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RESEARCH

# Investigation of *AMPD1* rs17602729, *PPAR-α* rs4253778, *ADRB2* rs1042713 and *ADRB3* rs4994 Polymorphisms in Diabetic Obese and Non-Obese Diabetic Groups

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## Abstract

Gene polymorphisms influencing mechanisms such as energy metabolism, fat storage, and insulin sensitivity can contribute to or have protective effects against the development of obesity and diabetes. Therefore, understanding the impact of genetic factors on the risk of obesity and diabetes is crucial for the development of individualized treatment and prevention strategies. We aimed to investigate the factors of obesity in diabetic patients in terms of *AMPD1, PPAR-α, ADRB2,* and *ADRB3* gene polymorphisms, as well as biochemical parameters. This case-control study included 99 diabetic obese patients and 99 non-obese diabetic patients. *AMPD1, PPAR-α, ADRB2* and *ADRB3* gene polymorphisms were detected using real-time polymerase chain reaction. Biochemical parameters were assayed using AU5800 Series Clinical Chemistry Analyzers. *AMPD1, ADRB3*, and *PPAR-α* gene polymorphisms were associated with BMI in diabetic patients ($p<0.05$). Non-obese diabetic patients with the G allele of the *PPAR*-α rs4253778 polymorphism showed an increase in BMI ($p=0.019$). In addition, carriage of the A allele of the *ADRB2* rs1042713 polymorphism was associated with approximately 7-fold higher odds of obesity compared with the GG genotype (OR=7.188, 95% CI: 2.383–21.675, $p<0.001$), whereas carriage of the C allele of the *ADRB3* rs4994 polymorphism was associated with approximately 2.5-fold higher odds of obesity compared with the TT genotype (OR=2.478, 95% CI: 1.254–4.895, $p=0.008$). The genetic variations observed in the studied genes, particularly their relationship with body mass index (BMI), propose a potential association with obesity risk in diabetic individuals. The development of obesity in diabetic individuals may vary from person to person, with genetic factors playing a significant role in this process.

**Keywords** Diabetes · Obesity · *AMPD1* · *ADRB2* · *ADRB3* · *PPAR-α*

## Introduction

Obesity is a significant and chronic disease that occurs when excess fat tissue accumulates in the body due to the imbalance between energy intake and expenditure [1, 2]. Obesity, which is caused by etiological factors such as unbalanced and incorrect nutrition, sedentary life, genetics, endocrine diseases, age, and gender, causes chronic diseases such as type 2 diabetes (T2DM), dyslipidemia, hypertension, cancer, and cardiovascular diseases. Polymorphisms emerge as potent contributors in forging a molecular bridge between obesity and T2DM, precipitating genetic alterations within these pivotal pathways. Specifically, genetic variants influencing insulin secretion and sensitivity exert a pronounced effect, augmenting the risk profile for both obesity and T2DM [3–5].

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Many candidate genes that can be associated with obesity have been identified to play a role in the molecular mechanisms of the conversion of carbohydrates and lipids into energy [6–9].

Adrenoceptor-β receptor genes (*ADRB1*, *ADRB2*, and *ADRB3*), known to be associated with energy metabolism, are found in blood vessels, heart, respiratory system, skeletal muscle, and adipose cells. *ADRB* genes play an important role in both the regulation of inflammatory cytokines and body mass index [10–12]. *ADRB2*, from this gene family, consists of 413 amino acids and is located on chromosome 5q31-32 [13]. The ADRB3 receptor gene is located on chromosome 8p11.1-p12, consists of 2 exons, and is encoded with 408 amino acids [14]. Polymorphisms in the *ADRB2* and *ADRB3* genes have been associated with alterations in energy metabolism and lipolysis in adipose tissue. While this situation causes an increase in BMI and obesity, it also increases the tendency to T2DM [10, 15–17].

The *AMPD1* gene is located on chromosome 1p13.1. It is closely related to energy metabolism, especially in striated muscles [18]. *AMPD1*, one of the important parts of energy metabolism, catalyzes the deamination of adenosine monophosphate (AMP) into inosine monophosphate (IMP) [19, 20].

The peroxisome proliferator-activated receptor (*PPAR-α*) gene is located on chromosome 22q13.3 [21]. *PPAR-α* gene has very important roles in the regulation of energy metabolism, especially in liver tissues, by affecting apolipoproteins through fatty acid binding and release, in addition to mitochondrial and peroxisomal β-oxidation [22, 23].

