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Research Article

Is high-sensitivity C-reactive protein involved in the cardiovascular comorbidities of acromegaly?

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Abstract. Objective: In addition to its involvement in the acute phase response, high-sensitivity C-reactive protein (hsCRP) is directly involved in the process of atherogenesis. The study set out to determine the serum levels of hsCRP in acromegaly, attempting to demonstrate a possible implication of its proatherogenic effect in the cardiovascular comorbidities of the disease. Material and Method: This cross-sectional research enrolled 65 acromegaly patients and 30 age- and body mass index (BMI)-matched healthy subjects (HS). According to the therapeutic response, the acromegaly group was categorized into two subgroups: group A (active disease, n=50) and group B (controlled disease, n=15). HsCRP was measured by the sandwich ELISA method. Results: Hypertension was the most common cardiovascular comorbidity in acromegaly patients (58.46%), followed by valvular heart disease (21.5%), acromegalic cardiomyopathy (16.92%), and arrhythmia (15.35%). Similar hsCRP values were observed in the acromegaly group and HS (p=0.706). A significant discrimination of hsCRP concentration between groups A and B was not identified (p>0.05). Similar concentrations of hsCRP were found in acromegaly patients with and without hypertension (p=0.925), valvular heart disease (p=0.835), acromegalic cardiomyopathy (p=0.826), and arrhythmia (p=0.325). No correlation was detected between hsCRP and components of the lipid metabolism. Conclusion: HsCRP does not play a major role in the cardiovascular pathogenesis of acromegaly, thus its cardiovascular comorbidities seem to be primarily caused by the excess of GH/IGF-1.

Key Words: atherogenesis, acute phase reactant, acromegaly, hsCRP, cardiovascular disease

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Introduction

Acromegaly is an endocrine and metabolic disease defined by a growth hormone (GH) overproduction, often generated by a pituitary adenoma (PA) (Asa et al 2021). The excess of GH leads to the hepatic synthesis of insulin-like growth factor 1 (IGF-1) that is the most accurate biomarker for diagnosing acromegaly. Both the hypersecretion of IGF-1 and GH contribute to the appearance of the disease's manifestations, such as osteoarticular abnormalities, metabolic alterations, cardiovascular changes and malignancies (Jung et al 2021). The risk of death for acromegaly patients has increased by over 60% compared to the general population, mainly due to cardiovascular complications (Yang et al 2021). Hypertension, acromegalic cardiomyopathy, and arrhythmia are the most common cardiovascular comorbidities of acromegaly (Yang et al 2021). Hypertension occurs in 15-60% of acromegaly patients and its severity is linked to the excess of GH (Vila et al 2020). The mechanisms underlying hypertension in acromegaly are still a subject of debate. It may be due to the long-term effects of GH/IGF-1 excess on the cardiovascular and renal systems, resulting in increased peripheral resistance and hydrosaline retention (Yang et al 2021). Even the activation of renin and aldosterone secretion by the hypersecretion of GH has been suspected by some researchers as a potential mechanism for the development of high blood pressure (BP) in acromegaly (Yang et al 2021). Moreover, Ronconi (2005) suggested that a decrease in the expression of endothelial nitric oxide synthase could have implications in the occurrence of hypertension in acromegaly. Additional factors that can aggravate hypertension in acromegaly should also be taken into account (e.g., insulin resistance, sleep apnea, myocardial hypertrophy, etc). The main components of acromegalic cardiomyopathy include concentric ventricular hypertrophy, myocardial fibrosis, and diastolic function impairment (Yang et al 2021). The arrhythmia in acromegaly patients is due to myocardial fibrosis and left ventricular hypertrophy (Mizera et al 2018). The most common arrhythmias in acromegaly are paroxysmal atrial fibrillation (AF), supraventricular tachycardia, and ventricular tachycardia (Fleseriu 2014). Valvular heart disease affects approximately 20% of acromegaly patients, being predominantly represented by mitral and aortic regurgitation (Ramos-Leví et al 2017). The mechanism of valvular heart disease in acromegaly is not fully understood yet, but it is suggested that it might be generated by the action of GH on the deposition of mucopolysaccharides and collagen, as well as the abnormal expression of metalloproteinases or dysregulation in proteoglycan synthesis (Mizera et al 2018).

