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Investigation of Polymorphisms in PPAR-Ɣ and TRHR Genes and their Impact on Turkish Diabetic and Obese Individuals

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Abstract

Obesity is a multifactorial global health concern strongly associated with metabolic disorders, including type 2 diabetes mellitus, cardiovascular diseases, and metabolic syndrome. Genetic determinants, particularly polymorphisms in the PPARγ and TRHR genes, have been implicated in susceptibility to obesity across diverse populations. This study aimed to investigate the genotype distributions of PPARγ (rs1801282) and TRHR (rs16892496) polymorphisms and to evaluate their associations with metabolic parameters in a Turkish cohort. Genotyping was performed using real-time polymerase chain reaction in a total of 239 individuals, comprising 160 patients with obesity and/or diabetes and 79 healthy controls. In the non-diabetic obese subgroup, individuals carrying the GG genotype showed significantly different body mass index (BMI) values compared with those carrying the CC and CG genotypes ($p = 0.008$). In the control group, carriers of the C allele exhibited significantly higher high-density lipoprotein (HDL) cholesterol levels than carriers of the G allele ($p = 0.034$). Furthermore, BMI values were significantly lower in A allele carriers compared with C allele carriers within the control group ($p = 0.026$). These findings suggest that genetic variation in PPARγ and TRHR may contribute to obesity- and diabetes-related phenotypes and could influence disease susceptibility. However, further large-scale, multi-ethnic studies are warranted to validate these associations and elucidate the underlying molecular mechanisms.

Keywords: Polymorphism; PPAR-γ; TRHR; Diabetes; Obesity

Introduction

Obesity and diabetes mellitus are chronic non-communicable diseases that impose a substantial burden on global healthcare systems. These conditions significantly reduce quality of life and contribute to increased morbidity, mortality, and healthcare expenditures. According to the World Health Organization (WHO), approximately 1.9 billion adults were overweight in 2016, of whom more than 650 million were classified as obese. Notably, the global prevalence of obesity has nearly tripled since 1975 [1]. Similarly, the prevalence of diabetes continues to rise at an alarming rate. The International Diabetes Federation (IDF) estimated that 463 million adults were living with diabetes

in 2019, a number projected to reach 700 million by 2045 [2].

Türkiye reflects this global trend. Data from the Turkish Diabetes, Hypertension, Obesity and Endocrinological Diseases Prevalence Study II (TURDEP II) reported an obesity prevalence of 32% and a diabetes prevalence of 13.7%. Compared with the earlier TURDEP I study conducted in 1998, these findings represent a 44% increase in obesity and a 90% increase in diabetes prevalence, highlighting the growing public health burden and the need for effective prevention strategies [3].

The etiology of obesity and diabetes is multifactorial, involving complex interactions between environmental and genetic factors. In recent years, genome-wide association studies (GWAS) have identified numerous genetic variants associated with susceptibility to these conditions. Among these, polymorphisms in the peroxisome proliferator-activated receptor gamma (PPARγ) and thyrotropin-releasing hormone receptor (TRHR) genes have attracted considerable attention [4].

PPARγ, located on chromosome 3p25, is a nuclear transcription factor that plays a central role in adipocyte differentiation, insulin sensitivity, and lipid metabolism [5]. Its high expression in adipose tissue underscores its importance in adipogenesis and metabolic regulation, where it promotes insulin sensitivity and modulates inflammatory responses [6]. The Pro12Ala (rs1801282) polymorphism in PPARγ has been investigated in relation to obesity and type 2 diabetes susceptibility. This missense variant, resulting in a proline-to-alanine substitution at codon 12, may influence transcriptional activity and insulin sensitivity [7]. However, evidence regarding its association with obesity remains inconsistent across populations, with some studies reporting increased risk associated with the Ala allele, while others failing to demonstrate a significant relationship [8].

