Biomarkers of Atherosclerosis and Indicators of Insulin Resistance in Non-Diabetic Acromegalic Patients

LAURA E. BOERO[1], MARCOS MANAVELA[2], LEONARDO A. GÓMEZ ROSSO[3], CLAUDIA INSÚA[4], NATALIA ELISSONDO[5], LUIS A. CUNIBERTI[6], FERNANDO D. BRITES[7]

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Address for reprints:
Bioq. Laura Boero
Departamento de Bioquímica Clínica. Facultad de Farmacia y Bioquímica
Universidad de Buenos Aires
(1113) Junín 956
Ciudad Autónoma de Buenos Aires, Argentina
Phone: 054 11 5950-8654 /
Fax: 05411 4508-3645
e-mail: lauraboero@fibertel.com.ar

ABSTRACT

Background

Cardiovascular, respiratory and metabolic comorbidities associated with acromegaly contribute to a significant increase in the mortality of this disease. Many of these patients are also diabetic.
Although it is frequent to find abnormal lipid and lipoprotein profiles in patients with acromegaly, controversial outcomes arise in an attempt to identify and/or establish the degree of the modifications of specific parameters.

Objectives

To assess the presence of biomarkers of atherosclerosis in non-diabetic patients with active acromegaly and its association with growth hormone (GH) and with insulin-like growth factor type 1 (IGF-1).

Material and Methods

The study included 14 patients and 14 healthy controls, pared by sex and age. Serum concentration of GH and IGF-1 were determined by immunoassays. Indicators of insulin resistance (glucose, insulin and HOMA) were measured, as well as lipoprotein profile, plasmatic levels of oxidized LDL (oxLDL), vascular cell adhesion molecule 1 (VCAM-1), endothelin-1 and lipoprotein-associated phospholipase A2 activity ($LpPLA_2$).

Results

Compared to controls, non-diabetic acromegalic patients had increased levels of GH ($p<0.05$) and IGF-1 ($p<0.001$), of indicators of insulin resistance (insulin $p<0.001$; HOMA $p<0.001$), triglycerides ($p<0.05$), apo B ($p<0.001$), oxLDL (117 ± 20 versus 89 ± 23 U/L; $p<0.05$) and endothelin-1 (0.9 ± 0.2 versus 0.7 ± 0.2 pg/ml; $p<0.05$). In addition, GH and IGF-1 were positively associated with (*r; p* <) insulin (0.40; 0.05 y 0.73; 0.001), HOMA (0.39; 0.05 and 0.74; 0.001), triglycerides (0.57; 0.05 and 0.64; 0.001), very low-density lipoprotein-cholesterol (VLDL-C) (0.54; 0.05 and 0.47; 0.05), apo B (0.40; 0.05 y 0.54; 0.05), oxLDL (0.59; 0.05 and 0.66; 0.05) and endothelin-1 (0.55; 0.05 y 0.51; 0.05).

Conclusions

Non-diabetic patients with active acromegaly presented an insulin resistance state, as well as subtle modifications of lipid profile and increased levels of oxLDL and endothelin-1. These alterations could explain why these patients are more likely to develop atherosclerotic cardiovascular disease in addition to acromegalic cardiomyopathy.

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Key words > Acromegaly - Atherosclerosis - Lipoproteins - Biological Markers

Department of Clinical Biochemistry, Institute of Physiopathology and Clinical Bichemistry, (INFIBIOC), Faculty of Pharmacy and Biochemistry, University of Buenos Aires (UBA). CONICET. Buenos Aires; Section of Endocrinology, Hospital de Clínicas "José de San Martín", UBA. Buenos Aires, Laboratory of the Section of Endocrinology. Hospital General de Niños "Dr. Pedro Elizalde". Buenos Aires; Universidad Favaloro. CONICET. Buenos Aires

[1] Biochemist specialized in Clinical Biochemistry, Area of Endocrinology Department of Clinical Biochemistry, Faculty of Pharmacy and Biochemistry, Institute of Physiopathology and Clinical Biochemistry, (INFIBIOC), UBA. Buenos Aires

[2] Medical Doctor, specialist in Endocrinology Section of Endocrinology, Hospital de Clínicas "José de San Martín", UBA. Buenos Aires

[3] Biochemist. Department of Clinical Biochemistry, Faculty of Pharmacy and Biochemistry, Institute of Physiopathology and Clinical Bichemistry, (INFIBIOC), UBA. Buenos Aires