The data regarding the relationship between excess GH or IGF-1 in the appearance of coronary artery disease (CAD) are contradictory. Thus, several studies conducted on small cohorts have

identified a low risk of CAD in acromegaly (Akutsu et al 2010; Bogazzi et al 2007; Cannavo et al 2006). Furthermore, Akutsu (2010) noted that achieving disease control did not modify the cardiovascular risk of affected patients. However, more recent studies have identified a high risk of CAD in acromegaly patients, considering the association of multiple atherogenic risk factors such as hypertension, dyslipidemia, hyperglycemia, insulin resistance, and sleep apnea (Berg et al 2010; Parolin et al 2018; Ragonese et al 2014).

High-sensitivity C-reactive protein (hsCRP) is one of the most well-known acute phase reactants belonging to the pentraxin family. This protein is an indicator of acute infections and inflammations. However, hsCRP can also increase in other pathologies such as cancers, trauma, autoimmune diseases, or metabolic disorders (Banait et al 2022). HsCRP is primarily synthesized by hepatocytes being stimulated by other proinflammatory cytokines namely tumor necrosis factor α, interleukin (IL) 6 and IL 1 (Banait et al 2022). HsCRP does not actually differ from traditional CRP but is a novel assay that detects extremely small concentrations of CRP in serum or plasma (Banait et al 2022). HsCRP is involved in endothelial dysfunction by increasing the recruitment of monocytes to atherosclerotic lesions, hindering the release of nitric oxide from the vascular endothelium (Banait et al 2022). Also, hsCRP increases the expression of some adhesion molecules (e.g., MCP1 and endothelin 1) and plasminogen activator inhibitor 1 (Banait et al 2022; Bassuk et al 2004). HsCRP contributes to the oxidation of LDL-cholesterol and mediates its uptake by macrophages (Banait T et al 2022; Bassuk et al 2004). Furthermore, hsCRP has a direct effect on the process of atherogenesis (Banait T et al 2022; Bassuk et al 2004). Taking into account its proatherogenic effects, a high level of hsCRP is considered a predictive factor for heart disease in apparently healthy subjects (HS), regardless of whether they have other cardiovascular risk factors or not.

The main research aim was to determine the serum hsCRP levels in a group of acromegaly patients who associate numerous cardiovascular risk factors including dyslipidemia, insulin resistance, and hyperglycemia. The secondary aim of the research was to demonstrate a possible involvement of the proatherogenic effect of hsCRP in the cardiovascular comorbidities of acromegaly.

Material and methods

A cross-sectional research was conducted at the Endocrinology Clinic from Cluj County Emergency Clinical Hospital, Cluj-Napoca between February 2017 and July 2021. Sixty-five acromegaly patients (39 females and 26 males) and 30 age- and body mass index (BMI)-matched HS (23 females and 7 males) were enrolled in the study.

The inclusion criteria of the acromegaly group were represented by adult patients diagnosed with acromegaly in conformity with the European Society of Endocrinology (Katznelson et al 2014). The acromegaly group was categorized into two subgroups according to the therapeutic response as follows: group A (active disease) included (1) treatment-naive patients with increased IGF-1 titers and lack of GH suppression after oral glucose tolerance test (OGTT) (GH > 1 ng/ml) and (2) therapeutically uncontrolled patients (having elevated IGF-1 titers and a random GH > 1 ng/ml). As a particularity, patients treated with GH receptor antagonists (GHRAs) were evaluated only by measuring IGF-1; group B (controlled disease) included treated patients who had a normal concentration of IGF-1 and a random GH < 1 ng/ml.

The exclusion criteria of the acromegaly group were represented by (1) acromegalic habitus, (2) normal somatotropic axis functionality, (3) immunosuppressive treatments, (4) uncontrolled diabetes mellitus (glycated hemoglobin > 10%), (5) uncontrolled hypertension under antihypertensive treatments (BP > 160/100 mmHg), and (6) active cancers.

The study was carried out respecting the Declaration from Helsinki and received approval from the Ethics Commission (No. 42/03.02.2017) of the "Iuliu Haţieganu" University of Medicine and Pharmacy, Cluj-Napoca. All subjects signed an informed consent before enrollment in the study.

Each patient was clinically assessed with the following measurements: weight (kg), height (cm), BP (mmHg) after 15 minutes of rest, waist circumference (cm), hip circumference (cm), and waist/hip ratio. All patients underwent pituitary magnetic resonance imaging (MRI) or computer tomography in case of contraindication to MRI.

The blood samples of the patients were collected from the cubital vein after a minimum of 8 hours of fasting. Afterward, the blood was incubated at room temperature for 40 minutes and centrifuged at 2000 rpm for 10 minutes. The obtained serum was stored at minus 80 degrees.

