ORIGINAL PAPERS

Adv Clin Exp Med 2016, **25**, 3, 449–455
DOI: 10.17219/acem/35639

ISSN 1899–5276

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Adiponectin and Cardiac Hypertrophy in Acromegaly*

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Abstract

Background. Adiponectin is an adipocytes-derived hormone which has been shown to possess insulin-sensitizing, antiatherogenic, and anti-inflammatory properties. In acromegaly, the data on adiponectin is contradictory. The relationship between adiponectin levels and cardiac parameters has not been studied.
Objectives. The aim of this study was to find out how adiponectin levels were affected in acromegalic patients and the relationship between adiponectin levels and cardiac parameters.
Material and Methods. We included 30 subjects (15 male, 15 female), diagnosed with acromegaly and 30 healthy (10 male, 20 female) subjects. Serum glucose, insulin, GH, IGF-1 and adiponectin levels were obtained and the insulin resistance of the subjects was calculated. Echocardiographic studies of the subjects were performed.
Results. We determined that adiponectin levels were significantly higher in the acromegalic group than the control group. In the acromegalic group, there was no statistically significant relation between serum adiponectin and growth hormone (GH), or insulin-like growth factor-1 (IGF-1) levels ($p = 0.3$, $p = 0.1$). We demonstrated that cardiac function and structure are affected by acromegaly. IVST, PWT, LVMI, E/A ratio, DT, ET, IVRT, VPR, and LVESV values were increased and the results were statistically significant. In the acromegalic group, adiponectin levels were positively related with left ventricle mass index (LVMI) but this correlation was found to be statistically weak ($p = 0.03$). In our study, there was a positive correlation between VAI and LVM. We also could not find any correlation between VAI and adiponectin levels.
Conclusions. Although insulin resistance and high insulin levels occur in active acromegaly patients, adiponectin levels were higher in our study as a consequence of GH lowering therapies. Our study showed that adiponectin levels may be an indicator of the cardiac involvement acromegaly. However, the usage of serum adiponectin levels in acromegalic patients as an indicator of cardiac involvement should be supported with other, wide, multi-centered studies (**Adv Clin Exp Med 2016, 25, 3, 449–455**).

Key words: acromegaly, insulin resistance, cardiac hypertrophy, echocardiography, adiponectin.

Adiponectin is an adipocyte-derived hormone and plays a role in insulin-sensitizing [1], antiatherogenic [2], anti-inflammatory properties [3, 4]. Reduced adiponectin levels have been reported in obesity (especially visceral obesity), diabetes, insulin resistance, hypertension [5, 6] and coronary artery disease [7, 8] as well as an increased risk of myocardial infarction.

Increased levels appear to reduce the overall cardiovascular risks [9]. Experimental evidence implies that adiponectin inhibits hypertrophic signaling in the myocardium [10] and may thus in-

* The study was funded by: Pamukkale University science investigation project 2009TPF002.

fluence cardiac remodeling [11, 12]. Low levels of adiponectin are associated with a further progression of left ventricular hypertrophy in patients presenting with hypertension, left ventricular diastolic dysfunction, and hypertrophy [13]. Adiponectin may serve to limit pathological cardiac remodeling, which leads to hypertrophy and diastolic dysfunction. Serum adiponectin levels are paradoxically higher in patients with chronic heart failure; they were an independent predictor of mortality [14, 15]. Adiponectin may play a role in the mechanism of heart failure. However, the effect of adiponectin seems to differ under different conditions and in different study populations.

Cardiovascular disorders are the leading causes of morbidity and mortality in patients with acromegaly [7, 8]. The growth hormone/insulin-like growth factor-1 (GH/IGF-1) axis has a direct endocrine effect on the myocardium, resulting in hypertrophy, enhancement of contractile performance, and elongation of the action potential of cardiac fibers [9]. Acromegaly involves complex mechanisms that interfere with the function of the heart, including coronary ischemia, chronic heart failure, and valvular disease.

Because acromegaly is also a systemic disorder characterized by morbidities similar to those of a metabolic syndrome, hypoadiponectinemia may be involved in the pathogenesis of insulin resistance and related metabolic disorders as well as cardiac changes present in active acromegaly [10–17]. Indeed, adiponectin levels in acromegalic patients have been reported variably as higher than [18] or similar to [19, 20] those in normal controls. The effect of GH-reducing therapy on serum adiponectin levels has also been studied [21, 22]. The relationship between adiponectin levels and cardiac parameters has not been studied.

