DOI: 10.24938/kutfd.1489519 Kırıkkale Üniversitesi Tıp Fakültesi Dergisi 2024;26(2):227-233
Original Article *Özgün Araştırma*

INSULIN RESISTANCE, SERUM ADIPONECTIN AND ADIPONECTIN GENE POLYMORPHISM IN FIRST- DEGREE RELATIVES OF INDIVIDUALS WITH TYPE 2 DIABETES MELLITUS

Tip 2 Diyabet Mellituslu Hastalarının Birinci Derece Akrabalarında İnsülin Direnci, Serum Adiponektin ve Adiponektin Gen Polimorfizmi

Yasemin KIRAÇ[1] **Murat YILMAZ**[2]

[1] *Department of Internal Medicine, Kırıkkale University School of Medicine, KIRIKKALE, TÜRKİYE*
[2] *Department of Endocrinology and Metabolism, Kırıkkale University School of Medicine, KIRIKKALE, TÜRKİYE*

ABSTRACT

Objective: Investigation of insulin resistance, serum adiponectin levels, and adiponectin gene polymorphism in first-degree relatives of type 2 Diabetes Mellitus (T2DM) patients.

Material and Methods: A total of 142 individuals (34 males, 108 females) meeting the inclusion criteria for first-degree relatives of T2DM patients were included in the study. A control group consisting of 80 (15 males, 65 females) healthy adults was formed. Blood pressure, waist and hip circumferences were measured for all participants. Fasting glucose and insulin levels, lipid profile, serum adiponectin level, and adiponectin gene T94P polymorphism were analyzed, and an oral glucose tolerance test with 75 grams of glucose was conducted. Insulin resistance was calculated using the HOMA-IR method.

Results: HOMA-IR value, total cholesterol, LDL-cholesterol, and triglyceride levels were significantly higher, while HDL-cholesterol level was significantly lower in first-degree relatives of T2DM patients compared to the control group. Glucose tolerance impairment was more prevalent in the study group. Serum adiponectin levels were significantly lower in the study group. Adiponectin gene polymorphism showed a similarity between the two groups.

Conclusion: The higher HOMA-IR and lower serum adiponectin levels detected in first-degree relatives of T2DM patients suggest impairment in metabolic functions in these individuals. However, the genotype distribution of adiponectin gene T94P polymorphism showed a similarity between the study and control groups. Further extensive studies supported by single gene polymorphism and multi-allele investigations, taking into account environmental factors and lifestyle, are needed to determine the effect of adiponectin gene polymorphism on diabetes development and impaired metabolic functions.

Keywords: *Insulin resistance, adiponectin, adiponectin gene polymorphism*

ÖZ

Amaç: Tip 2 Diyabet Mellitus (T2DM) hastalarının birinci derece akrabalarında insülin direnci, serum adiponektin seviyeleri ve adiponektin gen polimorfizminin araştırılması.

Gereç ve Yöntemler: T2DM'li bireylerin birinci derece akrabalarından dahil edilme kriterlerini karşılayan 142 kişi (34 erkek, 108 kadın) çalışmaya dahil edildi. Kontrol grubu 80 sağlıklı yetişkinden (15 erkek, 65 kadın) oluşturuldu. Tüm katılımcıların kan basıncı, bel ve kalça çevreleri ölçüldü. Açlık glukoz ve insülin seviyeleri, lipid profili, serum adiponektin düzeyi ve adiponektin geni T94P polimorfizmi çalışıldı ve 75 gram glukoz ile oral glukoz tolerans testi yapıldı. HOMA-IR yöntemiyle insülin direnci hesaplandı.

Bulgular: T2DM'li bireylerin birinci derece akrabalarında HOMA-IR değeri, Total-Kolesterol, LDL-Kolesterol ve trigliserid düzeyleri kontrol grubuna göre anlamlı yüksek, HDL-Kolesterol düzeyi anlamlı düşük bulundu. Glukoz tolerans bozukluğu çalışma grubunda daha yaygındı. Serum adiponektin düzeyleri çalışma grubunda anlamlı derecede daha düşüktü. Adiponektin geni T94P polimorfizmi için genotip dağılımı iki grup arasında benzerlik gösterdi.

