Cukurova Medical Journal
ÇUKUROVA ÜNİVERSİTESİ TIP FAKÜLTESİ

Cukurova Med J 2019;44(Suppl 1):100-107
DOI: 10.17826/cumj.553729

ARAŞTIRMA / RESEARCH

Aortic intima media thickness increases and is independently related to insulin-like growth factor-1 level in patients with acromegaly

Akromegalisi olan hastalarda aortik intima media kalınlığı artmıştır ve insulin benzeri büyüme faktörü-1 ile bağımsız olarak ilişkilidir

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Cukurova Medical Journal 2019;44(Suppl 1):100-107.

Abstract

Purpose: In our article, we aimed to identify whether there is an increase in intima-media thickness (IMT) measured from the abdominal aorta in patients with acromegaly and to identify the parameters closely related to the aortic IMT (AIMT).

Materials and Methods: 52 patients with acromegaly and 46 healthy controls were included. For all participants, all the necessary laboratory tests were done for acromegaly. On vascular ultrasound examination, the internal carotid IMT, common-carotid IMT, and aortic IMT (AIMT) were measured. The study population was divided into 3 different groups; control group (Group I), acromegaly patients in remission (Group II) and acromegaly patients with active disease (group-III).

Results: The incidence of hypertension, diabetes, and smoking was higher in Group-II-III than Group I. Insulin-like growth factor-1 (IGF-1) levels were increased from Group I to III and there was a significant difference between all groups. Common-carotid IMT and internal carotid IMT values were not significantly different between the groups. The AIMT value in Group III patients was statistically higher than the other two groups. The AIMT was similar between Groups I to II. Only the IGF-1 level was found to be independently associated with AIMT.

Conclusion: In patients with active acromegaly disease, AIMT is significantly elevated without elevation of carotid IMT, and AIMT is independently associated with serum IGF-1 levels. AIMT could be a useful study to show the presence of early subclinical atherosclerosis in acromegaly patients.

Keywords: Acromegaly, ultrasonography, aortic intima-media thickness, carotid intima-media thickness.

Öz

Amaç: Çalışmamızda akromegali hastalarında abdominal aorttan ölçülen intima-media kalınlığında (IMK) bir artış olup olmadığını ve aort IMK(AIMK) ile yakından ilişkili parametreleri tanımlamayı amaçladık.

Gereç ve Yöntem: Çalışmaya 52 akromegali hastası ve 46 sağlıklı kontrol dahil edildi. Tüm katılımcılara akromegali için gerekli tüm laboratuvar testleri yapıldı. Vasküler ultrason incelemesinde internal karotid IMK, kommon karotid IMK ve AIMK ölçüldü. Çalışmaya dahil edilenler 3 gruba ayrıldı; kontrol grubu (Grup I), remisyondaki akromegali hastaları (Grup II) ve aktif hastalığı olan akromegali hastaları(Grup-III).

Bulgular: Grup II-III'te hipertansiyon, diyabet ve sigara içme sıklığı Grup I'den daha yüksek saptandı. İnsülin benzeri büyüme faktörü-1 (IBBF-1) düzeyleri Grup I'den III'e doğru yükseliyordu ve tüm gruplar arasında anlamlı fark vardı. Gruplar arasında kommon-karotid IMK ve internal karotid IMK değerleri arasında anlamlı bir farklılık saptanmadı. Grup III hastalarında AIMK değerleri diğer gruplara göre istatistiksel olarak daha yüksek saptandı. AIMK grup I ve grup II hastalarında benzerdi. IBBF-1 düzeyi sadece AIMK ile bağımsız olarak ilişkili saptandı.

Sonuç: Aktif akromegali hastalığı olanlarda karotid IMK artışı olmadan aortik IMK'da belirgin bir artış olmaktadır ve bu artış serum IBBF-1 düzeyleri ile bağımsız olarak ilişkilidir. AIMK, akromegali hastalarında erken subklinik ateroskleroz varlığını göstermek için yararlı bir çalışma olabilir.

