ASSOCIATION OF POLYMORPHISMS IN LEPTIN AND LEPTIN RECEPTOR GENES WITH OBESITY IN POSTMENOPAUSAL WOMEN

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ABSTRACT

Objective: *Leptin is an adipokine that plays a key role regulating body weight. Common polymorphisms in the leptin (LEP) gene and leptin receptor (LEPR) gene are associated with obesity and its complications. This study investigated associations between the LEPR Q223R and LEP G-2548A polymorphisms and body mass index (BMI), plasma leptin levels, and biochemical parameters in postmenopausal women.*

Material and Method: *The study included 115 obese and 85 non-obese postmenopausal women. The G-2548A and Q223R polymorphisms were determined by polymerase chain reaction-restriction fragment length polymorphism. Plasma leptin levels, serum lipids, and anthropometric parameters were measured.*

Results: *Our results showed no association between obesity and the G-2548A and Q223R polymorphisms. The Q223R and G-2548A polymorphisms were significantly associated with total cholesterol in both groups. The G-2548A polymorphism was associated with high LDL-cholesterol levels in the non-obese group ($p<0.001$). Additionally, the Q223R polymorphism was associated with leptin levels ($p=0.021$), particularly in the obese group.*

Conclusion: *Our results suggest that the G-2548A and Q223R polymorphisms had no direct association with obesity in postmenopausal women. However, they had significant effects on lipid profiles in obese and non-obese subjects.*

Keywords: *Obesity, polymorphism, leptin, postmenopausal women, adipokine.* **Nobel Med 2017; 13(3): 34-40**

POSTMENOPOZAL KADINLARDA LEPTİN VE LEPTİN RESEPTÖR GENLERİNDEKİ POLİMORFİZMLER İLE OBEZİTE ARASINDAKİ İLİŞKİ

ÖZET

Amaç: Leptin, vücut ağırlığı düzenlenmesinde önemli rol oynayan bir adipokindir. Leptin (LEP) geni ve leptin reseptörü (LEPR) genindeki sık görülen polimorfizmlerin obezite ve obeziteden kaynaklı komplikasyonlarla ile ilişkili olduğu gösterilmiştir. Bu çalışmanın amacı postmenopozal kadınlarda LEPR Q223R ve LEP G-2548A polimorfizmleri ile obezite, vücut kitle indeksi (VKİ), plazma leptin seviyesi ve biyokimyasal parametreler arasındaki ilişkinin belirlenmesidir.

Materyal ve Metot: Çalışma 115 obez ve 85 obez olmayan postmenopozal kadın birey içermektedir. G-2548A ve Q223R polimorfizmlerinin belirlenmesi polimeraz zincir reaksiyonu-restriksiyon parça uzunluğu polimorfizmi (PCR-RFLP) ile gerçekleştirilmiştir. Çalışma kapsamında plazma leptin ve serum lipit seviyeleri, antropometrik parametrelerin ölçümü yapılmıştır.

Bulgular: Çalışma sonucunda G-2548A ve Q223R polimorfizmleri ile obezite arasında ilişki saptanmamıştır. Obez ve obez olmayan kişilerden oluşan her iki grupta da Q223R ve G-2548A polimorfizmleri ile total kolesterol seviyesi arasında istatistiksel olarak anlamlı ilişki gözlemlenmiştir. Obez olmayan kişilerden oluşan grupta, G-2548A polimorfizmi ile yüksek LDL-kolesterol seviyesi arasında ilişiki olduğu belirlenmiştir (p<0,001). Ayrıca obez grupta leptin seviyeleri ile Q223R polimorfizmi ilişki saptanmıştır (p=0,021).

Sonuç: Sonuçlarımız postmenopozal kadınlarda G-2548A ve Q223R polimorfizmleri ile obezite arasında direkt bir ilişkili olmadığını göstermektedir. Fakat polimorfizmlerin hem obez hem de obez olmayan bireylerde lipid profilleri üzerine önemli bir etkisinin olduğunu düşünülmektedir.