Sonuç: T2DM'li hastaların birinci derece akrabalarında daha yüksek HOMA-IR ve daha düşük serum adiponektin seviyelerinin saptanması bu bireylerde metabolik fonksiyonlarda bozulma olduğunu düşündürmektedir. Ancak adiponektin gen polimorfizmi çalışma ve kontrol grupları arasında benzerlik göstermiştir. Adiponektin gen polimorfizminin diyabet gelişimi ve bozulmuş metabolik fonksiyonlar üzerindeki etkisini belirlemek için, çevresel faktörler ve yaşam tarzı da dikkate alınarak, tek gen polimorfizmi ve multi allel incelemelerle desteklenen daha geniş çalışmalara ihtiyaç vardır.

Anahtar Kelimeler: *İnsülin direnci, adiponektin, adiponektin gen polimorfizmi*

Correspondence / Yazışma Adresi: **Yasemin KIRAÇ**
Department of Internal Medicine, Kırıkkale University School of Medicine, KIRIKKALE, TÜRKİYE
Phone / Tel: +905308768216 **E-mail** / E-posta: kiracyasemin@hotmail.com
Received / Geliş Tarihi: 27.05.2024 **Accepted** / Kabul Tarihi: 03.07.2024

KÜ Tıp Fak Derg 2024;26(2):227-233
Doi: 10.24938/kutfd.1489519

INTRODUCTION

In the pathophysiology of T2DM, there is insulin resistance in the liver, adipose tissue, and muscles, along with impaired insulin secretion in pancreatic beta cells. Insulin resistance disrupts glucose uptake in muscle and adipose tissues, leading to increased glucose output from the liver (1,2). It is known that insulin resistance is the earliest identifiable metabolic disorder that precedes hyperglycemia (3). Both genetic factors and acquired factors such as obesity, aging, and a sedentary lifestyle contribute to insulin resistance (4).

Adiponectin, first described in 1995, is a hormone secreted by adipocytes that plays a crucial role as a messenger in the cross-talk between adipose tissue and other organs (liver, pancreas, and muscles). It possesses insulin-sensitizing, anti-atherogenic, and anti-inflammatory properties. In recent years, numerous studies have investigated the physiological functions of adiponectin in obesity, diabetes, inflammation, atherosclerosis, and cardiovascular diseases. Adiponectin, triggered through appropriate receptors, suppresses glucose production in the liver and enhances fatty acid oxidation in skeletal muscles, thereby improving metabolic control. Beyond its metabolic role, adiponectin protects cells from apoptosis and reduces inflammation at the cellular level through receptor-mediated mechanisms (5).

The adiponectin gene has been identified as a sensitive gene for metabolic syndrome and T2DM. Mutations in the adiponectin gene have been observed to contribute to diabetes development and a decrease in adiponectin levels (6). The adiponectin gene is located on chromosome 3q27 locus and consists of 3 exons and 2 introns. In non-diabetic populations, three genetic polymorphisms have been identified in the adiponectin gene, one being common and the other two being rare: Silent T-G change at nucleotide 94 (exon 3) (prevalence approximately 25%),T-C change resulting from a faulty mutation at nucleotide 331 (exon 3), T-C change resulting from a faulty mutation at nucleotide 383 (exon 3) (7).

This study aims to evaluate insulin resistance, serum adiponectin level, and adiponectin gene T94P polymorphism in first-degree relatives of individuals with T2 DM.

MATERIALS AND METHODS

This study was conducted between October 2004 and April 2005 with patients who visited the Internal Medicine and Endocrinology outpatient clinics at Kırıkkale University Faculty of Medicine. The study protocol was approved by the Kırıkkale University Faculty of Medicine Ethics Committee with decision number 2005/104 on June 24, 2005. A total of 142 cases (34 males, 108 females; aged 18-65) were selected from the first-degree relatives of T2DM patients who presented to our outpatient clinic.The control group consisted of 80 healthy adults who presented to the internal medicine outpatient clinic for routine check-ups and did not have type 2 diabetes mellitus in first-degree relatives.

Individuals with known diabetes mellitus, controlled hypertension, malignancy, liver or kidney failure, congestive heart failure, and those with endocrine disorders such as hyperthyroidism, hypothyroidism, acromegaly, as well as those using insulin-sensitizing medications (metformin, thiazolidinediones) were not included in the study. This study protocol was approved by the Kırıkkale University Faculty of Medicine Ethics Committee. Written consent was obtained from all participants.

The weights of all cases included in the study were measured in kilograms (kg), and their heights were measured in centimeters (cm). Body Mass Index (BMI) was calculated using the formula weight (kg)/height^2(m^2). As a criterion for regional fat distribution, waist circumference was measured in centimeters between the lowest point of the ribs and the iliac crest, and hip circumference was measured in centimeters at the point of the maximum gluteal prominence; the waist/hip ratio was calculated.