The TRHR gene, located on chromosome 8q23.1, encodes the receptor for thyrotropin-releasing hormone and plays a key role in the hypothalamic–pituitary–thyroid axis [9]. Thyroid hormones are essential regulators of energy expenditure, metabolism, and body weight homeostasis [10]. Consequently, genetic variation in TRHR has been hypothesized to influence metabolic traits and obesity-related phenotypes. Previous studies have reported associations between TRHR variants and body composition as well as metabolic parameters [11]. In particular, the rs16892496 polymorphism has been linked to differences in muscle mass and strength; however, evidence regarding its relationship with obesity and diabetes remains limited and inconsistent [12].

In this study, we investigated the association of PPARγ (rs1801282) and TRHR (rs16892496) polymorphisms with obesity and diabetes in a Turkish population. A key strength of this work is the simultaneous evaluation of both variants, allowing assessment of their potential combined influence on metabolic phenotypes. We further examined their associations with relevant metabolic parameters to better characterize genotype–phenotype relationships.

Overall, this study aims to contribute to the understanding of genetic susceptibility to obesity and diabetes and to provide further insight into population-specific genetic variation. Elucidating these associations may help identify individuals at increased metabolic risk and support future research into personalized preventive and therapeutic strategies.

Materials and Methods

Study Population

This observational study was conducted at the Department of Endocrinology and Metabolic Diseases, Istanbul University Faculty of Medicine Hospital. A total of 239 participants were enrolled, comprising 80 individuals with both diabetes and obesity, 80 individuals with obesity without diabetes, and 79 healthy controls. Participants were classified as obese based on a body mass index (BMI) ≥30 kg/m^2. Diabetes mellitus was diagnosed according to the 2021 American Diabetes Association (ADA) criteria. Exclusion criteria included insulin therapy, familial participation within the same cohort, and the presence of endocrine disorders or chronic inflammatory diseases. BMI was used as the primary anthropometric measure of obesity and categorized according to World Health Organization (WHO) criteria: underweight (<18.5 kg/m^2), normal weight (18.5–24.9 kg/m^2), overweight (25.0–29.9 kg/m^2), obese (30.0–39.9 kg/m^2), and morbidly obese (≥40.0 kg/m^2).

Biochemical Analysis

Blood samples were centrifuged at 4500 rpm for 15 minutes at +4°C to obtain serum. Serum concentrations of glucose, HbA1c, total cholesterol, HDL-cholesterol, LDL-cholesterol, triglycerides, urea, creatinine, AST, and ALT were measured using an AU5800 Series Clinical Chemistry Analyzer (Beckman Coulter Inc., Brea, CA, USA), according to the manufacturer's instructions.

Genetic Analysis

Genomic DNA was extracted from peripheral blood samples using the RINA™ M14 automated extraction system (Rina Biotechnology, Istanbul, Türkiye). DNA concentration and purity were assessed using a NanoDrop 2000

spectrophotometer (Thermo Scientific, Wilmington, DE, USA). Only samples with A260/A280 ratios between 1.8–2.0 were included in the analysis [13].

Genotyping of PPARγ (rs1801282) and TRHR (rs16892496) polymorphisms was performed using real-time PCR on a Bio-Rad CFX96 Touch system. Each 20 µL reaction contained 2X SYBR Green PCR Master Mix, 0.5 µL of each primer (10 pmol), 2 µL of genomic DNA (50 ng), and nuclease-free water. The thermal cycling conditions were as follows: initial denaturation at 95°C for 10 minutes, followed by 40 cycles of 95°C for 15 seconds and 60°C for 1 minute.

Primer sequences were as follows:
PPARγ (rs1801282):
Forward 1: 5′-TCAGTGAAGGAATCGCTTTCTGG-3′
Forward 2: 5′-TCAGTGAAGGAATCGCTTTCTGC-3′
Reverse: 5′-TCAAGCCCAGTCCTTTCTGTGTT-3′

TRHR (rs16892496):
Forward 1: 5′-GTTGAAGAGCAAGCCCCCA-3′
Forward 2: 5′-GTTGAAGAGCAAGCCCCCC-3′
Reverse: 5′-TGGAAACTCCAAGGGTGAAGAA-3′

Primers were designed using Primer3 software.
All assays were performed in duplicate to ensure accuracy.