All patients were evaluated by measuring glucose, triglycerides, total cholesterol, and LDL-cholesterol levels using spectrophotometry. The level of HDL-cholesterol was obtained by applying Friedewald formula (HDL-cholesterol = total cholesterol - LDL-cholesterol - (triglycerides / 5). Patients were also evaluated by measuring insulin, GH, IGF-1, prolactin, thyroid-stimulating hormone (TSH), free thyroxine (FT4), testosterone (for males), estradiol (for females), gonadotropins, and basal cortisol through chemiluminescence immunoassay. The IGF-1 index was obtained by dividing the serum IGF-1 value by the upper limit of the reference range. IGF-1 index below 1 was considered normal. Estradiol, testosterone, and gonadotropins were measured solely to detect possible hypogonadotropic hypogonadism, and their concentrations were not compared between the acromegaly subgroups due to multiple sources of error (e.g., the postmenopausal status of women, testosterone replacement therapy, etc). The insulin resistance index (HOMA-IR) was calculated using the formula: glucose (mg/dl) x insulin (mUI/l)/405 (Matthews et al 1985). The serum hsCRP level was measured using the sandwich ELISA technique (Human hsCRP ELISA Kit, Elabscience (USA)), with a detection range between 15.63 and 1000 pg/ml.

The software MedCalc 19.3.1. was used for statistical analysis. Continuous variables with normal distribution were presented as mean ± standard deviation, while continuous variables with non-normal distribution were reported as median (interquartile range) (IQR). Categorical variables were presented as numbers (percentages). The comparison of continuous variables was performed using the independent samples T-test or the Mann-Whitney test, taking into consideration their distribution. The comparison of categorical variables was performed with Fisher's exact test. The correlations between two variables were obtained using the Pearson or Spearman correlation coefficient. A P value of less than 0.05 showed statistical significance.

Results

Statistically significant discrimination in weight, BMI, and diastolic BP were noted between the acromegaly group and the control group (CG) (Table 1). Similar hsCRP values were observed in the acromegaly group and the CG (p=0.706) (Table 1). The acromegaly group included 50 patients with active disease (group A) and 15 patients with uncontrolled disease (group B). In group A, 17 patients were treatment-naive, while the remaining 33 were therapeutically uncontrolled. Forty-one (63.07%) patients underwent surgical treatment, while 18 (27.69%) received radiotherapy. Thirty-nine (60%) patients were treated with medications from the class of somatostatin analogues (SSAs), GHRAs, or dopamine agonists. Fourteen (21.53%) patients required triple therapy (surgery, radiotherapy, and pharmaceutical treatment) (Table 2). Forty-nine (75.38%) patients had pituitary macroadenomas. Thirty-two (49.23%) of the PA were invasive. Forty-nine (75.38%) PAs showed T2 hyperintensity on pituitary MRI.

Table 1 - Features of acromegaly group and control group

Variables	Acromegaly group (n=65)	Control group (n=30)	P value
Female gender#	39 (60)	23 (76.66)	0.163
Age (years)^	52.06±12.41	49.46±15.34	0.421
Weight (kg)^	86.43±17.05	75.00±16.41	0.005
Height (cm)*	168 (163-175.2)	165 (164-170)	0.433
BMI (kg/m^2)^	30.05±5.38	27.09±5.88	0.023
Systolic BP (mmHg)*	130 (120-140)	120 (115-130)	0.061
Diastolic BP (mmHg)*	80 (80-90)	80 (70-85)	0.008
hsCRP (pg/ml)*	33.1 (18.35-67.34)	42.52 (18.46-105.2)	0.706

BP: blood pressure; BMI: body mass index; hs-CRP: high-sensitivity C-reactive protein; #numbers (percentages); ^mean ± standard deviation; *median (interquartile range)

The most common clinical manifestations of active acromegaly were acrofacial dysmorphism (92.3%), seborrhea (56.92%), visceromegaly (55.38%), hyperhidrosis (52.3%), osteoarticular manifestations (49.23%), and headache (49.23%) (Table 2). Pituitary insufficiency was present in 36% of group A and 40% of group B (Table 2). Diabetes mellitus (26%) and impaired glucose tolerance (20%) predominated in group A (Table 2). Colon polyps have been identified in 22% of patients from group A. Hypertension was the most common cardiovascular comorbidity in the acromegaly group (58.46%). A percentage of 21.5% of acromegaly patients have associated valvular heart disease and 16.92% of them have associated acromegalic cardiomyopathy. A percentage of 15.35% of acromegaly patients have presented arrhythmia. Three patients from group A had a previous hemorrhagic stroke.