Anahtar kelimeler: Obezite, polimorfizm, leptin, postmenopozal kadınlar, adipokin. **Nobel Med 2017; 13(3): 34-40**

INTRODUCTION

Obesity is a problem for women in all age groups, particularly after menopause. Menopause, which is a consequence of hormonal changes, including a decline in growth hormone and estrogens, involves an increased risk of overweight and obesity.[1] Hormonal changes that occur during menopause may contribute to higher accumulation of adipose tissue, particularly within the abdominal cavity.[2] Obesity and increased central fat are associated with increased morbidity and mortality.[3,4] Intra-abdominal fat cells produce a wide range of protein signals and factors called adipokines, such as leptin. Leptin is one of the most important adipose-derived hormones that plays a key role regulating energy intake and energy expenditure, including appetite control and metabolism; it is present in the circulation in amounts proportional to body fat mass.[5]

Postmenopausal women are characterized by elevated levels of leptin based on increased body fat mass, which is a consequence of the decline in estrogens.[6] Several studies have suggested that the percent of body fat may be the best adiposity-related predictor of serum leptin level in postmenopausal women.[7-9] Surprisingly, some studies have demonstrated the leptin could be involved in breast cancer, bone diseases, cardiovascular disease, and diabetes mellitus in postmenopausal women and enhance the progression of these conditions associated with obesity.[10-12]

The leptin (LEP) and leptin receptor (LEPR) genes have been extensively studied in search for genetic variants that could be important in the pathophysiology of human obesity, diabetes, and associated complications.[13,14] Several polymorphisms have been identified in these genes. One of these polymorphisms is a common G-2548A (rs7799039) leptin promoter variant, which results from a G to A substitution at nucleotide -2548 upstream of the ATG start site in the LEP gene.[15] The G-2548A polymorphism has previously been shown to be associated with adipocytes and increased leptin production and secretion.[16-18] The Q223R polymorphism (rs1137101) is located within the region encoding the extracellular domain of the leptin receptor and results from a change in a glutamine to an arginine at position 223 of the LEPR protein. The Q223R polymorphism is associated with a decrease in leptin binding activity resulting in leptin resistance.[19]

The associations between the Q223R and G-2548A polymorphisms in postmenopausal women with breast cancer and bone diseases have been investigated extensively, but studies involving healthy postmenopausal obese women are limited. The aim of this study was to investigate whether two common single polymorphisms in the leptin (LEP G-2548A) gene and its receptor (LEPR Q223R) are related to obesity in postmenopausal women. A further aim was to examine the influence of the LEP G-2548A and LEPR Q223R polymorphisms on lipid parameters,

Table 1. Baseline characteristics of the populations.

Parameter	Non-obese subjects (n=85)	Obese subjects (n=115)	*p*-value
Age	56.5±5.21	57.9±6.17	0.09
Age at menopause (y)	47.86±4.25	48.85±5	0.14
Menopausal period (y)	8±5.08	8.87±5.7	0.26
BMI (kg/m²)	23.7±1.5	33.7±7	<0.001
Waist circumference (cm)	85.94±9.8	109.7±16.4	<0.001
Hip circumference (cm)	98.5±6.4	118.8±13.8	<0.001
Fasting glucose (mg/dL)	93.75±5.8	104.3±17	<0.001
Total cholesterol (mg/dL)	210±22	230±31.8	<0.001
LDL-cholesterol (mg/dL)	125±17.4	136.5±28.6	0.0012
HDL-cholesterol (mg/dL)	59.2±7.7	51.4±8.71	<0.001
Triglycerides (mg/dL)	104±31	127.1±44.75	<0.001
HOMA-IR	1.91±0.7	3.51±1.78	<0.001
Leptin (ng/ml)	9.14±4.3	20.94±11.61	<0.001

Data are expressed as means ± standard deviation and were compared by the *t*-test.
BMI: body mass index, **LDL:** low-density lipoprotein, **HDL:** high-density lipoprotein, **HOMA-IR:** homeostasis model assessment of insulin resistance.

homeostasis model assessment-estimated insulin resistance (HOMA-IR), and plasma leptin levels in obese and non-obese subjects.

