ISSN 1022-7954, Russian Journal of Genetics, 2025, Vol. 61, No. 5, pp. 588–595. © Pleiades Publishing, Inc., 2025.

HUMAN GENETICS

Investigation of APOE2 rs7412 and APOA2 rs5082, APOA5 rs662799 and MTHFR rs1801133 Polymorphisms in Diabetic Obese and Non-Obese Diabetic Groups in Turkey

M. K. Ozyavuz[a], S. Durak[b], F. Celik[a], S. B. Aksoyer Sezgin[c], A. O. Gurol[d], Z. Dogan[e], and U. Zeybek[a, *]

[a] *Department of Molecular Medicine, Aziz Sancar Institute of Experimental Medicine, Istanbul University, Istanbul, 34093 Turkey*

[b] *Department of Medical Microbiology, Faculty of Medicine, Istanbul University Cerrahpasa, Istanbul, 34320 Turkey*

[c] *Department of Medical Biology and Genetics, Faculty of Medicine, Istanbul Yeni Yuzyil University, Istanbul, 34010 Turkey*

[d] *Department of Immunology, Aziz Sancar Institute of Experimental Medicine, Istanbul University, Istanbul, 34093 Turkey*

[e] *Programme of First and Emergency Aid, Vocational School of Health Services, Altınbaş University, Istanbul, 34217 Turkey*

**e-mail: zeybekumit67@gmail.com*

Received August 6, 2024; revised September 6, 2024; accepted September 16, 2024

Abstract—Obesity caused by an abnormal increase in adiposyte, is linked to type 2 diabetes. Diabetes is a metabolic-disease that is caused by insulin-deficiency. Type 2 diabetes is a serious implication of obesity and genetic polymorphisms. Apolipoprotein E2 (APOE2)(rs7412), Apolipoprotein A2 (APOA2) (rs5082), Apolipoprotein A5 (APOA5) (rs662799), Methylenetetrahydrofolate reductase (MTHFR) (rs1801133) polymorphisms which were determined to play role in the development of obesity and diabetes, were evaluated with the RT-qPZR in the study. We included 99 diabetic obese and 99 diabetic non-obese people. We investigated the effect of obesity on variants of all gene polymorphisms in diabetic patients. As a result, APOA2, APOE2 polymorphisms were significant, APOA5, MTHFR polymorphisms were not significant in genotype/allele frequency between groups. APOA2 CC-homozygous carriers had high low-density-lipoprotein-c, glucose, body-mass-index in diabetic-obese patients. APOE2 C-allele carriers had significantly high-Triglyceride and low high-density-lipoprotein versus TT-genotype in non-obese diabetic patients. The present study was first in the Turkey population and evaluates the polymorphisms of genes indicated in diabetic patients.

Keywords: diabetes, APOE2, APOA2, APOA5, MTHFR

DOI: 10.1134/S1022795425700115

INTRODUCTION

Obesity is a public health problem associated with adipocyte accumulation due to genetic, epigenetic, and environmental factors [1]. Diabetes Mellitus (DM) is a metabolic disease involving persistent hyperglycemia resulting from a defect in insulin production, insulin action, or both [2]. Genome-wide association studies report the association of different genetic polymorphisms with diabetes and obesity incidence in various ethnicities [3].

Apolipoprotein E (APOE) is a member of the polymorphic apolipoprotein family, consisting of 317 amino acid residues with a 36-kDa molecular mass, that plays a role in cholesterol transport, triglyceride metabolism, transport of lipoproteins between various tissues through plasma and interstitial fluid, and cell membrane maintenance and repair [4, 5]. There are also studies showing that APOE variants are highly associated with the risk of obesity [5, 6].

Genetic studies in humans show associations of obesity and triglyceride-rich lipoprotein with post-nutrition metabolism. Apolipoprotein A2 (APOA2) and Apolipoprotein A5 (APOA5) are genes that play a role in the development of obesity, dyslipidemia, and diabetes. The main function of the APOA5 gene, which is predominantly expressed in hepatocytes, is to retain and transport lipids through the blood, thus enabling the determination of the triglyceride level in the blood [7]. APOA5 gene rs662799, the single nucleotide polymorphism of the APOA5 gene, is one of the most studied, and also it is associated with high triglyceride and LDL-C levels and low HDL-C levels [8]. The APOA2 gene encodes the APOA2 protein, one of the most abundant proteins among HDL-C particles. The minor C allele of the –265T>C (rs5082) genetic variant located in the promoter of the apolipoprotein A-II gene (APOA2), with a frequency ranging from 0.2–0.4, directs APOA2 expression depending on the population [9, 10]. The study reported that this variant interacts with saturated fatty acid intake in

Table 1. Primer sequences for PCR amplification of APOE2 rs7412, APOA2 rs5082, APOA5 rs662790 and MTHFR rs1801133