Statistical Analysis

Statistical analyses were performed using SPSS version 22.0 (IBM Corp., Armonk, NY, USA), with a significance threshold set at $p < 0.05$. Continuous variables were expressed as mean ± standard deviation or median (minimum–maximum), depending on distribution, while categorical variables were presented as frequencies and percentages. Normality was assessed using the Kolmogorov–Smirnov test. One-way ANOVA was used for comparisons of normally distributed variables, whereas the Kruskal–Wallis test was applied for non-normally distributed variables. Categorical variables were analyzed using the chi-square test, with Bonferroni correction applied for post-hoc comparisons when appropriate.

Allele and genotype frequencies were calculated, and Hardy–Weinberg equilibrium was evaluated using the chi-square test. Genotype distributions between groups were compared using chi-square analysis. A priori power analysis was performed using G*Power 3.1 software to determine the minimum required sample size (effect size f = 0.25, power = 80%, α = 0.05).

Results

Demographic and Clinical Characteristics

The demographic and clinical characteristics of the 239 participants (80 with diabetes and obesity, 80 with obesity without diabetes, and 79 healthy controls) are presented in Table 1. Significant differences among the groups were observed in age, BMI, and several biochemical parameters. Post-hoc analyses revealed significant differences between the patient groups and the control group. The diabetic obese group showed significantly higher BMI, HbA1c, glucose, triglycerides, urea, and creatinine levels, and lower HDL cholesterol levels compared with the control group ($p < 0.001$ for most comparisons; $p = 0.001$ for HDL). The non-diabetic obese group also showed significantly higher BMI compared with the control group ($p < 0.001$). When comparing the diabetic obese and non-diabetic obese groups, significant differences were observed in glucose, HDL, HbA1c, triglycerides, urea, and creatinine levels ($p < 0.05$ for all comparisons) (Table 1).

	Sample 1-Sample 2	Test Statistic	Std. Eror	Std. Test Statistic	Sig.	*p*
BMI (kg/m²)	Control-Diabetic Obese	-94,100	9,088	-10,354	<0,001	**<0,001**
	Control-Nondiabetic Obese	-1,02,659	10,958	-9,369	<0,001	**<0,001**
	Diabetic Obese-Nondiabetic Obese	8,559	10,784	0,794	0,427	1,000
Glucose (mg/dl)	Nondiabetic Obese -Control	5,790	12,269	0,472	0,637	1,000
	Nondiabetic Obese- Diabetic Obese	-85,546	12,124	-7,056	<0,001	**<0,001**
	Control- Diabetic Obese	-79,756	8,181	-9,749	<0,001	**<0,001**
HDL (mg/dl)	Diabetic Obese- Nondiabetic Obese	39,558	11,998	3,297	0,001	**0,003**
	Diabetic Obese -Control	40,793	8,139	5,012	<0,001	**<0,001**
	Nondiabetic Obese -Control	1,235	12,144	0,102	0,919	1,000
Creatinine (mg/dl)	Nondiabetic Obese -Control	21,620	12,170	1,777	0,076	0,227
	Nondiabetic Obese- Diabetic Obese	-53,513	12,079	-4,430	<0,001	**<0,001**
	Control- Diabetic Obese	-31,893	8,148	-3,914	<0,001	**<0,001**