MATERIAL AND METHOD

Subjects

This prospective study enrolled patients who visited the outpatient clinic of the Obstetrics and Gynecology Department at Near East University Hospital. The two groups consisted of 115 obese postmenopausal women patients (mean age, 57.9±6.17 years; body mass index [BMI], 33.7±7 kg/m2) and 85 non-obese postmenopausal women (mean age, 56.5±5.21 years; BMI, 23.7±1.5 kg/m2). All women were considered postmenopausal because they had no menstruation for at least 1 year. Women with any of the following criteria were excluded: surgical menopause or ovarian surgery, early menopause at <40 years, underlying diseases known to affect age at menopause and previous or current use of estrogens. None of the participants had hypertension or liver, kidney, thyroid, cardiovascular, or any active inflammatory disease, and they were questioned about any medical therapy that might affect lipid and glucose metabolism. The participants did not receive any medications and did not participate in any diet or exercise program during the study. All subjects provided written informed consent before enrollment. The Near East University Research Ethics Committee approved the study (YDU/2016/38-306).

Anthropometric Measurements

All measurements were performed in the morning with the patients in a fasted state. Anthropometric measurements, including weight (kg), height (m), hip circumference (cm), and waist circumference (cm) were measured with the subjects barefoot and in light clothing. Hip circumference was measured by placing a tape around the patient's hips at the level of the prominences over the greater trochanters of both femurs. Waist circumference was measured midway between the lowest rib (laterally) and the iliocristale landmark with a tape. BMI was calculated as body weight (kg) divided by the square of height (m^2), and obesity was defined as a BMI ≥30 kg/m^2.[20]

Biochemical Parameters

Blood samples were obtained after an overnight fast. Levels of serum glucose, triglycerides, total cholesterol, high-density lipoprotein cholesterol (HDL-C), and low-density lipoprotein cholesterol (LDL-C) levels were measured using an automated clinical chemistry analyzer (Abbott ArchitectC8000; Abbott Park, IL, USA). Fasting insulin concentrations were measured using an electrochemiluminescence kit (Ref. 12017547; Elecsys Corp., Lenexa, KS, USA). Insulin resistance index values were calculated using the HOMA-IR, as the product of fasting insulin (μU/mL) and fasting glucose (mmol/L) divided by 22.5.[21]

Plasma leptin levels were measured using a commercially available enzyme-linked immunosorbent assay human leptin kit (EIA-2395; DRG International, Inc., Springfield Township, NJ USA). Human leptin kits were used according to the manufacturer's protocol. The results are expressed in ng/mL.

Genotyping

Genomic DNA was extracted from whole blood using a salting out procedure.22 Genotyping of the G2548A (rs7799039) and Q223R polymorphisms (rs1137101) was carried out using the polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) assay with primer pairs described previously.[15,23]

PCR reactions were performed in a total volume of 50 μl using 1 μg genomic DNA, 0.4 μM of each primer, 23.5 μl nuclease-free water (Fermentas International Inc., Quebec, ONT, Canada), and 25 μl DreamTaq PCR Master Mix (Fermentas International). PCR consisted of one cycle of initial denaturation for 2 min at 95°C, followed by 32 cycles of denaturation for 30 sec at 95°C, annealing for 30 sec at 54°C, extension for 30 sec at 72°C, and a final extension at 72°C for 10 min.

Table 2. Anthropometric and metabolic characteristics across LEPR Q223R genotypes of obese and non-obese postmenopausal women.

