



## Original Investigation

# Levels of serum leptin in patients with primary hand osteoarthritis<sup>☆</sup>



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### ABSTRACT

**Introduction:** Several studies have documented the statistical association between leptin and osteoarthritis (OA) especially in joints that support weight, such as hips and knees, demonstrating high concentrations of plasma leptin and synovial fluid. Few studies address the possible relationship between leptin and obesity/overweight with OA hand.

**Objectives:** To determine the relationship between serum leptin levels and the severity of OA in hands. Establish the association between obesity/overweight with the severity of OA, using radiographic scales.

**Methods:** Measurement of leptin levels by ELISA technique to 44 patients with primary OA of hand and 30 healthy controls. Analysis of hand radiographs using the classification system of Kellgren and Lawrence, and anthropometric measurements for the calculation of body mass index.

**Results:** Serum leptin levels in the group of patients with primary hand OA were higher compared to healthy controls ( $P=0.046$ ). No significant associations were found between the different degrees of severity of the disease measured by radiological scale of de Kellgren and Lawrence with the average leptin levels ( $P=0.94$ ) as well as the obesity/overweight categorization according to the body mass index ( $P=0.88$ ).

**Conclusions:** Serum leptin levels in the group of patients with primary hand OA in this study were higher compared to healthy controls, with a significant statistical difference. This difference was not maintained in relation to gender, as well as in the subgroup of patients with obesity or overweight.

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**Niveles de leptina sérica en pacientes con osteoartritis primaria de mano****R E S U M E N****Palabras clave:**

Osteoartritis  
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**Introducción:** Varios estudios han documentado la asociación estadística entre leptina y osteoartritis (OA), en especial en las articulaciones que soportan peso, como caderas y rodillas, y han demostrado concentraciones elevadas de leptina en plasma y líquido sinovial. Pocos estudios abordan la posible relación entre leptina y obesidad/sobrepeso con la OA de mano.

**Objetivos:** Determinar la relación entre el nivel sérico de leptina y la severidad de la OA en manos. Establecer la asociación entre obesidad/sobrepeso con la severidad de OA mediante escalas radiográficas.

**Métodos:** Medición del nivel de leptina por técnica de ELISA en 44 pacientes con OA primaria de mano y 30 controles sanos. Análisis de radiografías de manos mediante el sistema de clasificación de Kellgren y Lawrence y toma de medidas antropométricas para el cálculo del índice de masa corporal.

**Resultados:** El nivel sérico de leptina en el grupo de pacientes con OA primaria de manos fue mayor que el de los controles sanos  $p=0,046$ . No se encontraron asociaciones significativas entre los diferentes grados de severidad de la enfermedad medidos por escala radiológica de Kellgren y Lawrence y los niveles medios de leptina  $p=0,94$ , ni tampoco con la categorización de obesidad/sobrepeso de acuerdo con el índice de masa corporal  $p=0,88$ .

**Conclusiones:** El nivel sérico de leptina en el grupo de pacientes con OA de manos primaria de este estudio fue mayor que el de los controles sanos, con una diferencia estadística significativa. Esta diferencia no se mantuvo con relación al género, como tampoco en el subgrupo de pacientes con obesidad o sobrepeso.

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**Introduction**

Osteoarthritis (OA) is a chronic joint disease, frequent in middle-aged and elderly people, with a growing prevalence. It is considered one of the most common joint disorders and there is no established cure. In the past, it used to be thought as a simple "wear-out" process, and OA was known as a degenerative joint disease. However, it is currently acknowledged as a much more complex disease process, converging to an organized inflammatory process.<sup>1</sup>

A number of fatty tissue-secreted hormones called adipokines, with an effect initially restricted to metabolic activities, represent a newly identified family of compounds that could be considered the key actors in the complex network of soluble mediators involved in the pathophysiology of rheumatic diseases; in the case of OA, through inflammatory effects and catabolism of the cartilage.<sup>2,3</sup> A widely recognized hypothesis is how obesity increases the mechanical burden through the articular cartilage, leading to its degeneration. However, obesity is also associated with OA in non-weight-bearing joints, such as fingers and wrist joints, indicating that there are metabolic factors that also contribute to the high prevalence of OA in obese individuals, due to non-mechanical mechanisms.<sup>4-6</sup>