Triglyceride (mg/dl)	Nondiabetic Obese -Control	7,946	12,150	0,654	0,513	1,000
	Nondiabetic Obese- Diabetic Obese	-51,050	12,004	-4,253	<0,001	**<0,001**
	Control- Diabetic Obese	-43,104	8,143	-5,293	<0,001	**<0,001**
HbA1c (%)	Control- Nondiabetic Obese	-81,186	12,099	-0,015	0,988	1,000
	Control- Diabetic Obese	-81,741	8,215	-9,951	<0,001	**<0,001**
	Nondiabetic Obese - Diabetic Obese	-81,556	11,989	-6,803	<0,001	**<0,001**
Urea (mg/dl)	Nondiabetic Obese -Control	14,172	11,982	1,183	0,237	0,711
	Nondiabetic Obese - Diabetic Obese	-42,444	11,908	-3,564	<0,001	**0,001**
	Control- Diabetic Obese	-28,273	8,089	-3,495	<0,001	**0,001**

Post-hoc test was used for statistical analysis of the parameters used in the study between groups.
Bold font indicates significance p-values.
Table 1: Difference of significance according to biochemical parameters in study groups.

PPARγ (rs1801282) Genotype and Allele Distributions

Genotype and allele distributions of the PPARγ (rs1801282) polymorphism were analyzed using chi-square testing, and associations with clinical variables were assessed using ANOVA and Kruskal–Wallis tests. A significantly higher frequency of the GG genotype was observed in the diabetic obese group (62.5%) compared with the non-diabetic obese (33.75%) and control groups (35.45%) (p <0.001). The CG genotype was significantly more prevalent in the control group (59.5%) compared with the diabetic obese (35%) and non-diabetic obese groups (47.5%) (p <0.001). The CC genotype was more frequent in the non-diabetic obese group (18.75%) compared with the diabetic obese (2.5%) and control groups (5.06%) (p <0.001).

Regarding allele frequencies, the C allele was significantly more frequent in the control group (35%) compared with the diabetic obese group (20%) (p = 0.001). Similarly, the non-diabetic obese group (42.5%) showed a higher C allele frequency than the diabetic obese group (20%) (p <0.001). The G allele was more frequent in the diabetic obese group (80%) compared with the control group (65%); however, this difference was not statistically significant (p> 0.05). Allele and genotype distributions are summarized in Table 2.

PPAR-γ (rs1801282)	Control n (%)	Non-diabetic Obese n (%)	Diabetic Obese n (%)	χ^2	*p*
GG	28 (%35,45)	27 (%33,75)	50 (%62,5)	16,876	**<0,001**
CG	47 (%59,5)	38 (%47,50)	28 (%35,0)	28,390	**<0,001**
CC	4 (%5,06)	15 (%18,75)	2 (%2,5)	15,220	**<0,001**
C Allele	55 (%35)	68 (%42,5)	32 (%20)	0,050*	0,822*
				11,644**	**0,001****
				13,244***	**<0,001*****
G Allele	103 (%65)	92 (%57,5)	128 (%80)	0,077*	**0,008***
				0,719**	0,396**
				11,123***	**0,001*****

n: number of individuals, %: percentage. Gene calculation method and Chi-Square (χ 2) test were used for statistical analysis of genotypes and alleles of the genes in the study between groups. The genotype and allele distribution of the groups were calculated in a four-well table.
*Control&Non-diabetic Obese (for C allele χ2=0,050, p=0,822; For G allele χ2=0,077, p=0,008)
**Control&Diabetic Obese (for C allele χ2=11,644, p=0,001; For G allele χ2=0,719, p=0,396)
***Non-diabetic Obese&Diabetic Obese (For C allele χ2=13,244 p<0,001; for G allele χ2=11,123, p=0,001)
Table 2: Distribution of PPAR-γ (rs1801282) genotypes and alleles according to study groups.

PPARγ (rs1801282) and Biochemical Parameters

Analysis of the PPARγ rs1801282 polymorphism demonstrated significant associations between allele distribution and selected biochemical parameters. In the diabetic obese group, creatinine levels differed significantly between C (0.70 mg/dL) and G allele carriers (0.80 mg/dL) (p = 0.017). In the control group, HDL cholesterol levels were significantly higher in C allele carriers (55.0 mg/dL) compared with G allele carriers (53.0 mg/dL) (p = 0.034). In the non-diabetic obese group, urea levels differed significantly between C (25.0 mg/dL) and G allele carriers (23.5 mg/dL) (p = 0.042) (Table 3).