Parameter	Non-obese subjects				Obese subjects			
	QQ (n=38)	QR (n=25)	RR (n=22)	*p*-value	QQ (n=40)	QR (n=48)	RR (n=27)	*p*-value
Age	56±4.33	55±4.41	58±7	0.13	58.3±6.85	57.1±5.72	59±5.4	0.39
Age at menopause (y)	48±4.78	47.3±4.43	48.5±2.45	0.61	48.5±4.19	49.45±4.96	47.90±6.45	0.42
Menopausal period (y)	8±5.42	7.85±4.27	8.62±5.69	0.86	9.26±6.18	8.81±4.82	10.09±6.4	0.64
BMI (kg/m^2)	23.7±1.6	23±1.55	23.8±1.21	0.12	33.3±6.47	33.6±7.1	34.3±7.8	0.84
Waist circumference (cm)	85.2±11.86	84.9±5.82	85.5±11.2	0.98	104.4±13.25	107±20.3	109±7.93	0.49
Hip circumference (cm)	98.7±7.3	97.4±6.34	98.76±4.10	0.68	115.6±15.14	117.2±13.13	119±12.2	0.6
Fasting glucose (mg/dL)	94.86±7.34	92.36±3.84	94.25±5.4	0.26	100.9±11.14	107±21.5	105±10.8	0.21
Total cholesterol (mg/dL)	205±23.4	210.2±18.9	220±21.4[a]	0.04*	218±38.7	225.4±26.9	240.2±25.4[b]	0.019*
LDL-cholesterol (mg/dL)	125.8±17.6	123.1±16.8	130.9 ±15.58	0.28	135.6±35.12	137.3±24.34	136±23	0.95
HDL-cholesterol (mg/dL)	60.9±6.27	58±8.5	58±8.1	0.21	53.3±10	51.6±8.64	52.4±3.5	0.63
Triglycerides (mg/dL)	102±30.9	103.9±30.5	106±31.1	0.88	126.2±43.5	125.1±50.06	134.5±25.95	0.64
Leptin (ng/ml)	8.86±4.87	9.17±3.78	9.58±4.16	0.82	17.03±9.53	22±12.6	24.64±11.49[c]	0.021*
HOMA-IR	1.91± 1.07	1.87±0.48	1.98±0.26	0.88	2.98±1.67	3.66±1.89	3.94±2.78	0.07

Data are expressed as means ± standard deviation. Analysis of variance followed by Tukey's test was performed to compare subgroups. **BMI:** body mass index, **LDL:** low-density lipoprotein, **HDL:** high-density lipoprotein, **HOMA-IR:** homeostasis model assessment of insulin resistance. [a]: Significant difference from QQ genotype by post hoc Tukey's test. [b]: Significant difference from QQ genotype by post hoc Tukey's test. [c]: Significant difference from QQ genotype by post hoc Tukey's test. *: p <0.05

PCR products for the LEPR Q223R polymorphism were digested for 2 hours at 37°C with 5 U of the MspI restriction enzyme (Fermentas International). In cases of mutation, the MspI site was naturally created in a Q223R variant allele and produced fragments of 173 and 469 bp, which were separated on 2% agarose gels with ethidium bromide staining.

PCR products for the LEP G2548A polymorphism were digested for 2 hours at 37°C with 5 U of the HhaI restriction enzyme. In cases of mutation, the HhaI site was naturally created in the G2548A variant allele, and the resulting fragments were separated on 2.5% agarose gels with ethidium bromide staining.

Statistical Analysis

The distributions of continuous variables are expressed as means ± standard deviations. Differences in baseline characteristics between the groups were analyzed by Student's t-test and the $\chi 2$ test for continuous variables and categorical variables, respectively. Analysis of variance was used to compare the means of continuous variables among the three genotype subgroups. Differences among the three genotype subgroups in the mean values of the continuous variables were confirmed by a post hoc Tukey's test. A P value <0.05 was considered significant. All statistical analyses were performed using SPSS software (ver. 15.0; SPSS Inc., Chicago, IL, USA).

