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Trabajo Original

Obesidad y síndrome metabólico

Association of the leptin receptor rs1805134 polymorphism with obesity parameters, dietary intakes, and metabolic syndrome in Caucasian obese subjects

Asociación del polimorfismo del receptor de leptina rs 1805134 con parámetros de obesidad, ingesta alimentaria y síndrome metabólico en sujetos caucásicos con obesidad

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Abstract

Background: some studies have evaluated the association of the rs1805134 genetic variant of the *LEPR* gene with obesity.

Aims: the objective was to explore the association of the rs1805134 genetic variant of the *LEPR* gene with obesity measures and metabolic syndrome in obese Caucasian adults.

Methods*:* we conducted a cross-sectional study in 212 obese subjects with body mass index (BMI) greater than 30 kg/m^2. Measurements of adiposity parameters, blood pressure, fasting blood glucose, insulin concentration, insulin resistance (HOMA-IR), lipid profile, C-reactive protein, and prevalence of metabolic syndrome were determined.

Results*:* the distribution of rs1805134 was 128 TT (60.4 %), 77 TC (36.3 %), and 7 CC (3.3 %). C-allele carriers showed higher levels of BMI, body weight, body fat mass, waist circumference, insulin, HOMA-IR, triglycerides, total energy intake, and carbohydrate intake than non-C-allele carriers. A logistic regression analysis reported a high percentage of elevated waist circumference (OR = 2.22, 95 % CI = 1.201-4.97; p = 0.02), hyperglycemia (OR = 1.54, 95 % CI = 1.01-5.44; p = 0.01), and metabolic syndrome percentage (OR = 1.41, 95 % CI = 1.04-5.39; p = 0.03) in C-allele carriers.

Conclusions*:* subjects with the C-allele of the rs1805134 variant of the *LEPR* gene showed a worse metabolic pattern with a higher percentage of metabolic syndrome, central obesity and hyperglycaemia, probably related to higher energy intake.

Keywords:

Energy intake. rs1805134. *LEPR* gene. Metabolic syndrome.

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Statement of ethics: this study protocol was reviewed and approved by the HCVUA Committee, approval number No 6/2018. Written informed consent was obtained from all participants included in the study.

Consent to participate statement: a signed informed consent was obtained from all participants. This research complies with the guidelines for human studies in accordance with the World Medical Association Declaration of Helsinki.

Conflicts of interest statement: the authors have no conflicts of interest to declare.

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Data availability statement: all the data generated or analyzed during this study are included in this article. Further enquiries can be directed to the corresponding author.

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Resumen

Antecedentes: algunos estudios han evaluado la asociación de la variante genética rs1805134 del gen LEPR con la obesidad**.**

Objetivos: el objetivo fue explorar la asociación de la variante genética rs1805134 del gen LEPR con los parámetros de obesidad y síndrome metabólico en adultos caucásicos obesos.

Métodos: realizamos un estudio transversal en 212 sujetos obesos con índice de masa corporal (IMC) superior a 30 kg/m^2. Se determinaron los parámetros de adiposidad, presión arterial, glucemia en ayunas, concentración de insulina, resistencia a la insulina (HOMA-IR), perfil lipídico, proteína C-reactiva y prevalencia de síndrome metabólico.

Resultados: la distribución del rs1805134 fue de 128 TT (60,4 %), 77 TC (36,3 %) y 7 CC (3,3 %). Los portadores del alelo C mostraron niveles más altos de IMC, peso corporal, masa grasa corporal, circunferencia de la cintura, insulina, HOMA-IR, triglicéridos, ingesta total de energía y consumo de carbohidratos que los portadores sin alelo C. El análisis de regresión logística mostró un alto porcentaje de pacientes con elevada circunferencia de la cintura (OR = 2,22, IC 95 % = 1,201-4,97; p = 0,02), hiperglucemia (OR = 1,54, IC 95 % = 1,01-5,44; p = 0,01) y síndrome metabólico (OR = 1,41, IC 95 % = 1,04-5,39; p = 0,03) en los portadores del alelo C.