Biochemical Parameters	Diabetic Obese				Non diabetic Obese				Control			
	C Allele		G Allele		C Allele		G Allele		C Allele		G Allele	
	Median (min/max)	p	Median (min-max)	p	Median (min-max)	p	Median (min-max)	p	Median (min-max)	p	Median (min-max)	p
BMI (kg/m2)	35,21 (30-45)	0,181	34,83 (30-45)	0,380	32,87 (30-52)	0,004	34,73 (30-65)	0,852	25,82 (18-30)	0,105	25,33 (18-30)	0,783
Glucose (mg/dl)	182,0 (97-385)	0,279	176,0 (48-422)	0,183	90,0 (75-105)	0,594	90,0 (75-105)	0,141	92,5 (80-111)	0,935	92,0 (72-111)	0,177
HDL (mg/dl)	44,0 (26-60)	0,622	44,0 (23-66)	1,000	55,0 (34-111)	0,594	51,5 (20-73)	0,722	55,0 (33-75)	0,034	53,0 (32-80)	0,237
Weight (kg)	96,5 (68-125)	0,409	95,0 (68-140)	0,035	87,9 (73-160)	0,080	93,65 (73-160)	0,712	71,0 (53-96)	0,496	70,0 (50-98)	0,664
Creatinine (mg/dl)	0,70 (0,4-1,6)	0,017	0,80 (0,4-2,66)	0,337	0,58 (0,37-0,9)	0,967	0,57 (0,37-0,9)	0,227	0,66 (0,41-1,1)	0,602	0,68 (0,39-1,1)	0,743
Trygliceride (mg/dl)	168,0 (59-815)	0,371	165,0 (50-815)	0,136	84,5 (29-936)	0,712	99,5 (36-936)	0,273	100,5 (31-278)	0,924	100,5 (31-364)	0,695
Hba1c (%)	8,20 (5,5-13,7)	0,579	8,10 (5,1-13,7)	0,795	5,40 (4,9-6)	0,174	5,40 (4,5-6)	0,166	5,30 (4,8-5,9)	0,859	5,35 (4,7-6)	0,824
Urea (mg/dl)	29,0 (16-64)	0,041	31,5 (16-105)	**0,611**	25,0 (13-37)	0,652	25,0 (15-35)	0,042	26,5 (16-47)	0,627	26,0 (12-47)	0,916

Non-normally distributed parameters are shown as Median (min-max). ANOVA test and Kruskal-Wallis test were used for statistical analysis of the parameters used in the study between groups. Bold font indicates significance p-values.
Table 3: Distribution of demographic data in study groups according to PPAR-γ C and G alleles.

TRHR (rs16892496) Genotype and Allele Distributions

Genotype distributions of the TRHR (rs16892496) polymorphism are presented in Table 4. The AA genotype was the most frequent across all groups (40% in obese, 47.5% in non-diabetic obese, and 51.9% in controls), although differences were not statistically significant (p = 0.314).

The AC genotype was significantly more frequent in the diabetic obese group (37.5%) compared with the non-diabetic obese (20%) and control groups (35.45%) (p = 0.012). The CC genotype was more prevalent in the non-diabetic obese group (32.5%) compared with the diabetic obese (22.5%) and control groups (12.7%) (p = 0.011).

Regarding allele frequencies, the A allele was significantly more frequent in the control group (70%) compared with the non-diabetic obese group (57.5%) (p = 0.003). No statistically significant differences were observed in other intergroup comparisons (p>0.05). The C allele was most frequent in the non-diabetic obese group (42.5%), followed by diabetic obese (41.25%) and control groups (30%), although this difference did not reach statistical significance (p> 0.05).