[4] Biochemist. Laboratory of the Section of Endocrinology. Hospital General de Niños "Dr. Pedro Elizalde". Buenos Aires

[5] Biochemist. Specialist in Clinical Biochemistry, Area of Endocrinology Department of Clinical Biochemistry, Faculty of Pharmacy and Biochemistry, Institute of Physiopathology and Clinical Biochemistry, (INFIBIOC), UBA. Buenos Aires

[6] Doctor of the UBA. Universidad Favaloro. CONICET. Buenos Aires

[7] Doctor of the UBA. Department of Clinical Biochemistry, Faculty of Pharmacy and Biochemistry, Institute of Physiopathology and Clinical Biochemistry, (INFIBIOC), UBA. CONICET. Buenos Aires

Abbreviations >

Apo	Apolipoprotein	**oxLDL**	Oxidized low-density lipoprotein
CETP	Cholesteryl ester transfer protein	**Lp(a)**	Lipoprotein (a)
TC	Total cholesterol	**Lp-PLA$_2$**	Lipoprotein-associated phospholipase A$_2$
GH	Growth hormone	**CRP**	C-reactive protein
HDL	High density lipoprotein	**TG**	Triglycerides
HOMA	Homeostasis Model Assessment	**VCAM-1**	Vascular cell adhesion molecule-1
IGF-1	Type 1 insulin-like growth factor	**VLDL**	Very low-density lipoprotein
BMI	Body mass index		

BACKGROUND

Cardiovascular, respiratory and metabolic comorbidities associated with acromegaly contribute to a significant increase in the mortality of this disease, which doubles mortality rates of healthy populations. In fact, life expectancy of patients with active acromegaly is reduced approximately by 10 years. (1) Even more, between 10% and 30% of acromegalic patients present diabetes mellitus, (2) a condition that increases the complexity of the disease.

Systemic complications of acromegaly are associated with the chronic rise in the levels of growth hormone (GH) and type 1 insulin-like growth factor (IGF-1). (3) Studies performed in vitro and in vivo have widely demonstrated the effect that the increase in serum levels of GH and IGF-1 has on the structure and function of the heart. (4) Nevertheless, the poor prognosis associated with this condition is related not only with a specific cardiomyopathy,(5) but also with the presence of atherosclerotic disease.

Several studies agree to show abnormal lipid and lipoprotein profiles in acromegalic patients. In spite of that, the results are controversial while trying to identify and to establish the degree of modifications of the specific parameters.

Most studies have reported an increase in serum levels of lipoprotein (a) [Lp(a)], (6, 7), small dense low-density lipoprotein (LDL) particles (8, 9) and fibrinogen. (10) On the contrary, Sesmilo et al. (11) have found reduced levels of C-reactive protein (CRP), while homocysteine levels were within the reference range. According to our knowledge, no studies have been performed to evaluate other atherogenic or inflammatory markers, such as oxidized LDL (oxLDL), lipoprotein associated phospholipase A2 (Lp-PLA$_2$), endothelin-1 or soluble vascular cell adhesion molecules (VCAM-1) in acromegalic patients, compared to healthy controls.

The aim of the present study was to assess the presence of biomarkers of atherosclerosis in non-diabetic patients with active acromegaly and its association with GH and with IGF-1.

MATERIAL AND METHODS

Subjects

Fourteen patients with a diagnosis of active acromegaly were followed-up during one year at the Section of Endocrinology of the Hospital de Clínicas "José de San Martín". Patients included had a diagnosis of active acromegaly that comprised clinical examination and an increase in the serum levels of GH and/or IGF-1, according to age and sex. All those patients with diabetes, hypothyroidism, liver diseases, kidney diseases, adrenal insufficiency, hypogonadism, or under any treatment that might affect the metabolism of carbohydrates, the lipoprotein profile or the antioxidant status were excluded. None of the patients had a history of heart disease or cardiac symptoms.

The control group was constituted by 14 healthy men, matched by sex and age with the acromegalic patients. All the participants signed an informed consent form, and the protocol of this transversal study was approved by the Committees on Ethics of the Faculty of Pharmacy and Biochemistry and of the Hospital de Clínicas "José de San Martín" at the University of Buenos Aires.

Study protocol and samples

Blood samples were obtained from the antecubital vein between 8 AM and 9 AM and after a 12-hour fast. Samples were centrifuged at 1.500 × *g* for 15 minutes at 4 °C. Immediately after, glucose level was determined and the serum was kept at 4 °C for 24 hours for characterization of lipid and lipoprotein levels. Serum aliquots were also stored at -70 °C in order to perform determinations of the levels of insulin, GH, IGF-1, VCAM-1 and oxLDL and to assess the activities of the cholesteryl ester transfer protein (CETP) and LpPLA$_2$.