The aim of this study was to find out how adiponectin levels were affected in subjects with active and inactive acromegaly and any relationship between adiponectin levels and cardiac parameters in acromegalic patients.

Material and Methods

The study protocol conformed to the ethical guidelines of the Declaration of Helsinki as reflected in a prior approval by the institution's human research committee. The study was approved by the Ethics Committee of Pamukkale University.

Patient Characteristics

Thirty patients (15 male, 15 female) who were diagnosed with acromegaly and 30 healthy control subjects (10 male, 20 female) were included in the study. The subjects in both study groups were between 35 and 60 years old and both groups were similar with respect to mean age. Twenty-five patients were diagnosed with hypophyseal macroadenoma, and the remaining subjects were diagnosed with microadenoma during the first visit. Patients with nadir GH ≤ 1 μg/L after OGTT (oral glucose tolerance test) and normal IGF-1 levels according to age and sex were classified as inactive, and patients with nadir GH > 1 μg/L after OGTT and higher IGF-1 levels were classified as having active acromegaly. Three months before the evaluation, the patients stopped insulin-sensitizing treatment to avoid any interference with the analyzed metabolic parameters. Blood samples were collected and a cardiac analysis was performed before any treatment for this study. (All subjects in the patient group were treated with somatostatin analogs, and 22 subjects were also treated with surgery; 7 were treated with a combination of both surgery and radiotherapy). Twenty-three subjects with insulin resistance received insulin sensitizing therapy with either glitazones or metformin.

All of the healthy subjects had a normal body mass index (BMI), fasting plasma glucose levels (FPG), and IR parameters. None of the healthy subjects had drug usage or cardiac disease demonstrated with history, electrocardiography or echocardiography. None of the acromegalic group and control group had been diagnosed with hypertension. Anthropometric measurements (weight, height, waist circumference) of the subjects were obtained as they were in a prone position after 8 hours fasting.

Laboratory Methods

After 10 min of resting, arterial blood pressures were obtained with an aneroid sphygmomanometer. Blood samples for glucose, insulin, GH, IGF-1, and adiponectin were obtained after 8 h of fasting. Serum insulin levels of the subjects were analyzed by an Architect autoanalyzer using a commercially available, solid phase chemiluminescence immunometric procedure (Abbott, USA). Insulin resistance was calculated according to the HOMA method as follows: {[glucose(mg/dL)/18] X insulin (μU/mL)}/22.5 [23]. A HOMA-IR value above 2.7 was considered to show insulin resistance. Serum adiponectin, IGF-1 and GH concentrations were determined using ELISA kits.

The visceral adiposity index (VAI) was calculated as described [19], using the following formulas, differentiated according to sex, where triglyceride (TG) levels are expressed in millimoles per liter and HDL-cholesterol levels expressed in millimoles per liter:

for males, VAI: [WC/39.68 + (1.88 × (BMI)] ×
× (TG/1.03) × (1.31/HDL);

for females, VAI: [WC/36.58 + (1.89 × BMI)] ×
× (TG/0.81) × (1.52/HDL).

According to the specific, age-stratified cutoff points of VAI identifying patients with presumed visceral adipose dysfunction and cardiometabolic risk [24], we divided the patients into two groups: those with normal VAI (group A) and those with high VAI (group B)

M-mode, two-dimensional, and pulsed Doppler echocardiographic studies were performed with a commercial ultrasound system, Vivid 7, using a 2.5-MHz transducer during three to five consecutive cardiac cycles. The following measurements were recorded on an M-mode trace: left atrium diameter, left ventricular end-diastolic volume (LVEDV), left ventricular end-systolic volume (LVESV), interventricular septum thickness (IVST), left ventricular posterior wall thickness (PWT), left ventricular ejection fraction (LVEF), and fractional shortening. Left ventricle mass (LVM) was calculated with the Devereux Formula. We calculated LVM index by dividing LVM by the body surface area. The myocardial performance index (MPI) indicator of cardiac function is defined as the sum of isovolumetric contraction time (ICT) and isovolumetric relaxation time (IVRT) divided by ejection time (ET).