TRHR (rs16892496)					
Genotypes and Alleles	**Control n (%)**	**Non-diabetic Obese n (%)**	**Diabetic Obese n (%)**	χ^2	***p***
AA	41 (%51,9)	38 (%47,5)	32 (%40)	*2,316*	*0,314*
AC	28 (%35,45)	16 (%20,00)	30 (%37,50)	*12.889*	***0,012***
CC	10 (%12,7)	26 (%32,50)	18 (%22,50)	*8,948*	***0,011***
				*8,934**	***0,003****
A Allele	110 (%70)	92 (%57,5)	94 (%58,75)	*2,654***	*0,103***
				*2,006****	*0,157****
C Allele	48 (%30)	68 (% 42,5)	66 (%41,25)	*0,308**	*0,579**
				*2,266***	*0,132***
				*0,914****	*0,339****

n: number of individuals, %: percentage. Gene calculation method and Chi-Square(χ2) test were used for statistical analysis of genotypes and alleles of the genes in the study between groups. Bold font indicates significance p-values. The genotype and allele distribution of the groups were calculated in a four-well table.

*Control&Non-diabetic Obese (For A allele χ2=8,934, p=0,003; For C allele χ2=0,308, p=0,579)

**Control&Diabetic Obese (For A allele χ2=2,654, p=0,103; For C allele χ2=2,266, p=0,132)

*** Non-diabetic Obese&Diabetic Obese (For A allele χ2=2,006, p=0,157; For C allele χ2=0,914, p=0,339)

Table 4: Distribution of TRHR (rs16892496) genotypes and alleles according to study groups.

TRHR (rs16892496) and Biochemical Parameters

No statistically significant associations were observed between TRHR allele distribution and biochemical parameters, except for BMI, weight, and height. In the control group, the A allele was associated with significantly lower BMI (p = 0.026) and weight (p = 0.048) compared with the C allele. In the diabetic obese group, a significant difference in height was observed between A and C allele carriers (p = 0.044) (Table 5).

Biochemical Parameters	**Diabetic Obese**				**Non diabetic Obese**				**Control**			
	A Allele		**C Allele**		**A Allele**		**C Allele**		**A Allele**		**C Allele**	
	Median (min/max)	**p**	**Median (min-max)**	**p**	**Median (min-max)**	**p**	**Median (min-max)**	**p**	**Median (min-max)**	**p**	**Median (min-max)**	**p**
BMI (kg/m2)	34,71 (30-45)	0,592	33,33 (30-45)	0,582	36,61 (30-65)	0,359	37,49 (30-52)	0,638	25,22 (18-30)	0,026	25,60 (19-30)	0,947
Height (cm)	165,0 (148-184)	0,221	167,0 (149-184)	0,044	160,0 (120-192)	0,889	162,0 (153-186)	0,512	169,0 (150-186)	0,624	166,0 (155-181)	0,934
Glucose (mg/dl)	172,0 (48-422)	0,917	169,5 (48-390)	0,720	90,0 (75-105)	0,218	92,0 (82-105)	0,447	92,0 (72-111)	0,615	91,0 (80-111)	0,700
HDL (mg/dl)	44,0 (23-66)	0,574	44,0 (23-57)	0,220	54,0 (20-69)	0,249	55,0 (40-111)	0,581	53,0 (32-80)	0,974	53,5 (32-75)	0,760
Weight (kg)	95,5 (68-140)	0,205	95,0 (68-140)	0,366	95,5 (74-147)	0,269	98,7 (73-160)	0,695	69,0 (50-98)	0,048	72,0 (51-96)	0,778
Creatinine (mg/dl)	0,78 (0,4-2,6)	0,915	0,80 (0,5-2,6)	0,086	0,53 (0,34-0,82)	0,058	0,60 (0,4-0,9)	0,267	0,66 (0,39-1,07)	0,395	0,66 (0,39-0,92)	0,573
Trygliceride (mg/dl)	165,0 (59-815)	0,264	169,0 (50-815)	0,199	96,0 (46-936)	0,762	111,0 (29-166)	0,945	100,0 (31-364)	0,228	102,5 (43-266)	0,765
Hba1c (%)	8,2 (5,1-13,7)	0,301	8,05 (5,1-13,7)	0,626	5,2 (4,5-6)	0,150	5,40 (5,2-5,6)	0,278	5,4 (4,8-6)	0,146	5,30 (4,7-5,9)	0,308
Urea (mg/dl)	32,0 (16-105)	0,925	32,0 (16,6-92)	0,860	22,0 (13-37)	0,249	29,0 (13-36)	0,680	25,0 (12-47)	0,289	25,5 (12-40)	0,676