Analytic Determinations

Standardized methods with internal and external quality control procedures were used to determine the plasmatic levels of glucose, as well as lipid, lipoprotein and apolipoprotein profiles. Serum concentration of insulin was measured by enzyme immunoassay (MEIA, ABBOTT, Japan). The glucose/insulin ratio and the HOMA were calculated using the formula [Glucose (mmol/L) • Insulin (μU/ml)] / 22.5. Plasmatic levels of GH were measured with an ultrasensitive chemiluminescent assay (Accessâ, Beckman Coulter TM, USA) and serum concentrations of IGF-1 were determined with a solid-phase chemiluminescent enzyme immunoassay (Immulite 2000, Diagnostics Products Corp., Los Angeles, CA, USA). oxLDL levels were measured by enzyme immunoassay (Mercodia, Sylveniusgatan 8 A, SE-754 50 Uppsala, Sweden). Endothelin-1 and VCAM-1 levels were determined by enzyme immunoassay (R & D Systems, USA). White cell count was performed with an automatic particle counter (Coulter MAXM).

Cholesteryl ester Transfer Protein Activity

Cholesteryl ester transfer protein (CETP) activity was determined in serum samples according to the procedure previously described (12) with minimal modifications. Briefly, the capacity of a plasma sample to promote the transfer of

tritiated cholesteryl esters from a tracer amount of biosynthetically labeled HDL_3 (^{3}H-CE-HDL_3) (NEN Life Science Products, Boston, USA) towards plasma apoB-containing lipoproteins was evaluated.

Lipoprotein-Associated Phospholipase A2 Activity

Determinations of lipoprotein-associated phospholipase A2 activity ($LpPLA_2$) were performed using a radiometric assay described by Blank et al. (13) with minor modifications. Briefly, the radioactive acetate released by the lipid substrate was extracted and the radioactivity of the aqueous phase was measured thereafter.

Statistical analysis

The Shapiro-Wilk test explored the nature of the distribution of quantitative variables. Parametric data were expressed as mean ± standard deviation (SD) and the Student's *t* test was used to compare means. The results of non-parametric data were analyzed with the Mann-Whitney test and expressed as median and range. The correlation coefficient was analyzed by Pearson's test or Spearman's rank test according to the normality of data distribution A p value < 0.05 was considered to be statistically significant.

RESULTS

Table 1 shows the clinical characteristics, the biomarkers of insulin resistance and hormonal parameters of the 14 acromegalic patients and of the 14 healthy controls. Body mass index and waist circumference were significantly greater in acromegalic patients. Glucose and insulin levels, the glucose/insulin ratio and HOMA were also greater in patients than in controls. According to the inclusion criteria, serum concentrations of GH and IGF-1 were higher in acromegalic patients compared to controls.

Table 2 shows the levels of lipids, lipoproteins and apolipoproteins. Levels of triglicerids and apoB were significantly greater in acromegalic patients. Insulin resistance ratio, atherogenic index and the proportion of small dense LDL particles were also impaired in acromegalic patients. CETP activity was significantly greater in acromegalic patients compared to controls (168 ± 19 versus 148 ± 31%/ml.h, respectively; $p < 0.05$).

There was a significant increase in biomarkers of atherogenesis or inflammation - oxLDL and endothelin-1 - in acromegalic patients compared to healthy controls, as shown in Table 3. However, no differences were seen in LpPLA2 activity, in the concentrations of VCAM-1 or in white cell count.

The analysis of the association between the hormones that define acromegaly and the different biochemical parameters evaluated in the present paper showed significant correlations between GH and/or IGF-1 and most of the indicators of insulin resistance and lipid risk factors for atherosclerosis (Table 4). In addition, positive and significant correlations were observed with oxLDL and endothelin-1.

DISCUSSION

In the present study, a group of non-diabetic patients with active acromegaly, defined by their clinical manifestations and by the increase in the serum levels of GH and/or IGF-1, had lipid and lipoprotein profiles that were more atherogenic than those of healthy subjects, matched by sex and age. We assessed OxLDL, LpPLA2, endothelin-1, VCAM-1 and white cell count as biomarkers of cardiovascular disease. Acromegaly was associated with a significant increase in oxLDL and endothelin-1.

