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Original Article

Association of Epicardial Adipose Tissue Thickness with Cardiovascular Risk in Acromegaly

Akromegalide Epikardiyal Yağ Dokusu Kalınlığı ile Kardiyovasküler Risk Arasındaki İlişki

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ABSTRACT

Objective: Acromegaly is a rare disease associated with increased mortality. Reports on coronary artery disease in acromegaly are controversial. This study aimed to investigate the possible association of epicardial adipose tissue thickness with cardiovascular risk in patients with acromegaly.

Methods: The study included 38 patients followed up with the diagnosis of acromegaly and 29 healthy controls. Patients with acromegaly were divided into controlled and uncontrolled acromegaly groups based on insulin-like growth factor-1 levels. Epicardial adipose tissue thickness measurements were obtained from chest computed tomography, and laboratory data were extracted from patient files.

Results: Twenty-nine patients (76.3%) had controlled acromegaly. Eleven patients with acromegaly had diabetes mellitus (28.9%), 18 (47.4%) had hypertension, and 27 (71%) had a concomitant chronic disease. Epicardial adipose tissue thickness was significantly increased in the acromegaly group ($p<0.001$). No significant difference was observed between the controlled and uncontrolled acromegaly groups in terms of the epicardial adipose tissue thickness. Age was the only parameter that was significantly correlated with the epicardial adipose tissue thickness. When the Framingham risk score was calculated, the 10-year cardiovascular risk of patients with acromegaly was 5.63%.

Conclusions: The epicardial adipose tissue thickness is increased in acromegaly. However, this increase may not have clinical relevance in terms of cardiovascular risk.

Keywords: Acromegaly, cardiovascular risk, epicardial adipose tissue

ÖZ

Amaç: Akromegali, mortalitede artış ile seyreden nadir bir hastalıktır. Akromegalide koroner arter hastalığı görülmesi ile ilgili birbiriyle tezat yayınlar mevcuttur. Bu çalışmada, akromegali hastalarında epikardiyal yağ dokusu kalınlığı ile kardiyovasküler risk arasındaki olası ilişkiyi araştırdık.

Yöntemler: Çalışmaya akromegali tanısı ile takip edilen 38 hasta ve 29 sağlıklı kontrol olgu grubu dahil edildi. Akromegali hastaları, insülin benzeri büyüme faktörü-1 seviyelerine göre kontrollü ve kontrolsüz akromegali olmak üzere iki gruba ayrıldı. Epikardiyal yağ dokusu kalınlığı ölçümleri bilgisayarlı toraks tomografisinden yararlanılarak yapıldı, laboratuvar verilerine hasta dosyalarından ulaşıldı.

Bulgular: Yirmi dokuz hasta (%76,3) kontrollü akromegali idi. Akromegali hastalarının 11'inde diabetes mellitus (%28,9) ve 18'inde (%47,4) hipertansiyon mevcuttu. Eşlik eden kronik hastalığı olan 27 (%71) hasta vardı. Akromegali grubunda epikardiyal yağ dokusu kalınlığı anlamlı olarak artmıştı ($p<0,001$). Kontrollü ve kontrolsüz akromegali grupları arasında epikardiyal yağ dokusu kalınlığı açısından anlamlı fark gözlenmedi. Yaş, epikardiyal yağ dokusu kalınlığı ile anlamlı korelasyon gösteren tek parametreydi. Framingham risk skoru hesaplandığında akromegali hastalarının 10 yıllık kardiyovasküler riski %5,63 olarak bulundu.

Sonuçlar: Akromegalide epikardiyal yağ dokusu kalınlığı artmaktadır. Ancak bu artışın kardiyovasküler risk açısından klinik bir önemi olmayabilir.

Anahtar kelimeler: Akromegali, kardiyovasküler risk, epikardiyal yağ dokusu

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INTRODUCTION

Acromegaly, which results from excessive production of growth hormone (GH), has an incidence of 2-11 cases/million people/year[1]. It is associated with an increased risk of cardiovascular disease (CVD), possibly through concomitant CV risk factors[2,3]. In addition, excessive GH and insulin-like growth factor-1 (IGF-1) leads to endothelial dysfunction[4]. CV pathologies in acromegaly include hypertension, left ventricular hypertrophy, and cardiomyopathy[5,6]. However, reports on the incidence of coronary artery disease (CAD) in acromegaly are limited and controversial[7,8]. The epicardial adipose tissue (EAT) releases adipokines that play a role in the pathogenesis of atherosclerosis; thus, the EAT thickness (EATT) may be a potential marker of CVD[9].

