ORIGINAL ARTICLE

G(–2548)A leptin gene polymorphism in obese subjects is associated with serum leptin concentration and bone mass

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KEY WORDS

bone, leptin, leptin gene polymorphism, leptin receptor gene polymorphism

ABSTRACT

INTRODUCTION Clinical studies have shown either positive or in some other cases negative correlations between leptinemia and bone mineral density (BMD) or bone mineral content (BMC).

OBJECTIVES The aim of the present study was to assess whether these discrepancies might be associated with the effect of G(–2548)A leptin or A326G and A668G leptin receptor gene polymorphisms on serum leptin concentrations or BMD and BMC.

PATIENTS AND METHODS The study included 72 obese patients (39 women and 33 men, aged 46 ±8.8 years; body mass index [BMI] >30 kg/m^2). In all subjects, serum creatinine, glucose, lipids, leptin, and insulin were determined. Total fat mass (TFM), BMC, and BMD were assessed using dual energy X-ray absorptiometry (Lunar DPX-L).

RESULTS No significant correlations were observed between body mass composition parameters (TFM, lean mass, BMC) or BMD in relation to genotypes. A positive correlation was found between serum leptin concentration and BMI. An inverse association was observed between leptin concentrations and BMC. Multiple regression analysis showed independent correlations of leptinemia with sex (P <0.001), TFM (P <0.000 001), BMC (P = 0.0001), and the presence of (–2548)A allele of the leptin gene (P <0.05). These parameters together accounted for 83% of variability in serum leptin concentrations.

CONCLUSIONS In obese patients, serum leptin concentration shows an independent inverse correlation with BMD and male sex, but positively with TFM and the presence of –2548A allele of leptin gene. These parameters are responsible for 83% of leptin concentration variability. No correlations between the examined polymorphisms and BMC or BMD were found.

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INTRODUCTION Leptin is produced mainly by adipocytes of white adipose tissue and its serum concentration is higher in obese than in lean subjects.[1] It has been shown that osteoblasts express leptin receptors on their surface and that leptin may stimulate their proliferation and activity.[2] Therefore, it seems that there should be a positive correlation between serum leptin concentration and bone mineral density (BMD). However, a recent study by Karsenty[3] showed that in ob/ob mice, a lack of leptin is followed by increased BMD. It was observed that despite hypogonadism, the bone mass in those animals was not only preserved but mineralization was even increased.

Based on these results, it was concluded that leptin may decrease bone formation (via the central and sympathetic nervous system).[3,4]

The relationship between serum leptin concentrations and BMD in humans has already been examined. A number of studies have shown a weak positive or no correlation between these two parameters.[5-13] However, other authors have shown a negative correlation between leptin and BMD.[14-18] There may be at least two reasons for this discrepancy. Only in some of these studies the mean values of body mass index (BMI) exceeded 30 kg/m^2, and in obese patients the concentration of leptin in serum[1] and in cerebral fluid[19] is significantly higher than in subjects with normal body mass. Therefore, it is possible that higher leptin concentrations may exert a more potent effect on bone formation in obese patients than in lean ones. Another possibility is that these results might have been influenced by a number of factors that had not been examined, for example differences in leptin serum concentrations and/or function dependent on leptin and/or leptin receptor gene polymorphisms. The most widely studied and most functional are the polymorphisms of G(–2548)A leptin or A326G (K109R) and A668G (Q223R) leptin receptor genes.[20,21]

The aim of this study was to assess the effect of G(–2548)A leptin or A326G and A668G leptin receptor gene polymorphisms on serum leptin concentrations and on BMD and bone mineral content (BMC) in obese patients.

PATIENTS AND METHODS A total of 72 obese patients (BMI >30 kg/m^2) were included in the study. Hypertension was present in 53% of the patients. Subjects with diabetes and clinically relevant coronary heart disease were excluded. In all subjects blood samples were withdrawn in the morning after overnight fasting to measure serum creatinine, glucose, lipids, leptin, and insulin concentrations. The basic characteristics of the examined subjects are presented in TABLE 1.

Serum leptin concentrations were determined by radioimmunoassay (Linco Research Inc., United States). Total fat mass (TFM), total BMC and BMD were assessed using dual energy X-ray absorptiometry (Lunar DPX-L, GE, United States) of the total body. The study was approved by the local Ethics Committee and was performed in accordance with the Declaration of Helsinki. Informed consent was obtained from every participant.

