Mean platelet volume and arterial stiffness in patients with acromegaly

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ABSTRACT

Objective: There are still contradictory data in the literature whether patients with acromegaly are under risk in terms of atherosclerotic heart disease. Increased arterial stiffness develops before atherosclerosis and is evaluated to be a risk factor for atherosclerosis. Mean platelet volume (MPV) is currently gaining interest as a new independent cardiovascular risk factor. There are contrasting views about arterial stiffness in patients with acromegaly. There is no report in literature studying MPV in acromegaly patients. The aim of this study was to evaluate MPV and arterial stiffness in patients with acromegaly.

Methods: This study was designed as an observational cross-sectional, case-controlled study. Twenty-eight patients with acromegaly and 22 healthy volunteers were recruited for the study. The arteriography device Mobil-O-Graph® (IEM GmbH. Stolberg, Germany) which can perform oscillometric measurements was used to measure arterial stiffness. The Mann-Whitney U test, Student's t-test, Spearman's nonparametric correlation analysis and the chi-square test were used to statistical analyze.

Results: Aortic pulse wave velocity (PWV) value was found to be 6.41±2.12 m/s in the patient group with active acromegaly and 5.24±1.04 m/s in the healthy control group. The difference was statistically significant (p=0.03). The mean MPV value was found to be 9.68±1.11 in the patient group with active acromegaly and 8.53±1.18 in the healthy control group. There was a statistically significant difference between the two groups (p=0.004). In patients with acromegaly, a positive correlation was found between MPV and insulin-like growth hormone-I (IGF-1) level (p=0.021, r=0.434).

Conclusion: We determined an increase in aortic PWV and MPV in patients with acromegaly. In conclusion, evaluation of MPV and arterial stiffness in future studies could be beneficial in determining the risks for cardiovascular disease in patients with acromegaly.

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Key words: acromegaly, atherosclerosis, arterial stiffness

Introduction

Acromegaly is a rare disease caused by an adenoma which is localized in the pituitary gland and which releases growth hormone. The incidence is 3-4/million/year and the prevalence is 40-70/one million (1, 2). Meta-analysis have revealed a 72% increase in mortality in patients with acromegaly compared to the general population (1). Mortality evaluations show that approximately 60% of the patients with acromegaly die from cardiovascular disease (3-6). Atherosclerotic cardiovascular diseases constitutes an important part of this (5-8). Hypersecretion of growth hormone (GH) and insulin-like growth hormone-I (IGF-1) constitute a risk factors for atherosclerotic disease (9). Despite this adverse cardiovascular risk profile, contradictory data exist in the literature regarding whether patients with acromegaly are at risk in terms of atherosclerotic heart disease.

Increased arterial stiffness occurs before atherosclerosis and is evaluated to be a risk factor for atherosclerosis (10). Arterial stiffness is an index of total mortality. In addition, it is an important determinant for vascular diseases including cardiac failure, myocardial infarction, renal disease, stroke and dementia (11, 12). In a study by Matsuda et al. (13) there were decreased arterial stiffness in patients with acromegaly while elevated aortic stiffness was reported in the study by Nemes et al. (14).

Mean platelet volume (MPV) is gaining interest as a new independent cardiovascular risk factor (15). Mean platelet volume corresponds to the average of size of platelets in the blood. Mean platelet volume increases when there is increased platelet production (16). Platelets play a significant role in the pathophysiology of atherothrombotic disease (17). Large platelets are more active metabolically and enzymatically and have increased thrombotic potential (18). Additionally, MPV is an indicator of in-

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creased platelet activation (19). A correlation was reported between elevated arterial stiffness and MPV (20).

To our best knowledge, there is no report in literature studying MPV in acromegaly patients. There are contrasting views about arterial stiffness in patients with acromegaly in the previous studies. The aim of this study was to evaluate MPV and arterial stiffness in patients with acromegaly.

Methods

Study design

This study was designed as an observational, cross-sectional and case-controlled study.

Study population

Patients with acromegaly who were evaluated at the Department of Endocrinology, Medical Faculty of Adnan Menderes University, over a period of twelve months were enrolled into the study (September 2010-September 2011).