Insulin and HOMA-IR were significantly increased in patients from group A compared to group B (p=0.021 and p=0.027, respectively). Similarly, the IGF-1 level and IGF-1 index were significantly elevated in group A versus group B (p<0.0001). Additionally, a significantly higher level of random GH was noted in group A versus group B (p=0.0001). No statistically significant discrimination was detected in blood glucose, LDL-cholesterol, HDL-cholesterol, total cholesterol, and triglycerides among the two study acromegaly subgroups (p>0.05) (Table 3). In group A, an increased level of hsCRP was detected compared to group B (p=0.097), but without statistical significance. The median of hsCRP was lower in hypertensive acromegaly patients (32.64 pg/ml, IQR 17.83-67.11) compared to those with normal BP (34.63 pg/ml, IQR 18.67-67.48), although without statistical significance (p=0.925). Additionally, similar concentrations of hsCRP were observed in patients with and without valvular heart disease (median of 35.95 pg/ml, IQR 17.63-103.73 versus median of 32.18 pg/ml, IQR 18.88-61.47, p=0.835). The median hsCRP was lower in patients with acromegalic cardiomyopathy (median of 24.33 pg/ml, IQR 15.22-136.69) versus those without this complication (median of 33.86 pg/ml, IQR 18.46-67.11), but without statistical significance (p=0.826). There were no significant differences detected between acromegaly patients who had associated arrhythmias and those with normal sinus rhythm (median of 41.03 pg/ml, IQR 22.32-178.33 versus median of 32.64 pg/ml, IQR 17.93-64.46, p=0.325). No correlation was found between hsCRP and random GH (r=0.14, p=0.27), IGF-1 (r=0.16, p=0.19), IGF-1 index (r=0.13, p=0.29), or any component of the lipid panel (r=-0.003, p=0.97 for total cholesterol; r=0.07, p=0.57 for LDL-cholesterol; r=-0.17, p=0.16 for HDL-cholesterol; r=0.03, p=0.80 for triglycerides).

Discussion

Over time, literature has confirmed the risk of hypertension among patients with high levels of IL 6 and (hs)CRP (Jayedi et al 2019). A recent meta-analysis conducted on approximately 5,500 patients with AF and over 360,000 participants demonstrated a causal relationship between high CRP levels and the appearance of AF (relative risk of 1.49; 95% confidence intervals: 1.14-1.42) (Li et al 2022). Also, elevated values of this acute-phase reactant have been reported in patients with heart failure. The last patients with high levels of hsCRP have shown an unfavorable disease progression (Anand et al 2005).

The present study aimed to evaluate the level of hsCRP in acromegaly, attempting to identify a potential role of this protein in the cardiovascular comorbidities of the disease. The study noted similar concentrations of serum hsCRP in the acromegaly group and the CG. In the same manner, Potter (2008), Arikan (2009), and Ozkan (2012) did not find significant discrimination in hsCRP levels between acromegaly group and healthy controls (p>0.05). Vilar (2007) conducted a cross-sectional research, including 62 acromegaly patients and 36 HS matched by age, gender, and BMI. HsCRP had similar values in both groups. The acromegaly group included patients with uncontrolled (n=50) and controlled disease (n=12). Patients with uncontrolled disease had significantly decreased concentrations of hsCRP versus those with controlled disease (p<0.001). HsCRP was negatively correlated with GH (r=-0.324, p=0.039) and IGF-1 (r=-0.446, p<0.001) (Vilar et al 2007). Also, Ozkan (2015) detected lower CRP concentrations in 39 active acromegaly patients compared to 40 age-, gender-, BMI-, and cardiovascular risk factor-matched HS (p=0.01). Verhelst (2013) observed a decreased level of hsCRP in uncontrolled (n=95) versus controlled acromegaly patients (n=105) (p<0.001). Most