Genotyping Genomic DNA was amplified by polymerase chain reaction (PCR) with primers flanking polymorphic regions: 5'-TTTCCTGTAATTTTCCCGTGAG-3' as a sense primer and 5'- AAAGCAAAGACAGGCATAAA -3' as an antisense primer for G(–2548)A in the leptin gene, 5'-CTTTTGCCTGCTGGACTCTC.-3' as a sense primer and 5'-TAAAGAATTTACTGTTGAAACAAATGGC -3' as an antisense primer for A326G in the leptin receptor gene and 5'-TCCTGCTTTAAAAGCCTA ATCCAGTATTT-3' as a sense primer and 5'-AG CTAGCAAATATTTTTGTAAGCAAT.-3' as an antisense primer for A668G in the leptin receptor gene.[22,23] These primers yielded PCR products of 242 base pairs (bp), 213 bp, and 367 bp in length, respectively. The reaction was conducted in a total volume of 20 µl containing: 40 ng of template DNA, 4 pM of each primer, PCR buffer containing 1.5 mM $MgCl_2$, 2.5 µM each dNTP (MBI Fermentas, United States), and 0.5 U of Taq polymerase (MBI Fermentas, United States). The amplification was performed with initial denaturation at 94°C for 5 minutes, and then 36 cycles: denaturation at 94°C for 20 seconds, annealing at 54°C (leptin gene) and 58°C (leptin receptor genes) for 40 seconds, and extension at 72°C for 40 seconds. The final 72°C incubation was extended by 8 minutes. For restriction fragment length polymorphism assays, a PCR product was incubated at 37°C for 3 hours with 1 U *Cfo I*, *Hae III* and *Hpa II*, respectively. The fragments were separated by electrophoresis on 2% agarose gel, stained with ethidium bromide. Results were recorded with photographs of gels in UV light.

The PCR product of amplification containing –2548G wild-type allele was cleaved into 181 bp and 61 bp fragments. Thus leptin (*LEP*) –2548A allele was identified by lack of *Cfo I* restriction site. Substitution of adenine by guanine at 326 nucleotide of leptin receptor gene (LEPR) resulted in the formation of *Hae III* restriction site. The G326 allele was cleaved into 186 bp and 27 bp fragments, while the wild-type A326 allele was not cleaved. In the case of LEPR, the PCR product representing A668 allele was cleaved by *Hpa II* into 242 bp and 125 bp fragments, and the wild-type G668 allele was identified by the lack of *Hpa II* restriction site.

Statistical analysis Distribution of values of particular variables was examined using the Shapiro-Wilk test. The values were log-transformed because of skewed distribution. In all analyses of leptinemia, a logarithm of leptin concentrations, which showed a normal distribution, was used. The same transformation was applied for all variables with non-normal distribution (TABLE 1). The Student's t-test was used for the comparison between groups; if the number of groups was 2 or more (like in the case of genotypes), the analysis of variance (ANOVA) was applied. For a single variable analysis, the Pearson linear correlation was used. An optimal model of multiple regression (containing variables responsible for most of variability of leptinemia) was chosen. All analyses were performed using STATISTICA 6.1.

RESULTS The anthropometric and biochemical parameters of the study population are presented in TABLE 1. Compared with women, men were taller and heavier, had lower waist-hip ratio, while waist circumference was similar. Women had significantly greater TFM and serum leptin concentrations, but lower BMC.