In the literature review, it was determined that there are changes in the prevalence of obesity due to genetic predisposition in different ethnicities. This study aimed to examine the associations between *ADRB2*, *ADRB3*, *AMPD1*, and *PPAR-α* gene polymorphisms and obesity in diabetic patients.

## Materials and Methods

### Selection of Study Group

A total of 99 diabetic obese and 99 non-obese diabetic individuals were included in the present study. The diabetic obese group consisted of patients with type 2 diabetes mellitus (T2DM) diagnosed according to the criteria of the Turkish Diabetes Association and who met the criteria for obesity. Informed consent was obtained from all individual participants included in the study. Patients signed informed consent regarding the publication of their data. Experimental stages of the study were performed at Istanbul University, Aziz Sancar Experimental Medicine Research Institute, Department of Molecular Medicine. The Ethics Committee Approval of the present study was obtained from Istanbul University in accordance with the Declaration of Helsinki, Faculty of Medicine the Ethical Committee Decree No. 13.05.2016/09. Foundation: Research Fund of the Scientific and Technological Research Council of Turkey (TUBITAK 1003) (Project No: 116E827).

### Biochemical and Genetic Analyses

Five ml blood samples that were taken from individuals were centrifuged at 3000 g for 15 min and the serum samples were stored at −80° C until the analysis day. The samples were analyzed in terms of biochemical parameters such as glucose, urea, hemoglobin A1c (HbA1c), Aspartate Aminotransferase (AST), creatinine, Alanine Aminotransferase (ALT), Low-Density Lipoprotein (LDL), High-Density Lipoprotein (HDL), Triglyceride (TG), and Total Cholesterol (TC). The Real-Time Polymerase Chain Reaction Method was used to determine the gene polymorphisms of *ADRB2* rs1042713, *ADRB3* rs4994, *PPAR-α* rs4253778 *and AMPD1* rs17602729. The list of the primers that were used rs1042713&(*ADRB2*); F1: CCTTCTTG CTGGCACCCAATG/F2: CCTTCTTGCTGGCACCCAA TA/R: GCCAGGCCCATGACCAGA, rs4994&(*ADRB3*); F1ATCGTGGCCATCGCCT/F2: ATCGTGGCCATCGCC A/RGCACAGGGTTTCGATGCT, rs4253778&(*PPAR-α*); F1:TGTCATCAAACAGGCCATCCA/F2:CGACGAAGC AGACAAGACCG/R: CGACGAAGCAGACAAGACCA, rs17602729&(*AMPD1*); F1: GCAGCAAAAGTAATGCA ATACTCACG/F2:GCAGCAAAAGTAATGCAATACTC ACA/R: TGTAGACAAGCTGGAAGGCTGAG. For each SNP, the genotyping assay used two allele-specific forward primers (F1 and F2) and one common reverse primer (R). The data in the literature were used in the analyses. The device with which the reactions were performed was Bio-Rad CFX96 (Bio-Rad, Hercules, CA) and the program that was used for evaluation was CFX Maestro Manager Software (Bio-Rad, Hercules, CA).

### Statistical Analysis

The allele frequencies and genotype distributions of the investigated gene polymorphisms were compared between the diabetic obese and non-obese diabetic groups. A post hoc power analysis was performed using a chi-square contingency table approach ($\alpha = 0.05$, total sample size = 198, df = 2). The achieved statistical power ranged from 23.3% for *AMPD1* rs17602729 to 98.3% for *ADRB2* rs1042713 and was approximately 80% for *ADRB3* rs4994 and *PPAR-α* rs4253778. Statistical analyses were performed using SPSS version 29.0 (SPSS Inc., Chicago, IL, USA). Genotype and allele