RESULTS

Descriptive statistics for the anthropometric and metabolic characteristics of the study population are presented in Table 1. No differences were observed in mean age, age of menopause, or menopausal duration between the obese and non-obese subjects. Additionally, plasma glucose, total cholesterol, triglycerides, LDL-cholesterol, and leptin levels were significantly higher, whereas HDL-cholesterol was significantly lower (p<0.001), in obese subjects than in non-obese subjects. Non-obese subjects had significantly lower HOMA-IR compared to obese subjects (p<0.001).

Analysis of the LEPR gene produced three different genotype variants: QQ for the wild type, the heterozygote QR, and the homozygote RR for the polymorphism. The LEPR genotype frequencies were calculated and were 34.8% for QQ, 41.7% for QR, and 23.5% for RR in obese subjects. The frequencies of the QQ, QR, and RR genotypes were 44.7%, 29.4%, and 25.9%, respectively, in non-obese subjects. No differences in the Q223R polymorphism genotype frequencies were detected between obese and non-obese subjects.

The Q223R polymorphism allele frequencies were calculated. The frequencies of the Q allele of LEPR (found in 59.4% of non-obese subjects and 55.7% of obese subjects) and the R allele (found in 40.6% of non-obese subjects and 44.3% of obese subjects) did not differ between obese and non-obese subjects.

The Q223R polymorphism was significantly associated with levels of total cholesterol in non-obese subjects after adjustment for BMI and age (p=0.04). Post hoc comparisons in non-obese subjects showed that RR homozygotes had a significantly higher mean value compared to that of the QQ homozygotes. A significant association was found between Q223R and total cholesterol (p=0.019) and leptin (p= 0.021) levels in obese women. The post hoc Tukey's test showed significant differences in total cholesterol and leptin levels between the QQ and RR genotypes (p<0.05) but not between the QQ and QR genotypes of obese subjects (Table 2).

The frequencies of the G and A alleles in G-2548A were 56.5% and 43.5%, respectively, in the non-obese group and 53% and 47%, respectively, in the non-obese group. No differences in the allele frequencies of the G-2548A polymorphism were found between obese and non-obese subjects (p=0.54). The genotype frequencies of obese group subjects were 33% for GG, 40% for GA, and 27% for AA, whereas they were 40% for GG, 33% for GA, and 27% for AA in non-obese subjects. No differences in the genotype frequencies of the G-2548A polymorphism were detected between obese and non-obese subjects (p=0.51).

The G-2548A polymorphism was significantly associated with total cholesterol and LDL-cholesterol levels in non-obese subjects after adjustment for BMI and age (p<0.001). Post hoc comparisons in non-obese subjects showed that the AA homozygotes were associated with significantly higher total cholesterol and mean LDL-cholesterol levels compared to the GG and GA genotypes. Additionally, obese women homozygous for AA had significantly higher levels of total cholesterol (p=0.02) compared with women homozygous for GG and heterozygous for GA. The post hoc analysis revealed that women with the AA genotype had higher total cholesterol levels than did women with the GG genotype, and the mean total cholesterol values of the GA and AA genotypes did not differ significantly (Table 3).

DISCUSSION

Leptin is a hormone that reduces food intake and increases energy expenditure after binding to the leptin receptor.[24] Several studies have examined the association between LEP G-2548A polymorphisms and BMI in obese subjects and the potential association between this polymorphism and breast cancer in postmenopausal women.[25,26] We found no research on the association between the G-2548A polymorphism genotypes and BMI or on the influence of this association on the pathophysiology of obesity in postmenopausal women. Thus, this is the first study of the potential effect of the G-2548A polymorphism on obesity in postmenopausal women. Our results show no association between the G-2548A gene polymorphism and obesity. The results of studies that examined genetic changes in the LEP gene that could be related to obesity risk in women who were not postmenopausal are controversial. Yiannakouris *et al.* and Mammés *et al.* showed that the genotypes of the G-2548A polymorphism are not associated with BMI in Greek and French women.[18,27] In contrast, Li *et al.* reported that the -2548G/A polymorphism is associated with extreme obesity in northern Caucasian women.[28]