Conclusiones: los sujetos con alelo C de la variante rs1805134 del gen LEPR mostraron un peor patrón metabólico con mayor porcentaje de síndrome metabólico, obesidad central e hiperglucemia, probablemente relacionado con una mayor ingesta energética.

Palabras clave:

Ingesta energética.
rs1805134. Gen LEPR.
Síndrome metabólico.

INTRODUCTION

Obesity is currently a global epidemic and its prevalence has risen in a dramatic way, increasing different morbidities such as osteoarthritis, cardiovascular events, diabetes *mellitus* type 2 and cancer (1-2). Genetic advances have led to find a lot of genetic variants associated with obesity measures and other related traits. In addition, adipose tissue is an active organ that secretes a multitude of molecules, for example leptin. The leptin hormone is a cytokine synthesized in white adipose tissue (16 kDa peptide), and indicates the nutritional status of the brain. This adipokine acts through leptin receptors, which are located in the hypothalamus, which is the central regulatory centre of appetite regulation and energy homeostasis. The *LEPR* gene located in chr1p31 encodes these leptin receptors. Some mutations in this gene are related with monogenic forms of morbid, early-onset obesity and hyperphagia (3). Some single nucleotide polymorphisms (SNPs) of the coding region of the LEPR gene have been detected (4). Of these, the rs1805134 polymorphism occurs as a result of a non-conservative C to T substitution (Ser343Ser); this variant could alter leptin binding and perhaps leptin signalling (4). Rojano et al. (5) reported that the rs1805134 variant could be involved in the development of morbid obesity in Mexican subjects. In contrast, a protective influence in obesity comorbidities has been described with other SNPs located in the *LEPR* gene (6), increasing protection against having higher blood pressure levels. These contradictory findings are added to the fact that there are scarce studies in Caucasian populations; the lack of data in this area emphasizes the need for studies across different ethnic groups. Finally, we can mention metabolic syndrome (MS) as an entity associated with obesity. MS involves a constellation of risk entities including glucose intolerance or diabetes *mellitus,* abdominal obesity, hyperlipidemia, and high blood pressure levels (7). MS is considered a polygenic and multifactorial disorder due to numerous different genes together with environmental factors and, as above mentioned, fat mass is considered an endocrine and paracrine organ, and this tissue develops an important role in the presence of MS (8).

In this work, our objective was to explore the association of the rs1805134 genetic variant of the LEPR gene with obesity measures and metabolic syndrome in obese Caucasian adults.

PATIENTS AND METHODS

SUBJECTS

We conducted a cross sectional study with a non-probabilistic consecutive method to select 212 study subjects (30-65 years) among obese adults.

The study was conducted in a Health Area of the Castilla y Leon Autonomous Community in Spain. These patients were sent from 24 primary care health departments covering both rural and urban areas of residence to a tertiary hospital. The Caucasian obese subjects came for health examinations in our outpatient clinic to evaluate their obesity (body mass index ≥ 30 kg/m^2). A total of 212 obese subjects were informed about the objectives of the study, they agreed to participate in the investigation, and all these patients gave their informed consent. The study was carried out in accordance with the Declaration of Helsinki, and the Ethics Committee approved the protocol (code of registration 06/2018). Inclusion criteria for this study were 1) body mass index ≥ 30 kg/m^2, age in the range of 20-65 years, and the patient had been referred by a primary care physician.

The following data were exclusion criteria: severe illness (e.g., chronic kidney disease, liver disease, heart failure, previous cardiovascular events, and malignant tumours), heavy smokers, and a history of alcoholism; also, patients who had received a hypocaloric diet within the previous 6 months were excluded from the study.