Informed consent was obtained from all participants and the study protocol was approved by the Ethics Committee of Adnan Menderes University Medical Faculty.

Twenty-eight patients (17 females, 11 males) with acromegaly and twenty-two healthy volunteers (12 females, 10 males) were recruited for the study after exclusion criteria were applied. Since diabetes mellitus (DM) is observed frequently in patients with acromegaly, 29 patients with type 2 DM without complications (16 females, 13 males) were selected as the second control group to compare MPV values.

Patients with known congenital or acquired platelet disease, hematologic disease, active infection and acute stress, history of cerebrovascular event (CVE), myocardial infarction (MI) and those receiving anticoagulant and/or antiaggregant treatments, which may potentially affect MPV, were excluded from the study. Healthy volunteers with DM, hypertension, history of coronary artery disease, history of CVE, chronic obstructive lung disease, pregnancy were also excluded from the study.

Patients with complications (microvascular and macrovascular) in the control group with type 2 DM were excluded from the study.

The mean age was found to be 49.75±13.65 years old in patients with acromegaly, 49.55±14.57 years old in the healthy control group and 54.14±6.75 years old in the control group with a diagnosis of type 2 DM ($p>0.05$).

Study protocol

All participants were assessed with a detailed medical history, complete physical and echocardiographic examinations. All cases were examined by two cardiologists. Arterial stiffnes measurement were performed to all study participants.

Diagnosis of acromegaly

The diagnosis of acromegaly was established according to clinical and laboratory criteria, including increased serum GH and IGF-1 levels, and failure of serum GH to be suppressed below 1µg/L after a 75-g oral glucose load.

Blood investigations for disease activity

IGF-1 assessment was performed using an immunoradiometric method developed by Immunotech (Beckman Coulter, USA); intra-assay coefficient of variation (CV) and inter-assay CV of the kit were 6.3% and 6.8%, respectively. GH values were obtained via oral glucose tolerance test (OGTT) and as random levels. OGTT is not helpful for monitoring therapeutic responses while patients are receiving treatment with SSAs (3). GH was assessed using an immunoradiometric method developed by (CISBIO BIOASSAY, France); intra-assay and inter-assay CV were 2.1% and 4.5%, respectively. Biochemical control of acromegaly is generally defined as a normal IGF-1 for age and gender, and a GH level <1.0 ng/mL during an OGTT. Using sensitive assays, a GH level <0.4 ng/mL would be consistent with remission (3).

Echocardiographic study

Each subject underwent transthoracic echocardiography. Echocardiograms were performed with a Phillips HD-11XE (USA) using a standard technique in the left lateral decubitus position and were recorded on videotape. Echocardiograms were preliminarily evaluated by a first reader and subsequently re-evaluated by a highly experienced reader.

Measurement of arterial stiffness

An arteriography device performing oscillometric measurement (Mobil-O-Graph®, IEM GmbH. Stolberg, Germany) was used to measure arterial stiffness. Patients were allowed to rest for at least 15 minutes. They were asked not to smoke or take caffeinated beverages during the period of 30 minutes before measurement. Immediately prior to measurement the cuff appropriate for the patient's arm circumference belonging to the device was placed on the upper arm. The cuff was inflated by the device above the currently determined systolic pressure value (at least 35 mm Hg). Thus, brachial artery occlusion was achieved. During the period of measurement (approximately 8-20 s), blood flow was stopped as this was necessary for the procedure. In this stop-flow condition, a membrane forms in the brachial artery at the upper border of the cuff inflated at the place where blood flow is stopped. Whem early (direct, P1) and late (reflected, P2) systolic waves and the diastolic wave reach the region of occlusion, the pressure wave becomes prominent in the diaphragm similar to the striking of projected blood to a membrane. The upper arm tissue acts as a transmitter medium and transmits small but detectable changes which occur with the compression effect of the flowing fluid to the skin and cuff along the cuff border and allows for these changes to become generalized. Pressure sensors of the arteriograph with high resolution are strong enough to detect these small, weak changes. A special tonometer then amplifies and screens these changes. The signals obtained by the tonometer are transferred to a computer by an ultraviolet, wireless network. The informa-

tion is processed by a software developed for this objective. This software is independent of the person who uses the device. The compatibility and validity of the device using the protocols of European Society of Hypertension (ESH) and British Hypertension Society (BHS) have been previously proven by studies (21, 22).

