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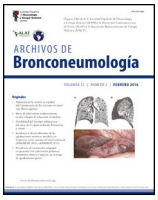

Scientific Letter

Serum leptin and ultrasound markers of early atherosclerosis in patients with sleep apnea hypopnea syndrome☆

Leptina sérica y marcadores ecográficos de aterosclerosis precoz en pacientes con síndrome de apneas e hipopneas del sueño

To the Editor:

Sleep apnea-hypopnea syndrome (SAHS) is a highly prevalent entity that occurs in up to 34% of men and 17% of women,[1] and remains underdiagnosed in many cases. SAHS has been associated with endothelial dysfunction and atherosclerosis, processes that are also aggravated by obesity and other metabolic problems closely associated with this respiratory disorder.

Leptin is a peptide hormone produced in adipose tissue that regulates energy homeostasis and satiety in the central nervous system; leptin levels indicate the degree of adiposity,[2] and there is increasing evidence of its role in the inflammatory cascade and in cardiovascular pathophysiology.[3]

SAHS leads to an increase in cardiovascular disease burden, and the detection of signs of early atherosclerosis in these patients could complement risk stratification. In addition, correlating leptin with ultrasound markers of atherosclerosis may provide information on the possible role of the hormone in the vascular wall thickening process.

We conducted a case-control study to investigate the relationship between serum leptin levels and Doppler ultrasound parameters in the common carotid artery in patients with SAHS. The protocol was approved by the local ethics committee and complied with the Helsinki Declaration. We included 28 individuals: 14 subjects who met criteria for moderate (apnea-hypopnea index [AHI] between 15 and 30) and severe (AHI > 30) on nocturnal polysomnography (PSG)[4] (Bitmed® model NGP-340), who formed the case group, were paired with 14 other healthy subjects of similar phenotype (age, body mass index [BMI], neck circumference), who formed the control group. Blood was drawn from all participants for laboratory analysis, including the determination of fasting baseline serum leptin (Leptin Human ELISA, Clinical Range® BioVendor, Czech Republic), and a Doppler ultrasound of both common carotid arteries was performed (MayLab 30 Esaote, 7.5 MHz linear transducer) by a cardiologist experienced in the technique and unfamiliar with the arm to which the patients had been assigned and the findings of the other tests. Intima-media thickness (IMT), peak wave velocity (PWV), and intraluminal diameter of the common carotid artery, right and left, 10 mm from the bifurcation were quantified. Continuous variables are shown as means (±standard deviation) and categorical variables are shown as frequencies and percentages. Comparisons between the groups were made using the Student t test for continuous variables and the Chi-squared test for categorical variables. Multivariate logistic and linear regression models were used to evaluate the associations between PSG parameters, leptin levels, and ultrasound markers. Statistical analysis was performed using the SPSS 20.0 statistical package (IBM Corp., Armonk, NY, USA).

Table 1
Clinical, polysomnographic, ultrasonographic, and clinical laboratory characteristics.

	Control group (n = 14)	SAHS group (n = 14)	p
Age (years)	44 ± 9)	43 ± 6	0.60
Women	6 (42.7%)	7 (38.9%)	0.59
Weight (kg)	102 ± 17)	110 ± 18	0.28
Height (m)	1.65 ± 0.09)	1.67 ± 0.09	0.63
BMI (kg/m²)	38 ± 6	39 ± 6	0.43
Neck circumference (cm)	39 ± 5	44 ± 5	0.006
Abdominal circumference (cm)	123 ± 16	126 ± 15	0.66
Epworth score >10	2 (14.3%)	12 (66.7%)	0.002
Nocturnal PSG			
AHI	1.7 ± 1.8	49.8 ± 34.9	0.0001
SaO_2%	95.8 ± 1.3	92.3 ± 4.3	0.01
TD90	0.2 ± 0.5	20.5 ± 24.3	0.005
Doppler ultrasound parameters			
Intima-media thickness (IMT) (mm)	0.75 ± 0.11	0.83 ± 0.07	0.01
Pulse wave velocity (PWV) (cm/s)	49 ± 14	49 ± 19	0.48
Artery diameter (mm)	7.45 ± 0.54	7.02 ± 0.67	0.04
Serum leptin (ng/mL)	30 ± 17	38 ± 32	0.19

AHI: apnea-hypopnea index; BMI: body mass index; SaO_2%: mean nocturnal O_2 saturation; SD: standard deviation.

Table 1 shows the characteristics and findings of both groups. There were no differences in gender or anthropometric characteristics, except for neck circumference, which was greater in the SAHS group. Carotid IMT was larger and intraluminal diameter smaller in patients with SAHS compared to the control group ($p < 0.05$). There was a significant correlation between higher AHI and lower SaO_2% with higher IMT and higher PWV (IAH-IMT $r = 0.54$, $p = 0.025$; IAH-PWV $r = 0.5$, $p = 0.007$; SaO_2%-IMT $r = -0.49$, $p = 0.007$; SaO_2%-PWV $r = -0.51$, $p = 0.006$). In terms of absolute values, leptin levels were higher in individuals with SAHS, but this difference did not reach statistical significance. Higher leptin levels were associated with lower mean nocturnal saturation (SaO_2%) ($r = -0.42$, $p = 0.02$), and serum hormone concentrations correlated positively with left common carotid artery IMT in the entire series ($r = 0.36$, $p = 0.03$).