The following adiposity parameters (weight, body mass index (BMI), fat mass by bioimpedance and waist circumference) and blood pressure were recorded. Blood samples were obtained from all subjects in this initial visit. During the same visit, 5 ml of venous blood after a 10-hour overnight fast were aliquoted in ethylene-diaminetetraacetic acid (EDTA)-coated tubes for biochemical assays and genotyping. The following parameters were determined: insulin, total cholesterol, LDL-cholesterol, HDL-cholesterol, triglycerides and C-reactive protein. The season at blood collection was registered. Dietary intake for 3 previous days was recorded, too. The Adult Treatment Panel III (ATPIII) criteria were used to classify subjects with metabolic syndrome (7). The diagnosis of MS requires at least 3 of the following data; elevated fasting glucose or treatment for diabetes *mellitus,* elevated tri-

glycerides (> 150 mg/dl) or treatment for hyperlipidemia, low HDL-cholesterol < 40 mg/dl (males) or < 50 mg/dl (females), elevated systolic or diastolic blood pressure (> 130/85 mmHg or antihypertensive treatment) and increased waist circumference (> 94 cm (males) or > 80 cm [females]).

ADIPOSITY PARAMETERS AND BLOOD PRESSURE

The same researcher determined all the parameters related to obesity to decrease interobserver variability. Waist circumference was determined using a flexible standard tape (Omrom, LA, CA). Body height (cm) was measured using a standard height measurement scale (Omrom, LA, CA, USA). Body weight was measured while the subjects were minimally unclothed and not wearing shoes, using digital scales (Omrom, LA, CA, USA). Body mass index (BMI) was obtained with the next equation: weight in kilograms divided by height in squared meters. Total fat mass was obtained by impedance with an accuracy of 5 g (9) (EFG BIA 101 Anniversary, Akern, It). This formula was used: (0.756 Height^2 / Resistance) + (0.110 x Body mass) + (0.107 x Reactance) – 5.463. Systolic and diastolic blood pressures were obtained thrice using a sphygmomanometer (Omrom, LA, CA, USA) after the subjects sat for 10 minutes. Finally, the mean of these three determinations was used.

BIOCHEMICAL PROCEDURES

Serum biochemistry analyses for glucose, insulin, C-reactive protein (CRP), total cholesterol, HDL-cholesterol, and triglyceride levels were conducted using the COBAS INTEGRA 400 analyser (Roche Diagnostic, Basel, Switzerland). LDL-cholesterol was calculated using Friedewald's formula (LDL-cholesterol = total cholesterol – HDL-cholesterol – triglycerides / 5) (10). Based on these parameters, the homeostasis model assessment for insulin resistance (HOMA-IR) was obtained using these values (glucose x insulin / 22.5) (11).

DIETARY INTAKES AND PHYSICAL EXERCISE

In all subjects, daily dietary intake for 3 previous days (2 weekdays and 1 weekend day) were registered with a computer-based data evaluation system (Dietosource®, Gen, Switzerland). This software is based on national composition food tables as reference (12). All subjects recorded their daily physical exercise in minutes per week with a self-reported questionnaire.

GENOTYPING rs1805134

DNA was obtained from cells of the oral mucosa using QIAamp® according to the manufacturer´s protocol. A method based on quantitative DNA polymerase chain reaction (qPCR) was used to evaluate the polymorphism rs1805134 of the *LEPR* gene. Genotyping was performed by real-time PCR and allelic discrimination using Taqman assays with the QuantStudio 12K Flex Real-Time qPCR instrument (Thermofisher, Pittsburg, Pens, USA). A total volume of 10 µl with 2.5 µl TaqMan OpenArray Master Mix (Applied Biosystems, Foster City, LA, CA, USA) and 2.5 µl human DNA sample were loaded and amplified on arrays following the manufacturer's instructions (Termocicler Life Technologies, LA, CA). Genotype calling and sample clustering for open array assays was performed in a TaqMan Genotyper (Life Technologies, Carlsbad, CA, USA). Ten percent of samples underwent a second genotyping to ensure reproducibility. Moreover, a negative control and control samples representing all genotypes were included in each reaction. Hardy Weinberg equilibrium was determined with a statistical test (Chi-squared). The variant of the *LEPR* gene was in Hardy Weinberg equilibrium ($p = 0.231$).