Non-normally distributed parameters are shown as Median (min-max). ANOVA test and Kruskal-Wallis test were used for statistical analysis of the parameters used in the study between groups. Bold font indicates significance p-values.

Table 5: Distribution of demographic data in the study groups according to TRHR A and C alleles.

Discussion

In this study, we investigated the association of PPARγ (rs1801282) and TRHR (rs16892496) polymorphisms with obesity and diabetes in a Turkish population. Our findings suggest that genetic variation in these loci may contribute to susceptibility to metabolic disorders, potentially through effects on lipid metabolism, insulin sensitivity, and energy homeostasis.

PPARγ plays a central role in adipocyte differentiation and insulin sensitivity. The Pro12Ala (rs1801282) polymorphism has been reported to reduce transcriptional activity of PPARγ, which may influence adipose tissue function and inflammatory signaling. Reduced PPARγ activity has been associated with increased activation of NF-κB pathways and elevated secretion of pro-inflammatory cytokines such as TNF-α, IL-6, and IL-1β, thereby contributing to insulin resistance and obesity-related metabolic dysregulation. In addition, PPARγ modulates adipokine secretion and fatty acid storage capacity, thereby influencing systemic insülin sensitivity and metabolic homeostasis [14,15].

In our cohort, significant differences were observed in anthropometric and biochemical parameters, including BMI, glucose, HbA1c, lipid profile, and renal function markers across study groups. These findings are consistent with previous reports demonstrating that obesity and diabetes are strongly associated with dyslipidemia, hyperglycemia, and impaired renal function [16-18].

Age was significantly higher in the diabetic obese group, consistent with the established relationship between aging and increased diabetes risk. BMI values were elevated across both obese groups compared with controls; however, no significant difference was observed between diabetic and non-diabetic obese individuals, suggesting that obesity severity alone may not fully explain diabetes development.

Consistent with prior studies, diabetic obese individuals exhibited significantly higher fasting glucose and HbA1c levels, along with elevated triglycerides and reduced HDL cholesterol, reflecting typical metabolic dysregulation associated with diabetes and obesity. Additionally, increased urea and creatinine levels suggest potential early renal involvement in diabetic individuals, in line with previous evidence linking metabolic disorders to renal dysfunction [19-21].

Regarding genetic associations, the GG genotype of PPARγ rs1801282 was significantly more frequent in the diabetic obese group, supporting its potential role in metabolic susceptibility. This finding is consistent with meta-analyses reporting associations between the Pro12Ala variant and obesity risk across multiple populations [22]. Furthermore, previous studies have suggested that the G allele may be associated with adverse metabolic profiles, including obesity and hyperlipidemia [23,24]. In the present study, higher BMI values in G allele carriers further support its potential involvement in adiposity-related phenotypes.

Interestingly, we observed higher HDL cholesterol levels in C allele carriers within the control group. This finding is consistent with the role of PPARγ in lipid metabolism and suggests that allele-specific differences may influence lipid homeostasis, potentially through modulation of adipose tissue function and lipoprotein metabolism [25,26].