Carotid ultrasound findings in patients with SAHS were closer to signs of incipient carotid atherosclerosis than in the control group, and while there were no differences in serum leptin levels between groups, higher levels were associated with worse SaO_2% and higher IMT. The association of SAHS with subclinical atherosclerosis on ultrasound has recently been reported in a large cohort of patients younger than 68 years.[2] Previous studies[3,5] have also found that patients with SAHS have higher levels of leptin compared with subjects without SAHS; the difference with our results may be explained by the small size of our sample, but we cannot rule out

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the possible role of circadian variation in hormone levels. High leptin levels have also been associated with greater alterations in polysomnographic parameters,[6] and one of the mechanisms that could mediate this phenomenon is intermittent hypoxia, which has a stimulating effect on the release of the hormone by adipose tissue.[7] Leptin is associated with an increase in sympathetic activity, an increase in blood pressure and heart rate, and also participates in inflammatory activity and oxidative stress,[3] processes that are involved in conjunction in the pathogenesis of atherosclerosis. These phenomena seem to mediate a greater presence of signs of subclinical atherosclerosis in patients with leptinemia. Further studies are needed to reinforce this hypothesis.

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Conflict of interests

The authors state that they have no conflict of interests.

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Pro-fibrotic Factors as Potential Biomarkers of Anti-fibrotic Drug Therapy in Patients With Idiopathic Pulmonary Fibrosis

Factores profibróticos como potenciales biomarcadores de la terapia antifibrótica en pacientes con fibrosis pulmonar idiopática

Dear Editor:

Idiopathic pulmonary fibrosis (IPF) is a chronic and progressive fatal fibrotic interstitial lung disease of unknown etiology characterized by progressive deposition of extracellular matrix and destruction of alveolar architecture.[1] It results in respiratory failure and patients have a poor prognosis, the median survival being about 3–5 years following diagnosis.[2] Lung transplantation is the only curative treatment for IPF. However, notable advances have been made in its pharmacological therapy during the last 5 years with the development of new agents designed to inhibit the processes that drive fibrosis.[3] Promising results have recently been made public from phase I and II clinical trials with the novel targets of the autotaxin-lysophosphatidic acid (ATX/LPA) pathway,[4,5] and the transforming growth factor-β (TGF-β) pathway[6,7] that are hypothesized to be central in the development of IPF.[8,9] Thus, the ATX inhibitor GLPG1690 was generally well tolerated and exhibited a safety profile similar to placebo, demonstrating favorable effects on mean change from baseline in forced vital capacity (FVC) at week 12 compared to placebo (25 mL vs −70 mL).[5] Two phase III trials are currently ongoing.[10] In the case of TGF-β suppression, GSK3008348 an αvβ6 integrin inhibitor administered as an inhaled solution, was also well tolerated with no reports of serious adverse events or clinically significant abnormalities that were attributable to study treatment.[6] Due to the increasing interest triggered by the new agents, reliable serum biomarkers would help to improve both diagnostic approach and monitoring of drug effects. Thus, serum levels of surfactant protein A (SP-A), a pulmonary collectin, have been shown to be useful in predicting prognosis or monitoring disease activity.[11,12] Even changes in serum SP-A levels could reflect the outcomes of anti-fibrotic drug therapy with pirfenidone or nintedanib.[13] The usefulness of serum biomarkers in patients undergoing anti-fibrotic drug therapy based on (ATX/LPA) and TGF-β pathways is not well characterized. The purpose of this study is to assess whether the pro-fibrotic compounds ATX, LPA and TGF-β, together with SP-A, could serve as potential biomarkers to monitor the therapeutic response of these novel IPF treatments.

We here report the results of a single-center study consisted of the measurement of serum levels of pro-fibrotic markers in 29 IPF confirmed patients recruited from the Interstitial Lung Diseases Unit at the Pneumology Service at University Hospital of Malaga 'Virgen de la Victoria' during 56 months. Thirty healthy individuals were included as comparison group and paired with sex, age, and smoking status with IPF patients. The local ethics committee approved this study. Prior to enrolment, participants were informed about the study, and provided written informed consent. A multidisciplinary group of Pneumologists, Radiologists and Pathologists established and discussed the diagnostics of IPF cases following the European Respiratory Society/American Thoracic Society/Japanese Respiratory Society/Latin American Thoracic Society criteria.[1]

The serum levels markers in IPF patients were compared with the levels found in healthy volunteers. The study included a single visit of participants. After providing the informed consent, a pulmonary function test was performed and a whole blood sample was drawn from a vein (venipuncture), and collected after