Fasting plasma glucose and insulin levels, lipid profile, and serum adiponectin levels were measured, and adiponectin gene T94P polymorphism was investigated. A 75-gram oral glucose tolerance test (OGTT) was conducted: after a 12-hour fasting period following a 3-day 300-gram carbohydrate diet, baseline serum glucose measurement was taken, and glucose levels were assessed at the 120th minute after the ingestion of 75 grams of oral glucose.

The criteria for diabetes diagnosis were as follows:

- Symptoms of diabetes (polydipsia, increased urine volume, unexplained weight loss) along with a randomly measured plasma glucose level of 200 mg/dL (11.1 mmol/L) or higher.
- Fasting plasma glucose level of 126 mg/dL (7.0 mmol/L) or higher after at least an 8-hour overnight fast.
- A 2-hour blood glucose level of 200 mg/dL or higher after a standard 75-gram glucose load (8).

Impaired fasting glucose (IFG) is defined as fasting plasma glucose level between 100-126 mg/dl after an overnight fast, with a blood glucose level below 140 mg/dl at the 2-hour mark of the OGTT; Impaired glucose tolerance (IGT) is characterized by 2-hour glucose level between 140-200 mg/dl, whether or not fasting plasma glucose is less than 100 mg/dl.

Insulin resistance was calculated using the HOMA-IR method (9). Insulin and blood sugar samples were collected at 0, 5, and 10 minutes after a 12-hour fast, and

KÜ Tıp Fak Derg 2024;26(2):227-233
Doi: 10.24938/kutfd.1489519

the average values were calculated. HOMA-IR was calculated using the formula: fasting glucose (mmol/liter) X fasting insulin (µU/ml)/22.5.

Serum lipid profile measurements, including serum total cholesterol (Total-C), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), and triglyceride (Tg) levels, were performed on all cases after a minimum 12-hour overnight fast using the Abbott Aeroset autoanalyzer and original kits.

Serum adiponectin levels were measured using the Elisa method with the B-Bridge International kit. Adiponectin gene T94P polymorphism was investigated using the PCR-RFLP method.

Blood samples from both the patient and control groups included in the study were collected in EDTA tubes. If immediate isolation from the blood samples was not possible, they were stored at -30°C and later isolated according to the specifications of the test kit (EZ DNA). For the determination of adiponectin T94G polymorphism, the forward primer 5' TAG AAG TAG ACT CTG CTG AGA TG 3 and the reverse primer 5' CTC CCT GTG TCT AGG CCT TAG 3' were selected. The PCR conditions applied according to the selected primers are as follows: 0.6 µl of each primer pair, 8 µl of MgCl2 (25 mM), 2 µl of dNTP (10 mM), 5 µl of PCR buffer, 0.3 µl of Taq DNA polymerase (5 U/50 µl), and 5 µl of DNA (250 ng) were combined with 34.1 µl of distilled water. After enzymatic digestion with *Bsp*HI restriction enzyme, the resulting products were loaded onto a 3% agarose gel and subjected to electrophoresis. Individuals with the wild-type genotype (TT) showed a 423 bp band, individuals with the homozygous mutant genotype (GG) showed bands at 265 and 158 bp, and individuals with the heterozygous genotype exhibited bands at 423, 265, and 158 bp (10).

The Mann-Whitney U test was employed to evaluate parametric measurements between groups. Pearson correlation analysis was performed to determine the relationship between variables. For the statistical evaluation of survey findings, Fisher's exact test or the continuity-corrected chi-square test was used to examine differences between qualitative variables in the two groups. A significance level of $p<0.05$ was considered.

RESULTS

Compared to the control group, there was no statistically significant difference in BMI and age among first-degree relatives of individuals with T2DM. Waist circumference and W/H ratio were found to be higher in the first-degree relatives of individuals with T2DM compared to the control group ($p<0.05$). The demographic and metabolic characteristics of the groups are presented in Table 1.

