

The visceral adiposity index, lipid accumulation product, and plasma atherogenic index are associated with subclinical atherosclerosis in patients with newly diagnosed acromegaly

Mustafa ÖZBEK* , Murat ÇALAPKULU , Sema HEPŞEN , Muhammed Erkam SENCAR ,
Hayri BOSTAN , İlknur ÖZTÜRK ÜNSAL , Erman ÇAKAL 

Department of Endocrinology and Metabolism, University of Health Sciences, Dışkapı Yıldırım Beyazıt Training and Research Hospital, Ankara, Turkey

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Background /aim: Acromegaly is a rare chronic endocrine disorder, the active form of which is associated with an increased risk of cardiovascular and metabolic disease. Therefore, early diagnosis and treatment of cardiovascular diseases in acromegaly patients are important in terms of morbidity and mortality. The aim of this study was to determine whether the visceral adiposity index (VAI), lipid accumulation product (LAP), and plasma atherogenic index (PAI) are early cardiovascular risk markers in patients with active acromegaly.

Materials and methods: The study included 45 patients newly diagnosed with acromegaly and 45 age–sex matched healthy control subjects. The VAI, LAP, and PAI values were calculated, and carotid artery intima media thickness (CIMT) was measured in both the patients and control groups.

Results: The PAI, VAI, LAP, and CIMT values were significantly higher in patients with acromegaly compared with the control subjects ($p < 0.004$, $p < 0.027$, $p < 0.012$, and $p < 0.001$, respectively). In the patient group, a significant positive correlation was found between the growth hormone (GH) and insulin-like growth factor I (IGF-I) levels, and between the VAI, LAP and PAI values. A significant positive correlation was determined between CIMT and LAP values in the patient group.

Conclusion: CIMT is a noninvasive method used to show early atherosclerosis. However, it is operator dependent. Therefore, VAI, LAP and PAI can be used as noninvasive, simple measurement methods to evaluate early atherosclerosis in patients with acromegaly.

Key words: Acromegaly, atherosclerosis markers, plasma atherogenic index, lipid accumulation product, visceral adiposity index, cardiovascular disease

1. Introduction

Acromegaly is a rare chronic endocrine disease, characterized by excessive growth hormone (GH) and increased insulin-like growth factor I (IGF-I) levels. In the vast majority of cases, the causative agent is generally a GH-secreting pituitary adenoma [1]. Overproduction of GH and IGF-I levels are associated with multiple comorbidities of various systemic (cardiovascular, hypertension, obstructive sleep apnea, colon polyposis, etc.) and metabolic complications [2]. In acromegaly, there are changes in protein, carbohydrate and fat metabolism due to excessively increased levels of GH and IGF-I [3,4]. Cardiovascular diseases are the primary cause of death in acromegaly, especially when it is active and uncontrolled [5]. This condition is further exacerbated in comorbid

conditions such as insulin resistance, type 2 diabetes, dyslipidemia and hypertension [4–7].

The visceral adipocyte index (VAI) is a recently developed mathematical index, calculated using simple, noninvasive parameters [(waist circumference (WC), body mass index (BMI), serum triglycerides (TG), high density lipoprotein cholesterol (HDL-C) levels)]. Studies have shown that it is significantly correlated with cardiovascular risk and metabolic syndrome [8], and similar studies have been conducted on active acromegaly patients [9,10]. Lipid accumulation product (LAP) is calculated based on the measurement of serum TG levels and WC [11] and has been used to predict cardiovascular risk in different disease populations (type 2 diabetes mellitus, insulin resistance, polycystic ovary syndrome) [12]. The plasma atherogenic

* Correspondence: mustafaozbek10@hotmail.com

index (PAI) is calculated using plasma TG and C levels, and studies have shown it to be an important indicator of atherosclerosis and coronary artery disease [13–15]. The measurement of carotid artery intima media thickness (CIMT) is a reliable, noninvasive, and simple method for the detection of subclinical atherosclerosis in patients with acromegaly [16].

The aim of this study was to investigate whether VAI, LAP and PAI may be useful markers in the evaluation of subclinical atherosclerosis in patients newly diagnosed with active acromegaly.