distributions were evaluated using contingency-table analyses, whereas biochemical and anthropometric parameters were compared using Student's t-test, as appropriate. Hardy–Weinberg equilibrium (HWE) was assessed separately in the diabetic obese and non-obese diabetic groups for each polymorphism using an exact test, with $p>0.05$ indicating consistency with HWE. Allelic distributions were compared using $2\times2$ contingency tables. In addition, allele-carrier models were evaluated by comparing carriers of the respective allele with the corresponding homozygous reference genotype, and unadjusted odds ratios (ORs) with 95% confidence intervals (CIs) were calculated. Pearson's chi-square test was used when expected cell counts were adequate. Fisher's exact test was used for $2\times2$ comparisons with expected cell counts $<5$, whereas the Fisher–Freeman–Halton exact test was applied to larger contingency tables with sparse expected cell counts. Simple linear regression analyses were performed separately in the diabetic obese and non-obese diabetic groups, with allele-carrier status as the independent variable and BMI or biochemical parameters as dependent variables. The Enter method was used, and model fit was evaluated using $R^2$, adjusted $R^2$, and the overall F-test. Bootstrap analyses based on 1,000 resamples with 95% percentile confidence intervals were also performed. A dominant inheritance model was used for the carrier analyses, in which individuals carrying at least one copy of the respective allele were compared with the corresponding homozygous reference genotype.

## Results

### Biochemical Parameters

A total of 198 participants were included and divided into two groups: non-obese diabetic patients ($n=99$, 50%) and diabetic obese patients ($n=99$, 50%). When comparing groups in terms of biochemical and anthropometric parameters it was observed that age, urea, ALT, TG, and BMI parameters were increased in the diabetic obese group and were statistically significant *($p<0.05$)*, whereas the HDL parameter was significantly increased in the non-obese diabetic group *(respectively, $50.89\pm1.76\rightarrow 46.29\pm1.02$; $p<0.05$)*. No significant difference was found between the groups in terms of AST, TC, LDL, glucose, and HbA1c serum levels (Data shown in Table 1).

### Genotype and Allele Frequencies

In our study, genotype and allele distributions of *AMPD1*, *ADRB2*, *ADRB3*, and *PPAR-α* gene polymorphisms were investigated in the study groups. Hardy–Weinberg equilibrium analysis showed that *AMPD1* rs17602729 was in equilibrium in both the non-obese diabetic and diabetic obese groups ($p=0.292$ and $p=0.065$, respectively). *PPAR-α* rs4253778 was in equilibrium in the non-obese diabetic group ($p=1.000$) but deviated from HWE in the diabetic obese group ($p=0.001$). *ADRB3* rs4994 showed significant deviation from HWE in both the non-obese diabetic and diabetic obese groups ($p=0.002$ and $p<0.001$, respectively). Similarly, *ADRB2* rs1042713 deviated significantly from HWE in both study groups ($p<0.0001$). The genotype distribution of the *ADRB3* gene rs4994 polymorphism was found to be statistically significant among the study groups ($p=0.008$). The T allele of the *ADRB3* gene rs4994 polymorphism exhibited a higher distribution in non-obese diabetic patients (respectively, 125 [63.1%] vs. 100 [50.5%]), while the C allele showed a higher distribution in the diabetic obese group (respectively, 98 [49.5%] vs. 73 [36.9%]), and the difference in allele frequencies was statistically significant ($p=0.011$). Moreover, in the carrier model, carriage of the C allele was associated with approximately 2.5-fold higher odds of obesity compared with the TT genotype (OR = 2.478, 95% CI: 1.254–4.895, $p=0.008$). Similarly, statistical significance was observed in the genotype distribution of the *ADRB2* gene rs1042713 polymorphism, and the AA genotype was not detected in the non-obese diabetic group ($p<0.001$). The G allele exhibited a higher distribution in non-obese diabetic patients (respectively, 122 [61.6%] vs. 98 [49.5%]), while the A allele was more frequent in the diabetic obese group (respectively, 100 [50.5%] vs. 76 [38.4%]), and the difference in allele frequencies was statistically significant ($p=0.015$). Furthermore, in the carrier model, carriage of the A allele was associated with approximately 7-fold higher odds of obesity compared with the GG genotype (OR = 7.188, 95%