As it was expected, body mass index and waist circumference were greater in patients with active acromegaly than in controls. The study design consid-

Tabla 1. Clinical characteristics, biomarkers of insulin resistance and hormonal parameters of acromegalic patients and healthy controls

	Acromegalic patients	Healthy controls
N	14	14
Women/men	11/3	11/3
Age (years)	47 ± 14	42 ± 12
BMI (kg/m^2)	29 ± 5	23 ± 3[a]
Waist circumference (cm)	94 ± 12	86 ± 18[b]
Glucosa (mg/dl)	97.5 ± 10.7	88.4 ± 7.5[b]
Insulin (mU/L)	15.8 ± 8.6	5.7 ± 2.4[a]
Glucose/insuline ratio	7.1 (3.4-14.6)	15.9 (8.8-51.1)[a]
HOMA	3.6 (1.1-8.2)	1.1 (0.5-2.2)[a]
GH (ng/ml)	7.0 (2.2-66.0)	2.6 (0.9-9.3)[b]
IGF-1 (ng/ml)	625 ± 2	154 ± 26[a]

IBMI: Body mass index. HOMA: Homeostasis Model Assessment. GH: Growth hormone. IGF-1: Type1 insulin-like growth factor. Results are expressed as mean ± SD, except for Glucose/insulin ratio, HOMA and GH, which are expressed as median (range).
[a] $p < 0,001$; [b] $p < 0,05$ versus non-diabetic acromegalic patients.

	Acromegalic patients (n = 14)	Healthy controls (n = 14)
TG (mg/dl)	116 ± 33	80 ± 26[a]
TC (mg/dl)	209 ± 37	203 ± 38
VLDL-C (mg/dl)	23 ± 8	19 ± 4
LDL-C (mg/dl)	138 ± 31	124 ± 30
HDL-C (mg/dl)	50 ± 13	56 ± 8
Non-HDL-C (mg/dl)	159 ± 31	140 ± 34
Apo B (mg/dl)	108 ± 20	79 ± 16[b]
Apo A-I (mg/dl)	151 ± 28	147 ± 13
TG/HDL-C	2.49 ± 0.98	1.41 ± 0.39[b]
TC/HDL-C	4.36 ± 0.89	3.51 ± 0.58[a]
LDL-C/HDL-C	2.87 ± 0.77	2.23 ± 0.54[a]
Apo B/Apo A-I	0.72 ± 0.16	0.55 ± 0.16[a]
LDL-C/Apo B	1.25 (1.00-2.10)	1.60 (1.30-1.80)[b]

TG: Triglycerides. TC: Total cholesterol. VLDL: Very low-density lipoprotein. LDL: Low-density lipoprotein. HDL: High-density lipoprotein. Apo: Apolipoprotein. Results are expressed as mean ± SD, except for LDL-C/Apo B, which is expressed as median (range).
[a] p < 0,05; b p < 0,001 versus non-diabetic acromegalic patients.

Tabla 2. Lipids, lipoproteins and apolipoproteins in non-diabetic acromegalic patients and healthy controls

	Acromegalic patients (n = 14)	Healthy controls (n = 14)
oxLDL (U/L)	117 ± 20	89 ± 23[a]
Lp-PLA_2 (µmol/ml.h)	8.5 ± 2.5	7.8 ± 1.7
Endothelin-1 (pg/ml)	0.9 ± 0.2	0.7 ± 0.2[a]
VCAM-1 (ng/ml)	41 ± 13	38 ± 7
White cell count (10^3/mm^3)	6.0 ± 1.2	6.5 ± 1.9

oxLDL: Oxidized low-density lipoprotein. Lp-PLA_2: Lipoprotein-associated phospholipase A_2. VCAM-1: Vascular cell adhesion molecule-1. Results are expressed as mean ± SD.
[a] p < 0.05 versus non-diabetic acromegalic patients.

Tabla 3. Markers of inflammation and atherogenesis in non-diabetic acromegalic patients and healthy controls

	GHr (p <)	IGF-1 r (p <)
Glucose	0.40 (0.05)	0.65 (0.05)
Insulin	0.40 (0.05)	0.73 (0.001)
HOMA	0.39 (0.05)	0.74 (0.001)
TG	0.57 (0.05)	0.64 (0.001)
VLDL-C	0.54 (0.05)	0.47 (0.05)
Non HDL-C	0.42 (0.05)	0.37 (NS)
Apo B	0.40 (0.05)	0.54 (0.05)
oxLDL	0.59 (0.05)	0.66 (0.05)
Endothelin-1	0.55 (0.05)	0.51 (0.05)

HOMA Homeostasis Model Assessment. GH: Growth hormone. IGF-1: Type1 insulin-like growth factor. TG: Triglycerides. VLDL: Very low-density lipoprotein. HDL: High-density lipoprotein. Apo: Apolipoprotein.