In this study, we aimed to investigate the association between EATT and CAD risk in patients with acromegaly.

MATERIALS and METHODS

This retrospective study included 38 patients diagnosed with acromegaly in the endocrinology outpatient clinic and 29 control patients of the same age and gender without CVD. The study was conducted in accordance with the Declaration of Helsinki and with the approval of Istanbul Medeniyet University Goztepe Training and Research Hospital Clinical Research Ethics Committee (decision no: 2017/0150, date: 06.06.2017).

The patients with acromegaly who had undergone chest computed tomography (CT) for any reason (e.g., pneumonia and suspected malignancy) were recruited for this retrospective study. EATT measurements were obtained from chest CT images. Laboratory data were extracted from patient files. Patients with acromegaly were divided into the controlled and uncontrolled groups. They were defined as having a "controlled" status if the IGF-1 values were within the reference interval for age and gender and "uncontrolled" if the IGF-1 levels were above the upper limit of normal. Body mass index (BMI) was calculated as weight (kg) divided by height in meters squared (m^2). Total cholesterol and triglycerides were measured by the enzymatic color test. Low-density lipoprotein and high-density lipoprotein cholesterol were studied with enzymatic color + immuno-inhibition test and glucose enzymatic UV test (HK G6P-DH). Serum thyroid-stimulating hormone (TSH) was examined in Beckmann-Coulter DXI-800 (CA, USA) immunoassay device by chemiluminescence immunoassay (CLIA) method. GH and IGF-1 were measured using a two-site chemiluminescent immunometric assay (Immulite 2000, Siemens Healthineers, Erlangen, Germany).

The 10-year risk prediction of CVD was calculated by the Framingham risk score (FRS). The 10-year CVD risk was defined as follows: low, FRS<10%; moderate, FRS=10-19%; and high, FRS≥20%[10].

Chest CT

The patients were evaluated with a multidetector (64 detectors) CT device (Discovery, GE Healthcare, Milwaukee, WI, USA) without contrast agent injection. A dose-reducing technique was applied during the scanning, and the applied dose values were changed according to the weight of the patient (range 45-60 mA and 90-120 kV). The slice thickness was 1.25 mm with a 0.75 reconstruction interval. The pitch factor was 0.67-1.72, the rotation time was 0.5-0.75 s, and the collimation was 64×0.625 mm.

EATT Measurements

One radiologist trained in cardiac imaging measured the EATT without knowledge of the patient's clinical information. EATT measurements were performed on multiplanar reconstructed images of axial chest CT at mediastinal window settings. EATT was measured at three points adjacent to the left ventricle (upper, anterosuperior wall; mid, lateral free wall; lower, postero-inferior wall) on short-axis view and midventricular segment adjacent to the right ventricle at the four-chamber view. EATT was measured between the myocardium and pericardium.

Statistical Analysis

Statistical analyses were performed using IBM SPSS Statistics for Windows, version 24.0 (IBM Corp., Armonk, NY, USA). Categorical variables were defined by frequency and percentage rate, and numerical variables were defined by mean ± standard deviation. The Shapiro-Wilk test was used to test conformity to normal distribution. Homogeneity of variances was examined by Levene's test. In dual independent group comparisons, Student's t-test was used for normally distributed numeric variables. Categorical variables were compared using the chi-square test. The correlations of EATT with laboratory and clinical parameters were evaluated by Pearson correlation analysis. The significance level was set at $p<0.05$.

RESULTS

A total of 38 patients with acromegaly (57.9% females, n=22) with a mean age of 49.9±11.2 years were included in the study (Table 1). The control group consisted of 29 participants with a mean age of 53.5±13.2 years.

Thirty-three patients (86.8%) had a history of surgery. Twenty-five patients (65.8%) received medical treatment: Specifically, 21 patients received somatostatin analog (SSA) only, 1 patient received dopamine agonist (DA) only, and 3 patients received both SSA and DA. Two patients had a history of radiotherapy, and 29 (76.3%) patients had controlled acromegaly.

Eleven patients with acromegaly had diabetes mellitus (28.9%), and 18 (47.4%) had hypertension. In total, there were 27 (71%) patients with a concomitant chronic disease including chronic obstructive pulmonary disease, obstructive sleep apnea syndrome, diabetes mellitus, and hypertension. The smoking rate was 18.4%. The mean 10-year CV risk of patients with acromegaly was 5.63% according to the FRS.