**Table 1** Demographic and biochemical data of diabetic obese and non-obese diabetic groups

| Study groups | Non-obese diabetic (n=99, 50%) | | | Diabetic obese (n=99, 50%) | | | Total (n=198) | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| Biochemical Parameters | Min | Max | (Mean±SE) | Min | Max | (Mean±SE) | Min | Max | (Mean±SE) | *p* value |
| Age (years) | 17 | 87 | 50.86±1.51 | 19 | 77 | 55.89±1.02 | 17 | 87 | 53.39±0.924 | ***0.006*** |
| ALT (U/L) | 6 | 71 | 19.60±1.01 | 8 | 71 | 23.27±1.25 | 6 | 71 | 21.45±0.81 | ***0.024*** |
| TG (mg/dL) | 40 | 583 | 139.64±8.53 | 51.5 | 815 | 189.82±13.42 | 40 | 815 | 164.33±8.09 | ***0.002*** |
| HDL (mg/dL) | 19 | 151 | 50.89±1.76 | 23 | 68 | 46.29±1.02 | 19 | 224.4 | 51.3±1.72 | ***0.025*** |
| BMI (kg/m2) | 17.7 | 29.7 | 24.801±0.31 | 30 | 48.9 | 35.996±0.44 | 17.7 | 48.9 | 30.4±0.48 | ***<0.0001*** |

The values given as Mean±SE in the table were analyzed using independent-samples t-tests (SE: standard error)

CI: 2.383–21.675, $p<0.001$). The genotype distribution of the *PPAR-α* gene rs4253778 polymorphism was found to be statistically significant between the study groups ($p=0.006$), and the GG genotype was not observed in the non-obese diabetic group. The G allele exhibited a higher distribution in non-obese diabetic patients (respectively, 12 [6.1%] vs. 6 [3.0%]), while the C allele was more frequent in the diabetic obese group (respectively, 192 [97.0%] vs. 186 [93.9%]); however, the difference in allele frequencies was not statistically significant ($p=0.148$). Moreover, in the carrier model, carriage of the G allele was associated with lower odds of obesity compared with the CC genotype (OR = 0.305, 95% CI: 0.095–0.982, $p=0.037$). No statistically significant difference was detected in the genotype and allele distribution of the *AMPD1* gene rs17602729 polymorphism ($p>0.05$). The genotype and allele distributions of the *AMPD1*, *PPAR-α*, *ADRB2*, and *ADRB3* genes are shown in Table 2.

## Biochemical Parameters and Genotypes Frequencies

### Diabetic Obese Patients

The genotype and allele distribution of the *AMPD1* gene rs17602729 polymorphism did not exhibit significant changes; however, an increased BMI was observed in patients with the T allele compared to those with the C allele in the diabetic obese group. Moreover, both alleles were found to be statistically significant concerning the BMI parameter *(respectively, BMI (kg/m$^2$) 37.91→35.9; T allele p = 0.001; C allele p = 0.003)* (Fig. 1). Regression analysis results indicated that the T allele of *AMPD1* gene was significantly associated with BMI (B = 3.267, $p<0.001$), suggesting that individuals carrying T allele have an average BMI that is 3.267 kg/m² higher (Data shown in Table 3). However, Regression analysis indicated that the C allele of *AMPD1* gene has a significant negative association with BMI (B = −13.036, $p=0.003$), suggesting that individuals carrying C allele genotype have an average BMI that is 13.036 kg/m² lower.

In diabetic obese patients carrying the C allele of the *ADRB3* gene rs4994, an increased BMI has been observed *(36.3 ± 0.5→34.2 ± 0.7; p = 0.023)*. However, Regression analysis indicated that, in diabetic patients, carrying the C allele has a positive but not statistically significant association with Body Mass Index (BMI) (B = 2.135, $p=0.078$) (Data shown in Table 3).

The presence of the *PPAR-α* gene rs4253778 G allele in diabetic obese patients was associated with decreased serum levels of ALT and BMI, which was statistically significant *(ALT (U/L) mean ± SE; 23.4 ± 1.3→19.5 ± 1.1; p = 0.043, BMI (kg/m2) mean ± SE; 36.1 ± 0.5→34.3 ± 0.3; p = 0.005)*. Regression analysis indicated that, in diabetic patients, carrying the G allele of rs4253778 has a negative but not statistically significant association with BMI and ALT (BMI; B = −1.715, $p=0.451$, ALT; B = −3.932, $p=0.533$). We observed that in