Tabla 4. Correlations between GH and/ IGF-1 with different parameters in non-diabetic acromegalic patients and healthy controls (n = 28).

ered the possibility of matching patients with controls according to their body mass index and waist circumference; however, as fat distribution in acromegalic patients and in subjects with central obesity and cardiovascular risk are not comparable, this criterion was not included. It has been demonstrated that patients with acromegaly present greater body mass indices and waist circumferences but a low proportion of fat; thus they have a concomitant gain of muscle mass. (14)

Carbohydrates metabolism presented an increase in insulin resistance with subsequent glucose intolerance, evident by high levels of glucose and insulin,

an increase in the glucose/insulin ratio, HOMA, and the triglyceride/HDL-C ratio; for this reason the latter has been proposed as an interesting marker to identify subjects with insulin resistance and high risk of cardiovascular disease. (15) Half of the acromegalic patients (7/14) presented plasmatic levels of insulin above the cut-point for our population and for the method used (15 mUI/ml) while insulin levels were normal in all controls. Insulin resistance is a frequent metabolic anomaly in acromegalic patients, (16, 17) and it may probably contribute with most of the cardiovascular risk associated with this disease. (18, 19) It has been demonstrated that, in the fasting state, the action of insulin on glucose utilization but not on lipolysis is impaired in adipose tissue of acromegalic patients because of a postreceptor defect. After glucose ingestion, the resistance to insulin in acromegaly is further enhanced and antilipolysis is also impaired. (20)

It is well known that insulin resistance, a condition that is present in disorders such as metabolic syndrome, type 2 diabetes mellitus and polycystic ovary syndrome, is responsible for the modifications in the metabolism of lipids and lipoproteins. (21) In the present study acromegalic patients presented higher levels of triglycerides, probably due to accumulation of particles of VLDL overloaded with triglycerides, and an increase in the concentrations of apo B compared to controls. This reflects the presence of more atherogenic lipid and lipoprotein profiles in acromegalic patients than in healthy subjects, which is also confirmed by higher values of the different atherogenic indices. The apo B/apo A-I ratio has been proposed as a marker of cardiovascular disease with a high positive predictive value. (22) Even more, the LDL-C/apo B ratio was significantly lower in acromegalic patients than in controls, suggesting an increase in the proportion of the more atherogenic small dense LDL particles. (23) Recently, Mc Laughlin et al. (24) have proposed to use the triglycerides/HDL-C ratio as a predictor not only of insulin resistance but also of the proportion of small dense LDL particles. Arosio et al. (9) also evaluated the physical properties of LDL by ultracentrifugation and they observed that LDL particles in patients with acromegaly were smaller and/or denser. These finding are similar to those reported by Tan et al. (8) and to our conclusions regarding the LDL-C/apo B ratio. CETP activity was greater in patients than in controls, as Tan et al. have also reported. (8) This lipid-transfer protein might be partially responsible for generating small dense LDL particles. (8) These results differ from other study that measured the transfer of cholesteryl esters from LDL to HDL particles. (6)

Insulin resistance may be crucial for modifying lipoprotein profile. Nevertheless, it must be noted that an increase in the activity of the GH/IGF-1 axis may amplify the insulin resistance state (25) and that GH has a direct effect on lipopoprotein metabolism. (26, 27) GH inhibits lipoprotein lipase in the adipose tissue and stimulates the hepatic lipase and the hormone-sensitive lipase; the latter is responsible for the release of free fatty acids from the adipose tissue, which are taken up by the liver and used to synthesize triglycerides. GH and IGF-1 were positively associated with plasmatic levels of glucose, insulin, HOMA, triglycerides, VLDL-C, non HDL-C, apoB, oxLDL and endothelin-1.

This paper describes the umpairment in the lipoprotein physiology in acromegalic patients, which has a more atherogenic profile compared to control subjects. Nevertheless, although some of the results obtained in the group of patients are higher than in the control group, they are within the reference values. Beentjes et al. (6) and Arosio et al. (9) analyzed the basal values of patients with acromegaly and of healthy subjects, and obtained similar results. It is clear that acromegaly poses a high risk for coronary artery disease. (28) In consequence, at the time of determining the absolute risk of a subject with acromegaly, the likelihood of considering this disease as an equivalent of coronary artery disease should be taken into account, as it was also suggested by the National Cholesterol Education Program, Adult Treatment Panel III (ATP III) for diabetes mellitus. (29) In this sense, the optimal levels of LDL, lipids and lipoproteins should be lower than the levels of patients without acromegaly or diabetes.