STATISTICAL ANALYSIS

The statistical analysis was performed using the SPSS ver.23 (IBM) software (SPSS Inc. Chicago, IL). Genotype numbers were determined manually from the allelic discrimination plots, and allele frequencies were determined from genotype frequencies. The *LEPR* rs1805134 genotype was analyzed using a dominant model (TT vs. TC + CC). Sample size was determined to detect differences over 3 kg of body weight with 90 % power and 5 % significance. Data distribution was tested using the Kolmogorov-Smirnov test. Descriptive statistics of all variable values are presented as mean ± standard deviation for continuous variables and as a percentage for categorical variables. Variables were analyzed with Student's t-test (for normally distributed variable) or the Kruskal-Wallis test (for non-normally-distributed variables). The Bonferroni test was applied for multiple testing to reduce type-I error in association analyses; logistic regression analyses were used to calculated odds ratios (OR) and 95% confidence intervals (CI) to estimate the association of rs1805134 with MS and its entities. P values below 0.05 were considered statistically significant.

RESULTS

We recruited 212 subjects with an average age of 59.5 ± 2.4 years (range: 35-61) and the mean body mass index (BMI) was 40.1.5 ± 2.2 kg/m^2 (range: 35.3-43.4). The distribution of the rs1805134 polymorphism in this sample was 128 TT (60.4 %), 77 TC (36.3 %) and 7 CC (3.3 %). The allele frequency was T (0.80) and C (0.20). Mean age for both genotype groups was similar (TT: 51.9 ± 4.9 years vs TC + CC: 51.0 ± 4.2 years: ns) as well as proportions of gender (TT 27.2 % males vs 72.8 % females vs TC + CC 31.2 % males vs 68.8 % females).

Table I summarizes the significant associations found between genotype groups and adiposity parameters. Applying the dominant

genetic model (TT *vs.* TC + CC), we observed statistical differences between both genotype groups in BMI (1.2 ± 0.1 kg/m^2; $p = 0.03$), body weight (4.2 ± 0.6 kg; $p = 0.02$), body fat mass (4.1 ± 0.1 kg; $p = 0.01$) and waist circumference (4.4 ± 0.5 cm; $p = 0.03$). C-allele carriers showed higher levels of these parameters when compared to non-C-allele carriers.

Biochemical characteristics according to genotype are summarized in table II. Fasting insulin levels, HOMA-IR and triglycerides were higher in C-allele carriers than in non-C-allele carriers in both genotypes. We observed statistical differences between both genotype groups in the above-mentioned parameters; insulin levels (6.6 ± 0.9 UI/L; $p = 0.03$), HOMA-IR (1.1 ± 0.2 units; $p = 0.02$) and triglycerides (31.4 ± 5.5 mg/dl; $p = 0.03$).

Table III summarizes dietary intakes and physical exercise. We reported statistical differences between both genotype groups in total energy intake (198.4 ± 83.5 cal/day; $p = 0.03$) and carbohydrate intake (59.4 ± 7.5 mg/dl; $p = 0.03$). C-allele carriers showed higher dietary intakes of these parameters versus non-C-allele carriers. Physical exercise was similar in both groups.

The percentage of patients with metabolic syndrome and its different components (central obesity, low-HDL cholesterol, hypertriglyceridemia, hypertension or hyperglycemia) has been summarized in table IV. According to the results of metabolic characteristics, the percentage of individuals who had high waist circumference (OR = 2.41, 95 % CI = 1.31-4.45; $p = 0.02$), hyperglycemia (OR = 1.80, 95 % CI = 1.01-3.18; $p = 0.01$) and metabolic syndrome percentage (OR = 1.77, 95 % CI = 1.11-3.12; $p = 0.03$) were higher in C-allele carriers than in non-C-allele carriers. Logistic regression analysis reported a high percentage of elevated values for waist circumference (OR = 2.22, 95 % CI = 1.201-4.97; $p = 0.02$), hyperglycemia (OR = 1.54, 95 % CI = 1.01-5.44; $p = 0.01$) and metabolic syndrome percentage (OR = 1.41, 95 % CI = 1.04-5.39; $p = 0.03$) in C-allele carriers after adjusting for energy intake, carbohydrate intake, gender, BMI, and age.