EATT was significantly increased in the acromegaly group compared with the control group (p<0.001). EATT measurements of the patient and control groups are presented in Table 2. Table 3 shows the comparison of controlled and uncontrolled groups. No significant difference was found between two groups in terms of EATT and laboratory findings. The TSH and cortisol levels of the controlled group were lower than those in the uncontrolled group (p=0.022, p=0.006, respectively). Results of the correlation analyses between EATT and other parameters are presented in Table 4. Age was found to be the only parameter significantly correlated with EATT (p=0.015 for the short-axis view-superior, p=0.007 for the short-axis view-mid, and p=0.01 for the four-chamber view midventricular measurements).

DISCUSSION

In this study, we found that patients with acromegaly had increased EATT compared with the healthy controls. However, no significant difference was noted between

Table 1. Demographic and laboratory characteristics of patients with acromegaly.

	Mean ± SD	Minimum	Maximum
Age (years)	49.89±11.18	19	70
Weight (kg)	80.63±14.25	56	110
BMI (kg/m^2)	29.26±3.60	22.6	36.3
Systolic BP (mmHg)	127.6±18.14	90	180
Diastolic BP (mmHg)	79.9±12.51	40	101
IGF-1 (ng/mL)	172.08±84.25	47	525
GH (ng/mL)	1.87±3.68	0.05	22.30
Cystatin-C (mg/L)	0.68±0.28	0.17	1.47
HDL-C (mg/dL)	46.61±11.31	32	81
LDL-C (mg/dL)	128.53±34.72	73	208
Triglyceride (mg/dL)	152.11±78.31	61	359
Glucose (mg/dL)	109.55±37.84	79	272
HbA1c (%)	6.08±1.21	4.5	11.2
Creatinine (mg/dL)	0.81±0.17	0.51	1.48
TSH (mIU/L)	0.998±0.71	0.25	2.42
fT4 (ng/dL)	1.066±0.22	0.66	1.88
Anti-TPO (IU/mL)	23.42±99.25	0.50	567.5
Anti-thyroglobulin (IU/mL)	33.46±158.57	0.55	842.00
ALT (U/L)	19.24±9.97	7	59
GGT (U/L)	29.12±36.142	8	183
Prolactin (ng/mL)	9.56±6.06	0.60	24.60
Cortisol (µg/dL)	10.41±2.26	8.00	16.00
Framingham risk score (%)	5.63±5.17	1	20
Time from symptom onset to diagnosis (years)	3.76±3.18	0.5	10

Anti-TPO: Anti-thyroid peroxidase, ALT: Alanine aminotransferase, BMI: Body mass index, BP: Blood pressure, IGF-1: Insulin-like growth factor-1, GGT: Gamma glutamyl transferase, GH: Growth hormone, HDL-C: High-density lipoprotein cholesterol, LDL-C: Low-density lipoprotein cholesterol, SD: Standard deviation, TSH: Thyroid-stimulating hormone

the controlled and uncontrolled groups in terms of EATT. EATT was associated with older age, but not with BMI, lipid profiles, glucose, HbA1c, FRS, or cystatin-C.

The EAT is an accumulation of visceral fat that is located between the myocardium and the visceral layer of the pericardium[11,12]. The EAT can be quantified by noninvasive methods such as echocardiography or CT[11,13]. Our finding about that EATT was increased in patients with acromegaly compared with healthy controls was in line with the literature[14]. Reyes-Vidal et al.[15] reported that the waist circumference and bodyweight of the patients increased when acromegaly was successfully treated. They attributed this change to increased ghrelin levels after acromegaly treatment, which has orexigenic effects. As controlled acromegaly constituted 76% of our study

Table 2. Epicardial adipose tissue thickness measurements of the patient and control groups.

	Patient group (n=38) mean ± SD	Control group (n=29) mean ± SD	p
SAV superior (mm)	5.842±1.519	4.241±1.481	<0.001*
SAV mid (mm)	6.161±1.579	4.017±1.508	<0.001*
SAV inferior (mm)	7.089±1.484	4.934±1.782	<0.001*
CHV mid ven (mm)	6.405±1.475	3.903±1.173	<0.001*

CHV: Four-chamber view midventricular segment alignment, SAV superior: Short-axis view, fat thickness measured at the anterosuperior wall level, SAV mid: Short-axis view, fat thickness measured from the level of the lateral free wall, SAV inferior: Short-axis view, fat thickness measured at the postero-inferior wall level, SD: Standard deviation, *Significance

Table 3. Comparison of patients with controlled and uncontrolled acromegaly.