Table 1. Demographic and metabolic characteristics of first-degree relatives of patients with type 2 diabetes mellitus

	Study (n=142)	**Control (n=80)**	**p**
Female/male	108/34	65/15	
Age (year)	37.70±10.84	36.60±12.34	>0.05
BMI (kg/m^2)	28.57±5.13	28.36±4.83	>0.05
Waist circumference (cm)	93.55±12.70	89.32±9.81	<0.05
Waist/hip	0.88±0.06	0.95±0.05	<0.05
Fasting glucose (mg/dl)	92.89±13.08	86.89±8.45	>0.05
Fasting insulin (µU/ml)	9.28±5.46	6.39±2.44	<0.05
HOMA-IR	2.26±1.29	1.67±1.01	<0.05
Total cholesterol (mg/dl)	185.15±42.01	158.9±39.34	<0.05
LDL-C (mg/dl)	111.28±29.52	93±18.45	<0.05
HDL-C (mg/dl)	46.82±10.89	54.31±19.16	<0.05
Triglycerides (mg/dl)	145.65±72.29	103.64+22.43	<0.05
Adiponectin (ng/ml)	1.12±0.94	3.05±1.38	<0.05

BMI:Body mass index, HOMA-IR: Homeostatic Model Assessment- Insulin Resistance, LDL-C:Low-density lipoprotein cholesterol, HDL-C: High-density lipoprotein cholesterol, p: Statistical significance level for the comparison between the two groups.

Glucose Tolerance Disorders - Insulin Resistance Parameters

In first-degree relatives of individuals with T2DM, total cholesterol, LDL-C, and triglyceride levels, HOMA-IR and fasting insulin levels were found to be higher, while HDL-C levels were found to be lower compared to the control group ($p<0.05$ respectively, Table 1, Graph 1). Among first-degree relatives of individuals with T2DM, according to OGTT, 74.1% (80 cases) of 108 female subjects had NGT, 9.3% (10 cases) had IFG, 14.8% (16

KÜ Tıp Fak Derg 2024;26(2):227-233
Doi: 10.24938/kutfd.1489519

cases) had BGT, and 1.8% (2 cases) were diagnosed with T2DM. Among 34 male subjects, 52.9% (18 cases) were classified as NGT, 32.3% (11 cases) as IFG, 11.7% (4 cases) as BGT, and 2.9% (1 case) as T2DM (Table 2). In the control group, 6.6% (1 case) of 15 male subjects had IFG, while 3.8% (2 cases) of 65 female subjects had BGT, and 1.5% (1 case) were diagnosed with T2DM (Table 2). When compared with first-degree relatives of individuals with T2DM, these rates were significantly lower in the control group ($p<0.05$).

Table 2: OGTT Results according to gender in participants enrolled in the study

	Study			Control		
OGTT	**Male**	**Female**	**Total**	**Male**	**Female**	**Total**
NGT, n /%	18/52.9	80/74.1	98/69.0	14/93.3	62/95.3	76/95
IFG, n/%	11/32.3	10/9.3	21/14.7	1/6.6	0	1.2
IGT, n/%	4/11.7	16/14.8	20/14.0	0	2/3.0	2.5
T2DM, n/%	1/2.9	2/1.8	3/2.1	0	1/1.5	1.2

OGTT: Oral glucose tolerance test, NGT: Normal glucose tolerance, IFG: Impaired fasting glucose, IGT: Impaired glucose tolerance, T2DM: Type 2 diabetes mellitus.

Adiponectin

Compared to the control group, a low level of serum adiponectin was found in first-degree relatives of individuals with T2DM ($p<0.05$) (Table 1) (Figure 1).

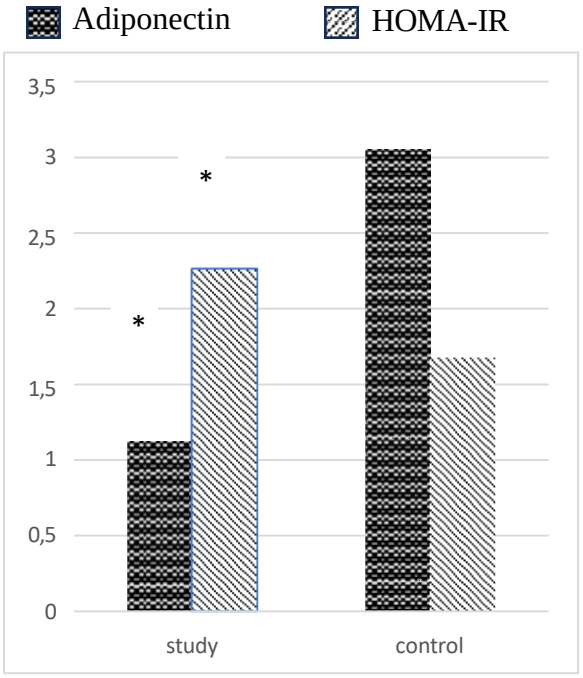

Figure 1: Serum adiponectin levels and HOMA-IR values in first-degree relatives of individuals with T2DM and the control group. *: $p<0.05$ compared to the control group

Adiponectin Gene T94P Polymorphism

In the first-degree relatives of individuals with T2DM, the adiponectin gene polymorphism was investigated in a total of 114 cases. Among these, the TT genotype was observed in 78% (89 cases), TG genotype in 17.5% (20 cases), and GG genotype in 4.3% (5 cases). In the control group, the TT genotype was found in 75% (60 cases), TG genotype in 20% (16 cases), and GG genotype in 5% (4 cases). There was no significant difference in the occurrence rates of adiponectin T94P gene polymorphism between first-degree relatives of individuals with T2DM and the control group (Graph 2, $p>0.05$). However, the GG genotype was slightly lower in the study group compared to the control group (Figure 2).

