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RESEARCH

The Investigation of Leptin (LEP) and Leptin Receptor (LEPR) Gene Variations in Obese Patients

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Abstract

Obesity is defined as a chronic public health problem that leads to deterioration in metabolic health. The leptin gene (LEP gene rs7799039) and leptin receptor (LEPR gene rs1137101) polymorphisms are thought to potentially be related to the pathophysiology of obesity and its complications. This study aimed to evaluate the role of critical gene polymorphism of the leptin gene in the pathogenesis of obesity. This study consisted of 4 groups including control ($n=49$), overweight ($n=50$), obese($n=50$), and morbid obesity ($n=49$). Real-time polymerase chain reaction was used for distributions of genotypes. We found statistically significant results in terms of genotype distribution of *LEP gene* and *LEPR gene* polymorphisms in the study groups ($p=0,031$; $p<0,001$, *respectively*) and showed an especially significant relationship between the *G allele* of the *LEPR gene* and increased BMI. Moreover, we found that the *GG genotype* of the *LEP gene* is statistically significant in terms of BMI in the obesity and morbid obesity groups ($p<0.001$). LEP and LEPR genes may serve as significant biomarkers in developing personalized treatments for obesity. Further studies with larger samples will shed light on the pathophysiology of obesity and enhance our understanding of leptin's role in obese patients.

Keywords Obesity · Leptin · Leptin receptor · Polymorphism · Gene

Introduction

Obesity is a chronic inflammatory disease developing because of unhealthy diets and inactive lifestyles when the energy taken is more than the energy spent and with environmental and genetic factors [1, 2]. Leptin, which is secreted mainly from adipose tissue in the body, is a product of the *ob* gene that is responsible for obesity and is encoded in the 7q31 region of the chromosome as an appetite-regulating hormone with a protein structure of 167 amino

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acids. This − 2548 G/A polymorphism has been shown to influence leptin gene transcription, leading to altered circulating leptin levels, which may have an impact on energy homeostasis and appetite regulation [3, 4]. The regulation of metabolic rate, nutritional behaviors, body weight homeostasis, thermoregulation, activation of the nervous system, stimulation of growth, and angiogenesis are among the basic functions of the leptin hormone, which is a member of the Type-I cytokine receptor family [5, 6]. Leptin performs all its metabolic functions via the central nervous system and its special receptors. These receptors are encoded through the LEPR gene and are responsible for 3% of obesity seen at an early age [6–10]. LEPR rs1137101 lies within exon 6 of the chromosome 1p31 leptin receptor gene. The Gln223Arg (A > G) missense mutation results in an amino acid substitution in the extracellular domain of the receptor that could have an impact on leptin binding affinity and consequent signaling. Resistance to leptin receptors and failure to cross the blood–brain barrier result in higher leptin levels in obese individuals. It was reported in a study that weight loss reduces leptin levels, and contrary leptin levels increase again [11–13]. It was shown that leptin is associated with insulin resistance, as well as obesity [14]. The relationship between leptin and insulin resistance was examined in a study that was conducted with 36 obese and 72 thin children. As a result of the study, it was reported that leptin levels were higher in obese children, and leptin levels were associated with insulin resistance [15].

Leptin deficiency or a deficiency in leptin receptors causes obesity by uncontrolled hunger, and leptin resistance could be considered a reason for obesity. Contrary to expectations, the reason why leptin levels in obese individuals are higher than in healthy and normal-weight individuals is leptin resistance [16, 17]. Also, some animal studies reported that the leptin hormone might have protective roles against increased adipose tissue and pancreatic damage [18, 19].

Epidemiological studies suggest that leptin regulates total body sensitivity to insulin and triglyceride levels in individuals who have leptin deficiency [20]. In the literature, the results of studies on the relationship between *LEPR gene rs1137101* polymorphism, *LEP gene rs7799039* polymorphism, and obesity are quite conflicting [12, 20–23].

The LEP and LEPR genes were selected because they play a central role in the regulation of energy balance and body weight through the leptin signaling pathway. Both genes have been implicated in the modulation of leptin production or receptor function by gene variants with a potential link to obesity susceptibility. The SNPs analyzed in the present study were chosen from the literature based on their functional significance as reported, allelic frequency in the population being studied, and probable association with obesity-related characteristics. Therefore, in the present study, the aim is to evaluate the relation in terms of biochemical parameters and the distribution of *LEPR gene rs1137101* and *LEP gene rs7799039* polymorphisms in obesity in obese patients.