The LEPR gene has been investigated in the search for gene variants potentially related to the pathophysiology of obesity in postmenopausal women, and conflicting results have been reported. Quinton *et al.* investigated the LEPR Q223R polymorphism in postmenopausal Caucasian women and reported an association with BMI.[19] In another study, Fairbrother *et al.* showed an association between Gln223Arg and BMI in postmenopausal Danish women.[29] Conversely, Lee *et al.* showed no significant association between the Q223R polymorphism and BMI in postmenopausal Korean women.[30] Our present results provide no evidence for a relationship between the Q223R polymorphism and BMI. These conflicting results may arise from interactions between the Q223R polymorphism and other polymorphisms in the leptin and/or leptin receptor genes, ethnicity, sample size of the population, or model used in the statistical analysis.

It is now well established that females are more protected from hypercholesterolemia-related diseases before menopause. The cessation of ovarian function after menopause results in a loss of estrogens, which disrupts homeostasis by, for example, decreasing leptin secretion and changing lipid metabolism, and which results in a total reduction in energy expenditure.[2] The metabolic effects of leptin and estrogen on cholesterol metabolism may be mediated by a common pathway involving activation of 5′-AMP-activated protein kinase (AMPK).[31] AMPK was initially identified as a protein kinase that inhibits 3-hydroxy-3-methylglutaryl coenzyme A reductase (HMG-CoAR). Leptin phosphorylates and activates AMPK via central and peripheral mechanisms.[32] Leptin signaling-deficient models show a loss of circadian rhythmicity in HMG-CoAR activity.[33] Takahashi-Yasuno *et al.* and Boumaiza *et al.* reported that the Q223R and G-2548A polymorphisms are associated with total cholesterol.[34,35] On the other hand, estrogen induces a decline in hepatic HMG-CoAR activity. Moreover, low HMG-CoAR expression in females indicates neo-synthesis of cholesterol and could be related to the well-known observation that females are more protected against hypercholesterolemia

Table 3. Anthropometric and metabolic characteristics across LEP G2548A genotypes of obese and non-obese postmenopausal women.

Parameter	Non-obese subjects (n=85)				Obese subjects (n=115)			
	GG (n=34)	GA (n=28)	AA (n=23)	*p*	GG (n=38)	GA (n=46)	AA (n=31)	*p*
Age	56.4±6.49	54.8±4.1	57.06±3.66	0.26	57.2±5.5	56.7±6.24	58.4±6.27	0.47
Age at menopause (y)	48.57±4.26	46.3±4.43	48.15±4.35	0.11	48.59±4.58	48.09±5.21	48.12±5.13	0.88
Menopausal period (y)	7.25±5	8.26±5.23	8±4.2	0.69	8.21±6.06	8.16±5.08	9.84±6.86	0.41
BMI (kg/m²)	23.6±1.64	23.7±1.45	24.13±1.13	0.38	32.2±5.88	35.3±8.4	34.41±6.42	0.13
Waist circumference (cm)	85.9±10.45	84.2±7.73	85.5±12	0.79	105.5±20.6	108±14.08	1 14.9±18.31	0.08
Hip circumference (cm)	97.64±7.4	98.8±6.77	98.56±8.41	0.81	116.3±16.49	119.5±12.81	117.8±15.9	0.62
Fasting glucose (mg/dL)	94.3±7.7	92.87±5.72	94.57±5.15	0.58	102.2±18.85	108±26.58	103.26±10.4	0.39
Total cholesterol (mg/dL)	198±15	212±21	229±19.09a	<0.001	219±33.7	226±25.1	238.9±33.52c	0.02*
LDL-cholesterol (mg/dL)	119±15.3	125±18.2	139±17.25b	<0.001	131.3±31.45	135.6±21.6	142±29.2	0.27
HDL-cholesterol (mg/dL)	57±7.94	61±6.56	60.1±8.44	0.10	52±8.29	51.3±6.86	53.32±10.72	0.59
Triglycerides (mg/dL)	102±24.45	104±35.75	109.6±25.27	0.61	119.3±41.63	127.5±51.21	136.7±33.24	0.26
Leptin (ng/ml)	9.87±4.61	8.98±4.38	7.85±3.92	0.23	22.42±13.15	21.04±11.12	19.74±10.49	0.63
HOMA-IR	1.89±0.43	1.87±0 .44	1.92±0.35	0.91	3.22±1.19	3.79±2.41	3.60±1.59	0.37