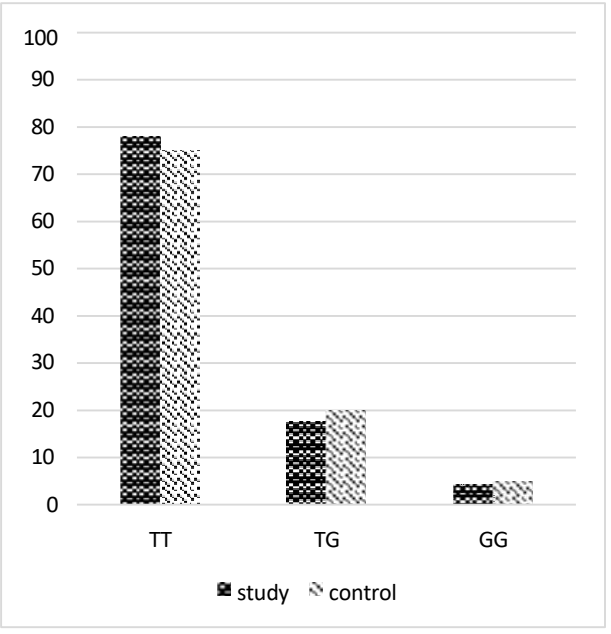

Figure 2: Percentage rates of adiponectinT94P gene polymorphism in first-degree relatives of T2DM cases and the control group

When looking at the cardiometabolic markers among the three gene polymorphisms in first-degree relatives of T2DM cases, no statistically significant difference was observed. Despite being statistically insignificant, the individuals with GG polymorphism had higher age but lower waist circumference, waist/hip ratio, fasting glucose, total cholesterol and triglyceride levels and higher HDL-C, fasting insulin and adiponectin levels when compared to other two polymorphism groups (Table 3).

KÜ Tıp Fak Derg 2024;26(2):227-233
Doi: 10.24938/kutfd.1489519

Table 3: Demographic and metabolic findings in subgroups of adiponectin gene polymorphism in first-degree relatives of T2DM cases.

	TT	GG	TG	Total	p
N	89	5	20	114	
Age	37.89±10.20	46.40±15.83	36.10±9.83	37.95±10.48	>0.05
BMI (kg/m^2)	29.14±5.49	29.50±3.77	28.25±3.79	29.00±5.15	>0.05
Waist circumference (cm)	94.51±12.93	93.00±8.15	93.10±8.86	94.19±12.08	>0.05
Hip circumference (cm)	105.64±12.11	109.00±10.04	107.25±13.32	106.07±12.18	>0.05
Waist/hip	0.88±0.06	0.85±0.03	0.86±0.06	0.88±0.06	>0.05
Fasting glucose (mg/dl)	93.15±12.13	92.40±11.99	93.05±18.30	93.10±13.26	>0.05
Fasting insulin (μU/ml)	9.33±5.73	11.08±4.29	10.35±4.73	9.59±5.50	>0.05
HOMA- IR	2.26±1.34	2.61±1.33	2.56±1.10	2.33±1.30	>0.05
Total cholesterol	185.83±40.61	179.60±44.46	171.20±41.16	182.99±40.87	>0.05
LDL-C	112.30±28.88	114.60±19.52	105.80±27.42	110.26±28.22	>0.05
HDL-C	46.24±11.36	50.40±8.29	46.05±7.72	46.39±10.66	>0.05
Triglycerides (mg/dl)	145.20±67.19	135.00±47.25	141.75±55.59	144.14±64.19	>0.05
Adiponectin (ng/ml)	1.04±0.92	1.24±1.01	1.06±0.85	1.05±0.90	>0.05

BMI:Body Mass Index, HOMA-IR: Homeostatic Model Assessment- Insulin Resistance, LDL-C: Low-density lipoprotein cholesterol, HDL-C: High-density lipoprotein cholesterol

DISCUSSION

The key findings of our study include the following points: The first-degree relatives of individuals with T2DM had higher waist circumference and waist/hip ratio when compared to healthy control cases. Additionally, HOMA-IR and serum fasting insulin levels, as well as total cholesterol, LDL-C and triglyceride levels were significantly elevated, while serum adiponectin and HDL-C levels were lower. However, in terms of BMI comparison, no significant difference was observed. Regarding the occurrence rates of adiponectin gene polymorphism, no significant difference was observed between first-degree relatives of individuals with T2DM and the control group.