Table 2. Features of acromegaly group according to therapeutic response

Variables	Group A (active disease) (n=50)	Group B (controlled disease) (n=15)	P value
Demographic data			
Female gender#	30 (60)	9 (60)	1
Age (years)^	51.2±12.45	54.93±12.25	0.31
Physical examination			
Weight (kg)^	87.55±17.11	82.7±16.87	0.005
Height (cm)^	170.2±10.79	167.4±10.14	0.375
BMI (kg/m^2)^	30.24±5.45	29.43±5.29	0.615
Diastolic BP (mmHg)*	80 (80-90)	90 (80-90)	0.605
Systolic BP (mmHg)*	128.75 (120-130)	130 (120-140)	0.58
Waist circumference (cm)*	100 (95.5-107)	98 (94.2-101.1)	0.367
Hip circumference (cm)*	110 (105-117)	106 (103-109.7)	0.233
Waist/hip ratio*	0.91 (0.88-0.94)	0.92 (0.87-0.95)	0.528
Clinical features			
Headache#	25 (50)	7 (46.66)	1
Acromegalic dysmorphism#	47 (94)	13 (86.66)	0.325
Osteoarticular manifestations#	26 (52)	6 (40)	0.557
Psychiatric manifestations#	7 (14)	3 (20)	0.685
Seborrhea#	29 (58)	8 (53.33)	0.773
Hyperhidrosis#	27 (54)	7 (46.66)	0.769
Hypertrichosis#	10 (20)	5 (33.33)	0.308
Visceromegaly#	30 (60)	6 (40)	0.238
Compression elements determined by PA			
Visual field defects#	8 (16)	3 (20)	0.706
Pituitary insufficiency#	18 (36)	6 (40)	0.77
Diabetes insipidus#	2 (4)	0 (0)	1
PA characheristics on MRI			
Macroadenoma#	37 (74)	12 (80)	0.744
Invasive character#	27 (54)	5 (33.33)	0.239
T2 hyperintensity#	35 (70)	14 (93.33)	0.09
Therapeutic modalities			
Surgery#	27 (54)	14 (93.33)	0.005
Radiotherapy#	13 (26)	5 (33.33)	0.742
Pharmaceutical treatment#	24 (48)	15 (100)	<0.0001
Monotherapy#	11 (22)	1 (6.66)	0.267
Double therapy#	13 (26)	9 (60)	0.027
Triple therapy#	9 (18)	5 (33.33)	0.282

BP: blood pressure; BMI: body mass index; PA: pituitary adenoma; MRI: magnetic resonance imaging; #numbers (percentages); ^mean ± standard deviation; *median (interquartile range)

patients were compared to a CG. Thus, 84 controlled patients were compared to 167 age-, gender- and BMI-matched HS, and no statistically significant discrimination in hsCRP levels were detected between these two groups (p=0.94). Sixty-five patients with uncontrolled disease were compared to 130 HS, and it was observed that the level of hsCRP was significantly decreased in active disease (p<0.001). Al-Shawk (2017) noted a low serum concentration of hsCRP in 30 active acromegaly patients versus 28 HS (p=0.001). The author observed a negative correlation between hsCRP and GH (r=-0.67, p=0.008). Andreassen (2007) investigated the pre- and post-therapeutic level of hsCRP in a group of 21 acromegaly patients compared to 42 HS. Before treatment, the researcher observed that the acromegaly group had significantly decreased hsCRP concentrations versus HS (p<0.001). The hsCRP level was below the

Table 3. Biochemical and hormonal profile, as well as serum hsCRP levels, in the two study subgroups, according to therapeutic response

Blood Tests	Group A (active disease) (n=50)	Group B (controlled disease) (n=15)	P value
Glucose (mg/dl)*	101.5 (89-117)	101 (97.25-113.25)	0.981
Insulin (µU/ml)^	18.3±11.16	11.3±4.64	0.021
HOMA-IR*	4.27 (2.38-6.63)	2.9 (2.14-3.66)	0.027
LDL-cholesterol (mg/dl)^	118±34.42	123.4±44.79	0.621
HDL-cholesterol (mg/dl)^	51.76±14.67	56.75±11.91	0.234
Total cholesterol (mg/dl)^	195.12±38.03	199.86±51.39	0.698
Triglycerides (mg/dl)*	126.5 (93-164)	109 (67.75-132.7)	0.105
Prolactin (ng/ml)*	8.95 (3.84-15.1)	9.5 (6.17-18.05)	0.744
TSH (µIU/ml)*	0.74 (0.47-1.27)	0.69 (0.42-1.11)	0.986
FT4 (ng/dl)*	1.04 (0.97-1.16)	1.06 (0.9-1.18)	0.93
Basal cortisol (µg/dl)^	12.53±5.55	11.54±3.28	0.517
IGF-1 (ng/ml)*	361.25 (260-607)	171 (81.35-195.7)	<0.001
IGF-1 index*	1.57 (1.18-2.8)	0.77 (0.37-0.88)	<0.001
Random GH (ng/ml)*	2.6 (1.68-8.1)	0.5 (0.45-0.73)	0.000
hsCRP (pg/ml)*	35.06 (19.3-79.52)	23.91 (14.65-46.15)	0.097