TABLE 1 Anthropometric and laboratory data of study patients

	Whole group (n = 72)	Women (n = 39)	Men (n = 33)	Significance of difference between men and women (*P*)
age (years)	46 ±8.8	47.2 ±7.2	44.6 ±10.3	NS
weight (kg)	101.7 ±14.5	98.4 ±15.4	105.6 ±12.5	<0.05
height (m)	1.69 ±0.08	1.63 ±0.05	1.76 ±0.06	<0.000001
BMI[a] (kg/m2)	35.7 ±5.0	37.0 ±5.7	34.2 ±3.4	<0.05
waist (cm)	112.4 ±11.7	112.2 ±13.5	112.7 ±9.3	NS
hip[a] (cm)	117 ±11.2	122 ±11.9	111.3 ±6.8	<0.0005
WHR	0.96 ±0.08	0.92 ±0.07	1.01 ±0.04	<0.0005
total body fat mass (g)	37,519 ±10,410	41,880 ±9820	32,366 ±8682	<0.0005
total body BMD (g/cm^2)	1.22 ±0.08	1.20 ±0.09	1.24 ±0.08	NS
spine BMD[a] (g/cm^2)	1.19 ±0.16	1.18 ±0.16	1.19 ±0.18	NS
total body BMC (g)	2951 ±525	2628 ±357	3333 ±428	<0.000001
leg BMC (g)	1204 ±227	1066 ±156	1367 ±186	<0.000001
trunk BMC[a] (g)	900 ±216	803 ±191	1015 ±187	<0.0005
serum creatinine (μmol/l)	82.9 ±15.9	76.4 ±15.1	88.7 ±14.3	<0.001
serum glucose (mmol/l)[a]	5.1 ±1.4	5.3 ±1.5	4.9 ±1.2	NS
total cholesterol (mg/dl)	234 ±56	224 ±43	248 ±68	NS
HDL cholesterol (mg/dl)	43.9 ±14.1	44.7 ±18.4	43.4 ±10.3	NS
LDL cholesterol (mg/dl)	151.2 ±49.5	143 ±38.8	157.2 ±56	NS
triglycerides (mg/dl)	205.6 ±148.8	178.3 ±130.9	240.2 ±164.6	<0.05
serum leptin (ng/ml)[a]	26.2 ±20.2	36.8 ±20.6	12.8 ±8.0	<0.0000001
serum insulin (mIU/ml)[a]	20.8 ±13.1	20.8 ±14.8	20.8 ±11.1	NS
leptin/TFM ratio[a]	0.644 ±0.399	0.861 ±0.396	0.370 ±0.167	<0.0000001

Data presented as mean ± standard deviation

a parameters that required log transformation for statistical analysis (see PATIENTS AND METHODS)

Abbreviations: BMC – bone mineral content, BMD – bone mineral density, BMI – body mass index, HDL – high-density lipoprotein, LDL – low-density lipoprotein, TFM – total fat mass, WHR – waist-hip ratio

TABLE 2 shows the frequency of particular alleles. ANOVA did not reveal any significant differences between the parameters of the body mass composition (TFM, lean mass, BMC) or BMD in relation to genotype. A single variable analysis showed a positive correlation of serum leptin concentration with BMI, but negative with BMC. A multiple regression analysis showed independent correlations of leptinemia with sex, TFM, BMC, and the presence of –2548 A allele of the leptin gene (TABLE 3). Together, the above-mentioned parameters are responsible for 83% variability in serum leptin concentrations (TABLE 3).

DISCUSSION High body mass (related mainly to high fat mass) is one of the factors exerting a positive effect on bone turnover, causing higher bone mineralization in obese patients. Leptin is produced predominantly by white adipose tissue. This fact implies a strong positive correlation between serum leptin concentration and fat tissue mass, which had been documented previously and confirmed also in this study.

In line with a number of studies[14-18] but in contrast to many others,[4-13] we observed a negative correlation between serum leptin concentration and bone mass (BMC). We have no data concerning the leptin concentration in cerebrospinal fluid in these patients. It is known, however, that a leptin concentration in cerebrospinal fluid in obese patients is only slightly higher in comparison with lean subjects, despite a much higher serum concentration of this hormone.[19] It might be speculated that even a slight increase in leptin concentrations in cerebrospinal fluid that occurs in obese patients is sufficient to activate

TABLE 2 Frequency of particular alleles in the study population (absolute number and percentage of patients is given)

Polymorphism/allele	AA	AG/GA	GG	A	G
G(–2548)A	12 (16.7%)	37 (51.4%)	23 (31.9%)	0.4236	0.5763
A326G (K109R)	33 (45.8%)	30 (41.7%)	9 (12.5%)	0.6761	0.3239
A668G (Q223R)	16 (22.2%)	42 (58.3%)	14 (19.5%)	0.5141	0.4859

TABLE 3 General linear model predicting serum leptin concentration

Independent variables	Regression coefficient[a]	95% confidence interval of regression coefficient	*P*	Model R^2
male gender	–0.197	–0.308 – (–0.087)	0.00067	0.826
LEP (–2548)A	+0.087	+0.007 – (+0.168)	0.034	
TFM (kg)	+0.0194	+0.0154 – (+0.0234)	<0.000001	
total body BMC (kg)	–0.204	–0.303 – (–0.106)	0.0001	

a Regression coefficients correspond to an average increase (or decrease for negative values) of the value of decimal logarithm of serum leptin concentration associated with the presence of qualitative variables or increase of quantitative variables by 1 unit.

Abbreviations: LEP (–2548)A – presence of allele A in (–2548) position of the leptin gene, others – see **TABLE 1**

a pathway in the central nervous system, decreasing bone formation via the sympathetic nervous system.[1,4]

A multivariate analysis showed that serum leptin concentrations are associated with sex, the presence of the LEP (–2548)A allele, higher TFM, and lower total body BMC. Together, these parameters are responsible for 83% of leptin concentration variability.