Insulin resistance plays an important role in the pathogenesis of T2DM (4). Volk et al., found that the frequency of insulin resistance among first-degree relatives of individuals with T2DM is 40%. In the same study, it was discovered that insulin-resistant first-degree relatives had significantly increased insulin secretion following oral glucose intake compared to insulin-sensitive first-degree relatives (11). Han et al. discovered that within the first-degree relatives of individuals with T2DM, 19.2% received a new diagnosis of T2DM based on WHO criteria following OGTT, while 19.2% exhibited IFG and/or IGT, and 51.2% had NGT (12). In our study, consistent with the literature, it was found that first-degree relatives of individuals with type 2 DM had higher rates of glucose intolerance and HOMA-IR values compared to the control group.

Adiponectin, also known as ADIPOQ, is an adipocyte-derived adipokine encoded by a gene located on chromosome 3q27, spanning 17 kb of the genome. It consists of 3 exons and 2 introns, and it encodes a protein containing 247 amino acids (13). Adiponectin plays a role in regulating glucose and lipid metabolism, cardiovascular function, and correcting insulin resistance. It possesses anti-inflammatory, anti-diabetic, and anti-atherogenic properties. Additionally, low levels of circulating adiponectin are associated with central obesity, insulin resistance, metabolic syndrome, and T2DM. When vascular endothelium is damaged, adiponectin interacts with collagen in the vascular intima, leading to its accumulation in the subintimal layer of the arterial wall. It has been found that adiponectin acts directly on endothelial cells, serving an anti-atherogenic function (6,7,14). In an experimental study conducted by Okamoto et al., it was demonstrated that the accumulation of subendothelial adiponectin in the region where vascular injury was induced via catheterization occurred, resulting in a decrease in serum adiponectin levels, while no accumulation did occur in healthy vascular areas (15). Adiponectin increases insulin sensitivity by disrupting TNF-α signaling. It has been found that adiponectin is under the control of PPAR-γ during adipocyte differentiation. PPAR-γ prioritizes an increase in serum adiponectin levels. Studies have shown a decrease in serum adiponectin levels in individuals with T2DM (10). In our study, serum adiponectin levels were found to be lower in first-degree relatives of individuals with T2DM compared to the control group. Additionally, some studies have reported a significant decrease in serum adiponectin levels in first-degree relatives of individuals with T2DM (15). In another study, serum fasting adiponectin levels were found to be significantly lower in first-degree relatives of individuals with T2DM

KÜ Tıp Fak Derg 2024;26(2):227-233
Doi: 10.24938/kutfd.1489519

compared to first-degree relatives with NGT and IGT (16). In another study, similar adiponectin levels were found in first-degree relatives of individuals with type 2 DM and the control group. However, in the first-degree relative group, there was no relationship found between serum adiponectin levels and insulin sensitivity. Nevertheless, in the same study, significantly lower serum adiponectin levels were observed in subcutaneous adipose tissue of first-degree relatives of individuals with type 2 DM compared to the control group (17). T2DM development involves complex mechanisms. However, abnormalities in adiponectin gene polymorphisms and plasma adiponectin levels have been associated with diseases. In this context, plasma adiponectin levels are closely correlated with insulin resistance and are decreased in patients with T2DM. Studies have reported on the relationship between single nucleotide polymorphisms (SNPs) in the *ADIPOQ* gene and metabolic diseases (18). The four most intriguing genetic variants of adiponectin have attracted increasing attention among researchers. These include +45T>G (rs2241766) located in exon 2, +276G>T (rs1501299) located in intron 2, and −11377C>G (rs266729) and −11391G>A (rs17300539) located in the promoter region (19). Many genetic variants have been identified in the adiponectin gene, and the association of these adiponectin polymorphisms with T2DM has been investigated through a series of studies conducted on various ethnic populations (20-23). However, the results are contradictory; while some studies show positive associations, others have shown the opposite. It has been observed that the +45T>G (rs2241766) and +276G>T (rs1501299) variants are closely associated with susceptibility to T2DM in the Japanese population (22). However, in French or Swedish Caucasians, this association has not been found (24,25). Again, in a meta-analysis, no significant association was found between the +45T>G (rs2241766) and +276G>T (rs1501299) variants and T2DM among Asians and Caucasians (26). In our study, the group consisting of a total of 114 individuals, who were first-degree relatives of individuals with type 2 DM, showed higher BMI and lower adiponectin levels. However, genotype distribution of adiponectin gene T94P polymorphism (TT, TG, GG) was observed to be similar to the control group. In a meta-analysis conducted by Panpan et al., it was revealed that individuals with the rs266729 G allele have a 13% higher risk of developing T2DM compared to those without the G allele. The rs266729 variant in the adiponectin gene was shown to be a susceptibility locus for T2DM, with individuals carrying the G allele being more prone to developing T2DM compared to those without the G allele. In the future, comprehensive examinations of gene-gene and gene-environment interactions should be explored to further elucidate the effects of multiple susceptibility genes on the development of T2DM (27). One possible explanation for this variation is that different populations may have experienced diverse environmental influences throughout their evolutionary processes. Additionally, it has been concluded that different lifestyles and sample sizes of studies may have contributed to this difference (26).