We assessed oxLDL, $LpPLA_2$, endothelin-1, VCAM-1 and white cell count searching for biomarkers with independent diagnostic and prognostic value to represent the underlying biology of blood vessels wall and, in particular, of the atherosclerotic process and its consequences. According to our knowledge, this would represent the first report of high levels of oxLDL and endothelin-1 in acromegalic patients compared to healthy subjects. This is an interesting finding as oxLDL might reflect the presence of oxidative processes in the arterial wall which are determinant for the development of the atheroma. In addition, endothelin-1, the most powerful vasoconstrictor in human beings, has atherogenic and inflammatory properties, such as the release of vasoactive substances, stimulation of mitogenesis in smooth muscle fibers and contraction of the heart. (30) oxLDL and endothelin-1 showed a positive correlation with GH and IGF-1, suggesting not only that there is an association between them but also the degree of activity of the disease.

To conclude, patients with active acromegaly present subtle modifications in lipid and lipoprotein profiles, and high concentrations of oxLDL and endothelin-1. All the conditions described in this paper could explain why these patients are more likely to develop atherosclerotic cardiovascular disease in addition to the specific acromegalic cardiomiopathy.

RESUMEN

Introducción
En la acromegalia, las comorbilidades cardiovasculares, respiratorias y metabólicas contribuyen a un aumento significativo de la mortalidad de los pacientes afectados. Asimismo, una proporción elevada de estos pacientes presentan diabetes mellitus.
Pese a que el hallazgo de un perfil lipídico y lipoproteico anormal en pacientes acromegálicos suele ser habitual, cuando se intenta identificar y/o establecer el grado de modificaciones de parámetros específicos, los resultados son controversiales.

Objetivos
Evaluar la presencia de biomarcadores de aterosclerosis en pacientes con acromegalia activa no diabéticos y su asociación con la hormona del crecimiento (GH) y el factor de crecimiento similar a la insulina tipo 1 (IGF-1).

Material y métodos
Se estudiaron 14 pacientes y 14 controles sanos pareados por sexo y edad. Se midieron las concentraciones de GH e IGF-1 por inmunoensayos. Se evaluaron indicadores de resistencia insulínica (glucosa, insulina y HOMA), perfil lipoproteico, niveles plasmáticos de lipo-proteínas de baja densidad oxidadas (LDLox), moléculas de adhesión celular vascular 1 (VCAM-1), endotelina-1 y actividad de fosfolipasa A_2 asociada con lipoproteínas ($LpPLA_2$).

Resultados
En comparación con los controles, los pacientes presentaron aumentos de GH ($p < 0,05$) e IGF-1 ($p < 0,001$), de los indicadores de resistencia insulínica (insulina $p < 0,001$; HOMA $p < 0,001$), triglicéridos ($p < 0,05$), apo B ($p < 0,001$), LDLox (117 ± 20 *versus* 89 ± 23 U/L; $p < 0,05$) y endotelina-1 ($0,9 \pm 0,2$ *versus* $0,7 \pm 0,2$ pg/ml; $p < 0,05$). Más aún, la GH y el IGF-1 se asociaron positivamente con (*r; p* <) insulina (0,40; 0,05 y 0,73; 0,001), HOMA (0,39; 0,05 y 0,74; 0,001), triglicéridos (0,57; 0,05 y 0,64; 0,001), colesterol de lipoproteínas de muy baja densidad (C-VLDL) (0,54; 0,05 y 0,47; 0,05), apo B (0,40; 0,05 y 0,54; 0,05), LDLox (0,59; 0,05 y 0,66; 0,05) y endotelina-1 (0,55; 0,05 y 0,51; 0,05).

Conclusiones
Los pacientes con acromegalia activa no diabéticos presentaron un estado de resistencia insulínica, así como modificaciones sutiles en el perfil lipoproteico y concentraciones elevadas de LDLox y endotelina-1. Las alteraciones descriptas podrían contribuir a un estado de mayor propensión al desarrollo de enfermedad cardiovascular aterosclerótica, la cual se sumaría a la miocardiopatía específica de la acromegalia.

Palabras clave > Acromegalia - Aterosclerosis - Lipoproteínas - Marcadores biológicos

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