Genes	Forward primers (5'–3') Forward/Reverse primers (5'–3')	Reverse primers (5'–3')
APOE2 (rs7412)	CCGATGACCTGCAGAAGC CCGATGACCTGCAGAAGA	CAGATGCGTGAAACTTGGTG
APOA2 (rs5082)	AATCCTGCTTCCTGTTGCAC AATCCTGCTTCCTGTTGCAA	TCTTTGGATGCTGCTCACAC
APOA5 (rs662799)	CAGGAACTGGAGCGAAAGTG CAGGAACTGGAGCGAAAGTT	AATGGGCAGGAGTGTGGTAG
MTHFR (rs1801133)	CTGCCCAGTCCCTGTGGTCTCT GCTGCGTGATGATGAAATCGG	GCTGCGTGATGATGAAATCGT

terms of obesity risk in various populations, and individuals with the CC genotype have a higher risk of obesity compared to carriers of the T allele [11, 12]. Most studies in the literature show that individuals homozygous for the C allele have higher levels of BMI, total cholesterol, and obesity. Allele-265T/C is also suggested to have a direct effect on triglyceride and free fatty acids metabolism [13, 14].

MTHFR (Methylenetetrahydrofolate reductase) plays a broad role in homocysteine and folate metabolism through the catalysis of 5,10-methylenetetrahydrofolate to 5-methyltetrahydrofolate. 5-Methyltetrahydrofolate is the circulating form of folate and is used in the remethylation of homocysteine to methionine. C→T transition mutation in exon 4 of the genomic polymorphism MTHFR C677T (rs1801133) plays an essential role in type 2 diabetes [15]. The C/C genotype of MTHFR has lower LDL, triglyceride, and total cholesterol levels; It has been reported that the T/T genotype has higher triglyceride, LDL and total cholesterol levels [16]. There are studies in the literature that MTHFR C677T (rs1801133) gene polymorphism may affect and is associated with the risk of T2DM [17, 18] and obesity [19].

MATERIALS AND METHODS

99 diabetic obese and 99 non-obese diabetic individuals were included in the study. The diabetic obese group was selected from individuals who were diagnosed with diabetes according to the criteria determined by the Turkish Diabetes Association and met the obesity criteria; Individuals with a history of chronic disease were excluded from the study. The origin of all individuals in the study is Turkish. The experimental stages of the study were carried out at Istanbul University Aziz Sancar Experimental Medicine Research Institute, Department of Molecular Medicine.

5 mL blood samples taken from everyone were centrifuged at 3000 *g* for 15 min, and then the serum samples obtained were stored at –80°C until the study day. Examples are 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). Evaluated in terms of biochemical parameters such as the Real-time polymerase chain reaction method was used to determine APOE2 rs7412, APOA2 rs5082, APOA5 rs662799, and MTHFR rs1801133 gene polymorphisms. The list of primers used for amplification of single nucleotide polymorphisms (SNPs) is given in Table 1. Qiagen FlexiGene commercial DNA kit (Qiagen, CA, USA) was used to perform genomic DNA isolation from whole blood. DNA purity was determined based on absorbance at 260 and 280 nm. The device in which the reactions were carried out is Bio-Rad CFX96 (Bio-Rad, Hercules, CA). The program used for evaluation is CFX Maestro Manager Software (Bio-Rad, Hercules, CA). Allele frequencies and genotype distributions of gene polymorphisms in diabetic obese and non-obese diabetic groups were compared. SPSS 21.0 program (SPSS Inc., Chicago, IL, USA) was used for statistical analysis of demographic information. Chi-square (χ^2) test, forward chi-square (χ^2) and Student's *t*-test were applied to show the significance of the difference between groups in terms of biochemical parameters and alleles. Ethics Committee approval for our study was received from Istanbul University Faculty of Medicine (Ethical Committee Decree no. 13.05.2016/09).

RESULTS

Analysis of Biochemical Parameters

The present study includes non-obese diabetics (n = 99, 50%) and diabetic obese people (n = 99, 50%). We compared the groups in terms of biochemical and anthropological parameters. We found that the diabetic obese group had significantly higher age, urea, ALT, and triglyceride parameters ($p < 0.05$), while the non-obese diabetic group had significantly higher HDL parameters ($p < 0.05$). Other parameters