Our study identified high HOMA-IR values and low adiponectin levels in first-degree relatives of individuals with T2DM, which is consistent with the literature. No significant difference was observed in the occurrence rates of adiponectin gene polymorphism between first-degree relatives of individuals with T2DM and the control group. However, the GG genotype was slightly lower in the study group compared to the control group. When examining the characteristics of the patients carrying the GG genotype, despite being at a more advanced age, lower waist circumference, lower waist-to-hip ratio, lower fasting glucose, lower total cholesterol and triglyceride levels, and higher HDL cholesterol and adiponectin levels were observed. These findings support the significance of the adiponectin gene in regulating glucose and lipid metabolism. In the future, more comprehensive studies are needed to understand the multiple gene interactions in the development of T2DM.

Conflict of Interest: The authors have no conflicts of interest to declare.

Researchers' Contribution Rate Statement: Concept/Design: YK, MY; Analysis/Interpretation: YK,MY; Data Collection: YK, MY; Writer: YK, MY; Critical Review: YK, MY; Approver: YK, MY

*Support and Acknowledgment***:** No financial support was received from any institution or person.

Ethics Committee Approval: The study protocol was approved by the Kırıkkale University Faculty of Medicine Ethics Committee with decision number 2005/104 on June 24, 2005.

REFERENCES

1. DeFronzo RA, Bonadonna RC, Ferrannini E. Pathogenesis of NIDDM. A balanced overview. *Diabetes Care.* 1992;15(3):318-368.
2. DeFronzo RA. Pathogenesis of type 2 diabetes mellitus. *Med Clin North Am.* 2004;88(4):787-835.
3. Pratley RE, Weyer C. The role of impaired early insulin secretion in the pathogenesis of Type II diabetes mellitus. *Diabetologia*. 2001;44(8):929-945.
4. Kitabchi AE, Temprosa M, Knowler WC, et al. Role of insulin secretion and sensitivity in the evolution of type 2 diabetes in the diabetes prevention program: Eeffects of lifestyle intervention and metformin. *Diabetes*. 2005;54(8):2404-2414.
5. Wang ZV, Scherer PE. Adiponectin, the past two decades. *J Mol Cell Biol*. 2016;8(2):93-100.
6. Menzaghi C, Ercolino T, Di Paola R, et al. A haplotype at the adiponectin locus is associated with obesity and other