Data are expressed as means ± SD. For the comparison of subgroups, analysis of variance followed by ANOVA was performed. **BMI:** body mass index, **LDL:** low-density lipoprotein, **HDL:** high-density lipoprotein, **HOMA-IR:** homeostasis model assessment of insulin resistance. [a]: Significant difference between GG genotype and GA genotype by post hoc Tukey test. [b]: Significant difference between GG genotype and GA genotype by post hoc Tukey test. [c]: Significant difference from GG genotype by post hoc Tukey test. *: $p<0.05$

before menopause. Unfortunately, we found no research on the influence of the Q223R and G-2548A polymorphisms on cholesterol metabolism in healthy postmenopausal women. Thus, this is the first study of the potential effect of the Q223R and G-2548A polymorphisms on total cholesterol levels. Taken together, the depletion of estrogen in combination with the LEPR and LEP gene substitutions after menopause could cause several metabolic changes in cholesterol metabolism that facilitate dyslipidemia and obesity.

The Q223R polymorphism is located within the extracellular domain of the leptin receptor, and the amino acid change affects the functional characteristics of the receptor and alters its signaling pathways. Quinton *et al.* showed that serum leptin binding activity and leptin levels are higher in postmenopausal Caucasian women who are carriers of the A allele than in those who are homozygous for the G allele.[19] Berezina *et al.* investigated metabolically healthy and unhealthy women carriers of the 223R allele in the leptin receptor gene and found higher leptin levels in this group than in individuals with the Q223Q genotype.[36] Furthermore, leptin levels are higher in metabolically unhealthy obese women with the R223R genotype than in women who are carriers of the 223Q leptin allele. We also found that obese postmenopausal women with the RR genotype had significantly higher plasma leptin levels than did subjects with the QR and QQ genotypes. Therefore, it can be concluded that the Q223R polymorphic variation in the LEPR gene may be associated with changes in ligand binding activity resulting in leptin resistance and differences in leptin levels.

The strength of the current study is that it was performed in a well-characterized cohort of postmenopausal women with and without obesity. The main limitations of this study were the lifestyle characteristics, which affected the relationships between gene variants and phenotype. Second, only a limited number of polymorphisms in the LEP and LEPR genes were analyzed.

CONCLUSION

In conclusion, our results suggest that the LEP G-2548A and LEPR Q223R polymorphisms are not associated with obesity, but they do have significant effects on lipid profiles and leptin levels. Based on the literature and our findings, the G-2548A and Q223R polymorphisms appear to play a role modulating energy homeostasis in postmenopausal women through an unknown feedback mechanism between leptin and estrogen signaling pathways. Indeed, there may be a cumulative effect when combining different factors, such as ethnicity, pleiotropic genotype effects, lifestyle, and nutritional factors, and this may affect energy homeostasis and explain the increase in BMI. Further assessment of this issue with a larger cohort that includes all possible polymorphisms and molecules that may play a role in the estrogen activity in adipose tissue is required.

*The authors declare that there are no conflicts of interest.

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