Statistical Analysis

The SPSS program (Statistical Package for Social Sciences, v. 11.0 for Windows) was used for statistical analysis and the results were expressed as mean ± standard deviation. Two-tailed 95% confidence intervals and p values were given, with $p < 0.05$ regarded as significant. In the statistical evaluations, 1-way analysis of variance test was used to observe any differences between the control group, active acromegaly and inactive acromegalic patient groups relating to blood values and cardiac parameters. In the determination of different groups, the Duncan multiple comparison method was used. In addition, Spearman Rank Correlation Coefficient, unpaired *t*-tests were used. Adjustments cannot be done because assumptions of multivariate normality are not achieved due to the small sample size.

Results

In this study, statistically significant differences were observed in fasting plasma glucose, insulin, HOMA-IR, growth hormone and adiponectin levels between the active and passive acromegalic groups. The clinical and biochemical findings of patients and controls are shown in Table 1. Adiponectin levels were higher in acromegalics than in the controls and this difference was statistically significant. Adiponectin levels did not correlate with GH and IGF-1 levels.

Among the patients, the mean VAI value was 1.8 ± 1.4. VAI directly correlated with LVM ($R = 0.55$, $p = 0.034$). No correlation was found regarding adiponectin. There was no correlation between IGF-1 and insulin. The adiponectin levels were also similar in groups A and B.

Table 1. Clinical and demographic properties between groups*

	Active (n = 19)	**Inactive (n = 11)**	**Control (n = 30)**	**p-value**
Mean age	54.11 ± 9.99	50.80 ± 4.15	48.53 ± 9.18	ns.
BMI (kg/m²)	27.66 ± 2.00[a]	31.76 ± 6.44[b]	25.06 ± 2.78 [a]	0.001
SBP (mm Hg)	123.33 ± 15.81[ab]	130.00 ± 20.00[a]	115.67 ± 10.06[b]	0.001
DBP (mm Hg)	83.88 ± 9.93	76.00 ± 15.16	75.67 ± 7.28	ns.
FPG (mg/dL)	106.33 ± 11.41[a]	123.00 ± 39.54[b]	89.20 ± 6.26[c]	0.001
Insulin (μIU/mL)	5.02 ± 2.24[a]	9.12 ± 4.29[b]	6.51 ± 2.45[a]	0.05
HOMA-IR	1.27 ± 0.59[a]	2.65 ± 1.22[b]	1.40 ± 0.53[a]	0.01
GH (ng/mL)	17.79 ± 17.70[a]	6.90 ± 2.52[b]	0.68 ± 1.29[b]	0.001
IGF-1 (ng/mL)	634.33 ± 504.00[a]	569.60 ± 335.41[a]	124.54 ± 44.86[b]	0.001
Adiponectin (μg/mL)	100.59 ± 100.59[a]	39.23 ± 39.18[ab]	28.84 ± 58.72[b]	0.001

* The differences between the means of groups carrying different letters in the same column are statistically significant.
BMI – body mass index; SBP – systolic blood pressure; DBP – diastolic blood pressure; FPG – fasting plasma glucose; HOMA-IR – homeostasis model assessment; GH – growth hormone; IGF-1 – insulin like growth factor-1.