Materials and Method

Participants and Ethics Statement

This study consisted of 4 groups including control (BMI < 25 kg/m^2), overweight (BMI ≥ 25 kg/m^2), obese (BMI ≥ 30 kg/m^2), and morbid obesity (BMI ≥ 35 kg/m^2) people. Two hundred whole blood samples were collected from Istanbul University, Istanbul Faculty of Medicine (Department of Internal Diseases and Department of General Surgery with the Complaint of Obesity. All study groups obtained their written assent to the investigation. The study was designed by following the Helsinki Declaration and confirmed by the Ethical Committee (Decree No. 13.05.2016/09). Funding source: Research Fund of the Scientific and Technological Research Council of Turkey (TUBİTAK 1003) (Project No:116E827).

DNA Isolation

The genomic DNA was obtained from 5 mL peripheral blood samples were obtained from each participant. DNA was extracted using a robotic system (RINATM M14; Bioeksen, Turkey). The instrument separates DNA from the sample by binding the DNA to magnetic beads, then physically and chemically disrupting them, digesting them enzymatically, and applying heat treatment, and there are washing steps involved. This was done according to protocols described in the literature.

qPCR Method

Genotyping was performed by using qPCR. Two forward primers and one reverse primer were designed for each SNP. Allele-specific forward primers were used for mutant and wild-type alleles. Genotyping was performed using allele-specific primers on a real-time PCR system (CFX96 Touch™ Real-Time PCR Detection System, Bio-Rad, USA) according to the manufacturer's instructions. The qPCR reactions contained 2 µL of template DNA, 3 µL oligo primer with Sybr Green, and 5 µL of qPCR Mix (Bioeksen, Turkey). Total reaction volume for qPCR was performed as 10 µL for each primer. The conditions were followed: 3 min at 95 °C, followed by 40 cycles at 95 °C for 10 s, 60 °C for 30 s.

Statistical Analyses

We used post-amplification fluorescent melting curve analysis [24] to detect the allelic types of SNP. Cq values obtained from qPCR and standard curves were detected by using CFXTM Manager Software version 3.1 (Bio-Rad Laboratories). Statistical analysis was performed by using the SPSS software package (revision 26.0; SPSS, Chicago, USA). Statistical significance was accepted as $p < 0.05$. The differences in BMI were found by using the 4×3 chi-square (x^2) test and one-way ANOVA test as a mean and standard deviation. The relationships and significance were shown by applying the post hoc test and Kruskal–Wallis test between biochemical parameters and genotyping of the study group.

Result

In the present study, 49 control, 50 overweight, 50 obesity, and 49 morbid obesity individuals were evaluated in terms of *LEP rs7799039* and *LEPR rs1137101* genotypes and biochemistry parameters. The demographic and biochemistry parameters of the study groups are shown in Table 1.

The study groups have a similar distribution of sex *($p > 0.05$).* We found a significant relationship between the study group regarding age parameters. The control group compared with the overweight group $p < 0.001$; the control group compared with the obese group $p < 0.001$; the control group compared with the morbid obesity group $p = 0.004$.

We found a negative correlation between high-density lipoprotein-cholesterol (HDL-c) plasma concentration according to body mass index (BMI) in the study groups *($p = 0{,}007$).* There was a statistically significant difference between the control and morbid obesity groups (the mean value of *HDL-c* $= 53{,}79 \rightarrow 43{,}27$ $p = 0.003$, *respectively*). We found a positive correlation of triglycerides (TC.) plasma concentration according to BMI in the study groups ($p < 0.001$; *the mean value of Trig* $= 120{,}7 \rightarrow 156{,}9 \rightarrow 201{,}9 \rightarrow 224{,}3$, *respectively*). However, no significant differences in aspartate transaminase (AST), total cholesterol, alanine transaminase (ALT), low-density lipoprotein cholesterol (LDL-c), and glucose plasma concentrations between the study groups *($p > 0.05$).*

The genotypes distribution of *LEP rs7799039* and *LEPR rs1137101* polymorphisms in the study groups is shown in Fig. 1. There were statistical differences according to genotype distribution of *LEP rs7799039* and *LEPR rs1137101* polymorphisms in the study groups ($p = 0.031$ *value of LEP rs7799039;* $p < 0.001$ *value of LEPR rs1137101, respectively*).