Table 2. Baseline characteristics of the study participants

	Total (n = 198) (Mean ± SE)	Non-obese diabetic (n = 99) (Mean ± SE)	Diabetic obese (n = 99) (Mean ± SE)	p-value
Age, years	53.39 ± 0.924	50.86 ± 1.51	55.89 ± 1.02	***0.006***
Urea, mmol/L	33.54 ± 1.03	31.37 ± 0.98	35.79 ± 1.82	***0.034***
Creatinine, mmol/L	0.81 ± 0.02	0.78 ± 0.02	0.85 ± 0.04	0.08
ALT, mmol/L	21.45 ± 0.81	19.60 ± 1.01	23.27 ± 1.25	***0.024***
AST, mmol/L	19.08 ± 0.54	18.10 ± 0.66	20.03 ± 0.84	0.075
TC, mmol/L	205.99 ± 5.02	200.50 ± 5.63	211.35 ± 8.26	0.281
TG, mmol/L	164.33 ± 8.09	139.64 ± 8.53	189.82 ± 13.42	***0.002***
HDL, mmol/L	51.3 ± 1.72	50.89 ± 1.76	46.29 ± 1.02	***0.025***
LDL, mmol/L	121.99 ± 2.83	122.01 ± 4.58	121.87 ± 3.33	0.968
Glucose, mmol/L	172.92 ± 4.81	163.98 ± 6.81	181.78 ± 6.71	0.064
HbA1c, mmol/L	8.24 ± 0.14	8.14 ± 0.22	8.33 ± 0.19	0.514
Height, cm	164.98 ± 0.66	167.33 ± 0.86	162.66 ± 0.96	***<0.0001***
Weight, kg	82.36 ± 1.29	69.597 ± 1.08	94.99 ± 1.47	***<0.0001***
BMI, kg/m^2	30.4 ± 0.48	24.801 ± 0.31	35.996 ± 0.44	***<0.0001***

The values given as Mean ± SE in the table were analyzed using independent samples t-tests. (Mean ± Standard Error (SE)); $P < 0.005$ values were accepted as significant between the study groups. TC—total cholesterol, TG—triglycerides, HDL—high-density lipoprotein cholesterol, LDL—low-density lipoprotein cholesterol, VLDL—very-low-density lipoprotein cholesterol, HbA1c—hemoglobin A1c, ALT—alanine aminotransferase, AST—aspartate aminotransferase.

showed no significant difference between groups ($p > 0.05$) (Table 2).

Genotype and Allele Frequencies

The genotype and allele distributions of the APOE2, APOA2, APOA4, and MTHR polymorphisms were compared between groups in our study. The genotype distribution of APOE2 polymorphism was found statistically significant between groups ($p < 0.0001$). The diabetes-obese group had a considerably increased T allele of the APOE2 polymorphism compared to the non-obese group (53.5% → 48.5%; $p = 0.002$). Furthermore, diabetic patients with the T allele of the APOE2 polymorphism had a nearly 3-fold increased risk of obesity (OR: 3.04; 95%CI: 1.503–6.131) (Fig. 1). The genotype distribution of the APOA2 polymorphism was statistically significant between study groups ($p = 0.011$). Moreover, diabetic individuals had T allele of the APOA2 polymorphism for the development of obesity was ~4.8 (55.1% → 53%, $p = 0.009$, CI: 1.33–17.5) (Fig. 2). There was no significant relation in terms of genotype and allele distribution of APOA5 and MTHFR polymorphisms in the study group ($p > 0.05$). The distribution of genotype and allele frequencies of APOE2 rs7412, APOA2 rs5082, APOA5 rs662799, and MTHR rs1801133 polymorphisms in study control groups were shown in Table 3.

Biochemical Parameters and Genotypes

We found that increased BMI in patients carrying with C allele of APOE2 polymorphism in the diabetic obese group (mean ± SE; 36.46 ± 0.53, $p = 0.007$). In diabetic obese patients, LDL levels were significantly increased in patients with the CC genotype compared to patients with the TT genotype of the APOA2 polymorphism (respectively, mean ± SE; 158 ± 20.2 → 114.46 ± 9.38, $p = 0.035$). Moreover, we found that in

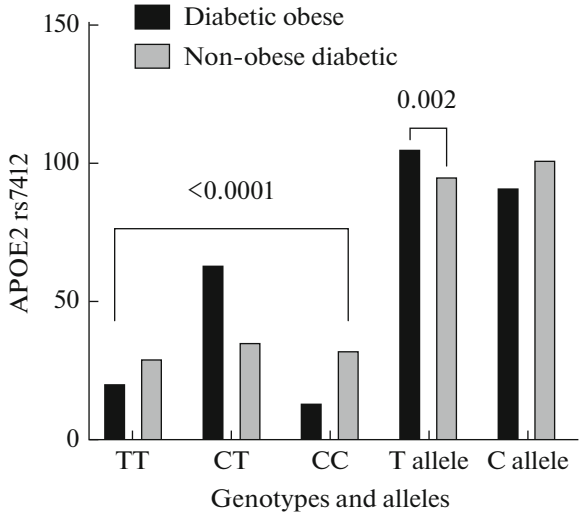

Fig. 1. Genotype and allele frequency of APOE2 rs7412 in the study group.