Several studies have suggested a potential relationship between leptin and OA of the weight-bearing joints, such as the hips and the knees, with diverse statistically significant relationships.<sup>7-18</sup> However, there are few studies on the probable relationship between leptin and obesity/overweight

with OA of the non-weight-bearing joints, such as the hands, which reveal associations or potential risk factor for OA affecting these areas.<sup>19,20</sup> The NHANES III<sup>19</sup> trial, conducted in North American population, failed to identify any association between leptin and hand OA. It is worth mentioning that no studies have been conducted in Latin America, and in Colombia in particular, that establish the cross-cutting association between leptin and hand OA. Hence, in view of the limited epidemiological evidence in that respect, we assume that leptin could be an important link between hand OA and obesity/overweight.

The objective of this study is to determine whether the serum concentration of leptin in a group of patients with primary hand OA is higher than in healthy controls and also to establish the relationship between obesity/overweight and the severity of the disease measured with a radiological scale.

**Methodology**

A cross-sectional, analytic study was conducted in Colombian patients over 18 years old, who met certain classification criteria of the American College of Rheumatology for hand OA,<sup>21</sup> and healthy individuals or controls. Blood samples were collected and hand X-rays were taken to both patients and controls, following identical protocols.

The inclusion criteria for patients with hand OA included: (a) a score  $\geq 2$  in Kellgren and Lawrence (KL) radiological severity scale<sup>22</sup>; (b) authorization to participate signing the

informed consent. For healthy controls: (a) patients with no clinical evidence of OA; (b) authorization to participate signing the informed consent.

The exclusion criteria for both groups of patients were: (a) patients with secondary OA (history of surgery, trauma, or injury of the joint ligament to be assessed); (b) active infection; (c) diagnosis of rheumatoid arthritis, systemic lupus erythematosus, reactive arthritis, spondyloarthritis, arthropathy due to deposition of crystals; (d) a clinical assessment by the treating physician indicating any other chronic inflammatory condition; (e) history of use of steroids in the last 3 months, and (f) obese or overweight patients participating in a weight loss program.

The AP X-rays of the hand were taken 6 months before drawing the blood sample and were analyzed by 2 physicians trained in accordance with the KL classification system: grade 0, with no radiological changes; grade 1, uncertain narrowing of the interarticular space and possible osteophytic formations; grade 2, defined osteophytes and possible narrowing of the articular space; grade 3, multiple moderate osteophytes, overt narrowing of the joint space, sclerosis and possible deformity of the bone contours; grade 4, large osteophytes, marked narrowing of the articular space, severe sclerosis and definite deformity of the bone contours.<sup>22</sup> Weight and height measurements were taken in an instrument calibrated to estimate the body mass index (BMI), using the formula  $BMI = \text{weight in Kg} / \text{height in cm}^2$ . A  $BMI \geq 25$  was considered obesity/overweight.

To quantify the level of leptin, blood samples were drawn (5 ml) per patient, collected in serum separator test tubes. The level of leptin was established with ELISA, using the Diasource Leptin Elisa 96 Tests kit, in accordance with the manufacturer's protocols (dual measurement per sample to avoid false readings associated with poor processing). The sensitivity was 0.1 ng/ml and the detection ranges were between 1 and 55 ng/ml.

The statistical analysis of the information was conducted using the Stata 13.0 software. The description of clinical variables with regards to age, sex, BMI and radiological changes of the joints, was processed via relative frequencies, totals and dispersion measures and summary, in accordance with the statistical distribution. Wilcoxon's range test was used to initially assess the statistical significance of the difference in serum leptin values between the 2 groups: sick patients and healthy controls. Likewise, a Kruskal-Wallis test was administered to radiographically assess the relationship between leptin and OA severity. Finally, the chi-square test was administered to assess the relationship between the presence of obesity/overweight and the severity of the OA based on a radiographic examination. A  $P < 0.05$  was considered statistically significant.

This protocol was approved by the ethics committees of the hospitals from which patients were selected. All of the participants submitted their written informed consents.