**Table 2** Genotype and allele frequencies of AMPD1 rs17602729, ADRB3 rs4994, ADRB2 rs1042713, and PPAR-α rs4253778 polymorphisms in the study groups

| Gene & SNPs | Genotypes and alleles | Non-obese diabetic (*n*, %) | Diabetic obese (*n*, %) | *p* value |
|---|---|---|---|---|
| *AMPD1* rs17602729 | TT | 4 (4.0%) | 1 (1.0%) | 0.385 |
| | CT | 42 (42.4%) | 40 (40.4%) | |
| | CC | 53 (53.5%) | 58 (58.6%) | |
| | T allele | 50 (25.3%) | 42 (21.3%) | 0.341 |
| | C allele | 148 (74.7%) | 156 (78.7%) | |
| *ADRB3* rs4994 | TT | 32 (32.3%) | 16 (16.2%) | ***0.008*** |
| | TC | 61 (61.6%) | 68 (68.7%) | |
| | CC | 6 (6.1%) | 15 (15.2%) | |
| | T allele | 125 (63.1%) | 100 (50.5%) | ***0.011*** |
| | C allele | 73 (36.9%) | 98 (49.5%) | |
| *PPAR-α* rs4253778 | GG | 0 (0.0%) | 2 (2.0%) | ***0.006*** |
| | GC | 12 (12.1%) | 2 (2.0%) | |
| | CC | 87 (87.9%) | 95 (96.0%) | |
| | G allele | 12 (6.1%) | 6 (3.0%) | 0.148 |
| | C allele | 186 (93.9%) | 192 (97.0%) | |
| *ADRB2* rs1042713 | GG | 23 (23.2%) | 4 (4.0%) | ***<0.001*** |
| | GA | 76 (76.8%) | 90 (90.9%) | |
| | AA | 0 (0.0%) | 5 (5.1%) | |
| | G allele | 122 (61.6%) | 98 (49.5%) | ***0.015*** |
| | A allele | 76 (38.4%) | 100 (50.5%) | |

Pearson's chi-square test was used when expected cell counts were adequate. Fisher's exact test was used for 2 × 2 comparisons with expected cell counts < 5, and the Fisher–Freeman–Halton exact test was applied to larger contingency tables with sparse expected cell counts. Bold p values indicate statistical significance ($p<0.05$)

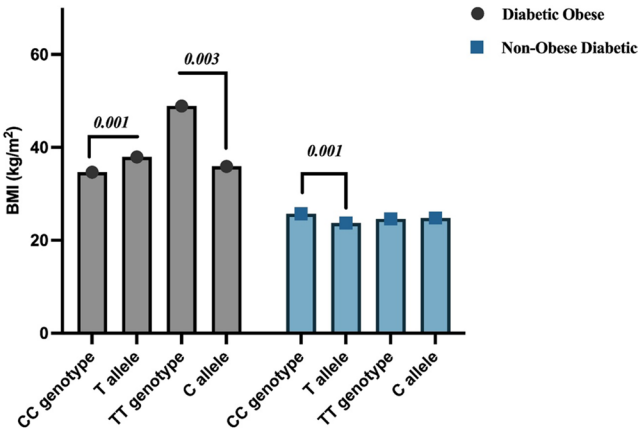


**Fig. 1** Comparison of BMI according to AMPD1 rs17602729 allele-carrier status in diabetic obese and non-obese diabetic patients. In diabetic obese patients, T-allele carriers showed higher BMI compared with the CC genotype group ($p=0.001$), whereas C-allele carriers showed lower BMI compared with the TT genotype group ($p=0.003$). In non-obese diabetic patients, T-allele carriers showed lower BMI compared with the CC genotype group (mean±SE: 23.7±0.4 vs. 25.7±0.4 kg/m²; $p=0.001$)

diabetic obese patients carrying the *PPAR-α* rs4253778 C allele, BMI values were increased, which was also statistically significant *(BMI (kg/m2) mean±SE; 34.9±0.01→36.019±0.4; p=0.016)*. Similar to the G allele, regression analysis indicated that, carrying the C allele of rs4253778 has a positive but not statistically significant association with BMI (B=1.119, $p=0.726$) (Data shown in Table 3).

The presence of the *ADRB2* gene rs1042713 polymorphism G allele in diabetic obese patients was found to be associated with elevated serum LDL levels, which was statistically significant (LDL (mg/dL) mean±SE;100±4.3→123.1±3.4; $p=0.002$) (Data shown in Table 3).

## Non Obese Diabetic Patients

Non-obese diabetic patients carrying the T allele of the *AMPD1* gene rs17602729 exhibit elevated serum LDL levels and decreased BMI *(*LDL (mg/dL) *Mean±SE; 111.7±5.01→134.1±7.7 p=0.014*, *BMI (kg/m2) Mean±SE; 25.7±0.4→23.7±0.4; p=0.001)* (Fig. 1). Carrying the T allele of rs17602729 has a significant negative association with BMI (B = −1.988, $p=0.001$), suggesting that individuals carrying this allele have an average BMI that is 1.988 kg/m² lower (Data shown in Table 4). Moreover, Carrying the T allele of rs17602729 has a significant positive association with LDL levels (B=22.432, $p=0.014$), suggesting that individuals carrying T allele have an average LDL level that is 22.432 mg/dL higher.