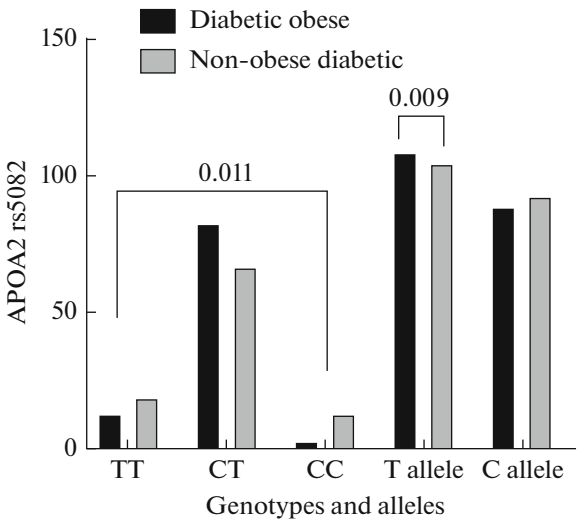

Fig. 2. Genotype and allele frequency of APOA2 rs5082 in the study group.

diabetic obese patients with carried CC genotype of APOA2 both glucose levels and BMI were significantly increased compared to the T allele (respectively, $p = 0.019$; $p < 0.0001$). Diabetic obese patients with the GA genotype of the APOA5 polymorphism were shown a significant increase in LDL (mean ± SE; 135.37 ± 8.51, $p = 0.043$). Furthermore, diabetic obese patients with the C allele of the MTHFR polymorphism were found a significant increase in both BMI and Weight (respectively, $p = 0.025$, $p = 0.015$) (Table 4).

HDL levels were increased in non-obese diabetic patients carrying the APOE2 polymorphism CC genotype and C allele, while increased TG levels were detected in patients carrying the TT genotype. An increase in glucose, TC and LDL levels was observed in non-obese diabetic patients carrying the APOA5 polymorphism AA genotype compared to patients carrying G allele and GA genotype. HDL levels were decreased in non-obese diabetic patients carrying the MTHFR polymorphism C allele, while increased TG levels were detected in patients carrying the T allele (Table 5). No significant association with APOA5 and biochemical parameters ($p > 0.05$).

DISCUSSION

Type 2 diabetes (T2DM) mellitus is a serious implication of obesity and genetic polymorphisms have an effect of a significant impact on biochemical alters such as glucose, lipid, and protein metabolism, may change insulin secretion, and ultimately lead to metabolic diseases. We investigated the effect of obesity on APOE2, APOA5, APOA2, and MTHFR gene polymorphisms in diabetic patients. Our study found that APOE2 rs7412 genotype and allele frequency have a significant relation among the study group. The literature has shown that APOE polymorphisms play an essential role in the increased risk of diabetes [20] and that there is a significant decrease in total and LDL cholesterol in people with the homozygous TT variant of APOE2 rs7412 [21]. Our study showed that C allele carriers had significantly high TG and low HDL versus TT genotype in non-obese diabetic patients. Moreover, the result of the C allele may lead to increased BMI in diabetic obese patients ($p < 0.05$).

The APOA2-265T>C polymorphism (rs5082) is one of the single nucleotide polymorphisms associated with obesity, insulin resistance, and plasma lipid level [22–24]. The study reported that APOA2-265T>C polymorphism and leptin and ghrelin levels, which play an essential role in appetite regulation and body energy balance, are effective in obesity, and serum ghrelin levels are high in patients with the CC genotype [22]. Based on the findings, the distribution of the APOA2 polymorphism genotype and allele frequency was statistically significant between study groups ($p < 0.05$). Moreover, CC homozygous carriers had high LDL-c, Glucose, and BMI in diabetic obese patients. Consistent with our findings, Abaj et al. reported that CC homozygotes were associated with an increased rate of BMI [14].

The literature reported that the frequency of allelic distribution of the APOA5 1131T-C polymorphism is related to the lipid profile, metabolic syndrome [25], diabetic nephropathy [26], cardiovascular disease in children and adolescents with obese [27]. APOA5 protein is considered an essential modulator of triglyceride metabolism and is associated with chylomicrons in plasma. In association studies, polymorphic variants in the gene and increased risk of obesity and metabolic syndrome were examined [28]. Dietary fat intake changes the effect of APOA5 gene polymorphism on serum triglyceride and cholesterol levels and obesity in young individuals [29].

We investigated the distribution of genotype and allele APOA5 polymorphism rs662790 and found no significant association in the study group. On the other hand, our study showed that while LDL, Glucose, and TC levels were found to be high in non-obese diabetic patients carrying the AA genotype, LDL levels were found to be low in diabetic obese patients carrying the AA genotype ($p < 0.05$). This suggests that the AA genotype of APOA5 polymorphism seen in diabetic patients may suggest a risk factor for metabolic syndrome in the study group. Among all single nucleotide polymorphisms identified in the human MTHFR gene, C677T (Ala222Val, rs1801133 C>T) is one of the most studied genetic variations [30].