## Results

Blood samples were drawn and hand x-rays were taken from a group of 44 patients with primary hand OA, in addition to

**Table 1 – Clinical characteristics of the group of patients with primary hand OA and healthy controls. Serum leptin levels in both groups.**

	Patients with hand OA (n = 44)	Control group (n = 30)	P
Females n (%)	42 (95)	19 (63)	
Median age in years (IQR)	63 (57–68)	61.5 (57–67)	
Median BMI (IQR)	25.15 (23.38–28.05)	25 (24–29)	
Obesity or overweight n (%)	22 (50)	13 (43)	
Median leptin ng/ml (IQR)	10.1 (2.6–21.4)	4.4 (1.6–21.4)	0.046
Mestizo n (%)	44 (100)	30 (100)	
Mechanical risk factor n (%)	1 (2.27)	0 (0)	

**Table 2 – Serum leptin level in the subgroup of women in the primary hand OA group and in the control group.**

	Patients with hand OA females (n = 41)	Control group females (n = 19)	P
Median leptin ng/ml (IQR)	10.4 (2.9–22.3)	6.5 (2.9–25)	0.81

blood samples and X-rays of 30 healthy controls who met the inclusion and exclusion criteria. The clinical characteristics of the groups are depicted in Table 1. There was a prevalence of females, with an average age of 62 years for both groups, at the time of the study. The BMI was similar in both groups, in addition to similar percentages for the distribution obesity/overweight. All of the patients were mestizos, and there was only one patient identified with mechanical risk factor.

The serum leptin level in the group of patients compared to the controls was higher, with statistical significance ( $P = 0.046$ ) (Table 1). The difference between the median and the interquartile ranges of the serum leptin levels in the females was higher in the group of patients, with a non-significant statistical difference ( $P = 0.81$ ) (Table 2). In the males subgroup, the difference in the average leptin level between patients with OA and healthy controls does not allow for a statistical analysis because of the small number of subjects. The level of leptin in the obese or overweight patients was higher than in patients with a normal BMI, with median and interquartile ranges of 19.05 (9.8–27.3) and 2.6 (0.9–10.4) respectively; with a  $P < 0.05$  in the Wilcoxon's range test (Table 3).

There were no statistically significant differences in the mean levels of leptin according to the different degrees of severity of the disease, classified under the KL radiographic scale ( $P = 0.94$ ); neither was there a statically significant association according to the classification of obesity/overweight or normal weight, in accordance with the BMI and the different levels of severity of the disease based on that radiographic scale ( $P = 0.88$ ) (Table 4).

**Table 3 – Average leptin levels in the primary hand OA and healthy control groups, with respect to obesity/overweight and normal weight.**

	Obesity or overweight (n = 40) ng/ml median (IQR)	Normal weight (n = 34) ng/ml median (IQR)
Patients*	19.05 (9.8–27.3)	2.6 (0.9–10.4)
Controls	9.05 (2.9–25)	(1.5–9.15)

\* P < 0.05 in Wilcoxon's range test.

**Table 4 – Mean leptin levels based on the severity of the primary hand OA classified according to Kellgren and Lawrence radiographic scale.**

Patients n = 44 (%)	Median leptin ng/ml (IQR)
KL grade 2 n = 5 (11)	19.9 (4.5–20.5)
KL grade 3 n = 23 (52)	10.4 (2.3–19.2)
KL grade 4 n = 16 (37)	8.15 (2.2–22.95)

## Discussion

OA is considered a chronic and disabling disease, with a high prevalence around the world. There is no clearly defined treatment because of the complexity of its etiopathogenesis. Mechanical and metabolic factors have been suggested and there is an epidemiological association with obesity and metabolic syndrome, with the participation of cytokines released from the adipose tissue called adipokines, which trigger a proinflammatory activity, in addition to disrupting the metabolism of the cartilage matrix and causing structural damage. Several studies have identified a statistically significant relationship between circulating leptin levels in the synovial fluid of the knees and hips (weight-bearing joints). Similarly, others have shown a wide heterogeneity in their primary outcomes, including radiological assessments, pain and functionality scales.<sup>14,16,23</sup>

