using systolic blood pressure (SBP ≥140 mmHg) and diastolic blood pressure (DBP ≥90 mmHg).

Blood Collection
Professional KSU nurses had collected 5 mL of the venous blood from both male and female participants. The withdrawn 5 mL of blood were transferred into 3 mL of coagulant vacutainer tube and the remaining 2 mL of blood were transferred into an ethylenediaminetetraacetic acid anticoagulant vacutainer and further used to measure the HbA1c and extraction of genomic DNA.

Plasma Analysis
The serum was extracted from coagulant blood collected in a plain vacutainer by centrifugation for 10 minutes at 3,000 rpm. The separated serum was used to measure FBG, PPBG, and lipid profile parameters such as high-density lipoprotein cholesterol (HDLC), low density lipoprotein cholesterol (LDLC), total cholesterol (TC), and triglycerides (TG). The HbA1c was evaluated using EDTA blood to detect average blood glucose levels for 90 days.

TaqMan Genotyping Analysis
A NanoDrop spectrophotometer was used to assess the purity of genomic DNA extracted from EDTA blood using the Qiagen kit. Purified genomic DNA was diluted into 10 ng/µL for 192 DNA samples and stored in the freezer until the TaqMan genotyping analysis was performed. Allelic discrimination with designed TaqMan probes was used to examine a couple of intronic SNPs (+10211T>G; rs17846866 in Intron 1 and +276G>T; rs1501299 in Intron 2) in the ADIPOQ gene. Genotyping was carried out for 25 µL using 10 µL of TaqMan master mix, 5 µL of purified H₂O, 5 µL of VIC/FAM probes, and 5 µL of 10 ng/µL of genomic DNA using an ABI 7500 RT-PCR system according to ABI instructions. The PCR was initiated with 95°C as incubation phase, 95°C as polymerase activation, 95°C denaturation, and 60°C as extension step. Genotyping was performed based on the previous studies. Randomly, ten DNA samples were regenotyped to make sure the results were accurate. All samples had the same genotyping analysis.

Statistical Analysis
The statistical analysis was performed using SPSS software (version 21.0). T-tests were used to compare variables between T2DM cases and controls. The Chi-square (χ²) test was calculated to investigate if the ADIPOQ variant genotypes were in Hardy–Weinberg equilibrium (HWE). Different genetic models, genotypes, and allele frequencies were calculated between T2DM cases versus healthy controls using odds ratio (OR), 95% confidence interval (95% CI), and a p-value. One-way ANOVA analysis was performed between +10211T>G and +276A>C variants and baseline features in T2DM cases. The significant p-value was set as <0.05 (p≤0.05).

Results
Analysis of T2DM Cases and Controls Subjects
The anthropometric, biochemical, and clinical parameters of T2DM cases and controls are shown in Table 1. This study included 96 cases of T2DM (59.4% males and 40.6% females) and 96 healthy controls (70.8% of males and 29.2% of females). Their ages ranged from 50–72 years in T2DM patients and 50–70 years in controls. In this study, age (p=0.01), weight (p=0.0001), BMI (p=0.0005), waist circumference (p<0.0001), HbA1c (p<0.0001), FBG (p<0.0001), PPBG (p=0.04), HDLC (p=0.002), and LDLC (p<0.0001) showed a significant association. Both TG (p=0.21) and TC (p=0.056) were not associated. Only SBP (p=0.001) levels were associated with a positive association and DBP (p=0.42) showed a negative association in T2DM cases when compared with controls.

HWE Analysis
Based on previous studies, rs17846866 and rs1501299 SNPs were selected for genotyping. The HWE analysis is defined in Table 2. The call rate of rs17846866/rs1501299 loci was found to be greater than 95%, contributing to the
predictability of the results. The HWE analysis on healthy volunteers found a significant association ($\chi^2=23.47$; $p=0.0001$) in rs1501299 and a lack of association ($\chi^2=1.38$; $p=0.23$) in rs17846866 SNPs.