**Table 3** Associations of AMPD1, ADRB2, ADRB3 and PPAR-α gene polymorphisms with biochemical parameters in diabetic obese patients

| Genes&SNPs | Genotypes and alleles | ALT (mmol/L) Mean±SE | LDL (mmol/L) Mean±SE | BMI (kg/m2) Mean±SE |
|---|---|---|---|---|
| AMPD1 rs17602729 | CC | 23.8±1.4 | 123.9±4.6 | 34.64±0.3 |
| | T allele | 22.4±2.3 | 119.2±4.8 | 37.91±0.87 |
| | *p1* | *0.581* | *0.488* | ***0.001*** |
| | TT | 15±2.4 | 97±4.3 | 48.9 |
| | C allele | 23.3±1.4 | 122.1±3.3 | 35.9±0.4 |
| | *p2* | *0.5* | *0.441* | ***0.003*** |
| ADRB3 rs4994 | CC | 21.9±2.7 | 124.7±9.2 | 37.2±1.1 |
| | T allele | 23.5±1.4 | 121.4±3.6 | 35.8±0.4 |
| | *p3* | *0.68* | *0.736* | *0.272* |
| | TT | 22.9±2.5 | 120.5±7.7 | 34.2±0.7 |
| | C allele | 23.3±1.4 | 122.1±3.7 | 36.3±0.5 |
| | *p4* | *0.898* | *0.864* | ***0.023*** |
| PPAR-α rs4253778 | CC | 23.4±1.3 | 122±3.4 | 36.1±0.5 |
| | G allele | 19.5±1.1 | 118.2±22.02 | 34.3±0.3 |
| | *p5* | ***0.043*** | *0.82* | ***0.005*** |
| | GG | 20.5±0.5 | 88±23 | 34.9±0.01 |
| | C allele | 23.3±1.2 | 122.6±3.3 | 36.019±0.4 |
| | *p6* | *0.749* | *0.134* | ***0.016*** |
| ADRB2 rs1042713 | AA | 19.8±4.3 | 100±4.3 | 34.6±1.1 |
| | G allele | 23.5±1.3 | 123.1±3.4 | 36.1±0.5 |
| | *p7* | *0.514* | ***0.002*** | *0.485* |
| | GG | 26.7±4.4 | 132±27.8 | 37±1.2 |
| | A allele | 23.1±1.2 | 121.4±3.2 | 36±0.4 |
| | *p8* | *0.564* | *0.731* | *0.654* |

The difference between the groups was analyzed by the student's t-test. The values given as Mean±SE in the table and bold values of $p<0.05$ indicate statistical significance. p1 value represents of T allele and CC genotype; p2 value represents of C allele and TT genotype; p3 value represents of T allele and CC genotype; p4 value represents of C allele and TT genotype; p5 value represents of G allele and CC genotype; p6 value represents of C allele and GG genotype; p7 value represents of G allele and AA genotype; p8 value represents of A allele and GG genotype

**Table 4** Associations of AMPD1, ADRB2, ADRB3 and PPAR-α gene polymorphisms with biochemical parameters in non-obese diabetic patients