	Controlled acromegaly (n=29) Mean ± SD	Uncontrolled acromegaly (n=9) Mean ± SD	p
Age (years)	50.28±12.17	48.67±7.57	0.711
SAV superior (mm)	5.793±1.5292	6.000±1.566	0.726
SAV mid (mm)	6.031±1.4663	6.578±1.934	0.371
SAV inferior (mm)	6.931±1.4338	7.600±1.613	0.243
CHV mid ven (mm)	6.314±1.5054	6.700±1.414	0.500
BMI (kg/m^2)	28.88±3.85	30.49±2.43	0.246
IGF-1 (ng/mL)	140.21±43.19	274.78±103.68	0.004*
GH (ng/mL)	1.2659±1.50	3.8067±7.00	0.311
HDL-C (mg/dL)	45.21±9.009	51.11±16.67	0.334
LDL-C (mg/dL)	126.62±30.720	134.67±47.104	0.640
Triglyceride (mg/dL)	153.66±82.366	147.11±67.68	0.830
Glucose (mg/dL)	107.97±39.846	114.67±32.059	0.649
HbA1c (%)	5.945±1.2947	6.544±0.798	0.199
Creatinine (mg/dL)	0.82±0.17	0.76±0.14	0.373
Cystatin-C (mg/L)	0.7197±0.275	0.5567±0.291	0.135
TSH (mIU/L)	0.964±0.687	1.101±0.805	0.022*
Cortisol (ug/dL)	9.59±1.489	12.90±2.572	0.006*
Prolactin (ng/mL)	9.48±5.905	9.78±6.878	0.899
FRS (%)	6.03±5.388	4.33±4.44	0.500

CHV: Four-chamber view midventricular segment alignment, BMI: Body mass index, FRS: Framingham risk score, IGF-1: Insulin-like growth factor-1, GH: Growth hormone, HDL-C: High-density lipoprotein cholesterol, LDL-C: Low-density lipoprotein cholesterol, SAV superior: Short-axis view, fat thickness measured at the anterosuperior wall level, SAV mid: Short-axis view, fat thickness measured from the level of the lateral free wall, SAV inferior: Short-axis view, fat thickness measured at the postero-inferior wall level, SD: Standard deviation, TSH: Thyroid-stimulating hormone, *Significance

Table 4. Correlation analyses between the epicardial adipose tissue thickness and cardiovascular parameters.					
		SAV superior	**SAV mid**	**SAV inferior**	**CHV midventricular**
Age (years)	r	0.39	0.428	0.259	0.421
	p	0.015*	0.007*	0.116	0.010*
BMI (kg/m^2)	r	0.211	0.170	0.171	0.232
	p	0.204	0.308	0.304	0.167
Cystatin-C (mg/L)	r	0.122	0.153	0.031	0.162
	p	0.467	0.358	0.852	0.338
HDL-C (mg/dL)	r	-0.002	-0.070	0.171	0.006
	p	0.992	0.677	0.305	0.974
Triglyceride (mg/dL)	r	-0.004	-0.040	-0.041	0.004
	p	0.982	0.813	0.805	0.979
Glucose (mg/dL)	r	0.043	0.045	-0.147	0.111
	p	0.797	0.789	0.378	0.512
HbA1c (%)	r	0.135	0.170	-0.034	0.260
	p	0.420	0.308	0.841	0.120
TSH (mIU/L)	r	0.320	0.049	0.085	0.086
	p	0.053	0.772	0.618	0.617
FRS (%)	r	0.049	0.237	0.051	0.208
	p	0.768	0.152	0.762	0.217

CHV: Four-chamber view midventricular segment alignment, BMI: Body mass index, FRS: Framingham risk score, HDL-C: High-density lipoprotein cholesterol, SAV superior: Short-axis view, fat thickness measured at the anterosuperior wall level, SAV mid: Short-axis view, fat thickness measured from the level of the lateral free wall, SAV inferior: Short-axis view, fat thickness measured at postero-inferior wall level, TSH: Thyroid-stimulating hormone, *Significance

participants, our findings are possibly caused by the increased EATT along with the increased bodyweight.