Pulse wave velocity (PWV) which is one of the indexes of arterial stiffness and aortic augmentation index (AIX) are noninvasive methods used to determine the severity of vascular damage. Measurement of the velocity of propagation of pulse wave is one of the important methods used to determine the elastic properties of the arteries. It is based on the principle of measurement using two ultrasounds or pressure-sensitive transducers placed on the skin along the tracings of two arteries with a certain distance between each other (carotid-femoral arteries). Aortic pulse wave propagation velocity (v) can be measured by determining pulse wave progression time (t) occuring between two points (most commonly between the carotid artery and femoral artery) by systolic ejection pressure and the distance between the two points (s). PVW can be calculated using v=s/t formula as meter/second (m/s) (23).

Augmentation index=AIX

Augmentation index is a parameter used for measurement of arterial stiffness like pulse wave velocity. It is the value obtained by dividing the difference between the two systolic wave peaks observed in the arterial pulse wave namely the amplitudes of the direct (early systolic) wave P1 which occur as a result of ejection and the reflected (late systolic) second wave (P2) to the pulse pressure and multiplying this by 100 (24).

Mean platelet volume measurement

Patients' MPV's were analyzed using two different blood samples, drawn in test tubes with EDTA using automated whole blood counter Beckman Coulter LH 780 (Miami, FL, USA). The samples were analyzed within 2 hours. Quality controls in our laboratory documented a good reproducibility of MPV measurements, with intra-assay and inter-assay coefficients of variation ≤2.2% on commercial controls. The reference range of this device for MPV was 6.5-11.6 femtoliters (fL).

Statistical analysis

All statistical analysis were carried out using Statistical Package for the Social Sciences (SPSS version 16.0, SPSS Inc., Chicago, IL, USA). The Mann-Whitney U test was used to analyze inter-group difference in cases where the variables did not demonstrate a normal distribution. Data was presented as median and 25-75% percentiles. For data with normal distribution, Student's t-test was used for inter-group analysis and the data was presented as mean and standard deviation. Correlation estimations of groups without normal distribution were performed with Spearman's nonparametric correlation analysis. The chi-square test was used to compare rates between groups. Statistical significance was set at $p<0.05$.

Results

Clinical characteristics

The mean time after diagnosis in patients with acromegaly was 100.7 months (min 0, max 372) and 5 patients had newly diagnosed disease. Sixteen of these patients had undergone hypophysis surgery. Gammaknife treatment had been administered in 4 patients. Seventeen patients were receiving octreotide, 3 patients were receiving lanreotide and 2 patients were receiving pegvisomant treatment. Eight of the patients who were receiving somatostatin analogues had not undergone hypophysis surgery. Eleven of the patients were in remission (39.29%). Twelve patients had active disease (42.86%). Five patients had newly diagnosed disease (17.86%). When treatments of the 11 patients in remission were evaluated, it was found that 3 patients had received octreotide treatment following hypophysis surgery, 5 patients had received only octreotide treatment and 3 patients had undergone only hypophysis surgery.

Seventeen of the patients with acromegaly (60.7%) had DM and 4 (14.3%) had impaired glucose tolerance. Eighteen of these patients (64.3%) had a diagnosis of hypertension. 58.82% of the patients with active acromegaly had hypertension and 58.82% had DM. 72.73% of the patients in remission had hypertension and 63.64% had DM.

The mean body mass index was found to be 27.64±3.91 kg/m^2 in the patients with acromegaly, 26.84±4.87 kg/m^2 in the healthy control group and 26.88±3.88 kg/m^2 in the type 2 DM control group. No significant difference was found between three groups ($p>0.05$).

The mean disease time in the type 2 DM control group was 7.07±7.2 years. The diagnosis of hypertension was present in 55.17% of the type 2 DM control group and no significant difference was found compared to the patient group with acromegaly ($p>0.05$).