Table 2. Echocardiographic findings obtained between groups*

	Active (n = 19)	Inactive (n = 11)	Control (n = 30)	p-value
IVST (mm)	10.11 ± 1.61[a]	11.00 ± 1.22[a]	6.93 ± 2.93[b]	0.001
PWT (mm)	9.77 ± 1.98[a]	10.80 ± 1.48[a]	6.93 ± 3.03[b]	0.001
LVM (g)	219.70 ± 46.78[a]	257.40 ± 109.08[a]	128.46 ± 37.13[b]	0.001
LVMI (g/m²)	118.58 ± 20.82[a]	145.00 ± 35.99[b]	76.65 ± 15.08[c]	0.001
E-velocity (mm/s)	0.80 ± 0.15[a]	0.60 ± 0.15[b]	0.77 ± 0.14[a]	0.05
A-velocity (mm/s)	0.83 ± 0.17[a]	0.67 ± 0.07[b]	0.67 ± 0.13[b]	0.05
E/A ratio	0.98 ± 0.29	0.92 ± 0.29	1.19 ± 0.36	ns.
DT	214.66 ± 58.45	210.00 ± 38.25	191.06 ± 32.9	ns.
ET	307.33 ± 37.07[a]	311.20 ± 35.84[a]	276.93 ± 26.72[b]	0.001
IVRT	112.88 ± 14.47[a]	110.60 ± 14.17[a]	97.00 ± 11.73[b]	0.001
VPR	56.55 ± 17.32[a]	56.00 ± 14.12[a]	45.06 ± 8.87[b]	0.01
MPI	0.77 ± 0.19	0.65 ± 0.38	0.66 ± 0.14	ns.
LVEDV	74.77 ± 32.88[a]	112.40 ± 40.25[b]	102.46 ± 23.86[b]	0.05
LVESV	34.44 ± 7.69[a]	46.00 ± 16.43[b]	31.90 ± 11.06[a]	0.05
EF (%)	64.55 ± 8.15	63.80 ± 8.19	64.06 ± 5.63	ns.

* The differences between the means of groups carrying different letters in the same column are statistically significant. ns. – non-significant. IVST – thickness of interventricular septum in diastole; PWT – thickness of left ventricular posterior wall in diastole; LVM – left ventricular mass; LVMI – left ventricular mass index; E – early transmitral maximal flow velocities; ET – ejection time; A – atrial transmitral maximal flow velocity; IVRT – isovolumetric relaxation time; DT – deceleration time of E-wave; VPR – velocity of mitral flow propagation; MPI – myocardial performance index; LVEDV – left ventricle end-diastolic volume; LVESV – left ventricle end-systolic volume; EF – left ventricular ejection fraction.

Table 3. Adiponectin levels in the acromegalic group in relation to LVM, LVMI, ET, MPI, LVEDV and LVESV

	LVM	LVMI	ET	MPI	LVEDV	LVESV
Adiponectin (μg/mL)	0.306	0.404	–0.202	0.189	0.084	0.011
	0.107	0.030*	0.285	0.316	0.659	0.399

* p-value < 0.05; statistically significant. IVST – thickness of interventricular septum in diastole; PWT – thickness of left ventricular posterior wall in diastole; LVM – left ventricular mass; LVMI – left ventricular mass index; E – early transmitral maximal flow velocities; A – atrial transmitral maximal flow velocity; IVRT – isovolumetric relaxation time; DT – deceleration time of E-wave; VPR – velocity of mitral flow propagation; MPI – myocardial performance index; LVEDV – left ventricle end-diastolic volume; LVESV – left ventricle end-diastolic volume; EF – left ventricular ejection fraction.

The echocardiographic findings between groups are shown in Table 2. IVST, PWT, LVM, left ventricular mass index (LVMI), early transmitral maximal flow velocity/atrial transmitral maximal flow velocity (E/A) ratio, deceleration time of E-wave (DT), ejection time (ET), isovolumetric relaxation time (IVRT), velocity of mitral flow propagation (VPR), and LVESV values were significantly greater in acromegalic patients (Table 2). In the acromegalic group, adiponectin levels were positively related (p = 0.03) (Table 3).

Discussion

The most common feature of acromegalic cardiomyopathy is concentric biventricular hypertrophy [25, 26]. Cardiac valve disease is also underestimated: Lie and Grossman [27] found mitral and aortic abnormalities in 19% of their autopsy series. Colao et al. demonstrated a high prevalence of both mitral and aortic valve dysfunction in patients with active acromegaly [28]. Cardiac valve abnormalities were associated with left ventricular hypertrophy [28, 29]. Increased stroke volume and cardiac output and decreased end-systolic stress

and systemic vascular resistance were observed in some studies [30, 31]. In our study, IVST, PWT, LVM, LVMI, DT, ET, IVRT, VPR, and LVESV values were significantly greater in acromegalic patients showing biventricular hypertrophy and impairment of diastolic and systolic function.