In this study, EATT correlated with the age of patients with acromegaly. However, no association was observed between EATT and hypertension, HbA1c, lipid parameters, or BMI. The ratio of the adipose tissue increases with increasing age due to decreased basal metabolic rate and physical activity levels[16]. Pascot et al.[17] reported that age-associated increase in visceral adipose tissue causes deterioration in CV health in premenopausal women.

Acromegaly is associated with CVD and reduced life expectancy, particularly if it is uncontrolled[2,3]. Despite the presence of CV risk factors, successful disease control improves survival[18]. Excessive GH and IGF-1 production impairs the vascular system[7,19,20] subsequently leading to CV events[4]. Despite the well-known CV risk factors associated with acromegaly, no clear evidence links acromegaly with CAD[7,8]. Patients with acromegaly were reported to have increased coronary calcifications[21]. However, several studies have reported lower risk rates for CAD in acromegaly[7,8]. Contradictory findings also exist in terms of carotid intima-media thickness (CIMT). Several studies have associated acromegaly with increased CIMT[22,23], whereas others reported decreased or unchanged CIMT[8,24].

Numerous publications have confirmed that adipose tissue is not only an inert energy storage pool but also has metabolic functions. Visceral adipose tissue secretes adipokines that may cause chronic subclinical inflammation and thus lead to CVD[9]. Since the EAT is in direct contact with the coronary vascular system and the myocardium, it has paracrine effects as well[25]. Adipokines secreted from the EAT may increase the risk of CAD by causing systemic inflammation[9]. Therefore, we hypothesized that increased EATT may be associated with increased CV risk. However, the results of our study showed that the EATT did not have clinical relevance in terms of CV risk. Similar to the results of Dos Santos Silva et al.[26] who reported low FRS in patients with acromegaly, we found that, although the mean BMI was high, the 10-year CV risk of patients with acromegaly was low with an FRS of 5.6%. No significant difference was noted between the controlled and uncontrolled groups with regard to FRS. The low CV risk of patients may be due to the effective follow-up and treatment of diabetes in our clinic. The potential anti-inflammatory effect of IGF-1 might also explain the lower CV risk in patients with

acromegaly[19,27]. However, this hypothesis requires more comprehensive studies with a larger number of patients because this hypothesis contradicts the increased CV risk in patients with uncontrolled acromegaly. Another possible explanation is that SSAs may have had a beneficial effect on the CV system[28-30], as 65.8% of the patients in our study were receiving medical treatment. All these cardioprotective factors may have counteracted the paracrine and systemic effects of the EAT on the CV system. In accordance with our results, Ozkan et al.[14] revealed that although the CIMT and EATT were significantly increased, the inflammatory markers were low in patients with acromegaly. They suggested that in acromegaly, inflammation might not be responsible for atherosclerosis and that the pathophysiology of CAD may differ from the population in general[19].

Aulinas et al.[31] studied 35 patients with acromegaly and showed that cystatin-C can be used in patients with high CV risk but without coronary symptoms. However, cystatin-C levels were not associated with EATT in the present study, which may be due to small sample size.

The TSH and cortisol levels of patients with controlled acromegaly were significantly lower than in those with uncontrolled acromegaly. Surgery or radiation therapy to the pituitary gland may have reduced TSH and cortisol levels in patients with controlled acromegaly.

This study has several limitations. First, the number of patients was relatively small. Second, EATT measurements were obtained from chest CT images with a multiplanar reconstructed image rather than with electrocardiography (ECG)-gated cardiac CT. Images that were acquired randomly in any phase of the cardiac cycle rather than in the diastolic phase on ECG-gated CT might have led to slight inaccuracies. However, although the ECG-gated CT is an accurate technique in EATT assessment, increased radiation exposure is a major disadvantage in clinical practice. Third, given the retrospective design of the study, CV outcomes could not be investigated. A prospective study with a long follow-up period could reveal an association of EATT with CV risk.

CONCLUSIONS

The EATT is increased in acromegaly. However, the increased EATT in patients with acromegaly may not have clinical relevance in terms of CV risk. Similar to the general population, clinicians caring for patients with acromegaly should aim for lifestyle changes, achieving ideal weight, cessation of smoking, and effective treatment of diabetes and dyslipidemia for CV risk reduction.

Ethics

Ethics Committee Approval: The study was conducted in accordance with the Declaration of Helsinki and with the approval of Istanbul Medeniyet University Goztepe Training and Research Hospital Clinical Research Ethics Committee (decision no: 2017/0150, date: 06.06.2017).

Informed Consent: Retrospective study.

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Author Contributions

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