HOMA-IR: insulin resistance index; LDL: low density lipoprotein; HDL: high density lipoprotein; TSH: thyroid-stimulating hormone; FT4: free thyroxine; IGF-1: insulin-like growth factor 1; GH: growth hormone; hs-CRP: high-sensitivity C-reactive protein; ^mean ± standard deviation; *median (interquartile range)

detection limit in over 50% of these patients. The CRP concentrations in the acromegaly group increased post-therapy (p<0.001). Delaroudis (2008) evaluated the hsCRP titer in 18 acromegaly patients at baseline and after a period of six months of therapy with SSAs versus 15 HS. The author observed a low level of hsCRP in acromegaly compared to the CG (p<0.001). The hsCRP value increased significantly after therapy with SSAs (p<0.001), however this level remained lower compared to the CG.

Wolters TLC (2021) identified significantly decreased plasma hsCRP concentrations in treatment-naive acromegaly patients (n=12) versus patients with active disease (n=35), controlled disease (n=74), and HS (n=56) (p<0.001).

Sesmilo G (2002) monitored the effects of GHRAs on inflammation and cardiovascular risk factors in active acromegaly. Thus, the author identified a low concentration of CRP in 48 active acromegaly patients compared to 47 age- and BMI-matched HS. CRP levels increased after the introduction of GHRAs. This type of medication blocks the activation of the GH receptor, preventing intracellular signaling and causing a decrease in IGF-1 concentration. Thus, the increased CRP could be due to a decrease in IGF-1 production or the direct action of GHRAs (Sesmilo G et al 2002).

In cross-sectional research, Fedrizzi (2011) evaluated the risk factors linked with the occurrence of hypertension in 44 acromegaly patients (21 with active disease and 23 with controlled or cured disease). Hypertension was identified in 33% of patients with uncontrolled disease and in 65% of those who were controlled or cured. In the group of patients with uncontrolled disease, IGF-1 positively correlated with systolic BP (r=0.48, p<0.05), but no statistically significant differences in hsCRP levels were identified between hypertensive acromegaly patients and those who were normotensive (p=0.76). Similar to Fedrizzi's study, the present research did not identify a significant discrimination in serum hsCRP titers between hypertensive acromegaly patients and those with normal BP. Also, approximately similar concentrations of hsCRP were identified in acromegaly patients with and without acromegaly cardiomyopathy, arrhythmia or valvular heart disease.

Contrasting with the rest of the studies mentioned above, Ozisik (2023) detected a significantly higher level of hsCRP in 30 active acromegaly patients versus 41 HS (p<0.05). In the current study, active acromegaly patients had an increased level of hsCRP versus controlled patients, but without statistical significance.

The literature has shown discordant aspects of hsCRP concentrations in acromegaly. In this study, the similar level of hsCRP in the acromegaly group and CG, corroborated with the lack of correlation between hsCRP and the lipid profile components, suggest that hsCRP is not an independent cardiovascular risk factor in acromegaly. Moreover, the low level of hsCRP identified by some researchers in active acromegaly reinforces the idea that cardiovascular disease (CVD) in acromegaly is not due to its proatherogenic effect. Thus, the involvement of atherosclerosis in the occurrence of CVD in acromegaly seems to be less and less plausible. A postmortem study conducted on 27 acromegaly patients did not identify a pronounced atherosclerosis compared to the same age and gender population (Lie JT 1980). Moreover, in another study, the intima-media thickness of the carotid artery, indirectly reflecting the presence of atherosclerosis, was decreased in acromegaly patients versus the CG (Otsuki et al 2021). These data lead to the hypothesis that cardiovascular comorbidities of acromegaly are not due to the proatherogenic effect of hsCRP, but rather they are dependent on GH or IGF-1 hypersecretion (Andreassen et al 2007).

The limited number of patients and the cross-sectional design of the study were the main limitations of the present research. Thus, future prospective studies conducted on large cohorts will be able to provide additional data about the possible relationship between hsCRP and CVD in acromegaly.

Conclusions

This research suggests that the cardiovascular comorbidities of acromegaly are not determined by the proatherogenic effect of hsCRP, even though it is considered an independent cardiovascular risk factor. Therefore, hypertension, acromegalic cardiomyopathy, valvular heart disease, and arrhythmia seem to be primarily dependent on the excess of GH/IGF-1.

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