| SNPs | Genotypes and alleles | LDL (mmol/L) Mean ± SE | Glucose (mmol/L) Mean ± SE | BMI (kg/m2) Mean ± SE |
|---|---|---|---|---|
| AMPD1 rs17602729 | CC | 111.7 ± 5.01 | 154.8 ± 7.7 | 25.7 ± 0.4 |
| | T allele | 134.1 ± 7.7 | 174.8 ± 11.5 | 23.7 ± 0.4 |
| | *p1* | ***0.014*** | 0.155 | ***0.001*** |
| | TT | 90 ± 24.8 | 122 ± 9.7 | 24.6 ± 0.1 |
| | C allele | 123.5 ± 4.6 | 165.8 ± 7 | 24.8 ± 0.3 |
| | p2 | 0.147 | 0.205 | 0.653 |
| PPAR-α rs4253778 | CC | 120.1 ± 4.6 | 161.1 ± 7.3 | 24.6 ± 0.3 |
| | G allele | 136 ± 18.2 | 184.5 ± 18 | 26.3 ± 0.6 |
| | *p3* | 0.257 | 0.262 | ***0.019*** |
| | GC | 136 ± 18.2 | 184.5 ± 18 | 26.3 ± 0.6 |
| | CC | 120.1 ± 4.6 | 161.1 ± 7.3 | 24.6 ± 0.3 |
| | *p4* | 0.257 | 0.262 | 0.07 |
| ADRB2 rs1042713 | GG | 113.5 ± 8 | 136.1 ± 10.3 | 25.2 ± 0.7 |
| | GA | 124.6 ± 5.4 | 172 ± 8 | 24.7 ± 0.4 |
| | *p5* | 0.315 | ***0.027*** | 0.512 |
| | GG | 113.5 ± 8 | 136.1 ± 10.3 | 25.2 ± 0.6 |
| | A allele | 124.6 ± 5.4 | 172 ± 8 | 24.7 ± 0.3 |
| | *p6* | 0.315 | ***0.027*** | 0.512 |

The difference between the groups was analyzed by the student's t-test. The values given as Mean ± SE in the table and bold values of $p < 0.05$ indicate statistical significance. p1 value represents of T allele and CC genotype; p2 value represents of C allele and TT genotype; p3 value represents of G allele and CC genotype; p4 value represents of CC and GC genotype; p5 value represents of GG and GA genotype; p6 value represents of A allele and GG genotype in non-obese diabetic patients

No statistical significance was observed in terms of biochemical parameters in non-obese diabetic patients with the *ADRB3* gene rs4994 polymorphism ($p > 0.05$). (Data shown in Table 4).

Non-obese diabetic patients with the G allele of the *PPAR-α* gene rs4253778 polymorphism showed an increase in BMI (BMI (kg/m2);24.6 ± 0.3→26.3 ± 0.6; $p = 0.019$). However, Regression analysis indicated that, in diabetic patients, carrying the G allele of rs4253778 has a positive but not statistically significant association with BMI (B = 1.744, $p = 0.070$) (Data shown in Table 4).

Non-obese diabetic patients carrying the A allele of the *ADRB2* gene rs1042713 polymorphism exhibited increased glucose and HbA1c serum levels (Glucose (mg/dL) Mean ± SE= 136.1 ± 10.3→172 ± 8; $p = 0.027$, HbA1c (%) Mean ± SE = 7.3 ± 0.3→8.4 ± 0.3; $p = 0.022$). Regression analysis indicated that, in diabetic patients, carrying the A allele of rs1042713 has a significant positive association with glucose levels (B = 35.898, $p = 0.027$). Moreover, carrying the A allele of rs1042713 has a significant positive association with HbA1c levels (B = 1.028, $p = 0.046$).

## Discussion

Obesity and T2DM present formidable global health challenges, with increasing recognition of the pivotal role played by genetic factors in their pathogenesis. Recent research endeavors have made substantial headway in pinpointing genetic variations that escalate susceptibility to obesity and T2DM [3]. These variations, typically manifesting as polymorphisms, serve as linchpins in elucidating the intricate nexus between genetic predisposition and disease manifestation. In the current study, we analyzed selected genes of the *AMPD1*, *ADRB2*, *ADRB3* and *PPAR- α gene* polymorphism in patients with diabetic obese and non-obese diabetic patients.

*PPAR-α* plays a significant role in lipid and carbohydrate metabolism by regulating metabolic processes such as fatty acid metabolism, glucose homeostasis, and anti-inflammatory responses. Polymorphisms in the *PPAR-α* gene can influence the function of this receptor and thus affect lipid and glucose metabolism [23]. Raj et al. found that the *PPAR-α* G allele exhibited a protective effect against T2DM, whereas the C allele increased susceptibility to the development of T2DM [24]. Ortega et al. showed that the rs4253778 SNP was significantly associated with serum LDL levels [25]. In our study, while statistically significant differences were found in ALT serum levels and BMI values between individuals carrying the C allele of the *PPAR-α* gene rs4253778 in diabetic obese patients, regression analysis indicated that the association was not statistically significant.