Echocardiographic findings

The most common echocardiographic finding in the patients with acromegaly was mitral failure (57.14%). The left ventricular myocardium was found to have concentric hypertrophy (LVMH) in 21.43% of the patients. Echocardiographic findings were found to be normal in all subjects in the healthy control group. The control group with type 2 DM was not evaluated in terms of echocardiography and arterial stiffness.

Arterial stiffness measurements

No significant difference was found between the patient group with acromegaly and the healthy control group in terms of peripheral systolic blood pressure, peripheral main arterial pressure, pulse, peripheral pulse pressure, central systolic blood pressure, central diastolic blood pressure, central PWV, cardiac output, peripheral resistance, cardiac index, arterial stiffness, augmentation pressure, augmentation index and reflection magnitude ($p>0.05$). PWV value was found to be sig-

nificantly higher (p=0.006). When the patient group with active acromegaly (n=17) was compared with the healthy control group after excluding the patients in remission in terms of arterial stiffness, a significant difference was found only in terms of PWV value (p=0.03) (Table 1). Higher PWV in the patient group with acromegaly compared to the group with active acromegaly was explained by the fact that the number of patients with a diagnosis of hypertension was higher in the patient group in remission. Therefore, the group with acromegaly accompanied by hypertension (n=18) was compared with the healthy control group in terms of PWV value (Table 2). PWV value was found to be 7.28±1.58 in the hypertensive patients with acromegaly and 5.24±1.04 in the healthy control group. A statistically significant difference was found between

Table 1. Comparison of the patient group with active acromegaly and the control group in terms of arterial stiffness and MPV

	Patient group with active acromegaly (n=17)	Control group (n=22)	*P*
MPV, fL	9.68±1.11	8.53±1.18	0.004¥
Peripheral systolic blood pressure, mm Hg	125.06±15.69	116.77±15.23	>0.05¥
Peripheral diastolic blood pressure, mm Hg	79.94±13.94	73.23±13.02	>0.05¥
Peripheral main arterial pressure, mm Hg	100.53±13.55	93.23±12.81	>0.05¥
Peripheral pulse pressure, mm Hg	45 (39-52)	41.5 (34.75-51.25)	>0.05¥¥
Pulse, min	79.77±16.63	76.68±10.9	>0.05¥
Central systolic blood pressure, mm Hg	115.47±18.14	108.09±15.14	>0.05¥
Central diastolic blood pressure, mm Hg	81.94±14.22	74.68±13.06	>0.05¥
Central pulse wave velocity, m/s	33.71±15.16	33.41±9.16	>0.05¥
Peripheral resistance, s/*mm Hg/mL	1.24 (1.15-1.35)	1.24 (1.13-1.38)	>0.05¥¥
Cardiac output, l/min	4.37±0.7	4.25±0.56	>0.05¥
Cardiac index, l/min*1/m^2	2.25±0.38	2.3±0.28	>0.05¥
Augmentation pressure, mm Hg	3 (1.5-5.5)	4.5 (2-8)	>0.05¥¥
Augmentation index, %	17 (4.5-24)	15 (-1.5-27.5)	>0.05¥¥
Reflection magnitude, %	60.29±10.12	64.91±9.09	>0.05¥
PWV, m/s	6.41±2.12	5.24±1.04	0.03¥

¥Values are mean±SD for data with normal distribution. Student's t-test was used and statistical significance was set at *P*<0.05.
¥¥Values are median and 25th-75th percentile for data without normal distribution. The Mann-Whitney U test was used and statistical significance was set at *P*<0.05.
MPV - mean platelet volume; PWV - pulse wave velocity

Table 2. Comparison of hypertensive patients with acromegaly and the healthy control group in terms of arterial stiffness