Several recent findings have suggested that adiponectin is able to influence cardiac remodeling in pathologic states. Under normal circumstances, adiponectin would restrain the resulting hypertrophy. In a large group of Japanese men, adiponectin was inversely and independently associated with electrocardiographic evidence of LVH [32]. An inverse relationship between plasma adiponectin and LVM index was described in patients with type 2 diabetes [33] and essential hypertension [13]. Hypoadiponectinemia or functional adiponectin resistance perhaps secondary to downregulation of adiponectin receptors [34] may contribute to an exaggerated hypertrophic response to hemodynamic load and to inappropriate LVH [35]. In our study, adiponectin levels in the acromegalic group were found to correlate positively with LVMI ($p = 0.03$). Although we expected to find an inverse correlation between adiponectin levels and LVMI, in our study the positive correlation between adiponectin levels and LVMI may have been due to somatostatin analog treatment.

Data regarding adiponectin levels in active acromegaly available in the literature is variable as lower than [22], higher than [18] or similar to [19, 20] those in normal controls. The effect of GH-reducing therapy on serum adiponectin levels has also been studied [21, 22]. Olarescu et al. measured adipokines in 37 patients with active acromegaly before and after treatment. At baseline, they found that total body lean mass was correlated negatively with high-molecular weight adiponectin (HMWAD), adiponectin and leptin. No significant changes were observed in the fasting glucose, adiponectin and leptin levels following treatment. In the transsphenoidal surgery (TS) group, adiponectin, vascular endothelial growth factor-A (VEGF-1), monocyte chemotactic protein 1 (MCP1), and thioredoxin (TRX) decreased significantly. In the somatostatin analogs (SA), group leptin increased, while in the pegvisomant (PGV) group HMWAD increased significantly [21]. Silha et al. found increased, rather than decreased, adiponectin levels in a study involving 18 patients with acromegaly compared to BMI- and sex-matched controls. In that study, insulin resistance and fasting serum glucose were not significantly different between the acromegalic patients and control subjects, with fasting insulin in the patients being only 24% higher than in the control group [18]. In accordance with that study, we found the increased adiponectin levels and also HOMA-IR values of patients and controls were similar. They stated that these results may be due to the small sample size, we confirmed their results with a larger sample size. On the other hand, Lam et al. stated that the patients in their study were significantly more insulin resistant and had lower adiponectin levels, which are reversible with GH-lowering therapies [22]. The discrepancies in serum insulin and adiponectin levels in acromegaly patients may be due to the therapy that patients were taking for the control of GH.

GH excess also causes alterations in body composition, leading to reduced fat mass and increased lean body mass, which are reversible with treatment for acromegaly. Treatment with octreotide (or Sandostatin) is accompanied by an increase in total body fat [36]. The serum adiponectin level has been shown to vary inversely with total body fat in large population-based studies [38]. BMI does not distinguish between fat mass and lean body mass. Not measuring and monitoring the body fat change by bioelectrical impedance analysis is a limitation of our study. To bypass this limitation, we calculated VAI. It is proposed that, based on simple anthropometric and metabolic parameters, VAI as a surrogate marker of adipose tissue function and distribution independently correlated with cardiometabolic risk in the general population. Further, acromegaly may reflect a condition of cardiometabolic risk, characterized by an altered production of adipocytokines, IR, and inadequate insulin secretion [19]. In our study, group A and group B patients had similar adiponectin levels. We also could not find any correlation between VAI and adiponectin levels. On the other hand, Ciresi et al. [24] found lower adiponectin levels in group B and a strongly significant inverse correlation between VAI and adiponectin. In our study, there was a positive correlation between VAI and LVM. This may be an important way for VAI to assess cardiac risk in acromegalics.

The authors have concluded that acromegaly is a systemic disorder that affects glucose tolerance, body composition, cardiac structure, and cardiac function. This study showed that adiponectin levels were also affected in acromegaly. Adiponectin levels were three-fold higher in active acromegalic patients than inactive acromegalic patients. Adiponectin levels may be useful for the evaluation of acromegaly as well as active and inactive acromegaly.

Adiponectin levels may be an indicator of the cardiac involvement of acromegaly. However, the usage of serum adiponectin levels in acromegalic cardiomyopathy as an indicator of cardiac involvement should be supported with other, wide, multicentered studies.

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Conflict of interest: None declared

Received: 1.07.2014
Revised: 14.12.2014
Accepted: 4.03.2015