We found a significant association between BMI and genotype distribution of *LEP gene rs7799039 ($p < 0.05$).* Even if the genotype significance of the groups could not

Table 1 Demographic and biochemistry parameters of the study groups

Variable	Control				Overweight				Obese				Morbit Obesity				X^2	*p*
	Min	Max	Median	IQR	Min	Max	Median	IQR	Min	Max	Median	IQR	Min	Max	Median	IQR		
Age (yr)	17	67	49	26	39	75	62	14	40	73	58	9	39	66	54	13	29.47	***<0.001***
Glucose (mmol/L)	79	238	174	75	70	316	163	60	109	319	166	52	104	312	170	76	6.671	*0.083*
TC (mmol/L)	40	246	160	152	70	583	133	81	67	815	148	86	76	671	191	197	24.12	***<0.001***
Total-c (mmol/L)	123	328	192	117	130	396	196	66	144	314	207	72	149	289	206	57	1.374	*0.712*
HDL-c (mmol/L)	19	84	54	15	26	151	48	18	29	68	48	10	23	62	43	9	4.217	***0.007***
LDL-c (mmol/L)	60	215	117	106	67	275	119	48	66	199	132	56	63	193	125	51	2.448	*0.485*
ALT (mmol/L)	11	28	17	15	10	57	19	12	10	43	17	16	12	58	18	16	7.04	*0.071*
AST(mmol/L)	14	22	17	7	12	50	19	6	12	36	19	6	11	71	20	9	1.259	*0.739*

The groups were analyzed by a One-Way ANOVA and Kruskal–Wallis test. Bold values of $p < 0.05$ indicate significant differences