TaqMan Genotyping Analysis in rs17846866 and rs1501299 SNPs
The discrepancy between T2DM cases and healthy controls was shown to be statistically significant in the presence of TaqMan genotyping in rs17846866 and rs1501299 SNPs. Table 3 defines the allele, genotype, and various genetic models used to compare T2DM cases and controls. The TT (homozygous genotype), TG (heterozygous), and GG (homozygous variant) genotype frequencies in rs17846866 SNP were 52.1%, 33.4%, and 14.0% in T2DM cases and in controls, TT, TG, and GG genotype frequencies were 71.9%, 23.9%, and 4.2%, respectively. Both heterozygous (TG vs TT; OR=1.92; 95% CI=1.01–3.66; $p=0.004$) and homozygous variant (GG vs TT; OR=4.83; 95% CI=1.50–15.55; $p=0.004$) was associated in T2DM cases. Dominant, co-dominant, and recessive models of genotype frequencies were found to be 47.9%, 66.6%, and 85.5% in T2DM cases and 28.1%, 76.1%, and 95.8% in healthy controls. Only the dominant model (OR=2.35; 95% CI=1.29–4.27; $p=0.004$) revealed a positive association, while the co-dominant (OR=0.63; 95% CI=0.33–1.18; $p=0.15$) and recessive models (OR=0.25; 95% CI=0.08–0.80; $p=0.01$) did not. Wild allele (T) and variant

| Table 1 Demographic Data of T2DM and Healthy Controls |
|------------------------------------------------------|
| **T2DM Patients** (n=96)                            |
| Age (years)                                         | 58.6±5.66 |
| Gender (F:M)                                        | 39 (40.6%) | 57 (59.4%) |
| Weight (kg)                                         | 73.4±11.23 |
| Height (cm)                                         | 158.9±7.87 |
| BMI (kg/m²)                                         | 29.1±4.41 |
| Waist Circumference (cm)                            | 93.3±8.01 |
| FBG (mmol/L)                                        | 6.0±2.23 |
| PPBG (mmol/L)                                       | 9.18±16.91 |
| HbA1c (%)                                           | 7.8±0.76 |
| Systolic Blood Pressure (mmHg)                      | 129.1±14.42 |
| Diastolic Blood Pressure (mmHg)                     | 79.47±9.75 |
| HDLC (mmol/L)                                       | 0.66±0.25 |
| LDLC (mmol/L)                                       | 3.72±0.97 |
| Total Cholesterol (mmol/L)                          | 4.96±1.31 |
| Triglycerides (mmol/L)                              | 1.66±0.84 |
| **Healthy Controls** (n=96)                         |
| Age (years)                                         | 56.5±5.57 |
| Gender (F:M)                                        | 28 (29.2%) | 68 (70.8%) |
| Weight (kg)                                         | 64.6±11.34 |
| Height (cm)                                         | 157.2±6.38 |
| BMI (kg/m²)                                         | 26.0±3.89 |
| Waist Circumference (cm)                            | 87.4±6.76 |
| FBG (mmol/L)                                        | 3.81±0.61 |
| PPBG (mmol/L)                                       | 5.16±10.19 |
| HbA1c (%)                                           | 5.4±0.45 |
| Systolic Blood Pressure (mmHg)                      | 119.1±16.43 |
| Diastolic Blood Pressure (mmHg)                     | 78.4±8.29 |
| HDLC (mmol/L)                                       | 0.55±0.30 |
| LDLC (mmol/L)                                       | 2.61±0.76 |
| Total Cholesterol (mmol/L)                          | 4.61±1.21 |
| Triglycerides (mmol/L)                              | 1.52±0.72 |
| **P-value**                                         | 0.01 |

| Table 2 HWE Analysis for rs17846866 and rs1501299 SNPs in ADIPOQ Gene |
|---------------------------------------------------------------|
| **SNPs**           | **Minor Allele** | **p^2** | **2pq** | **q^2** | **X^2** | **HW p-value** |
|-------------------|-----------------|---------|---------|---------|---------|----------------|
| rs17846866        | G               | 0.703   | 0.271   | 0.026   | 1.38    | 0.23           |
| rs1501299         | C               | 0.305   | 0.495   | 0.201   | 23.47   | 0.0001         |

TaqMan Genotyping Analysis in rs17846866 and rs1501299 SNPs
The discrepancy between T2DM cases and healthy controls was shown to be statistically significant in the presence of TaqMan genotyping in rs17846466 and rs1501299 SNPs. Table 3 defines the allele, genotype, and various genetic models used to compare T2DM cases and controls. The TT (homozygous genotype), TG (heterozygous), and GG (homozygous variant) genotype frequencies in rs17846866 SNP were 52.1%, 33.4%, and 14.0% in T2DM cases and in controls, TT, TG, and GG genotype frequencies were 71.9%, 23.9%, and 4.2%, respectively. Both heterozygous (TG vs TT; OR=1.92; 95% CI=1.01–3.66; $p=0.004$) and homozygous variant (GG vs TT; OR=4.83; 95% CI=1.50–15.55; $p=0.004$) was associated in T2DM cases. Dominant, co-dominant, and recessive models of genotype frequencies were found to be 47.9%, 66.6%, and 85.5% in T2DM cases and 28.1%, 76.1%, and 95.8% in healthy controls. Only the dominant model (OR=2.35; 95% CI=1.29–4.27; $p=0.004$) revealed a positive association, while the co-dominant (OR=0.63; 95% CI=0.33–1.18; $p=0.15$) and recessive models (OR=0.25; 95% CI=0.08–0.80; $p=0.01$) did not. Wild allele (T) and variant
allele (G) showed as 0.68 and 0.32 allelic frequencies in T2DM cases and 0.84 and 0.16 in healthy controls and positive association (G vs T; OR=2.36; 95% CI=1.44–3.85; p=0.0005) was detected when compared between two groups.