TT genotype frequency was determined to be highest in Turks (30%), followed by Chinese (18–20%), North Indians (15–17%), and Brazilians (9–13%) [31]. Pathak et al. reported that the MTHFR mutant TT genotype and heterozygous CT genotype were independently associated with an increased risk of T2DM. The results of the current study demonstrated that no significant association were found between the groups in terms of genotype and allele distributions of

Table 3. Genotype and allele frequencies of APOE2 rs7412 and APOA2 rs5082, APOA5 rs662799 and MTHFR rs1801133 polymorphisms in diabetic obese and non-obese diabetic patients

Gene variations	Genotypes and alleles	Diabetic obese, *n* (%)	Non-obese diabetic? *n* (%)	*p*-value
APOE2 rs7412	TT	21 (21.2%)	30 (30.3%)	**<0.0001**
	CT	64 (64.6%)	36 (36.4%)	
	CC	14 (14.1%)	33 (33.3%)	
	T allele	106 (53.5%)	96 (48.5%)	**0.002**
	C allele	92 (46.5%)	102 (51.5%)	0.14
APOA2 rs5082	TT	13 (13.1%)	19 (19.2%)	**0.011**
	TC	83 (83.8%)	67 (67.7%)	
	CC	3 (3.1%)	13 (13.1%)	
	T allele	109 (55.1%)	105 (53%)	**0.009**
	C allele	89 (44.9%)	93 (47%)	0.247
APOA5 rs662799	AA	77 (77.8%)	85 (85.9%)	0.282
	GA	19 (19.2%)	11 (11.1%)	
	GG	3 (3%)	3 (3%)	
	A allele	173 (87.4%)	181 (91.4%)	0.659
	G allele	41 (12.6%)	25 (8.6%)	0.14
MTHFR rs1801133	CC	12 (12.1%)	19 (19.2%)	0.362
	CT	79 (79.8%)	74 (74.7%)	
	TT	8 (8.1%)	6 (6.1%)	
	T allele	103 (52%)	112 (56.5%)	0.579
	C allele	95 (48%)	86 (43.5%)	0.171

The difference between the groups was analyzed by Chi-square (χ^2) test; bold values of $p < 0.05$ indicate statistical significance; $p < 0.005$ values were accepted as significant between the study groups.

Table 4. Biochemical parameters according to APOE2 rs7412, APOA2 rs5082, APOA5 rs662790 and MTHFR rs1801133 polymorphisms in diabetic obese group

Diabetic obese				
Gene variations	Variables	Genotype and allele	Mean ± standard error	*p*-value
APOE2 rs7412	BMI, kg/m^2	TT	34.27 ± 0.61	0.007
		C allele	36.46 ± 0.53	
APOA2 rs5082	LDL, mmol/L	CC	158 ± 20.2	0.035
		TT	114.46 ± 9.38	
	Glucose, mmol/L	CC	267 ± 70.87	0.019
		T allele	179.11 ± 6.49	
	BMI, kg/m^2	CC	37.133 ± 1.93	<0.0001
		T allele	35.96 ± 0.46	
APOA5 rs662790	LDL, mmol/L	AA	118.54 ± 3.52	0.043
		GA	135.37 ± 8.51	
MTHFR rs1801133	BMI, kg/m^2	TT	33.913 ± 0.76	0.025
		C allele	36.18 ± 0.48	
	Weight, kg	TT	89.25 ± 1.76	0.015
		C allele	95.5 ± 1.59	

ANOVA and independent samples *t*-tests were used for inter-group statistical analysis of the parameters used in the study; $p < 0.005$ values were accepted as significant between the study groups.

Table 5. Biochemical parameters according to APOE2 rs7412, APOA5 rs662790, and MTHFR rs1801133 polymorphisms in non-obese diabetic group