2. Materials and methods

This retrospective study, included 45 patients newly diagnosed with acromegaly patients (26 females, 19 males; average age 49.8 ± 11.7 years), and 45 age-sex matched healthy control subjects (28 females, 17 males; average age 46.2 ± 5.2 years) were included in this study. Exclusion criteria were defined as the presence of mixed hormone secreting adenoma, a history of acromegaly therapy, the presence of one or more anterior pituitary hormone deficiencies, or severe hypertriglyceridemia. Disease activity was determined according to plasma GH and IGF-I levels. Pituitary magnetic resonance imaging (MRI) scan was performed in all patients to detect pituitary adenoma.

Approval for the study was granted by the local ethics committee and all participants provided informed consent before participation. This study was carried out in the Department of Endocrinology and Metabolism Diseases at the Dışkapı Training and Research Hospital in Ankara.

The diagnosis of acromegaly was based on the Endocrine Society Clinical Practice Guidelines [17] as follows: 1) typical acromegaly clinical manifestations, 2) lowest serum GH concentration of > 1 ng/mL after a 75-g oral glucose tolerance test (OGTT) or fasting GH value of > 2.5 ng/mL, 3) serum IGF-I levels above the normal age-adjusted range, and 4) contrast-enhanced MRI showing a pituitary tumor in the sellar area.

All blood samples were drawn at 8 a.m. glycated haemoglobin (HbA1c) was measured using the high-performance liquid chromatography (HPLC) method. The IGF-I and GH concentrations were measured using chemiluminescence on an IMMULITE 2000 Xpi device (Siemens Health-care Diagnostics Inc). Serum IGF-I levels were compared with the age-sex-adjusted normal reference values. Plasma levels of TG, HDL, low-density lipoprotein (LDL), glucose, and creatinine were evaluated using an automated chemistry analyzer (Aeroset, Abbott, Holliston, MN, USA) using commercially available kits (Abbott, USA). LDL-C levels were calculated using the Friedewald formula ($TC=LDL+HDL+TG/5$).

2.1. Anthropometric measurements

All measurements were performed by the same researcher. The anthropometric measurements included height, weight, and waist and hips circumference. BMI was calculated by dividing body weight (kg) by the square of height (m^2). WC was measured at the midpoint between the iliac crests and the lowest rib while standing. Hip circumference was measured at the widest part of the hips. The average of these two values were calculated as the waist-hip-ratio (WHR).

VAI (TG and HDL-C levels expressed in millimoles per liter), and LAP were calculated to evaluate abdominal adiposity [8,11]. PAI values were calculated using the \log_{10} TG/HDL formula [13]. The following formulas were used:

$$VAI \text{ (males)} = [WC \text{ (cm)} / 36.58 + (1.88 \times BMI)] \times (TG / 1.03) \times (1.31 / HDL-K)$$

$$VAI \text{ (females)} = [WC \text{ (cm)} / (36.58 + (1.88 \times BMI))] \times (TG / 0.81) \times (1.52 / HDL-K)$$

$$LAP \text{ (males)} = (WC \text{ (cm)} - 65) \times TG$$

$$LAP \text{ (females)} = (WC \text{ (cm)} - 58) \times TG$$

$$PAI = \log_{10} TG / HDL \text{ formula}$$

Patients diagnosed with diabetes mellitus, dyslipidemia, metabolic syndrome, obesity, systolic or diastolic hypertension for the first time at the time of the diagnosis of acromegaly did not receive any specific treatment before the anthropometric measurements.

2.2. Measurement of CIMT

The CIMT was derived from a noninvasive ultrasound of the common carotid arteries, using a high-resolution B-mode ultrasound machine (EUB 7000 HV; Hitachi, Tokyo, Japan) with a 13 MHz linear array transducer. CIMT was defined as the distance between the blood-intima and media-adventitia boundaries on B-mode imaging. Three measurements were performed from 1 cm proximal to both main carotid artery bifurcations, and CIMT measurements were taken only from the posterior wall. The average CIMT was calculated from the average of three measurements taken from both arteries. All these examinations were performed by one of the authors (M.O.).