Previous studies showed positive and negative correlations of leptinemia and the presence of the (–2548)A allele.[24,25] In obese adolescent girls, a positive correlation of obesity and the (–2548)G allele was shown, and serum leptin concentration was 25% lower in subjects with AA genotype.[25] In contrast, Hoffstedt et al.[21] showed that in non-obese subjects, the presence of AA genotype correlated positively with serum leptin levels.

Despite these discrepancies, it might be concluded that G(–2548)A leptin gene polymorphism may influence leptin levels, and as a confounding factor should be assessed in all the studies that examine the leptin levels.

The K109R and Q223R leptin receptor gene polymorphisms showed no relationship with leptin levels, which is in line with the results of a meta-analysis conducted by Paracchini et al.[20]

Our study has a number of limitations. It was impossible to assess the body mass of the examined subjects prior to the study. However, all study subjects reported that their weight was stable over the previous 5 years. We may assume that also the fat mass was stable over that time. As leptin production depends mainly on the amount of white adipose tissue, we assume that also leptin levels were rather stable during the previous 5 years. Another limitation concerns the interpretation of a negative relationship between leptinemia and BMC or BMD – it should take into account the effect of immobilization on osteogenesis in obese patients. Obesity-induced low physical activity could be one of the main factors that impair bone formation in obese patients. It cannot be excluded that this factor may also affect an inverse correlation between BMC or BMD and leptinemia. Moreover, the study group was relatively small, which precluded a separate multiple regression analysis in women and men and limited the reliability of the results.

In conclusion, serum leptin concentrations in obese patients are independently and negatively correlated with BMD and male sex but positively correlated with TFM and the presence of –2548A allele of the leptin gene. All of the above parameters account for 83% of leptin concentration variability. No correlations between the studied polymorphisms and BMC or BMD were observed.

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ARTYKUŁ ORYGINALNY

Polimorfizm G(–2548)A genu leptyny jest związany ze stężeniem leptyny w surowicy oraz masą kości u otyłych pacjentów

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SŁOWA KLUCZOWE

kość, leptyna, polimorfizm genu leptyny, polimorfizm genu receptora leptyny

STRESZCZENIE

WPROWADZENIE Badania kliniczne wykazały zarówno dodatnie jak i ujemne korelacje pomiędzy stężeniem leptyny we krwi oraz gęstością i zawartością mineralną kości (*bone mineral density* – BMD, *bone mineral content* – BMC).

CELE Celem pracy było ustalenie, czy u podłoża tych rozbieżności może leżeć wpływ polimorfizmu G(–2548)A genu leptyny czy też polimorfizmu A326G i A668G genu receptora leptyny na jej stężenie w surowicy krwi oraz na wartości BMD i BMC.

PACJENCI I METODY W badaniach uczestniczyło 72 otyłych pacjentów (39 kobiet i 33 mężczyzn w wieku 46 ±8,8 lat ze wskaźnikiem masy ciała [*body mass index* – BMI] >30 kg/m^2). U wszystkich pacjentów zbadano poziom kreatyniny, glukozy, lipidów, leptyny i insuliny w surowicy. Oceniono całkowitą masę tłuszczową (*total fat mass* – TFM) oraz BMC i BMD za pomocą dwuwiązkowej absorpcjometrii rentgenowskiej aparatem Lunar DPX-L.

WYNIKI Nie zaobserwowano statystycznie istotnych korelacji pomiędzy badanymi parametrami biometrycznymi (TFM, masa sucha, BMC) lub BMD a genotypem. Zaobserwowano dodatnią korelację pomiędzy stężeniem leptyny w surowicy a BMI, natomiast ujemną – między stężeniem leptyny a BMC. Regresja wielokrotna wykazała niezależne korelacje między stężeniem leptyny we krwi a płcią pacjenta (P <0,001), TFM (P <0,000 001), BMC (P = 0,0001) oraz obecnością allelu A w pozycji (–2548) genu leptyny (P <0,05). Wyżej wymienione parametry odpowiadają za 83% zmienności w stężeniu leptyny w surowicy.

WNIOSKI U pacjentów otyłych występuje niezależna ujemna korelacja między stężeniem leptyny a BMD oraz płcią męską, oraz dodatnia między stężeniem leptyny a TFM i obecnością allelu A w pozycji (–2548) genu leptyny. Parametry te odpowiadają za 83% zmienności w stężeniu leptyny. Nie stwierdzono korelacji pomiędzy badanymi polimorfizmami a BMC i BMD.

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