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Original article

Leptin Reference Values and Cutoffs for Identifying Cardiometabolic Abnormalities in the Spanish Population

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ABSTRACT

Introduction and objectives: Estimate leptin reference values and calculate leptinemia cutoff values for identifying cardiometabolic abnormalities in Spain.
Methods: Cross-sectional study carried out between 2008 and 2010 in 11 540 individuals representing the Spanish population aged ≥ 18 years. Data were obtained by standardized physical examination and analyses were performed at a central laboratory. Leptinemia was measured using ELISA. Cardiometabolic abnormality was defined as the presence of at least two of the following: high blood pressure, high triglycerides, reduced high density lipoprotein cholesterol, high insulin resistance values, and elevated C-reactive protein and glucose.
Results: Leptin values were higher in women than men (geometric mean, 21.9 and 6.6 ng/mL; $P < .001$). The median [interquartile range] was 24.5 [14.1-37.0] ng/mL in women, and 7.2 [3.3-14.3] ng/mL in men. In the multivariate analysis, leptin was significantly associated with anthropometric measures, insulin, and C-reactive protein, and inversely associated with age, smoking, and physical activity in women ($r^2 = 0.53$; $P < .001$) and in men ($r^2 = 0.61$; $P < .001$). The leptin values that identified cardiometabolic abnormality were 23.75 ng/mL in women (area under the curve, 0.722; sensitivity, 72.3%; specificity, 58.7%) and 6.45 ng/mL in men (area under the curve, 0.716; sensitivity, 71.4%; specificity, 60.2%).
Conclusions: These results facilitate the interpretation of leptin values in clinical and population studies. Leptin has moderate sensitivity and specificity for identifying cardiometabolic abnormalities.

Valores de referencia y puntos de corte de leptina para identificar anormalidad cardiometabólica en la población española

Palabras clave:
Leptina
Obesidad
Factores de riesgo cardiovascular
Anormalidad cardiometabólica

RESUMEN

Introducción y objetivos: Estimar los valores de referencia de leptina y calcular los puntos de corte de leptinemia que identifiquen anormalidad cardiometabólica en España.
Métodos: Estudio transversal realizado de 2008 a 2010 sobre 11.540 individuos representativos de la población española de edad ≥ 18 años. La información se obtuvo mediante examen físico estandarizado y las analíticas se realizaron en un laboratorio central. La leptinemia se midió por enzimoinmunoanálisis. Se definió anormalidad cardiometabólica como la presencia de al menos dos de las siguientes: presión arterial elevada, triglicéridos elevados, colesterol unido a lipoproteínas de alta densidad bajo, valores altos de resistencia a insulina y proteína C reactiva y glucosa elevadas.
Resultados: Los valores de leptina fueron mayores en mujeres que en varones (media geométrica, 21,9 y 6,6 ng/ml; $p < 0,001$). En mujeres la mediana [intervalo intercuartílico] fue 24,5 [14,1-37,0] ng/ml y en varones, 7,2 [3,3-14,3] ng/ml. En el análisis multivariable, la leptina estuvo significativamente asociada con las medidas antropométricas, la insulinemia y la proteína C reactiva y en relación inversa con la edad, el tabaquismo y la actividad física en mujeres ($r^2 = 0,53$; $p < 0,001$) y en varones ($r^2 = 0,61$; $p < 0,001$). Los valores de leptinemia que identificaron anormalidad cardiometabólica fueron 23,75 ng/ml en mujeres (área bajo la curva, 0,722; sensibilidad, 72,3%; especificidad, 58,7%) y 6,45 ng/ml en varones (área bajo la curva, 0,716; sensibilidad, 71,4%; especificidad, 60,2%).

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Conclusiones: Estos resultados facilitan la interpretación de los valores de leptinemia en estudios clínicos y poblacionales. La leptina tiene sensibilidad y especificidad moderadas para identificar anormalidad cardiometabólica.

INTRODUCTION

Leptin, a peptide described in 1994, is synthesized by adipocytes, and its serum concentration reflects the body's energy reservoir[1]. Leptin acts on the hypothalamic receptors and influences the expression of different neuropeptides that regulate energy balance by decreasing food intake and increasing energy expenditure and sympathetic tone in response to normal weight gain[1].