	Hypertensive patients with acromegaly (n=18)	Control group (n=22)	*P*
Peripheral systolic blood pressure, mm Hg	128.06±14.54	116.77±15.23	0.023¥
Peripheral diastolic blood pressure, mm Hg	83.44±11.87	73.23±13.02	0.014¥
Peripheral main arterial pressure, mm Hg	103.89±11.92	93.23±12.81	0.01¥
Pulse, 1/min	81.78±19.73	76.68±10.9	>0.05¥
Central systolic pressure, mm Hg	118.17±16.69	108.09±15.14	>0.05¥
Central diastolic pressure, mm Hg	85.5±12.11	74.68±13.06	0.011¥
Central pulse wave velocity, m/s	31 (23.75-35.5)	30.5 (24.75-42)	>0.05¥¥
Peripheral resistance, s*mm Hg/mL	1.26 (1.15-1.31)	1.24 (1.13-1.38)	>0.05¥¥
Cardiac output, l/min	4.61±0.76	4.25±0.56	>0.05¥
Cardiac index, l/min*1/m^2	2.44±0.5	2.3±0.28	>0.05¥
Augmentation pressure, mm Hg	5.65 (1.53-5.3)	4.5 (2-8)	>0.05¥¥
Augmentatation index, %	13.11 (3.75-23.25)	15 (-1.5-27.5)	>0.05¥¥
Reflection magnitude, %	57.89±11.36	64.91±9.09	0.036¥
Pulse wave velocity, m/s	7.28±1.58	5.24±1.04	<0.001¥

¥Values are mean±SD for data with normal distribution. Student's t-test was used and statistical significance was set at *P*<0.05
¥¥Values are median and 25th-75th percentile for data without normal distribution. The Mann-Whitney U test was used and statistical significance was set at *P*<0.05

the two groups (p<0.001). There was no significant difference between the patients with and without LVMH in terms of arterial stiffness (p>0.05). No significant difference was found between the patients with acromegaly who received and did not receive somatostatine analogue in terms of arterial stiffness (p>0.05).

Mean platelets volume measurements

The mean MPV value was found to be 9.22±1.2 fL in the patient group with acromegaly and 8.53±1.18 fL in the healthy control group (Table 3). There was a significant difference between the two groups (p=0.047). The mean MPV value was found to be 8.99±0.95 fL in the group with type 2 DM which was not significantly different from the patient group with acromegaly (p>0.05). The mean MPV value was found to be 9.68±1.11 fL in the patient group with active acromegaly which was statistically significantly different from the healthy control group (p=0.004). There was a significant difference between the patient group with active acromegaly and the type 2 DM control group in terms of MPV (p=0.03). When the patient group with acromegaly were compared with the healthy control group, no significant difference was found in terms of hemoglobin, white blood cells, platelets, CRP and erythrocyte sedimentation rate (p>0.05) (Table 4).

Lipid parameters

In the patient group with acromegaly, 3 patients were using atorvastatin for hyperlipidemia. After excluding these 3 patients the group with acromegaly and the control group were compared in terms of lipid parameters. In the patient group with acromegaly (n=25), the mean LDL value was found to be 118.89±31.44 mg/dL, the mean HDL value was found to be 44.88±11.94 mg/dL and the mean serum triglyceride value was found to be 140±54.22 mg/dL which were not significantly different from the control group (p>0.05). When the patient group with active acromegaly (n=17) was compared with the control group, no significant difference was found in terms of LDL and HDL levels. The median serum triglyceride level was found to be 133 mg/dL (122-165.5) in the patient group with acromegaly and 115 mg/dL (82-146) in the control group. The difference between the two groups was significant (p=0.039).

Correlation analysis

In patients with acromegaly, a positive correlation was found between MPV and IGF-1 level (p=0.021, r=0.434) (Fig. 1). A positive correlation was present between MPV and GH levels during OGTT with 75 g. No correlation was found with random GH value, however a correlation was present between MPV and GH at the 30th minute (p=0.014, r=0.461), GH at the 60th minute (p=0.024, r=0.427),

Table 3. Comparison of the patient groups with acromegaly and the control group in terms of arterial stiffness and MPV

	Control group (n=22)	Patient group with active acromegaly vs. control (n=17)	*P*	Hypertensive patients with acromegaly vs. control (n=18)	*P*	Patient group with total acromegaly vs. control (n=28)	*P*	Diabetic patients with acromegaly vs. control (n=17)	*P*
Mean platelet volüme, fL	8.53±1.18	9.68±1.11¥	0.004	9.34±1.34¥	0.048	9.22±1.2¥	0.047	9.41±1.29¥	0.033
Augmentation index, %	15 (-1.5-27.5)	17 (4.5-24)¥¥	>0.05	13.11 (3.75-23.25)¥¥	>0.05	16 (4.25-22.75)¥¥	>0.05	7 (2-22)¥¥	>0.05
Pulse wave velocity, m/s	5.24±1.04¥	6.41±2.12¥	0.03	7.28±1.58¥	<0.001	6.44±1.74¥	0.006	6.54±1.39¥	0.002