Anahtar kelimeler: Akromegali, ultrasonografi, aortik intima-media kalınlığı, karotid intima-media kalınlığı.

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Geliş tarihi/Received: 15.04.2019 Kabul tarihi/Accepted: 21.06.2019 Çevrimiçi yayın/Published online: 24.09.2019

INTRODUCTION

Acromegaly is a chronic disease associated with growth hormone (GH)-secreting pituitary adenoma, characterized by insulin-like growth factor-1 (IGF-1) increase and excess protein synthesis and excessive tissue growth due to these hormones[1]. Chronically elevated levels of IGF-1 in patients with acromegaly cause structural and functional changes that are specific for the disease[1]. This disease may cause mortality if left untreated, and cardiovascular diseases are the most common cause of mortality in this disease[1]. Hypertension (HT), diabetes mellitus (DM), smoking coronary artery disease (CAD) due to similar risk factors, myocardial infarction and presence of stroke are independent determinants of intima-media thickness (IMT) measurement[2,3].

In patients with acromegaly, the frequency of HT, DM, and hyperlipidemia (HL) is increased that is closely associated with increased IMT[1,4-8]. Although some of these studies have shown an increased CIMT[9-13], such an increase could not be found in some of these studies [14,15]. To detect the development of early atherosclerosis, abdominal aortic IMT measurement can be used[16]. We couldn't find any study in the literature on abdominal AIMT evaluation of patients with acromegaly. For this reason, in patients with acromegaly, we also hypothesized that the increase in IMT due to high IGF-1 might increase A-IMT earlier and more prominently than CIMT. We aimed to investigate whether there is an increase in AIMT values measured from the abdominal aorta in addition to traditional CIMT in patients with acromegaly in our study and to identify parameters closely related to AIMT in the same patient group.

MATERIALS AND METHODS

Study population

In our study 52 patients with Acromegaly (mean-age: 40.2 ± 8.9 years, female / male: 21/31) and 46 healthy controls (mean-age: 41.4 ± 10.9 years, female / male: 21/25) were included. Current guideline information's are used to diagnose, treat and classify the patients with acromegaly (1). The study population was divided into 3 different groups; control group (Group I), patients with acromegaly in remission since 6 months or Group II (The patients treated surgery and/or medical treatment and who were in remission for acromegaly after these treatment), and acromegaly patients with active disease or group III (de novo patients or the patients who were treated with surgery and/or medical and who were not in remission for acromegaly with these treatments). Ten of the Group III patients were de novo diagnosed and 14 patients did not enter the remission with surgical and / or medical treatment. Presence of secondary HT, malignant HT, vascular plaques, aortic aneurysm, aortic dissection, acute or chronic heart failure, cerebrovascular disease, valvular heart disease, malignancy, pregnancy, active thyroid disorder, hepatic and kidney failure were also excluded from both groups. The study protocol was approved by the Local Ethics Committee and written informed consent form was given to each participant and their consent was obtained.

First of all, a detailed medical history was taken and complete physical examination of the entire study population was performed. Subjects age, gender, and presence of HT, DM, CAD-family history, HL, current smoking status, CAD and body mass index (BMI) were recorded. White blood cell concentrations, hematocrit, fasting plasma glucose, blood urea nitrogen (BUN), creatinine, total cholesterol, low density lipoprotein cholesterol, high density lipoprotein (HDL) cholesterol, triglyceride, thyroid stimulated hormones (TSH), GH and IGF-1 levels were measured (Abbott, Aeroset, USA and commercial kits).