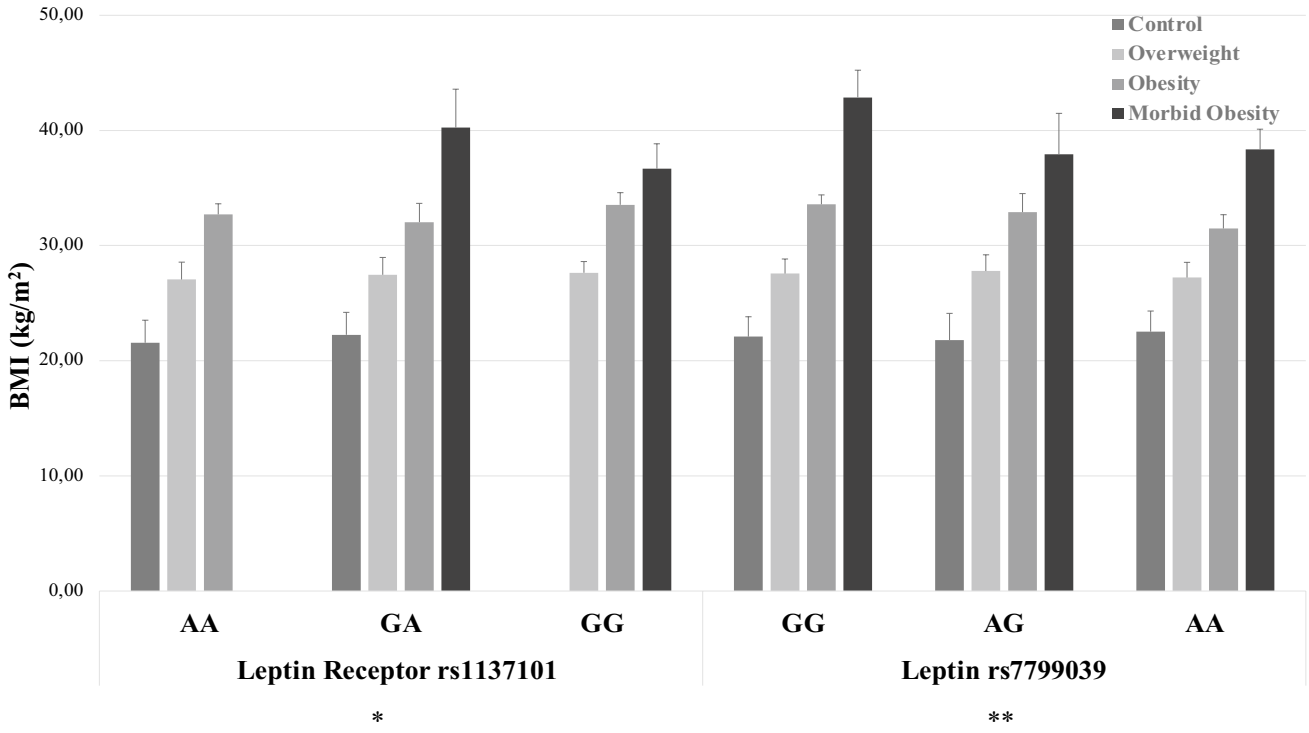

Fig. 1 LEP rs7799039 and LEPR rs1137101 genotypes in the study groups. The difference between and within the groups was analyzed by chi-square (×2) test *p*-value of LEPR rs1137101 polymorphisms * < 0.0001 and *p*-value of LEP rs7799039 polymorphisms ** = 0.031

be determined in advanced statistical analysis, we detected that *LEP gene rs7799039* is statistically significant in terms of BMI between GG genotype compared to AA genotype *(p < 0.001)* in the obesity group. In addition, GG genotype of *LEP gene rs7799039* is statistically significant in terms of BMI in the morbid obesity group compared to *AA and GA genotypes* (*BMI mean of GG genotype → 42.8; AA genotype → 38.36;GA genotype → 37.91; p < 0.001).*

The chi-square (× 2) test showed that carried GG homozygotes and G allele increased BMI and are highly associated with obesity in *LEPR gene rs1137101* polymorphisms of the study groups, are shown in Table 2 *(p < 0.05)*. We found that distribution of G allele control; 41 (20.5%) → overweight; *54(27%) → obese; 49(24,5%) → morbid obesity; 58(29%), respectively.*

Moreover, we found that AA homozygote genotype of *LEPR gene rs1137101* polymorphism might have a protective effect against obesity between morbid obesity and control *(AA homozygotes genotype; morbid obesity = 0 → control = 16,3%; p < 0,001, respectively).*

Table 2 LEPR rs1137101 GG genotypes and G allele distribution in the study groups

SNPs/groups		Control *n* = 49 (%)	Overweight *n* = 50 (%)	Obese *n* = 50 (%)	Morbid obesity *n* = 49 (%)	χ^2	*p*
LEPR rs1137101	AA	8 (16.3%)	14 (28%)	11 (22%)	0	41.722	**< 0.001**
	GA	41 (87.7%)	18 (36%)	29 (58%)	40 (81.6%)		
	GG	0	18 (36%)	10 (20%)	9 (18.4%)		
	A allele	57 (28.5%)	46 (23%)	51 (25.5%)	40 (20%)	*17	***< 0.001**
	G allele	41 (20.5%)	54 (27%)	49 (24.5%)	58 (29%)	**26.7	****< 0.001**
						***12.0	***** = 0.001**
						****21.7	******** < 0.001**
						*****12.7	********* < 0.001**

The groups were analyzed by chi-square (×2) and post-hoc test. Bold values of $p < 0.003$ indicate significant differences. * < 0.001, *p*-value of A allele between morbid obesity and controls; ** < 0.001, *p*-value of G allele between overweight and controls; *** = 0.001 *p*-value of G allele between obese and controls; **** < 0.001; ***** < 0.001 *p*-value of G allele between morbid obesity and controls

There were no significant results found between the biochemistry parameters and *LEP rs7799039* and *LEPR rs1137101* polymorphisms in the study groups *(p > 0.05)*.

Discussion

Leptin is a product of the obese (ob) gene and regulates BMI, food, and reproductive functions, playing important roles in fetal growth, proinflammatory immune responses, angiogenesis, and lipolysis [25]. Leptin also binds to and activates the leptin receptor by synthesizing and secreting from white adipose tissue cells. Decreased signal transduction and expression of leptin receptors cause leptin not to reach the targeted cells, and therefore, the development of leptin resistance [26]. Leptin resistance is also characterized by decreased satiety, excessive food consumption, and increased BMI, leading to obesity [27].