2.3. Statistical analysis

Statistical analyses were performed using SPSS software (version 23.0, SPSS, IBM Corporation, NY, USA). The Kolmogorov–Smirnov test was applied to assess conformity of the data to normally distribution. Categorical data were summarized as frequency and percentage (%). All continuous variables as mean \pm standard deviation (SD) values for normally distributed variables and as median (range) for nonnormally distributed variables. The independent samples t-test was used to compare continuous variables with normal distribution, and the Mann–Whitney U test for nonnormally distributed variables. A associations between categorical variables were examined using chi-square analysis, and the association between

numerical variables with Pearson's correlation analysis. Results were given with a 95 % confidence interval and a value of $p < 0.05$ was considered statistically significant.

3. Results

The demographic, anthropometric and biochemical characteristics of the patients newly diagnosed with acromegaly and the control subjects are shown in Table 1. The acromegaly group (n=45) comprised of 26 females and 19 male with a mean age of 49.8 ± 11.7 years. The control group (n= 45) comprised 28 female, and 17 males with a mean age of 46.2 ± 5.2 years. Routine biochemical and hormonal parameters including fasting blood glucose (FBG), HbA1c, TC, LDL-C, TG, GH, and IGF-I levels were significantly elevated in the patients with acromegaly compared with the control subjects. Significantly higher anthropometric parameters of WC, weight and BMI were

determined in the acromegaly group than in the control group ($p < 0.004$, $p < 0.001$, and $p < 0.001$, respectively).

VAI values were significantly elevated in acromegalic patients compared to the control subjects [4.7 (1.67-25.95), 2.6 (0.96-15.3), $p < 0.027$, respectively]. LAP values were significantly elevated in patients with acromegaly compared with the control subjects [41.3 (13.77-339.1), 28.2 (1.89-174.9), $p < 0.012$, respectively]. PAI values were significantly elevated in patients with acromegaly when compared with control subjects [0.49 (-0.02-1.13), 0.2 (-0.23-1.05), $p < 0.004$, respectively]. WHR values were significantly elevated in patients with acromegaly compared with the control subjects (0.59 ± 0.08 , 0.53 ± 0.08 , $p < 0.004$, respectively). CIMT levels were significantly elevated in the acromegaly group when compared with the control group (0.77 ± 0.13 , 0.51 ± 0.11 , $p < 0.001$, respectively).

Table 1. Demographic, metabolic and laboratory findings of the acromegaly and control groups.

	Acromegaly (n = 45)	Control (n = 45)	p-value
Sex (female/ male)	26/19	28/17	0.66
Age(years)	49.8 ± 11.7	46.2 ± 5.2	0.08
Height (cm)	165.3 ± 8.4	165.6 ± 8.4	0.89
Weight(kg)	84 ± 17	73 ± 12	0.001
BMI (kg/ m ²)	31 ± 6.6	26.6 ± 4.4	0.001
WC(cm)	97.6 ± 13.8	88 ± 13	0.004
HC(cm)	108 ± 15.1	105.4 ± 9.2	0.42
VAI	2.6 (0.96-15.3)	4.7 (1.67-25.95)	0.027
PAI	0.49 (-0.02-1.13)	0.2 (-0.23-1.05)	0.004
LAP	41.3 (13.77-339.1)	28.2 (1.89-174.9)	0.012
WHR	0.59 ± 0.08	0.53 ± 0.08	0.004
IGF-I	559.5 (329-1581)	-	-
GH	8.4 (1.59-55.7)	-	-
FBG (mg/dL)	113.6 ± 34	92.1 ± 8.5	<0.001
HbA1c (%)	6.7 ± 1.9	5.4 ± 0.4	<0.001
TC (mg/dL)	185.1 ± 31	170 ± 33.9	0.04
LDL-C (mg/dL)	126.9 ± 24.2	108.5 ± 28.9	0.002
HDL-C (mg/dL)	46.3 ± 12.1	49.8 ± 15.1	0.26
TG (mg/dL)	128 (61-527)	82.6 (27-397)	0.001
CIMT(mm)	0.77 ± 0.13	0.51 ± 0.11	<0.001

Abbreviations: WC, waist circumference; HC, hip circumference; BMI, body mass index; CIMT, carotid intima-media thickness; FPG, fasting blood glucose; TC, total cholesterol; TG, triglyceride; HDL-C, high density lipoprotein cholesterol; LDL-C, low density lipoprotein cholesterol; HbA1c, hemoglobin A1c; GH, growth hormone; IGF-I, insulin-like growth factor I; PAI, plasma atherogenic index; LAP, lipid accumulation product; VAI, visceral adiposity index; WHR, waist-hip ratio.