Non-obese diabetic				
Gene variations	Variables	Genotype and allele	Mean ± standard error	*p*-value
APOE2 rs7412	HDL, mmol/L	CC	56.694 ± 4.09	0.02
		T allele	48.033 ± 1.59	
		TT	43.103 ± 2.21	0.001
		C allele	54.363 ± 2.22	
		TT	43.103 ± 2.21	0.002
		CC	56.694 ± 4.09	
		TT	43.103 ± 2.21	0.029
		CT	52.238 ± 2.03	
	TG, mmol/L	TT	173.28 ± 21.34	0.036
		C allele	124.344 ± 7.11	
		TT	173.28 ± 21.34	0.02
		CC	124.077 ± 9.34	
		TT	173.28 ± 21.34	0.018
		CT	124.58 ± 10.7	
APOA5 rs662790	Glucose, mmol/L	AA	169.5119 ± 7.55	0.01
		G allele	130.7564 ± 11.6	
	TC, mmol/L	AA	205.1081 ± 5.87	0.05
		G allele	174.3077 ± 16.1	
		AA	205.1081 ± 5.87	0.013
		GA	161.6 ± 16.2	
	LDL, mmol/L	AA	125.388 ± 4.92	0.027
		GA	91.9 ± 11.74	
MTHFR rs1801133	HDL, mmol/L	TT	35 ± 4.93	0.031
		C allele	51.782 ± 1.79	
		TT	35 ± 4.93	0.029
		CC	53.778 ± 2.64	
		TT	35 ± 4.93	0.039
		CT	51.276 ± 2.15	
	TG, mmol/L	CC	108.742 ± 9.31	0.007
		T allele	147.26 ± 10.21	
		CC	108.742 ± 9.31	0.003
		TT	225.017 ± 60.6	
		TT	225.017 ± 60.6	0.015
		CT	140.689 ± 9.63	

ANOVA and independent samples *t*-tests were used for inter-group statistical analysis of the parameters used in the study; $p < 0.005$ values were accepted as significant between the study groups.

MTHFR polymorphism rs1801133 ($p > 0.05$). Despite the no significant results, we found a significant association between the TT genotype effect of low HDL levels and high TG levels in the non-obese diabetic group ($p < 0.05$). On the other hand, the C allele leads to increased BMI in the diabetic obese group ($p < 0.05$).

CONCLUSIONS

The frequency of Diabetes mellitus (DM) is thought to be mostly related to the increasing prevalence of worldwide obesity but the prevalence of non-obese patients with DM is increasing. The pathophysiology of non-obese diabetic patients remains inadequately investigated, and these influences define the patient's treatment. The presented study showed that polymorphic and biochemical differences occur in the presence and absence of obesity in diabetic patients. We found that some genetic polymorphisms are associated with biochemical parameters in diabetic patients and that these vary depending on obesity status. Future studies need to be conducted with a larger sample to better understand the pathophysiology of obesity in diabetic patients. Future studies need to be conducted with a larger sample to better understand the pathophysiology of obesity in diabetic patients. The present study was first in the Turkey population and evaluates the distribution of critical polymorphisms of the genes of APOE2, APOA2, APOA5, and MTHFR in diabetic patients and will contribute to the literature in this manner.

ACKNOWLEDGMENTS

We thank the Scientific and Technological Research Council of Turkey (TUBITAK) for supporting our work. We would also like to thank all the authors who took part in our study for their contributions.

AUTHOR CONTRIBUTION

All authors contributed to the study conception and design. Study concept and design: Mustafa Kerem Ozyavuz and Umit Zeybek; acquisition of data: Sermin Durak, Ramazan Cakmak; analysis and interpretation of data: Saadet Busra Aksoyer Sezgin, Umit Zeybek, Sermin Durak, Faruk Celik and Zeliha Dogan; drafting of the manuscript: Mustafa Kerem Ozyavuz, Saadet Busra Aksoyer Sezgin and Faruk Celik; critical revision of the manuscript: Umit Zeybek and Ali Osman Gurol; statistical analysis: Sermin Durak; study supervision: Umit Zeybek; Funding: Research Fund of the Scientific and Technological Research Council of Turkey (TUBITAK 1003).

FUNDING

This work was supported by the Scientific and Technological Research Council of Turkey (TUBITAK 1003) (Project no. 116E827).

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. The study was approved by the Istanbul University Clinical Research Ethics Committee Decree no. 13.05.2016/09. The authors declare no competing interests. This research involving human participants. Informed consent was obtained from all individual participants included in the study. Patients signed informed consent regarding publishing their data.

CONFLICT OF INTEREST

The authors of this work declare that they have no conflicts of interest.