Ehap et al. reported lipid concentrations including HDL-c, TC, LDL-c, and VLDL, showing significant correlation among obesity groups compared with non-obese groups *(p < 0,001)* [28]. Similar to this study, our results showed a significant negative correlation concerning plasma concentration of HDL-c with increased BMI and found a positive correlation of TC plasma concentration with BMI in the study groups *(p < 0,05)*. Moreover, we found a statistically significant association between the study group regarding *LEP gene rs7799039* polymorphism and increased BMI *(p < 0,05)*. However, the level of significance of genotypes between the groups could not be determined in advanced statistical analysis. İman et al. reported that the AA genotype of *Leptin rs7799039* increased obesity risk in the study group *(LEP gene rs7799039 AA genotype obese; 28.12%, non-obese; 13.6% p = 0.001)*. Furthermore, there was more frequency in terms of GG genotype of *LEP rs7799039* polymorphism in non-obese than in the obese group *(49,12% → %29,39; p = 0.002)* [29]. Similar to this disruption, our result genotype of *LEP rs7799039* was totally *AA;44,4% → AG;28,4 → GG;26,7% p = 0.031*. Shruti et al. reported that the *AA genotype of the LEP gene* was more positively associated with BMI than *GA and GG genotypes*. Moreover, individuals with the AA genotype of the *LEP gene rs7799039* were found to have higher serum leptin levels than GA and GG. In our study, we found a significant association between *LEP gene rs7799039* polymorphism and BMI *(p < 0.001)*. Especially *GG genotype* of *LEP gene rs 7799039* is statistically significant in the obesity group and morbid obesity group. On the other hand, the other study in the Turkish population reported no significant association between *LEP gene rs7799039 polymorphism* and obese children and adolescents [30] *(p > 0.05)*. However, they found a significant association between *LEPR gene rs1137101* polymorphism and obesity *(p < 0.05)*. Apart from this, Raskiliene et al. reported that GG genotype of *LEP gene rs7799039* polymorphism was associated with higher BMI compared to A allele carried in obese males [22].

The deficiency in leptin receptors causes obesity by causing uncontrolled food intake, and leptin resistance also causes obesity. Campa et al. found no statistically significant difference in terms of *LEPR gene rs1137101* genotype between non-obese and overweight/obese individuals *(p > 0.05)* [31]. İmen et al. found an association with overweight individuals in GG genotype of *LEPR gene rs1137101 polymorphism* ($p = 0.037$). Moreover, they showed a negative correlation between HDL-c and the GG genotype of *LEPR polymorphism* [29]. The other study reported that there is a significant relationship between obesity and the GG genotype of *LEPR gene rs1137101* polymorphism compared with non-obese controls *(17.3% → 6.6% p = 0.009, respectively)*. Apart from the GG genotype of *LEPR gene rs1137101*, the frequency of the G allele was significantly higher among obese individuals compared to non-obese control *(36.4% → 21.3% p < 0.001, respectively)*. However, they found no significant relationship between genotypes and biochemical parameters in study groups *(p > 0.05)* [29]. The present study showed that carrying GG homozygotes genotype and G allele of *LEPR gene rs1137101* polymorphism increased BKI *(p < 0.001)*. On the other hand, there was no significant association between the distribution of genotype and biochemical parameters *(p > 0.05)*. Similar to other studies in the Turkish population, it was revealed that there is a significant association of the G allele of *LEPR gene rs1137101* polymorphism with an increased risk of obesity *(38,5% → 30,4%; p < 0,05 respectively)* [32].

Conclusions

Consequently, we found a significant association between *LEP gene rs7799039* and *LEPR gene rs1137101* polymorphisms in study groups, and especially G allele of *LEPR gene rs1137101* polymorphism might carry a relationship with increased BMI in the study groups. One limitation of the present study is that it has a relatively small sample population, with approximately 50 participants in each of the two groups. With a small number of participants, the statistical power of the analyses can be decreased and generalizability of the outcomes to large populations can be restricted. More diverse and larger cohorts are required for future investigations to validate and expand on the associations observed in the present study. Future studies are needed to be conducted with a larger sample size, including the serum levels of Leptin and gene expression activity, to better understand the role of Leptin in obesity. The present study evaluates in the Turkish population the distribution of

critical polymorphisms of the genes of leptin metabolism in obesity and will contribute to the literature in this manner.

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

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

Declarations

Ethics Approval The study was confirmed by Istanbul University's Ethics Committee. All participants obtained their written assent to the study's procedures.

Competing interests The authors declare no competing interests.

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