KÜ Tıp Fak Derg 2024;26(2):227-233
Doi: 10.24938/kutfd.1489519

features of the insulin resistance syndrome. *Diabetes.* 2002;51(7):2306-2312.
7. Stumvoll M, Tschritter O, Fritsche A, et al. Association of the T-G polymorphism in adiponectin (exon 2) with obesity and insulin sensitivity: Interaction with family history of type 2 diabetes. *Diabetes.* 2002;51(1):37-41.
8. American Diabetes A. Screening for type 2 diabetes. *Diabetes Care*. 2003;26 Suppl 1:S21-24.
9. Matthews DR, Hosker JP, Rudenski AS, Naylor BA, Treacher DF, Turner RC. Homeostasis model assessment: Insulin resistance and beta-cell function from fasting plasma glucose and insulin concentrations in man. *Diabetologia*. 1985;28(7):412-419.
10. Yang WS, Hsiung CA, Ho LT, et al. Genetic epistasis of adiponectin and PPAR gamma2 genotypes in modulation of insulin sensitivity: A family-based association study. *Diabetologia*. 2003;46(7):977-983.
11. Volk A, Renn W, Overkamp D, et al. Insulin action and secretion in healthy, glucose tolerant first degree relatives of patients with type 2 diabetes mellitus. Influence of body weight. *Exp Clin Endocrinol Diabetes*. 1999;107(2):140-147.
12. Han XY, Ji LN, Zhou XH. Insulin sensitivity and beta function in the first-degree relatives of type 2 diabetic patients. *Zhonghua Yi Xue Za Zhi*. 2004;84(21):1777-1780.
13. Yuan HP, Sun L, Li XH, et al. Association of adiponectin polymorphism with metabolic syndrome risk and adiponectin level with stroke risk: A meta-analysis. *Sci Rep*. 2016;6:31945.
14. Weyer C, Funahashi T, Tanaka S, et al. Hypoadiponectinemia in obesity and type 2 diabetes: Close association with insulin resistance and hyperinsulinemia. *J Clin Endocrinol Metab*. 2001;86(5):1930-1935.
15. Okamoto Y, Arita Y, Nishida M, et al. An adipocyte-derived plasma protein, adiponectin, adheres to injured vascular walls. *Horm Metab Res.* 2000;32(2):47-50.
16. Osei K, Gaillard T, Schuster D. Plasma adiponectin levels in high risk African-Americans with normal glucose tolerance, impaired glucose tolerance, and type 2 diabetes. *Obes Res.* 2005;13(1):179-185.
17. Lihn AS, Ostergard T, Nyholm B, et al. Adiponectin expression in adipose tissue is reduced in first-degree relatives of type 2 diabetic patients. *Am J Physiol Endocrinol Metab*. 2003;284(2):E443-448.
18. Palit SP, Patel R, Jadeja SD, et al. A genetic analysis identifies a haplotype at adiponectin locus: Association with obesity and type 2 diabetes. *Sci Rep.* 2020;10(1):2904.
19. Gable DR, Hurel SJ, Humphries SE. Adiponectin and its gene variants as risk factors for insulin resistance, the metabolic syndrome and cardiovascular disease. *Atherosclerosis.* 2006;188(2):231-244.
20. Gonzalez-Sanchez JL, Zabena CA, Martinez-Larrad MT, et al. An SNP in the adiponectin gene is associated with decreased serum adiponectin levels and risk for impaired glucose tolerance. *Obes Res.* 2005;13(5):807-812.
21. Vasseur F, Helbecque N, Dina C, et al. Single-nucleotide polymorphism haplotypes in the both proximal promoter and exon 3 of the APM1 gene modulate adipocyte-secreted adiponectin hormone levels and contribute to the genetic risk for type 2 diabetes in French Caucasians. *Hum Mol Genet.* 2002;11(21):2607-2614.
22. Hara K, Boutin P, Mori Y, et al. Genetic variation in the gene encoding adiponectin is associated with an increased risk of type 2 diabetes in the Japanese population. *Diabetes.* 2002;51(2):536-540.
23. Hivert MF, Manning AK, McAteer JB, et al. Common variants in the adiponectin gene (ADIPOQ) associated with plasma adiponectin levels, type 2 diabetes, and diabetes-related quantitative traits: The Framingham offspring study. *Diabetes.* 2008;57(12):3353-3359.
24. Gu HF, Abulaiti A, Ostenson CG, et al. Single nucleotide polymorphisms in the proximal promoter region of the adiponectin (APM1) gene are associated with type 2 diabetes in Swedish caucasians. *Diabetes.* 2004;53 Suppl 1:S31-35.
25. Vasseur F, Helbecque N, Lobbens S, et al. Hypoadiponectinaemia and high risk of type 2 diabetes are associated with adiponectin-encoding (ACDC) gene promoter variants in morbid obesity: Evidence for a role of ACDC in diabesity. *Diabetologia*. 2005;48(5):892-899.
26. Han LY, Wu QH, Jiao ML, et al. Associations between single-nucleotide polymorphisms (+45T>G, +276G>T, -11377C>G, -11391G>A) of adiponectin gene and type 2 diabetes mellitus: A systematic review and meta-analysis. *Diabetologia*. 2011;54(9):2303-2314.
27. Sun P, Liu L, Chen J, et al. The polymorphism of rs266729 in adiponectin gene and type 2 diabetes mellitus: A Meta-Analysis. *Medicine (Baltimore).* 2017;96(47):e8745.