The correlations between serum GH, IGF-I, CIMT and laboratory and anthropometric parameters of all the study participants are shown in Table-2.

In the acromegaly group a significant positive correlation was found between CIMT and HbA1c ($r = 0.42, p = 0.002$), GH ($r = 0.76, p < 0.001$), IGF-I ($r = 0.698, p < 0.001$), LAP ($r = 0.372, p = 0.006$) and WHR ($r = 0.506, p < 0.001$). A significant positive correlation was found between GH and HbA1c ($r = 0.604, p < 0.001$), IGF-I ($r = 0.763, p < 0.001$), VAI ($r = 0.29, p = 0.012$), PAI ($r = 0.357, p < 0.001$), LAP ($r = 0.288, p = 0.013$) and WHR ($r = 0.243, p = 0.037$) in patients with acromegaly. A significant positive correlation was found between IGF-I and HbA1c ($r = 0.537, p < 0.001$), GH ($r = 0.763, p < 0.001$), VAI ($r = 0.307, p = 0.008$), PAI ($r = 0.344, p = 0.002$), LAP ($r = 0.300, p = 0.009$) and WHR ($r = 0.232, p = 0.04$) in patients newly diagnosed with acromegaly patients.

4. Discussion

In patients with active acromegaly, mortality is generally significantly higher than in the general population [18]. Mortality rates are increased especially by cardiovascular diseases (60% cardiovascular, 25% respiratory disease, and 10% malignancy) [5]. Acromegalic cardiomyopathy is disease specific, and it is associated with the duration of the disease. It depends on the long-term GH / IGF-I effect [19]. High serum GH levels are a more important independent risk factor in mortality than IGF-1 levels [20].

The results of this study showed that, traditional biochemical and anthropometric cardiovascular risk factors, such as FBG, HbA1c, TC, LDL-C, TG, weight, BMI, and WC were significantly higher in patients with active acromegaly compared to control subjects.

In this study VAI, LAP, PAI and CIMT levels were evaluated in patients with newly diagnosed acromegaly and in control subjects.

Recent studies have shown that high VAI levels are a strong independent risk factor associated with the development of cardiovascular and cerebrovascular events.

It has also been emphasized that VAI is a good indicator for the development of diabetes [8,21].

In a recent study, Cirese A, et al concluded that VAI is associated with disease activity, and may be a useful marker for early metabolic risk in patients with newly diagnosed active acromegaly [9] and is independently influenced by GH levels [9].

It has been suggested that VAI may be a useful marker for the evaluation of cardiometabolic risk in postmenopausal patients with active acromegaly [10]. Giordano C et al. reported that active acromegaly is strongly associated with visceral adiposity dysfunction, and VAI indirectly shows adipose tissue dysfunction [22]. In another study, VAI and CIMT were found to be correlated independently of other cardiovascular risk factors, and it was concluded that the calculation of VAI may provide a better estimation of early atherosclerosis than the insulin resistance marker [23].

In this study, similar to the literature, we found higher VAI levels in the active acromegalic patients than control subjects. There was statistically significant positive correlations between GH / IGF-I and VAI levels ($r = 0.29, p = 0.012, r = 0.307, p = 0.008$, respectively). High levels of VAI in our study can also be attributed to the findings of metabolic syndrome parameters. In this study, there was no correlation between CIMT and VAI levels.

In our study, similar to the literature, VAI levels may be associated with disease activity in active acromegaly. VAI may be a marker for early atherosclerosis in active acromegalic patients.

LAP is a new index to predict the deposition of central lipid tissue and is used in detection of metabolic syndrome. It was shown that LAP was better than BMI in predicting insulin resistance and cardiovascular risk [24,25]. In another study reported that LAP was the best predictor of metabolic syndrome, according to VAI, triglyceride to glucose index and WHR [26].