B-mode ultrasonography evaluation for intima-media thickness

Aort and carotid arteries were examined with a high-resolution ultrasound system (Philips EPIQ 7) equipped with a 5-1 and 12-5 MHz high resolution linear and convex converter (Philips Health Care, Bothell, WA, USA) respectively. To visualize the IMT, all arteries were scanned longitudinally on the posterior or distal wall of the artery. Frozen images were used for all measurements. Two images of the best quality were selected for analysis on each study. The distance from the anterior margin of the first echogenic line to the anterior margin of the second echogenic line was defined as IMT. The first line represents the intima-lumen interface and the second line represents the top layer of adventitia that contains collagen. In the presence of two independent and blind observers, vascular IMT was measured using ultrasonic calipers. All IMT values

were calculated as averages of six measurements. The patients were examined in the supine position. Patients rotated their heads by 45° from where they were scanned for the examination of the carotid arteries. IMTs measured from 10-20 mm proximal before bifurcation (for the common carotid artery) were accepted as CCIMT and 10-20 mm distal segment of the right and left common carotid artery in the distal segment after bifurcation (for the IC artery) were accepted as ICIMT. AIMT was accepted as IMT measured from the posterior wall of the abdominal artery (Figure 1a-c). All USG examination time was approximately 30-40 minutes. Subjects were evaluated by a 1 well experienced radiology specialist for conventional, Doppler and SWE examinations. Specialist had more than 12 years of experience in USG studies and at least 500 SWE procedures in a year.

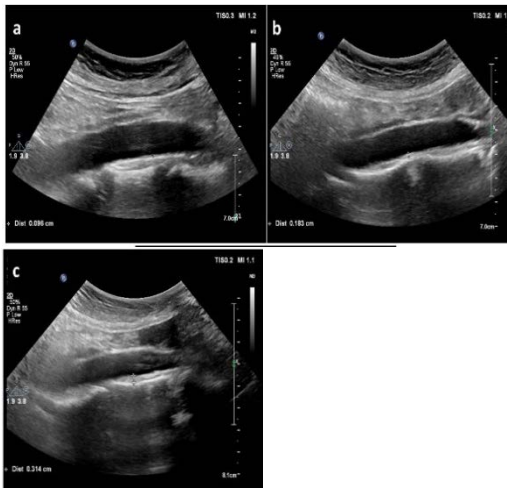

Figure 1. Abdominal AIMT measurement by B-mode ultrasound (a) normal abdominal AIMT measurement as 0.96 mm in control subjects; (b) increased abdominal AIMT measurement as 1.83 mm in patient with Acromegaly in remission; (c) significantly increased abdominal AIMT measurement as 3.14 mm in patient with active Acromegaly

Statistical analysis

All analyses were made by using SPSS 22, 0 (Chicago, IL, USA) statistical software. Continuous variables in group data were expressed as mean ± standard deviation. Categorical variables were expressed as numbers and percentiles. Student t test or One way ANOVA were used to compare continuous variables in groups. While Mann-Whitney U test or Kruskal-Wallis 1-way ANOVA test were used for not normally distributed samples. For normally distributed data, Scheffe and Games-Howell tests were used for multiple comparisons of groups with respect to homogeneity of variances. For non-normally distributed data, Bonferroni adjusted Mann Whitney U test was used for multiple comparisons of groups. The chi-square ($\chi 2$) test was used to compare categorical variables. Pearson correlation analysis was used for single variable correlation analysis. Linear regression analysis was used to determine markers found in the single variable analysis which were independent from parameters related to AIMT. ROC curve analysis was performed to reassess markers that independent for identifying patients to be an active disease for acromegaly. The value of the area under the curve was used as the accuracy criterion of the test.

RESULTS

The mean duration of disease was 66.84 ± 51.84 months in patients with active acromegaly and the mean duration of remission was 54.61 ± 47.53 months in patients with acromegaly in remission.