In another rs1501299 SNP, the AA (homozygous genotype), AC (heterozygous genotype), and CC (homozygous variant) genotype frequencies were 19.8%, 41.7%, and 38.5% in T2DM patients, respectively, 42.7%, 25%, and 32.3% in controls. T2DM was attributed with both heterozygous (AC vs AA; OR=3.59; 95% CI=1.71–7.56; p=0.0005) and homozygous variant (CC vs AA; OR=2.57; 95% CI=1.24–5.31; p=0.009). Dominant, co-dominant, and recessive genotype frequency models were found to be 80.2%, 58.3%, and 61.5% in T2DM cases, and 57.3%, 75%, and 67.7% in healthy controls, respectively. Only the dominant model (OR=3.02; 95% CI=1.58–5.75; p=0.0006) exhibited a positive association, while the co-dominant (OR=0.46; 95% CI=0.25–0.86; p=0.01) and recessive (OR=0.76; 95% CI=0.42–1.37; p=0.36) did not. When comparing the two groups, the wild allele (A) and variant allele (C) revealed 0.59 and 0.41 allelic frequencies in T2DM cases and 0.45 and 0.55 in healthy controls, respectively, and a positive association (C vs A; OR=1.83; 95% CI=1.22–2.74; p=0.003) was detected.

### Genotyping Detection in T2DM Baseline Characteristics with ANOVA Analysis

One-way ANOVA analysis was carried out between genotype frequencies of rs17846866 (+10211T>G) and rs1501299 (+276A>C) SNPs and characteristic features of T2DM patients and displayed in Table 4. Baseline characteristics such as age, weight, height, BMI, waist circumference, HbA1c, FBG, PPBG, and lipid profile parameters such as HDLC, LDLC, TG, and TC were compared between the three genotypes in +10211T>G SNP. The TT genotype levels were found to be high in HbA1c (7.94 ±0.82), PPBG (10.96±23.30), HDLC (0.67±0.25), LDLC (3.94±1.07), and TG (5.13±1.48), and the TG genotype levels were extreme in age (58.75±6.46), weight (58.75±6.46), height (160.47±7.36), waist circumference (94.00±8.19), FBG (6.25±2.44),

| Genotypes/Allele (rs17846866) | T2DM (n=96) | Controls (n=96) | ORs | 95% CI | p-value |
|-------------------------------|-------------|----------------|-----|--------|---------|
| TT (Genotype) | 50 (52.1%) | 69 (71.9%) | 1.92 | 1.01–3.66 | 0.04 |
| TG (Genotype) | 32 (33.4%) | 23 (23.9%) | 4.83 | 1.50–15.55 | 0.004 |
| GG (Genotype) | 14 (14.5%) | 04 (4.2%) | 2.35 | 1.29–4.27 | 0.004 |
| TG+GG vs TT (Dominant Model) | 46 (47.9%) | 27 (28.1%) | 2.57 | 1.24–5.31 | 0.009 |
| TT+GG vs TG (Co-Dominant Model) | 64 (66.6%) | 73 (76.1%) | 0.25 | 0.33–1.18 | 0.15 |
| TT+TG vs GG (Recessive Model) | 82 (85.5%) | 92 (95.8%) | 0.08–0.80 | 0.01 |
| T (allele) | 132 (0.68) | 161 (0.84) | 2.63 | 1.44–3.85 | 0.0005 |
| G (allele) | 60 (0.32) | 31 (0.16) | 1.83 | 1.22–2.74 | 0.003 |

| Genotypes/Allele (rs1501299) | T2DM (n=96) | Controls (n=96) | ORs | 95% CI | p-value |
|-------------------------------|-------------|----------------|-----|--------|---------|
| AA (Genotype) | 19 (19.8%) | 41 (42.7%) | 3.59 | 1.71–7.56 | 0.0005 |
| AC (Genotype) | 40 (41.7%) | 24 (25%) | 2.57 | 1.24–5.31 | 0.009 |
| CC (Genotype) | 37 (38.5%) | 31 (32.3%) | 0.46 | 0.25–0.86 | 0.01 |
| AC+CC vs AA (Dominant Model) | 77 (80.2%) | 55 (57.3%) | 0.42–1.37 | 0.36 |
| AA+AC vs CC (Recessive Model) | 58 (58.3%) | 72 (75%) | 0.76 | 1.22–2.74 | 0.003 |

