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Brief report

Association between leptin and disease activity in patients with rheumatoid arthritis☆,☆

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ABSTRACT

Background and objective: Multiple studies have found a direct relationship between leptin concentrations and disease activity in rheumatoid arthritis.
Patients and methods: We studied 77 patients with the diagnosis of rheumatoid arthritis; the leptin determination was through an enzyme immunoassay. Disease activity was assessed by the DAS-28 CRP. A multivariate logistic regression model was used to determine the association between significant variables and leptin concentrations.
Results: 40.3% of the patients were in remission, 41.6% were mildly active, 11.7% were moderately active and 6.5% were severely active. The results show an independent association between higher concentrations of leptin and disease activity (OR 1.7; 95% CI 1.4–3.2; *p* 0.03), the number of swollen joints (OR 4.6; 95% CI 1.7–8.3; *p* 0.000), the number of painful joints (OR 3.4; 95% CI 1.6–4.6; *p* 0.000), and the presence of metabolic syndrome (OR 1.3; 95% IC 1.2–1.9; *p* 0.045).
Conclusion: The data suggest that serum leptin is elevated in patients with active RA.

Asociación de la leptina con la actividad de la enfermedad en pacientes con artritis reumatoide

Palabras clave:
Artritis reumatoide
Leptina
Actividad de la enfermedad

RESUMEN

Introducción y objetivo: Múltiples estudios han encontrado una relación directa entre las concentraciones de leptina y la actividad de la enfermedad en artritis reumatoide.
Pacientes y métodos: Se estudiaron 77 pacientes con artritis reumatoide, la determinación de la leptina fue a través de inmunoanálisis enzimático. Se evaluó la actividad de la enfermedad mediante el DAS-28 PCR. Se realizó un modelo de regresión logística multivariante para determinar la asociación entre las variables significativas y las concentraciones de leptina.
Resultados: El 40,3% de los pacientes estaban en remisión, el 41,6% actividad leve, el 11,7% actividad moderada y el 6,5% actividad grave. Se encontró una relación independiente entre mayores concentraciones de leptina y la actividad de la enfermedad (RR 1,7; IC al 95%: 1,4-3,2; p = 0,03), el número de articulación tumefactas (RR 4,6; IC al 95%: 1,7-8,3; p = 0,000), el número de articulaciones dolorosas (RR 3,4; IC al 95%: 1,6-4,6; p = 0,000) y a presencia de síndrome metabólico (RR 1,3; IC al 95%: 1,2-1,9; p = 0,045).
Conclusiones: Los datos obtenidos sugieren que la leptina sérica está elevada en pacientes con AR activa.

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Introduction

With the discovery of leptin in 1994[1] a new approach was established for the study of adipocyte biology, considering it as a tissue with endocrine, autocrine and paracrine functions, beyond its role in energy regulation and lipid storage.[2] Increased leptin levels have been observed during infectious processes and inflammation, playing a significant role in both inflammatory and immune responses.[1,2]

Due to the functional and biological characteristics of leptin, it has been recognized as a possible participant in rheumatoid arthritis (RA). However, although its important role in the inflammatory and immunological response is already known, nowadays the information about the leptin-RA association is still inconclusive. Therefore, we conducted this study in order to determine the association between the activity of the disease in RA and serum leptin levels.

Patients and methods

Patients with the diagnosis of RA were studied according to the ACR/EULAR 2010 criteria,[3] 10 ml of blood was drawn in the morning from veins in the antecubital fossa to determine the values of triglycerides, total cholesterol, high-density lipoprotein (c-HDL), C-reactive protein (CRP), glucose, serum leptin. The low-density lipoprotein (c-LDL) values were obtained through the Friedewald formula.

The determination of leptin and IL-6 was carried out through enzyme immunoassay (ELISA) with the TECO® and Thermo scientific® Test Kits, respectively, which use two specific high-affinity monoclonal antibodies with a sandwich type quantitative test. The absorbance was measured at 450 nm and leptin and IL-6 concentrations were established through a standard curve. Values higher than 17 ng/ml were considered hyperleptinemia, while 0–5 pg/ml were considered normal IL-6 values.