Traditionally, body mass index (BMI) has been used to assess the degree of obesity. However, BMI has limitations in detecting adiposity in individuals with BMI < 30[2–4]; recent studies have highlighted the usefulness of leptin for improving the accuracy of BMI in assessing the percentage of body fat when dual-energy X-ray absorptiometry (DXA) is not available, and may represent a future marker for obesity.[5] The association between leptin and hypertension has also been studied,[6,7] and it has been suggested that it may activate the sympathetic nervous system, increasing blood pressure[8,9] or even increasing risk of hypertension.[10–12] Leptin has also been found to be related to biological cardiovascular risk factors[13] and to the development of cardiovascular disease.[14–20] Finally, it has been reported that consumption of fiber and vegetables, physical activity, and smoking are inversely associated with leptinemia.[21–24]

There are few population-based studies, particularly in samples of a reasonable size and representing entire countries, on the link between leptin concentrations and obesity and other cardiovascular risk factors.[14–16,25–32] This information could be relevant for more precise estimates of fat mass and its potential role in mediating cardiometabolic risk. Moreover, there are no studies that explore the ability of leptin to predict cardiometabolic abnormality. Therefore, the aim of this study was to estimate the leptin reference values and calculate leptinemia cutoff values for identifying cardiometabolic abnormalities in women and men from the general population of Spain.

PARTICIPANTS AND METHODS

Data were obtained from The Nutrition and Cardiovascular Risk in Spain Study, the methodology of which was previously described.[33] In brief, the study was conducted between June 2008 and October 2010, and included 12 948 people representing the noninstitutionalized Spanish population aged $\geq$ 18 years. Participants were selected by stratified cluster sampling. Data on sociodemographic and lifestyle variables were collected via telephone interview, and personal interviews, physical examinations, and collection of blood and urine samples were performed during two home visits. Data collection staff received training in the study's procedures.

Written informed consent was obtained from all participants. The study was approved by the Clinical Research Ethics Committees of Hospital Universitario La Paz (Madrid), and Hospital Clinic (Barcelona).

Study Variables

We used reported data on age, sex, educational level, smoking and diagnosed morbidity. In addition, we obtained a computerized dietary history on normal food consumption during the previous year, and calculated the number of kcal/day and the Healthy Eating Index (HEI).[34] The following cutoff points were considered: poor diet (< 59.5), adequate (59.5-63.7), good (63.8-65.5), very good (65.6-67.5) and excellent (> 67.5).

Physical activity was measured using the EPIC Study questionnaire, which combines physical activity at work and during leisure time (Cambridge index).[35] This index has been shown to accurately estimate cardiovascular risk and all-cause mortality.[36] We also evaluated compliance with physical activity guidelines from the European Union and the World Health Organization (EU/WHO)[37], which recommend $\geq$ 2.5 hours of moderate intensity activity or $\geq$ 1 hour of vigorous intensity activity per week.

We measured each individual's weight, height, and waist circumference using electronic scales (Seca 841; precision, 0.1 kg), portable extendable stadiometers (KaWe44 444Seca), and non-elastic flexible measuring tapes with buckles, respectively. Blood pressure was measured using validated automatic devices (Omron Model M6) according to standard procedures.[38]

Samples of blood and urine were obtained from each participant at home after 12 hours fasting. We measured glucose, C-reactive protein (CRP), glycosylated hemoglobin (HbA_{1c}), insulin, total cholesterol, triglycerides, high-density lipoprotein cholesterol (HDL-C), and low-density lipoprotein cholesterol (LDL-C), which was calculated using Friedewald formula. Serum leptin was measured by enzyme immunoassay using two monoclonal antibodies (DBC, Diagnosis Biochem Canada, Inc.), automated using a BEST2000 robot. The sensitivity of this test was 0.5 ng/mL, and the intra- and inter-assay variation coefficients were 7.47% and 9.6%, respectively. These analyses were carried out using standardized methods at a central laboratory.

Cardiovascular Risk Factors

The BMI was calculated as weight in kilos divided by the square of height in meters. Abdominal obesity was defined as waist circumference $>$ 102 cm in men and $>$ 88 cm in women. Hypertension was defined as blood pressure $\geq$ 140/90 mmHg or if the patient was taking antihypertensive medication; diabetes mellitus as casual blood glucose $\geq$ 126 mg/dL, $HbA_{1c} \geq 6.5\%$, or treatment with oral antidiabetic agents or insulin; hyperlipidemia as LDL-C $\geq$ 115 mg/dL or lipid-lowering drug treatment, and smoking as any level of tobacco consumption.

According to the harmonized definition,[39] the diagnosis of metabolic syndrome requires meeting at least 3 of the following 5 criteria: waist circumference $\geq$ 102 cm for men and $\geq$ 88 cm for women; fasting glucose $\geq$ 100 mg/dL; blood pressure $\geq$ 130/85 mmHg; triglycerides $\geq$ 150 mg/dL, and HDL-C $<$ 40 mg/dL in men, and $<$ 50 mg/dl in women. Insulin resistance was estimated using the Homeostasis Model Assessment-Insulin Resistance