In the present study, LAP measurements were found significantly increased in patients with active acromegaly than control subjects. In our results, LAP measurements

Table-2. Correlation analyses results between CIMT, GH, IGF-I and anthropometric values.

Correlation graphic		HbA1c	GH	IGF-1	VAI	PAI	LAP
CIMT	r value	0.42	0.716	0.698	0.204	0.182	0.372
	p value	0.002	<0.001	<0.001	0.143	0.19	0.006
GH	r value	0.604	1.000	0.763	0.29	0.357	0.288
	p value	<0.001	-	<0.001	0.012	<0.001	0.013
IGF-I	r value	0.537	0.763	1.000	0.307	0.344	0.300
	p value	<0.001	<0.001	-	0.008	0.002	0.009

were also correlated with both CIMT, GH and IGF-I levels. Furthermore, in this study CIMT values were positive correlated with HbA1c levels. As a result of these findings, we can say that LAP measurements are indirectly related to dysglycemia and insulin resistance. And also, in patients with acromegaly, LAP measurements may be used as a surrogate marker for predicting subclinical atherosclerosis.

According to many evidence, dyslipidemia is the most important major risk factor for coronary artery disease [27]. PAI has been found to be associated with metabolic syndrome and obesity in many studies [28,29]. In another study, Zhu et al. demonstrated that PAI is positively correlated with diabetes mellitus [30]. The findings of the studies showed that PAI is a powerful indicator of the risk for atherosclerotic cardiovascular disease [31–33]. In another study, PAI was found to be positively correlated with cardiovascular diseases in postmenopausal women [34]. PAI values differ in previous studies. This situation is attributed to different ethnic groups in the studies [34].

In our study, PAI values were found significantly increased in patients with active acromegaly than control subjects. According to correlation analysis, there was a positive correlation between the PAI and GH levels in patients with acromegaly. And also, there was a positive correlation between the PAI and IGF-I levels in patients with acromegaly. There was no correlation between PAI and CIMT levels in acromegaly patients.

CIMT level is a reliable, noninvasive and easy indicator, which can be applied in ultrasonographic evaluations. It could be recommended as a potential measurement method to detect subclinical atherosclerosis, which has been shown in many studies [35–37]. In previous studies, higher CIMT measurements have been found in acromegaly patients, as an indicator of early atherosclerosis [16,38].

In this study, CIMT levels were significantly elevated in acromegalic patients when compared with control subjects (0.77 ± 0.13 , 0.51 ± 0.11 , $p < 0.001$, respectively). A significant positive correlation was found between CIMT and HbA1c ($r = 0.42$, $p = 0.002$), GH ($r = 0.76$, $p < 0.001$), IGF-I ($r = 0.698$, $p < 0.001$), LAP ($r = 0.372$, $p = 0.006$) and WHR ($r = 0.506$, $p < 0.001$) in patients with acromegaly.

In our study, higher CIMT measurements seem to be associated with blood glucose dysregulation, metabolic syndrome parameters, obesity, and higher levels of GH and IGF-I in patients with newly diagnosed acromegalic patients.

5. Conclusion

Our study is the first study evaluating LAP and PAI measurements in newly diagnosed acromegaly patients. Our results show that LAP and PAI values, which are a simple measurement method, can be used easily to evaluate early atherosclerosis in patients with acromegaly. According to their advantage, LAP and PAI measurements are not operator dependent. The measurements are performed with cheaper routine biochemical and anthropometric data. Well-planned prospective studies with a large number of cases are needed on this subject.

Acknowledgements/disclaimers/conflict of interest

This research received no outside support. The authors have no financial interest with any organization. The authors have no conflicts of interest to declare.

Informed consent

This study conformed to the Helsinki Declaration. The study was approved by Dışkapı Yıldırım Beyazıt Training and Research Hospital Ethics Committee (No: 09.12.2019 – 77/05). All participants were informed about the research protocol, and they declared their voluntary attendance by signed written consent.

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Contribution of authors

M. O, S.H, H. B, M.C, M.E.S participated in data collection, M.O., I, O, U, M.C contributed to interpretation of results, data analyzes, M O, wrote and edited the manuscript. M.O., M.C, contributed to the discussion. M, O, E.C contributed to study design, reviewed and edited the manuscript. All authors read and approved the final manuscript.

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