REFERENCES

1. Ali, E.M.M., Diab, T., Elsaid, A., et al., Fat mass and obesity-associated (*FTO*) and leptin receptor (*LEPR*) gene polymorphisms in Egyptian obese subjects, *Arch. Physiol. Biochem.*, 2021, vol. 127, no. 1, pp. 28–36. https://doi.org/10.1080/13813455.2019.1573841
2. American Diabetes Association, Diagnosis and classification of diabetes mellitus, *Diabetes Care*, 2014, vol. 37, suppl. 1, pp. S81–S90.
3. Cheng, M., Mei, B., Zhou, Q., et al., Computational analyses of obesity associated loci generated by genome-wide association studies, *PLoS One*, 2018, vol. 13, no. 7. https://doi.org/10.1371/journal.pone.0199987
4. Liu, S., Liu, J., Weng, R., et al., Apolipoprotein E gene polymorphism and the risk of cardiovascular disease and type 2 diabetes, *BMC Cardiovasc. Disorders*, 2019, vol. 19, no. 1, p. 213. https://doi.org/10.1186/s12872-019-1194-0
5. Alharbi, K.K., Syed, R., Alharbi, F.K., et al., Association of apolipoprotein E polymorphism with impact on overweight university pupils, *Genet. Test Mol. Biomarkers*, 2017, vol. 21, no. 1, pp. 53–57. https://doi.org/10.1089/gtmb.2016.0190
6. Galal, A.A., Abd Elmajeed, A.A.A., Elbaz, R.A., et al., Association of apolipoprotein E gene polymorphism with the risk of T2DM and obesity among Egyptian subjects, *Gene*, 2021, vol. 15, no. 769. https://doi.org/10.1016/j.gene.2020.145223
7. Ye, H., Zhou, A., Hong, Q., et al., Positive association between *APOA5* rs662799 polymorphism and coronary heart disease: a case–control study and meta-analysis, *PLoS One*, 2015, vol. 10, no. 8. https://doi.org/10.1371/journal.pone.0135683
8. Talmud, P.J., Hawe, E., Martin, S., et al., Relative contribution of variation within the *APOC3/A4/A5* gene cluster in determining plasma triglycerides, *Hum. Mol. Genet.*, 2002, vol. 11, no. 24, pp. 3039–3346. https://doi.org/10.1093/hmg/11.24.3039
9. van't Hooft, F.M., Ruotolo, G., Boquist, S., et al., Human evidence that the apolipoprotein A-II gene is implicated in visceral fat accumulation and metabolism of triglyceride-rich lipoproteins, *Circulation*, 2001,