*AMPD1* gene polymorphisms may contribute to the development of obesity by affecting energy metabolism [20, 26]. Safranow et al. reported that the *AMPD1* polymorphism CC genotype has been associated with a decreased frequency of obesity and diabetes in coronary artery disease [26]. Nemati et al. found that the frequency of hypertension was

9.94 times higher in the T allele carriers than in the C carriers and no TT genotype was observed in the control group [27]. In our study, it was observed that diabetic individuals carrying the T allele of *AMPD1* gene rs17602729 exhibited an increased BMI in the obese subgroup, whereas a decreased BMI was noted in the non-obese subgroup with the T allele. Furthermore, a significant association was observed between elevated LDL serum levels and the T allele of *AMPD1* gene rs17602729 in non-obese diabetic patients.

*ADRB2* gene may affect energy expenditure and adipose tissue metabolism, thereby increasing the risk of obesity [11, 28, 29]. Tellechea et al. reported an association between ADRB2 haplotypes and insulin resistance-related traits in women with PCOS [30]. Mitra et al. reported that obese patients with the G allele of *ADRB2 gene rs1042713* had significantly higher total cholesterol and LDL cholesterol levels [28]. We found that the G allele of ADRB2 gene rs1042713 polymorphism in diabetic obese patients associated with elevated serum LDL levels. Furthermore, the A allele of *ADRB2 gene rs1042713* was found to be significant in terms of glucose and HbA1c parameters in non-obese diabetic individuals. Similarly, a previous study reported that the *ADRB2 gene rs1042713* (Arg16Gly) polymorphism is associated with the development of T2DM, and this relationship occurs through changes in BMI and HbA1c [28]. In our study, *ADRB3* gene polymorphism was not found to be associated with biochemical parameters in terms of genotype and allele distribution in non-obese diabetic individuals, while *ADRB3* gene C allele was associated with BMI in diabetic obese patients.

## Conclusion

In our study, the genotype and allele distribution of the examined genes were evaluated along with biochemical parameters, presenting the first data obtained from the Turkish population. The development of obesity in diabetic individuals may vary from person to person, with genetic factors playing a significant role in this process. Specifically, the investigated gene polymorphisms may be associated with pathways related to energy metabolism, fat storage, and insulin sensitivity and may therefore be linked to differences in obesity susceptibility. Therefore, understanding the role of genetic factors in the development of obesity in diabetic individuals may be crucial in developing individualized treatment and prevention strategies. The genetic variations observed in the examined genes, particularly their association with BMI, suggest a potential link with obesity risk in diabetic individuals. These findings are believed to make a significant contribution to the literature as they represent the first data obtained from the Turkish population.

## Limitations

This study has several limitations. First, it was conducted at a single center and employed a case-control design without independent replication, which may limit the generalizability of the findings. Second, multiple comparisons were performed across four gene polymorphisms and several biochemical parameters without adjustment for multiple testing, potentially increasing the risk of type I error. In addition, the study groups were not matched for age, sex, or diabetes duration. A significant age difference was observed between the diabetic obese and non-obese diabetic groups, while data on sex distribution and diabetes duration were not available for further adjustment. Finally, deviations from Hardy–Weinberg equilibrium were observed for some polymorphisms, and these findings should be taken into consideration when interpreting the genetic association results. The relatively low statistical power observed for AMPD1 rs17602729 may have limited the ability to detect smaller genetic effects. Information on medication use and additional glycemic control criteria beyond HbA1c was not available. In addition, formal assessment of population stratification was not performed, and the single-center recruitment strategy may have introduced selection bias.

**Author Contributions** Authors' Contributions: All authors contributed to the conception and design of the study. Study concept and design: S.D. and U.Z.; acquisition of data: S.D., M.K.O. and S.B.A.S.; analysis and interpretation of data: S.D., U.Z., and F.C.; drafting of the manuscript: S.D.; critical revision of the manuscript: U.Z., A.O.G.; statistical analysis: F.C.; study supervision: U.Z.

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**Data Availability** No datasets were generated or analysed during the current study.

## Declarations

**Ethics approval and consent to participate** The Ethics Committee Approval of the present study was obtained from Istanbul University in accordance with the Declaration of Helsinki, Faculty of Medicine the Ethical Committee Decree No. 13.05.2016/09.

**Consent to participate** Informed consent was obtained from all individual participants included in the study. Patients signed informed consent regarding the publication of their data.

**Competing interests** The authors declare no competing interests.

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