Table 3 Genotype and Allele Frequencies of rs17846866 and rs1501299 SNPs in the ADIPOQ Gene Were Compared Between T2DM and Healthy Controls

![Table 3](https://doi.org/10.2147/DMSO.S377057)
and TC (6.25±2.44), while only BMI (30.58±3.52) was found in GG genotype. None of the ANOVA analysis revealed a positive association between +1021 T>G SNP and baseline groups (p>0.05). In the +276 A>C SNP, FBG (6.54±2.46), TC (5.01±1.38), and TG levels (1.73±1.08) were shown to be extremely high in the AA genotype. The AG genotype had elevated levels of weight (1.73±1.08), height (159.32±7.43), BMI (30.11±3.87), waist circumference (94.18±8.01), and HDLC levels (94.18±8.01), whereas the CC genotype had increased levels of age (59.15±5.47), HbA1c (7.93±0.75), PPBG (11.45±26.09), and LDLC (3.95±1.06), but there was no statistical association using ANOVA analysis (p>0.05).

**Discussion**

The **ADIPOQ** gene was selected in this study to analyze the genetic role of rs17846866 and rs1201599 SNPs in a Saudi population with patients confirmed with T2DM. Adiponectin has been attributed to metabolic disorders, specifically T2DM/obesity, which is a risk factor. Adiponectin is widely known to be an insulin sensitizing agent, rather than increasing insulin resistance. Several observational studies have indicated that serum adiponectin levels are lower in chronic diseases where insulin resistance is a prominent risk factor. Adiponectin levels are hypothesized to be important in the development of T2DM.\(^2\) Diabetes, particularly T2DM, is becoming more common in the Kingdom. No studies were documented after a rapid screening between **ADIPOQ** gene SNPs in T2DM patients in Saudi Arabia, and thus this study was planned with TaqMan genotyping analysis adopted with VIC and FAM probes.

The basic findings from this study were observed when Table 1 details were compared between both groups and confirmed the major difference between age, weight, height, BMI, waist circumference, FBG, PPBG, HbA1c, HDLC, and LDLC (p<0.05). HWE analysis found a significant association in rs1501299 genotype assay (p<0.05). The TaqMan genotyping analysis confirmed the positive association with rs17846466 (TG+GG vs GG; OR=2.35; 95% CI=1.29–4.27; p=0.004) and rs1501299 SNPs in **ADIPOQ** gene (AC+CC vs AA; OR=3.02; 95% CI=1.58–5.75; p=0.0006). However, ANOVA analysis with rs17846466 and rs1501299 SNPs in the **ADIPOQ** gene in T2DM patients has no effect on any of the involved parameters (p>0.05). Table 3 in this study highlights positive associations in allele frequency, dominant model, heterozygous and homozygous variants, as well as a negative association in co-dominant and recessive models in both rs17846466 and rs1501299 SNPs.

The **ADIPOQ** gene does not directly cause disease but can enhance the effect of environmental factors. SNPs and haplotypes of the **ADIPOQ** gene are associated with obesity, which is a common risk factor for T2DM.\(^2\) The **ADIPOQ**