vol. 104, no. 11, pp. 1223–1228.
https://doi.org/10.1161/hc3601.095709

10. Delgado-Lista, J., Perez-Jimenez, F., Tanaka, T., et al., An apolipoprotein A-II polymorphism (−265T/C, rs5082) regulates postprandial response to a saturated fat overload in healthy men, *J. Nutr.,* 2007, vol. 137, no. 9, pp. 2024–2028.
https://doi.org/10.1093/jn/137.9.2024
11. Corella, D., Peloso, G., Arnett, D.K., et al., APOA2, dietary fat, and body mass index: replication of a gene–diet interaction in 3 independent populations, *Arch. Intern. Med.*, 2009, vol. 169, no. 20, pp. 1897–1906.
https://doi.org/10.1001/archinternmed.2009.343
12. Corella, D., Tai, E.S., Sorli, J.V., et al., Association between the *APOA2* promoter polymorphism and body weight in Mediterranean and Asian populations: replication of a gene–saturated fat interaction, *Int. J. Obesity*, 2011, vol. 35, no. 5, pp. 666–675.
https://doi.org/10.1038/ijo.2010.187
13. Jafari Azad, B., Yaseri, M., Daneshzad, E., et al., Interaction between Apo A-II -265T>C polymorphism and dietary total antioxidant capacity on some anthropometric indices and serum lipid profile in patients with type 2 diabetes mellitus, *J. Nutr. Sci.*, 2021, vol. 10, p. 9.
https://doi.org/10. 1017/jns.2020.61.
14. Abaj, F., Esmaeily, Z., Naeini, Z., et al., Dietary acid load modifies the effects of ApoA2-265T>C polymorphism on lipid profile and serum leptin and ghrelin levels among type 2 diabetic patients, *Endocr. Disord.*, 2022, vol. 22, no. 1, p. 190.
https://doi.org/10.1186/s12902-022-01083-7
15. Ménézo, Y., Patrizio, P., Alvarez, S., et al., MTHFR (methylenetetrahydrofolate reductase: EC 1.5.1.20) SNPs (single-nucleotide polymorphisms) and homocysteine in patients referred for investigation of fertility, *J. Assist. Reprod. Genet.*, 2021, vol. 38, no. 9, pp. 2383–2389.
https://doi.org/10.1007/s10815-021-02200-6
16. Lapik, I.A., Ranjit, R., and Galchenko, A.V., Impact of *KCNJ11* rs5219, *UCP*2 rs659366, and *MTHFR* rs1801133 polymorphisms on type 2 diabetes: a cross-sectional study, *Rev. Diabetic Stud.*, 2021, vol. 17, no. 1, pp. 21–29.
https://doi.org/10.1900/RDS.2021.17.21
17. Meng, Y., Liu, X., Ma, K., et al., Association of *MTHFR* C677T polymorphism and type 2 diabetes mellitus (T2DM) susceptibility, *Mol. Genet. Genomic Med.*, 2019, vol. 7, no. 12.
https://doi.org/10.1002/mgg3.1020
18. Pathak, D., Shrivastav, D., Verma, A.K., and Alsayegh, A.A., Role of metabolizing MTHFR gene polymorphism (rs1801133) and its mRNA expression among type 2 diabetes, *J. Diabetes Metab. Disord.*, 2022, vol. 21, no. 1, pp. 511–516.
https://doi.org/10.1007/s40200-022-01001-7
19. Sarkar, P., Chatterjee, D., and Bandyopadhyay, A.R., Effect of *MTHFR* (rs1801133) and *FTO* (rs9939609) genetic polymorphisms and obesity in T2DM: a study among Bengalee Hindu caste population of West Bengal, India, *Ann. Hum. Biol.*, 2021, vol. 48, no. 1, pp. 62–65.
https://doi.org/10.1080/03014460.2021.1876920
20. Alharbi, K.K., Khan, I.A., and Syed, R., Association of apolipoprotein E polymorphism with type 2 diabetes mellitus in a Saudi population, *DNA Cell Biol.*, 2014, vol. 33, no. 9, pp. 637–641.
https://doi.org/10.1089/dna.2014.2461
21. Smolkova, B., Bonassi, S., Buocikova, V., et al., Genetic determinants of quantitative traits associated with cardiovascular disease risk, *Mut. Res.*, 2015, vol. 778, pp. 18–25.
https://doi.org/10.1016/j.mrfmmm.2015.05.005
22. Basiri, M.G., Sotoudeh, G., Alvandi, E., et al., *APOA2*− 256T>C polymorphism interacts with saturated fatty acids intake to affect anthropometric and hormonal variables in type 2 diabetic patients, *Genes Nutr.,* 2015, vol. 10, no. 3.
https://doi.org/10.1007/s12263-015-0464-4
23. Noorshahi, N., Sotoudeh, G., Djalali, M., et al., APOA II genotypes frequency and their interaction with saturated fatty acids consumption on lipid profile of patients with type 2 diabetes, *Clin. Nutr.,* 2016, vol. 35, no. 4, pp. 907–911.
https://doi.org/10.1016/j.clnu.2015.06.008
24. Jafari Azad, B., Yaseri, M., Daneshzad, E., et al., Interaction between Apo A-II-265T>C polymorphism and dietary total antioxidant capacity on some anthropometric indices and serum lipid profile in patients with type 2 diabetes mellitus, *J. Nutr. Sci.*, 2021, vol. 10, p. 9.
https://doi.org/10. 1017/jns.2020.61
25. Ajjemami, M., Ouatou, S., Charoute, H., et al., Haplotype analysis of the apolipoprotein A5 gene in Moroccan patients with the metabolic syndrome, *J. Diabetes Metab. Disord.,* 2015, vol. 14, no. 1, p. 29.
https://doi.org/10.1186/s40200-015-0160-3
26. Elabd, D. and Fayad, T., ApoA5-1131T→C polymorphism and its effect on triglyceride level in type 2 diabetes patients with nephropathy, *Comp. Clin. Pathol.*, 2014, vol. 23, no. 1, pp. 145–150.
https://doi.org/10.1007/s00580-012-1586-3
27. Zhu, W.F., Wang, C.l., Liang, L., et al., Triglyceride-raising *APOA5* genetic variants are associated with obesity and non-HDL-C in Chinese children and adolescents, *Lipids Health Dis.,* 2014, vol. 13, p. 93.
https://doi.org/10.1186/1476-511X-13-93
28. Ong, K.L., Jiang, C.Q., Liu, B., et al., Association of a genetic variant in the apolipoprotein A5 gene with the metabolic syndrome in Chinese, *Clin. Endocrinol.* (Oxford), 2011, vol. 74, no. 2, pp. 206–213.
https://doi.org/10.1111/j.1365-2265.2010.03899.x
29. Dominguez-Reyes, T., Astudillo-Lopez, C.C., Salgado-Goytia, L., et al., Interaction of dietary fat intake with *APOA2, APOA5* and *LEPR* polymorphisms and its relationship with obesity and dyslipidemia in young subjects, *Lipids Health Dis.*, 2015, vol. 14, p. 106.
https://doi.org/10.1186/s12944-015-0112-4
30. Liew, S.C. and Gupta, E.D., Methylenetetrahydrofolate reductase (MTHFR) *C677T* polymorphism: epidemiology, metabolism and the associated diseases, *Eur. J. Med. Genet.*, 2015, vol. 58, no. 1, pp. 1–10.
https://doi.org/10.1016/j.ejmg.2014.10.004
31. Zhong, J.H., Rodrıguez, A.C., Yang, N.N., et al., Methylenetetrahydrofolate reductase gene polymorphism and risk of type 2 diabetes mellitus, *PLoS One*, 2013, vol. 8, no. 9.
https://doi.org/10.1371/journal.pone.0074521

Publisher's Note. Pleiades Publishing remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.
AI tools may have been used in the translation or editing of this article.