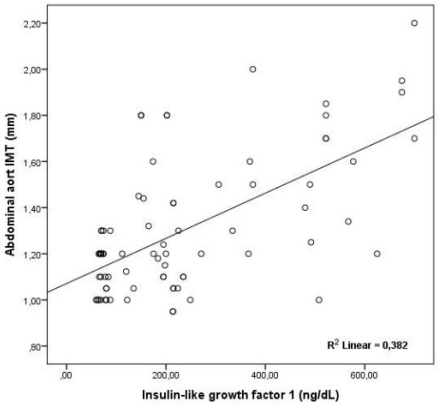

Figure 2. There is significant correlation between abdominal aortic intima-media thickness (IMT) and insulin-like growth factor 1 level.

Presence of HT, DM and smoking, systolic and diastolic blood pressure were found to be higher in Group II and III than Group I. Heart rate was significantly higher in Group III than Group I. Glucose, BUN and HDL cholesterol levels were highest in Group III and statistical significance was found only between Group III and Group I (Table 1).

Creatinine and TSH levels were significantly higher in both Acromegaly groups than controls. GH levels were the highest in Group III and statistical significance was found between Group III and the other two groups (Table 1).

Serum IGF-1 and triglyceride levels increased significantly from Group I to Group III. It was determined that serum IGF-1 and triglyceride levels were statistically different between all study groups (Table 1).

Table 1. All study parameters according to study groups

Variable	Group I n=46	Group II n=28	Group III n=24	p
Age (year)	40.1 ± 8.9	40.5 ± 12.4	42.1 ± 9.3	0.747
Gender (female)	13	10	11	0.582
Hypertension, n (%)	0 (0%)	4 (15%)	10 (39%)	**< 0.001**
Diabetes mellitus, n (%)	0 (0%)	6 (23%)	8 (31%)	**0.004**
Current smoker, n (%)	0 (0%)	6 (23%)	9 (%)	**0.002**
Hyperlipidemia, n (%)	0 (0%)	4 (15%)	4 (15%)	0.069
Coronary artery disease, n (%)	0 (0%)	4 (15%)	4 (15%)	0.069
Systolic blood pressure (mmHg)	111 ± 7.1 α, β	126 ± 13	132 ± 19	**<0.001**
Diastolic blood pressure (mmHg)	72 ± 6.2 α, β	80 ± 9.1	84 ± 15	**<0.001**
Basal heart rate (pulse/minute)	68 ± 3.6 α	73 ± 7.2	82 ± 11.3	**<0.001**
Body mass index (kg/m²)	28.1 ± 1.9	28.2 ± 2.1	28.8 ± 2.3	0.561
WBC (µL)	6.52 ± 1.55	5.94 ± 1.23	6.82 ± 1.94	0142
Hematocrit (%)	38.8 ± 2.6	38.5 ± 2.8	39.9 ± 4.3	0.288
Fasting plasma glucose (mg/dL)	93 ± 6.2 α	104 ± 25	110 ± 24	**0.011**
Blood urea nitrogen (mg/dL)	25.1 ± 5.0 α	28.4 ± 7.2	31.8 ± 8.9	**0.006**
Creatinine (mg/dL)	0.57 ± 0.08 α, β	0.66 ± 0.11	0.75 ± 0.21	**< 0.001**
Total Cholesterol (mg/dL)	198 ± 24	210 ± 39	216 ± 39	0.203
LDL cholesterol (mg/dL)	123 ± 32	131 ± 24	125 ± 14	0.136
HDL cholesterol (mg/dL)	51 ± 12 α	47 ± 11	43 ± 10	**0.002**
Triglyceride (mg/dL)	101 ± 26 α, β	148 ± 40 ¥	222 ± 53	**< 0.001**
TSH (uIU/mL)	1.96 ± 0.76 α, β	1.16 ± 0.84	1.04 ± 0.54	**<0.001**
IGF-1 (ng/dL)	72.1 ± 7.8 α, β	184 ± 37 ¥	454 ± 159	**<0.001**
Growth hormone (ng/mL)	1.02 ± 0.52 α	1.59 ± 1.78 ¥	10.3 ± 15.7	**0.001**
Common CIMT (mm)	0.63 ± 0.11	0.64 ± 0.15	0.70 ± 0.21	0.160
Internal CIMT (mm)	0.58 ± 0.12	0.59 ± 0.14	0.64 ± 0.16	0.167
AIMT (mm)	1.13 ± 0.11 α	1.21 ± 0.24 ¥	1.58 ± 0.32	**<0.001**