Table I. Adiposity parameters and blood pressure

Parameters	TT n = 128	TC + CC n = 84	p
BMI	39.0 ± 0.3	40.2 ± 0.4	0.03
Weight (kg)	102.4 ± 2.1	106.6 ± 1.8	0.02
Fat mass (kg)	44.5 ± 1.2	49.1 ± 1.0	0.01
WC (cm)	118.0 ± 3.0	122.4 ± 2.1	0.03
SBP (mmHg)	135.9 ± 2.2	133.6 ± 3.1	0.37
DBP (mmHg)	81.4 ± 4.1	80.7 ± 4.2	0.41

BMI: body mass index; DBP: diastolic blood pressure; SBP: systolic blood pressure; WC: waist circumference.

Table II. Biochemical parameters (mean ± SD)

Parameters	TT n = 128	TC + CC n = 84	p
Fasting glucose (mg/dl)	105.2 ± 2.1	108.7 ± 4.0	0.31
Total cholesterol (mg/dl)	196.8 ± 11.8	206.1 ± 7.2	0.18
LDL-cholesterol (mg/dl)	116.4 ± 8.0	114.8 ± 7.1	0.22
HDL-cholesterol (mg/dl)	53.3 ± 2.0	50.7 ± 2.1	0.19
Triglycerides (mg/dl)	136.1 ± 11.0	167.7 ± 8.1*	0.03
Insulin (mIU/L)	17.6 ± 1.5	24.2 ± 1.1*	0.02
HOMA-IR	5.2 ± 0.3	6.3 ± 0.2*	0.03
CRP	4.2 ± 0.4	4.4 ± 0.9	0.41

*HOMA-IR: homeostasis model assessment of insulin resistance. CRP: C-reactive protein. *p < 0.05 between genotypes in a dominant model (TT vs TC + CC).*

Table III. Dietary intakes and physical activity (mean ± SD)

Parameters	TT n = 128	TC + CC n = 84	p
Calories (cal/day)	1631.4 ± 224.2	1808.9 ± 131.9	0.01
Carbohydrates (g/day)	191.2 ± 13.1	251.1 ± 21.0	0.01
Proteins (g/day)	80.4 ± 5.3	81.1 ± 7.2	0.41
Lipids (g/day)	61.3 ± 4.1	62.2 ± 2.1	0.42
Fiber (g/day)	13.2 ± 2.1	13.1 ± 2.3	0.41
Cholesterol (mg/day)	273.1 ± 80.1	254.1 ± 57.1	0.28
Saturated fatty acids (g/day)	17.2 ± 2.0	16.9 ± 1.1	0.32
Monounsaturated fatty acids (g/day)	29.2 ± 4.1	29.9 ± 4.3	0.40
Polyunsaturated fatty acids (g/day)	6.8 ± 3.3	7.0 ± 3.2	0.21
Physical activity (minutes/week)	117.9 ± 6.2	119.4 ± 4.1	0.33

Table IV. Metabolic syndrome and components of metabolic syndrome

Parameters	TT n = 128	TC + CC n = 84	p
Percentage of MetS	36.0 %	50.0 %*	0.03
Percentage of central obesity	57.1 %	76.1 %*	0.02
Percentage of hypertriglyceridemia	31.2 %	57.1 %*	0.01
Low HDL-cholesterol	18.2 %	20.1 %	0.49
Percentage of hypertension	71.0 %	71.4 %	0.35
Percentage of hyperglycaemia	30.4 %	44.2 %*	0.01

*The cutoff points for the criteria of: central obesity (waist circumference > 88 cm in female and > 102 in male), hypertension (systolic BP > 130 mmHg or diastolic BP > 85 mmHg or specific treatment), hypertriglyceridemia (triglycerides > 150 mg/dl or specific treatment) or hyperglycaemia (fasting plasma glucose > 110 mg/dl or drug treatment for elevated blood glucose). *p < 0.05 between genotypes in a dominant model (TT vs TC + CC).*

DISCUSSION

We conducted a cross-sectional study to evaluate the potential association between *LEPR* rs1805134 SNP and obesity-related measures in a Caucasian obese population. Our results demonstrate that presence of the variant "C allele" of the SNP rs1805134 is associated with greater adiposity parameters, HOMA-IR, insulin, triglycerides and energy/carbohydrates intakes as compared to non-C-allele carriers.