Stannus et al.<sup>9</sup> found that the serum leptin level was related with reduced cartilage thickness in various knee compartments, measured with nuclear magnetic resonance in STIR sequences (*short tau inversion recovery*) and T1 in cases of OA, in a group of 163 patients, mostly females; this was an indication that these outcomes were leptin mediated. Karnoven-Guteriez et al.,<sup>10</sup> in a population-based study of a cohort in Michigan, found that the leptin serum level was associated with OA: a 5 ng/ml rise in the leptin serum level was linked to a higher probability of knee OA. Lübbecke et al.<sup>24</sup> conducted a cross-sectional study including 219 patients with primary hip and knee OA, treated with joint replacement and measured the concentration of leptin in the synovial fluid obtained the day of surgery. The main outcome was the severity of pain measured before the procedure using the WOMAC (*The Western Ontario and McMaster Universities Osteoarthritis Index*) and VAC (*Visual Analog Scale*) scales, in addition to the finding that joint pain was associated with an elevated leptin concentration. Zhang et al.,<sup>25</sup> in a meta-analysis of 11 clinical trials, with a total of 3625 patients, showed that an increase in the level of expression of leptin was associated with the severity of the disease, in patients with OA, particularly among the female patients.

In contrast to the large number of trials that showed the relationship between leptin and OA in weight-bearing joints, there are few *in vivo* studies that conclusively demonstrate the relationship between hand OA and leptin. Our study showed that hand OA is more prevalent in females, with a late presentation in the natural history of the disease, with a mean age of 63 years, which is consistent with the epidemiological results worldwide. The average serum leptin levels in the group of patients with primary hands OA were higher than in healthy controls, with a statistically significant association ( $P=0.046$ ), just as was shown by Veenbrin et al.<sup>26</sup> in their

paper presented before the meeting of the American College of Rheumatology in San Diego (California) in 2017. In this study they concluded that leptin is partially involved in the relationship between BMI and hand OA, in contrast to previous studies, such as Yusuf et al.<sup>27</sup> and Massengale et al.<sup>19</sup> who conducted a population-based study (National Health and Nutrition Examination Survey, NHANES III), and failed to find any statistical evidence supporting the hypothesis that serum leptin was associated with hand OA. In this study, we found no significant associations between the various levels of hand OA severity measured with the KL radiological scale and the mean serum leptin levels ( $P=0.94$ ). Neither did we find a positive statistical relationship between the serum leptin level of patients classified as obese/overweight, based on the BMI ( $P=0.88$ ); these findings were also described by Yusuf et al.<sup>27</sup>

We would like to highlight that this paper is the first study in a population of Colombian and Latin American patients including patients with primary hand OA, in which the serum leptin level is assessed in terms of its potential association with the disease. It is also remarkable that hand OA is not only caused by mechanical factors, but there are metabolic factors as well, that could be involved in its pathogenesis, as has been shown in knee and hip OA.

We are aware of the limitations of this trial, including the small number of patients, which could impact the detection of other epidemiological variables with significant differences between patients and controls. Since this is a cross-sectional study, it is only possible to establish associations and not a causal relationship. Further studies will be required with enough statistical power and adequate designs, to confirm the probable etiopathogenic role of leptin in hand OA. It is however interesting that the difference in the average leptin levels between the 2 groups was not statistically significant, when comparing patients versus controls, in accordance with their classification as obese/overweight or normal weight. Hence, based on these findings, it is not possible to support the recently demonstrated hypothesis of the positive relationship between these metabolic factors and the disease. Finally, this trial showed no association between the severity of the disease measured with the radiological scale, and the levels of leptin, neither indirectly through the presence of obesity or overweight. The cross-sectional design of the trial limits the weight of this finding.

## Conclusions

In conclusion, serum leptin levels in the group of patients with primary hands OA in our study were higher as compared to healthy controls, with a statistically significant association. This difference was not maintained in the subgroup of females, neither in the subgroup of obese or overweight patients. No statistically significant differences were found between the different levels of severity of the disease according to the KL radiographic scale and the mean levels of leptin, neither with obesity/overweight or normal weight. These findings could indicate the potential relevance of leptin in hand OA and should be interpreted with caution because of the limi-

tation of the study. This also highlights the need to conduct further research.

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## Conflict of interest

The authors have no conflicts of interest to disclose.

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