For the TRHR rs16892496 polymorphism, genotype distributions showed significant differences between groups, although allele-level associations were less consistent. Previous genome-wide association studies have reported associations between TRHR variants and BMI, waist-hip ratio, and obesity risk [27,28]. In our study, A allele carriers in the control group demonstrated lower BMI values, supporting a possible role of TRHR in body weight regulation.

TRHR is involved in the hypothalamic–pituitary–thyroid axis, which regulates thyroid hormone secretion and energy expenditure. Therefore, genetic variation in TRHR may influence metabolic rate and body weight regulation through modulation of thyroid hormone signaling pathways. Alterations in TRHR signaling may also indirectly influence leptin-mediated appetite regulation, further linking thyroid axis dysregulation with obesity-related phenotypes [29-31]. However, the precise functional consequences of rs16892496 remain unclear and require further investigation.

Although PPARγ and TRHR operate through distinct biological pathways, both have been independently associated with metabolic phenotypes in this and previous studies. This suggests that obesity and diabetes are likely influenced by multiple genetic factors acting through complementary mechanisms rather than a single pathway. In addition, gene–environment interactions, including lifestyle factors such as physical activity, may modify the phenotypic expression of these polymorphisms [32].

The strengths of this study include a well-characterized cohort, inclusion of both diabetic and non-diabetic obese individuals, and comprehensive biochemical and genetic analyses. Importantly, this is among the first studies to evaluate PPARγ and TRHR polymorphisms jointly in a Turkish population.

However, several limitations should be acknowledged. The relatively modest sample size may limit statistical power for detecting weaker associations. The cross-sectional design

prevents causal inference. Additionally, lack of detailed dietary intake and physical activity data limits assessment of gene–environment interactions.

Future studies with larger, multi-ethnic, and longitudinal designs are needed to validate these findings and further elucidate the functional mechanisms underlying these genetic associations. However, due to the observational design, causal relationships cannot be inferred.

Although PPARγ and TRHR act through distinct biological pathways, both converge on energy balance regulation through lipid metabolism and endocrine control. This suggests that multiple genetic determinants may interact in shaping individual susceptibility to metabolic disorders.

Conclusion

This study investigated the association of PPARγ (rs1801282) and TRHR (rs16892496) polymorphisms with obesity and diabetes in a Turkish population. Our findings suggest that these genetic variants may contribute to inter-individual susceptibility to metabolic disorders through their effects on lipid metabolism, insulin sensitivity, and energy regulation. The PPARγ rs1801282 GG genotype was more prevalent in diabetic obese individuals and was associated with higher BMI, supporting its potential role in obesity-related metabolic risk. In addition, higher HDL cholesterol levels observed in C allele carriers suggest a possible protective effect of this variant on lipid metabolism.

For TRHR rs16892496, A allele carriers showed lower BMI values in the control group, indicating a potential role in body weight regulation, possibly mediated through thyroid hormone signaling pathways. Overall, these findings support the hypothesis that genetic variation in PPARγ and TRHR contributes to metabolic phenotypes, although their effects appear to be modest and likely influenced by additional genetic and environmental factors. Further large-scale, longitudinal studies are required to confirm these associations and to clarify the functional mechanisms underlying these gene variants in obesity and diabetes.

Declarations

Ethics Approval

This research, conducted in accordance with the Helsinki Declaration and relevant ethical standards, was approved by the Istanbul University Clinical Research Ethics Committee (Approval Number: 2020/342).

Conflict of Interest

The authors declare no competing interests.

Consent to Participate

Informed consent was obtained from all participants, including written consent for data publication.

Contributions

All authors contributed to the conception and design of the study; data acquisition: V.A., S.D., R.C. and S.B.A.S.; data analysis and interpretation: V.A., Ü.Z., S.D. and F.Ç.; manuscript drafting: V.A., S.D.; manuscript critical revision: Ü.Z., A.O.G., H.A.E. and M.K.O.; statistical analysis: M.D.; study supervision: Ü.Z. and V.A.

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