¥Values are mean±SD for data with normal distribution. Student's t test was used and statistical significance was set at *P*<0.05.
¥¥Values are median and 25th-75th percentile for data without normal distribution. The Mann-Whitney U test was used and statistical significance was set at *P*<0.05

Table 4. Laboratory findings in the patients with acromegaly and the healthy control group

	Patient group with acromegaly (n=28)	Control group (n=22)	*P*
Fasting glucose, mg/dL	106.5 (90-128)	71.5 (66.75-81.5)	<0.001¥¥
Post-prandial glucose, mg/dL	139 (123.5-200.75)	113 (104-125)	<0.001¥¥
HbA1c, %	6.5 (5.38-7.58)	5.2 (5-5.4)	<0.001¥¥
HDL, mg/dL	44.61±11.57	46.59±9.79	>0.05¥
LDL, mg/dL	117.21±32.33	122.96±24.66	>0.05¥
TG, mg/dL	133.5 (107.75-151.5)	115 (82-146)	>0.05¥¥
CRP, mg/dL	0.4 (0.2-1.37)	0.55 (0.25-1.01)	>0.05¥¥
ESR, mm/h	26.73±14.26	20.96±12.78	>0.05¥
Platelets, /mm^3	247000 (202250-317250)	260000 (221250-3115000)	>0.05¥¥
White blood cells, /mm^3	6604±1732	6357±1202	>0.05¥
Hemoglobin, g/dL	13.15 (11.43-13.95)	13.2 (12.75-14.05)	>0.05¥¥

¥Values are mean±SD for data with normal distribution. Student's t-test was used and statistical significance was set at *P*<0.05.
¥¥Values are median and 25th-75th percentile for data without normal distribution. The Mann-Whitney U test was used and statistical significance was set at *P*<0.05.
CRP - C-reactive protein; ESR - erythrocyte sedimentation rate; HbA1c - glycosylated hemoglobin; HDL - high density lipoprotein; LDL - low-density lipoprotein; TG - tryglyceride

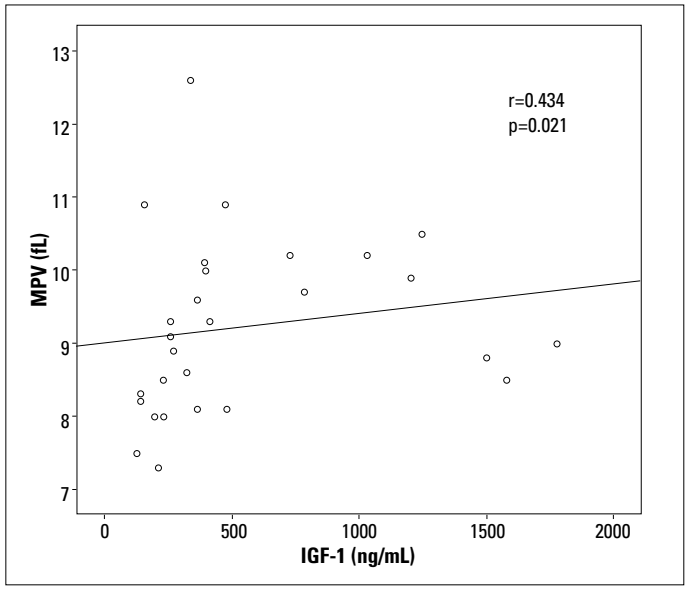

Figure 1. In patients with acromegaly, a positive correlation was found between IGF-1 level and MPV (Spearman's nonparametric correlation analysis)
IGF-1 - insulin growth factor-1; MPV - mean platelet volume

GH at the 90th minute (p=0.042, r=0.388) and GH at the 120th minute (0.049, r=0.375). A positive strong correlation was found between age and PWV value (p<0.001, r=0.739). No correlation was found between IGF-1 level, random GH value, GH at the 30th minute, GH at the 60th minute, GH at the 90th minute and GH at the 120th minute with PWV value (Table 5).