WBC: white blood cell; HDL: high density lipoprotein; LDL: low density lipoprotein; TSH: thyroid stimulated hormones; IGF-1: insulin-like growth factor 1; CIMT: carotid intima-media thickness; AIMT: aortic intima-media thickness.
Group I: control; Group II: acromegaly patients with remission; Group III: acromegaly patients with active disease; α = p value < 0.05 between the Group I and III; β = p value < 0.05 between the Group I and II; ¥ = p value < 0.05 between the Group II and III.

Table 2. The study parameters associated with AIMT

	Univariate analyze		Multivariate analyze	
	p	r	p	β
SBP (mmHg)	0.046	0.227	0.508	0.073
Heart rate (bpm)	< 0.001	0.398	0.157	0.165
Creatinine (mg/dL)	0.004	0.323	0.531	0.067
Triglyceride	0.001	0.355	0.388	0.101
TSH (uIU/mL)	0.039	−0.234	0.874	0.016
IGF-1 (ng/dL)	< 0.001	0.618	0.001	0.491
Growth hormone (ng/mL)	< 0.001	0.404	0.291	122

IGF-1: insulin-like growth factor 1; SBP: systolic blood pressure; TSH: thyroid stimulated hormones.

CCIMT and ICIMT values were similar among the groups. Abdominal AIMT levels were ~~the~~ highest in Group III and statistical significance was found between Group III and the other two groups (Table 1). There was a positive correlation between AIMT and systolic blood pressure, heart rate, creatinine, TSH, IGF-1, and GH levels. In these parameters, only level of IGF-1 was independent determinant of AIMT value in linear regression analysis (Table 2, Figure 2). The mean duration of disease in patients with active acromegaly and remission duration of patients with inactive acromegaly had no significant correlation with any IMT parameters.

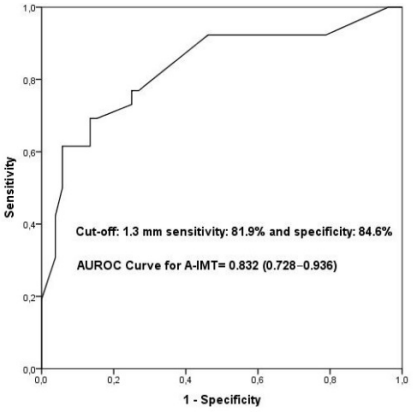

Figure 3. The ROC curve of values for common and internal carotid IMT and aortic IMT for determining patients with active acromegaly.

In the ROC analysis, the area under the curve was 0.584, 0.506, and 0.832 ICIMT, CCIMT and AIMT respectively (p=0.291, p=0.506 and p <0.001, respectively). When the AIMT cut-off values were taken as 1.3 mm, it determines the patients with active acromegaly with 81.9% sensitivity and 84.6 specificity (Figure 3). In group I, II and III, 3 (12%), 6 (23%) and 21 (81%) patients had AIMT value ≥ 1.3 mm respectively.

DISCUSSION

Our study was the first study to evaluate the relation between parameters about acromegaly and AIMT in the presence of cardiovascular disease in patients with acromegaly. The main consequence of this study is in patients with active acromegaly; IMT is significantly higher than ~~in~~ the control group and patients with acromegaly in remission. Another important finding is that the parameters most closely related to AIMT are serum IGF-1 levels. In our study, for the first time in the literature, we found that there was an independent, strong and positive relationship between AIMT and IGF-1 level.