| Table 4 One-Way Anova Analysis Studies in Diabetes Patients |
|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|
|                | +1021 TT (n=50) | +1021 TG (n=32) | +1021 GG (n=14) | +276 AA (n=19) | +276 AC (n=40) | +276 CC (n=37) | p-value         |
| Age (years)    | 58.66±5.39      | 58.75±6.46      | 58.14±4.95      | 0.94           | 57.47±4.47      | 58.62±6.41      | 0.57           |
| Weight (kg)    | 72.01±13.05     | 75.02±8.71      | 74.98±10.03     | 0.41           | 73.23±14.39     | 76.23±10.43     | 0.71           |
| Height (cm)    | 158.54±8.64     | 160.47±7.36     | 156.68±5.49     | 0.29           | 157.86±8.78     | 159.32±7.43     | 0.79           |
| BMI (kg/m²)    | 28.70±5.15      | 29.22±3.32      | 30.58±3.52      | 0.37           | 29.28±4.70      | 30.11±3.78      | 0.15           |
| Waist Circumference (cm) | 93.44±8.05 | 94.00±8.19      | 91.64±7.65      | 0.65           | 90.84±6.83      | 94.18±8.01      | 0.30           |
| HbA1c (%)      | 7.94±0.82       | 7.81±0.74       | 7.75±0.56       | 0.61           | 7.8±0.77        | 7.8±0.76        | 0.76           |
| FBG (mmol/L)   | 5.83±2.10       | 6.25±2.44       | 6.03±2.24       | 0.70           | 6.54±2.46       | 5.81±1.76       | 0.48           |
| PPBG (mmol/L)  | 10.96±23.30     | 7.41±2.26       | 6.85±1.95       | 0.56           | 7.31±1.35       | 7.69±2.48       | 0.52           |
| HDLC (mmol/L)  | 0.67±0.25       | 0.65±0.24       | 0.63±0.26       | 0.84           | 0.63±0.22       | 0.69±0.25       | 0.57           |
| LDLC (mmol/L)  | 3.94±1.07       | 3.49±0.77       | 3.42±0.85       | 0.055          | 3.66±1.08       | 3.49±0.75       | 0.75           |
| Total Cholesterol (mmol/L) | 1.63±0.88 | 1.72±0.86       | 1.65±0.67       | 0.89           | 5.01±1.38       | 4.92±0.96       | 0.96           |
| Triglycerides (mmol/L) | 5.13±1.48 | 4.79±0.99       | 4.72±1.23       | 0.39           | 1.73±1.08       | 1.67±0.97       | 0.90           |
gene variant rs17846866 (SNP +10211) was correlated with changes in circulatory adiponectin levels. The TT genotype may be the primary factor for elevated levels of circulating adiponectin in T2DM patients. T2DM etiology is linked to rs1501299 polymorphism of the ADIPOQ gene at position 276 (SNP276). The rs1501299 SNP at intron 2 (G-T) demonstrated intriguing phenotypes with regard to plasma adiponectin levels, insulin resistance, and T2DM susceptibility. Patients with GG genotype at 276 had lower plasma adiponectin levels, a higher insulin resistance index, and a greater likelihood of developing T2DM compared to those with TT genotype. T2DM conversion is more likely in people with impaired glucose tolerance who have the SNP rs1501299 T-allele. The rs1501299 variant in ADIPOQ gene is not associated with the size of the impact of twice-weekly exercise training on total and high molecular weight adiponectin levels, despite the fact that regular exercise is recommended for patients with T2DM. A wide range of genetic studies have been published between T2DM patients and ADIPOQ genetic variants. This study identified genetic variants (rs17846866 and rs1501299 SNPs) to be significantly associated, confirming from prior studies on rs17846866 SNP. However, Saxena et al.'s studies showed a negative association. The rs1501299 SNP was found to be associated both positively and negatively in the global studies. A previous meta-analysis of three cohorts of T2DM patients carrying the ADIPOQ gene was previously carried out by the Peter group. Haplotype-based analyses were also consistent with the results of rs10937273, rs12637534, rs16861209, rs822395, rs17366568, rs3774261, rs6444175, and rs17373414 SNPs selection. The ADIPOQ genetic variations have been thoroughly explained. In a multi-SNP genotypic risk score for ADIPOQ alleles, three separate SNPs were shown to be associated with T2DM after correcting for adiponectin levels (OR=0.86, 95% CI=0.75–0.99, p=0.0134). An European–Australian community with T2DM did have an increased risk of insulin resistance and MetS because of genetic diversity in ADIPOQ and its receptors, according to the findings of this study. Dong et al. conducted a meta-analysis study on T2DM patients with rs2241766 and rs1501299 SNPs in the ADIPOQ gene. In the end, 53 publications were included, which consist of 9,285 cases with rs2241766 and 14,156 controls, as well as 7,747 cases with rs1501299 and 10,607 controls. The subgroup analysis of the rs2241766 locus revealed a strong association among the three models. For the genetic models of rs1501299 locus, no statistically significant association was found. One of the strengths of this study was the incorporation of sample size calculation, recruitment, and the TaqMan genotyping analysis.

In conclusion, this case-control study in the Saudi population verified the positive association between rs17846866 and rs1501299 SNPs in the ADIPOQ gene with T2DM risk. The limitation of this study was it investigated only two SNPs, missing of adiponectin levels and limited sample size. This study significantly implies that ADIPOQ genetic variants play an important influence in the Saudi capital population. Future studies are required to evaluate whether the additional SNPs identified in the ADIPOQ gene are susceptible markers in the Saudi population.

**Ethical Consideration**

Ethical approval was obtained from the authors previous institute (KSU); the author is presently working in SEU.

**Disclosure**

The author declares there is no conflict of interest towards this study.

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