The results in the literature are scarce and contradictory in this topic area. Only one study by Rojano et al. (6) evaluated the relationship of rs1805134 with adiposity. In this previous study (6), of the six *LEPR* SNPs analysed, only allele C of rs1805134 was associated with obesity. The results are similar to those found in our study, but in a Mexican population. As far as we know, these are the only two studies in the literature that have analysed this relationship. Interestingly, when association between serum lipids and *LEPR* gene SNPs in obese Japanese children was evaluated, the rs1805134 variant showed a significant association with serum lipid levels, since lower triglycerides levels were reported in CC homozygotes (13). Our results show a relationship between allele C and increased triglyceride levels and insulin resistance. One hypothesis to explain these contradictory results is the presence of other polymorphisms, probably located in introns close to the rs1805134 SNP, which might regulate the expression of the exons of *LEPR* gene (14) and modify the response of its related complex pathways. Another theory is that potential associations of this SNP with biochemical parameters may have been modulated or masked due to unmeasured environmental factors. And finally, the different ethnicities evaluated in the studies, as well as the ages of the patients and BMI, can explain the differences in the literature.

Our findings indicate that the effects of the *LEPR* polymorphism on obesity and metabolic impairment status with a high percentage of MS in C-allele carriers could be related with a high caloric intake related to high carbohydrate intakes. The fact that there are associations between polymorphisms of the *LEPR* gene and different dimensions of eating behaviour is consistent with the functions that these genes perform at the brain level, where there are different motivations that regulate eating behaviour, which can be related to food energy balance (15). Food intake associated with the *LEPR* polymorphism could be explained because leptin modulates neuronal activation in striated regions of the brain, related to feelings of food gratification (non-homeostatic) due to the direct action of leptin on the dopamine centres in the brain (16). Subjects with *LEPR* polymorphisms may have some resistance to the action of leptin and therefore impairment in these brain circuits. Moreover, these relationships would explain the fact that in obese people there would be alterations in the response to internal satiety signals (homeostatic) and an increased response to food (17). For example, Macarena et al. (18) reported that the dimensions "Slow eating", "emotional eating", "enjoyment of food" and "uncontrolled eating" were significantly associated with certain polymorphisms of *LEPR*. Finally, this relationship between SNPs of the *LEPR* gene and the above-mentioned eating behavior has been translated into a direct relationship of the LEPR223Arg allele (rs1137101) with higher daily energy intake (19) and other specific eating patterns (20). In our study, patients carrying the C-allele ingested more calories at the expense of carbohydrates, and this positive energy balance may explain the greater weight and worsening of biochemical parameters. For example, Illagasekera et al. (21) found that in this type of study the biochemical measures tested are also influenced by unmeasured lifestyle factors. In our study we show this relationship with caloric intake.

Limitations of our study are as follows: one is that the study was designed for adult obese subjects, so the data are not generalizable to children or overweight subjects. Second, the cross-sectional design does not allow to extract causality. The third limitation is that dietary intake was determined with a diet questionnaire, which would lead to biases in the estimation of intake. Finally, we have not determined the LEPR expression in tissues or leptin levels in blood samples. The strengths of our study were that we studied a representative population of mid-aged obese patients, predominantly women with intermediate obesity.

In summary, subjects with the C allele of the rs1805134 variant in the *LEPR* gene showed a worse metabolic pattern with a higher percentage of metabolic syndrome, central obesity and hyperglycaemia, probably related to a higher energy intake.

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