Increased GH and IGF-1-altered metabolic and vascular functions in patients with acromegaly which lead to over-hyper filtration on the kidney and excessive Na absorption that causes HT, as well as decreased GH-bound insulin sensitivity and insulin resistance that causes increased DM frequency[1,4,17]. DM and HT frequency were reported to be 15-38% and 33-46%, respectively, in this disease[5-7,17]. Dyslipidemia is mostly associated with TG elevation[8]. As a result, increased HT, DM frequency, dyslipidemia, endothelial dysfunction and concomitant direct effects of IGF-1 are accelerating the progressive cardiovascular (CV) diseases and atherosclerotic process[18,19]. Close follow-up is recommended in the acromegaly guideline in terms of HT, DM, dyslipidemia, sleep apnea syndrome and CV disease development for this disease[1]. Although IMT measurement is not routinely recommended in the acromegaly guideline, the common target organ damage of CV risk factors such as ~~increased~~ HT, DM, and HL in patients with acromegaly is IMT. Furthermore, IMT increase in patients with acromegaly can be explained by vascular effects of increased IGF-1 and increased production of collagen[20]. Because collagen fibers are key ingredients in the construction of arteries[21].

When the presence of collagen in the vein wall is examined; there are thin collagen fibril bundles in the subendothelial intima layer, more in the tunica media layer among the smooth muscle cells and much in the adventitia layer[21]. The most frequent causes of death in patients with acromegaly ~~is~~ are CV events and CV mortality is doubled compared to the normal population[1-4]. Therefore, it is important to diagnose these patients with increasing IMT at the stage of subclinical or asymptomatic atherosclerosis. In our study, the IMT measured from the carotid and abdominal aorta is higher in patients with acromegaly compared to the control group but only AIMT was found to be statistically higher. There is no study in the literature comparing the IMT value in different regions except the carotid region in patients with acromegaly. The most important reason for this is that the AIMT assessment is more difficult than the CIMT and there is no routine AIMT measurement while following the patients with acromegaly. The most important problem about the AIMT assessment in

research studies is that AIMT measurement cannot be done clearly and there are not enough devices that provide adequate tissue penetration[22,23]. However, this measurement can be done clearly after 6 hours of fasting and in non-obese patients[2]. Atherosclerosis begins with fatty streaks in childhood, which can be detected early by sensitive vascular imaging techniques[16,24]. Autopsy studies have shown that the first atherosclerotic lesion begins from the dorsal surface of the distal abdominal aorta[24]. For this reason, in our study, patients with acromegaly examined for AIMT measurement in addition to both ICIMT and CCIMT measurements. With new USG devices and high-resolution probes, the abdominal aorta can be clearly visualized and AIMT can be easily measured.

We think that the result of the studies without CIMT increase may depend on these reasons: I) The number of patients included in the studies about acromegaly is between 30-50; II) Some of the patients were taken in remission; III) The duration of exposure to active disease and the duration of HT, DM, HL are very variable and cannot be fully specified, which may lead to late involvement, especially in the carotid region; IV) the frequency and the onset time of HT, DM, HL, depending on the increased IGF-1 may be different; V) early diagnosis of the disease in routine biochemical tests, early surgical or medical treatment may have prevented IMT involvement.

Abdominal AIMT is affected by systemic diseases earlier than other vascular regions. For this reason, we wanted to measure abdominal AIMT, the largest vascular IMT that can be measured and the earliest affected area of the IMT in our study. Because we anticipated that this initiative will be affected early in the disease process and will determine the development of subclinical atherosclerosis before. For this reason, AIMT may be a sign of earlier involvement in patients with acromegaly. We did not find any association between AIMT and patients with acromegaly in the literature. Our study showed that there was a significant AIMT increase in patients with acromegaly without significant CIMT increase. In addition, patients with acromegaly who were treated surgically or medically due to acromegaly and who were in remission were evaluated. And also, patients with active acromegaly disease were also evaluated. In our study, it was found that the significant AIMT increase was detected in patients with acromegaly who have active disease. However, patients with acromegaly who were in remission were found to have similar CIMT and AIMT according to the control group.