The body mass index (BMI) was calculated using the weight/height formula^2 (kg/m^2), and the results were classified as low weight: <18.5 kg/m^2; normal: 18.5–24.9 kg/m^2; overweight: 25–29.9 kg/m^2; obesity >30 kg/m^2. With the patient in the standing position, the waist circumference was measured with a tape measure according to WHO guidelines. Blood pressure was taken with a manual mercury sphygmomanometer with the patient sitting, after a rest of 20 min. Patients were classified with the presence of metabolic syndrome (MS) according to the ATP-III criteria.[4] The factors related to the disease were determined, such as time of progression, the activity of the disease was evaluated by DAS-28 CRP, according to the following classification; remission <2.3; mild activity ≥2.3 to <3.8, moderate activity ≥3.8 to <4.9 and severe activity ≥4.9. Values above 15 IU/ml were considered a positive rheumatoid factor.

Statistic analysis

The SPSS 22.0 software package was used. A value of $p \leq 0.05$ was considered a significant result. The categorical variables were expressed as frequencies and percentages and were compared with the Chi square test. The normal distribution was evaluated by the Kolmogorov–Smirnov test. The continuous variables were presented as mean and standard deviation or as median and interquartile range; and were compared using the Student's *t* test or the Mann–Whitney *U* test, as the case may be. Finally, a multivariate logistic regression model was performed, using the Forward Stepwise regression method.

Table 1
General characteristics of the population.

Variables	No. (77)
Age *X* (SD)	50.9 ± 11.9
Median BMI (IQR)	30.3 (26.5–33.3)
Cholesterol *X* (SD)	187.6 ± 42.2
Median triglycerides (IQR)	139 (109–186)
Median glucose (IQR)	90.5 (85–103)
c-LDL *X* (SD)	113.4 ± 36.8
c-HDL median (IQR)	40 (37–45)
Median CRP (IQR)	1.2 (0.5–4.2)
DAS-28 median CRP (IQR)	2.6 (1.9–3.3)
Duration of the disease X (SD)	6.2 ± 4.1
IL-6 *X* (SD)	2.07 ± 8.5
Median leptin (IQR)	43.5 (10.9–61.7)
Median NPJ (IQR)	2 (0–4)
Median NSJ (IQR)	3 (0–4)

c-HDL: high density lipoprotein; c-LDL: low density lipoprotein; DAS-28 CRP: *disease activity score*; SD: standard deviation; IL-6: interleukin 6; BMI: body mass index; NPJ: number of painful joints; NSJ: number swollen joints; CRP: C-reactive protein; IQR: interquartile range; *X*: mean.

Results

We studied 77 patients, 93.5% of whom were women. Regarding the BMI, 46.8% were obese, 32.5% were overweight, 18.2% had normal weight and 2.5% were underweight. 40.3% of patients were in remission, 41.6% had mild activity, 11.7% had moderate activity and 6.5% had severe activity. The general characteristics of the population studied can be seen in Table 1. The relationship of serum leptin levels and biochemical parameters, disease activity, MS and the treatment used was evaluated, the results can be seen in Table 2. A multivariate logistic regression was performed (Table 3) with leptin as the dependent variable. An independent relationship was found between higher levels of leptin and the activity of the disease, the presence of MS and the number of swollen and painful joints.

Discussion

Our study reports a positive association between disease activity and serum leptin levels. Some studies report no relationship between the activity of the disease and serum leptin levels.[5,6] Most of them are studies performed in small samples, generally less than 40 patients or in which there is no difference between the levels of leptins and the presence of other inflammation parameters or situations that could increase it independently of the activity, as gender, age or other inflammatory cytokines or the methods used to measure activity. The controversial results between the relationship of leptin and RA reported in the literature may be down to the impossibility of comparing the different studies due to differences in the duration of the disease, age, race, gender, BMI, coexistence of other autoimmune pathologies or that produce chronic inflammation or to the different methods used to measure leptin values. Finally, our results coincide with those found in three meta-analyses. Lee et al.[7] performed a meta-analysis to evaluate the relationship between serum leptin levels and RA activity, including 13 studies with a total of 648 patients with RA and 426 controls, finding a small but significantly positive correlation between the level of circulating leptin and DAS-28 (correlation coefficient = 0.275, 95% CI = 0.076–0.452, $p = 0.007$). Tian et al.[8] performed a meta-analysis, in which they evaluated 20 studies that included 998 patients with RA and 692 controls, where patients with RA had higher levels of leptin, and found that the region, race, age, BMI, duration of disease and disease activity were positively associated with plasma levels of leptin in patients with RA. Cao et al.[9] studied whether serum leptin levels correlated with disease activity in patients with RA, included