The aim of this study is to investigate the effect of abnormal course of acromegaly on IMT without CV risk factors. In some studies, in the control group who have similar risk factors like patients with acromegaly, no increased AIMT was detected[14]. Conversely, although the risk factors are similar, IMT value is still elevated compared to controls with equal CV risk factors like patients with acromegaly[9,10]. Because of these consequences, only healthy controls without CV risk factors were taken in our study so as not to be confused with the concept.

Biochemical parameters such as IGF-1[14], urotensin II[9] and procalcitonin[15] in patients with acromegaly have been shown to be associated with vascular involvement. Some of the studies about acromegaly reported that IGF-1 and GH levels did not correlate with CIMT[12]. However, in this study, the number of patients with active disease who were acromegaly was 14 and a similar number of controls were obtained. A recently study by Yaron M. et al[14] reported a positive and independent association between IGF-1 serum level and CIMT in a similar number of patients with acromegaly that close to our study. The increased IGF-1 level was thought to have a negative effect on the vessel wall by increasing vascular stiffness and impairing vascular vasodilatation[14]. In our study, it was also found that serum IGF-1 and AIMT increase were closely and independently related. Our work supported the study conducted by Yaron and et al. In addition, this close relationship between serum IGF-1 levels and AIMT supports the hypothesis that the previously mentioned, increase in vascular colloid causes increased IMT in patients with active acromegaly. In patients with acromegaly, the increase in AIMT is more closely associated with the IGF-1 level. Furthermore, when we evaluated only patients with acromegaly, it was determined that AIMT independently determined patients with active acromegaly, together with IGF-1 level.

There are some important limitations in this study. The first limitation is the number of patients taken in our study is limited, however very few patients were included in this group of studies in the literature. Patients were not followed up in this study, and there was no efficacy in the effect of the treatment on the IMT value. There are studies that

the medical treatment applied in patients with acromegaly result with regressing and not in increasing CIMT values[11,13].

In conclusion, it is thought that AIMT measurement may be more useful than CIMT in showing the presence of asymptomatic atherosclerosis for the early diagnosis and treatment of CV diseases that are the most frequent cause of mortality and morbidity in patients with acromegaly. The AIMT measurement may be a routine follow-up examination for the earlier recognition of the presence of CV diseases in patients with acromegaly. To show the relationship with AIMT measurement acromegaly is the first in the literature; however, it is necessary to support existing data with a new study with more patients.

Yazar Katkıları: Çalışma konsepti/Tasarımı: HES, DD; Veri toplama: HES, DD; Veri analizi ve yorumlama: HES, DD; Yazı taslağı: HES, DD; İçeriğin eleştirel incelenmesi: HES; Son onay ve sorumluluk: HES, DD; Teknik ve malzeme desteği: HES, DD; Süpervizyon: HES, DD; Fon sağlama (mevcut ise): yok.
Bilgilendirilmiş Onam: Katılımcılardan yazılı onam alınmıştır.
Hakem Değerlendirmesi: Dış bağımsız.
Çıkar Çatışması: Yazarlar çıkar çatışması beyan etmemişlerdir.
Finansal Destek: Yazarlar finansal destek beyan etmemişlerdir.

Author Contributions: Concept/Design: HES, DD;; Data acquisition: HES, DD; Data analysis and interpretation: HES, DD; Drafting manuscript: HES, DD; Critical revision of manuscript: HES, Final approval and accountability: HES, DD; Technical or material support: HES, DD; Supervision: HES, DD; Securing funding (if available): n/a.
Informed Consent: Written consent was obtained from the participants.
Peer-review: Externally peer-reviewed.
Conflict of Interest: Authors declared no conflict of interest.
Financial Disclosure: Authors declared no financial support

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