Table 5. Correlation analysis of MPV and PWV

	MPV, fL		PWV, m/s	
Variables	***P***	**r**	***P***	**r**
IGF-1 level	0.021	0.434	0.393	-0.171
GH (random)	0.088	0.721	0.077	-0.346
GH (at 30 min.)	0.014	0.461	0.582	-0.111
GH (at 60 min.)	0.024	0.427	0.372	-0.179
GH (at 90 min.)	0.042	0.388	0.377	-0.177
GH (at 120 min.)	0.049	0.375	0.212	-0.248
Duration of disease (months)	0.574	-0.111	0.143	0.284

¥Spearman's nonparametric correlation analysis were used to correlation analysis.
GH - growth hormone; IGF-1 - insulin growth factor-1; MPV - mean platelet volume; PWV - pulse wave velocity

Discussion

In our study, MPV was found to be significantly higher in the active acromegaly group compared to the control group and the patient group with type 2 DM. When the patient group with acromegaly was compared with the healthy control group in terms of arterial stiffness, PWV value was found to be significantly higher in the patient group.

It is not whether if patients with acromegaly are at risk in terms of atherosclerotic heart disease despite an advers cardiovascular risk profile (8). There is no consensus about the prevelance of atheroslerotic heart disease in patients with acromegaly.

Thickening in intramural vessels was described in 22% of the cases in postmortem studies (25). Cannavo et al. (26) evaluated patients with acromegaly using the Framingham score and coronary CT scan measurement. They showed that 41% of the patients carried a risk of coronary atherosclerosis risk. Calcified plaques were shown in approximately half of the patiens in this risk group (26). In the study performed by Colao et al. (27) increased intimal media thickness was found before the development of atherosclerotic plaques in patients with acromegaly.

Arterial stiffness is used to define the visco-elastic properties of the vessel wall (10). Arterial stiffness is currently regarded as an independent predictor of cardiovascular morbidity and mortality (11). Increased arterial stiffness increases left ventricular load by increasing systolic blood pressure, contributing to left ventricular hypertrophy and leads to a decrease in perfusion pressure in coronary arteries by decreasing in diastolic blood pressure and causing myocardial ischemia (12, 13). The 2007 Arterial Hypertension Treatment Notice of the European Society of Hypertension reported that high blood pressure is an important determinant for cardiovascular events in the presence of cardiovascular risk factors in the age group above 55 years. Increased vessel wall stiffness namely increased pulse wave propagation velocity by itself can put patients into the high/very high risk group (28). In a meta-analysis, patents between 20 and 90 years of age were classified as low, moderate and high risk patients in terms of cardiovascular disease risk and their PWV was evaluated. Mean PWV was found to be 8.86 m/s (95% CI) in the low risk group, 10.64 m/sn in the moderate risk group and 14.9 m/s (95% CI) in the high risk group (29).

In a study performed in patients without cardiovascular disease, a characteristic relation was found between increased PWV value and carotid plaque which can be demonstrated on ultrasonography also in subclinical or asymptomatic patients (30). PWV has also been proven to be related to asymptomatic coronary atherosclerosis. Kullo et al. (31) showed that confirmed the role of aortic PWV in measuring the cardiovascular risk in asymptomatic individuals who were independent of the classic risk factors. In a long-term study (9.4 years) performed by Hansen et al. (32) in more than 1600 asymptomatic patients, where the main end-points were cardiovascular mortality, fatal and non-fatal coronary disease, it was demonstrated that increased aortic PWV herald poor cardiovascular prognosis independent of classic risk factors and more efficiently compared to classic factors.

Augmentation index is a significant and independent index of cardiovascular events. An increase of 10% in the augmentation index increases the mortality risk due to coronary disease by 28%. Augmenation index has strong prognostic value together with classic risk factors and has been shown to strongly predict cardiovascular events in the absence of classic risk factors (33). In a study performed by Smith et al. (34), it was shown that acro-

megaly was associated with changes in the central arterial pressure waveform, suggesting large artery stiffness. It was shown that large artery stiffness decreased in patients cured of acromegaly and that large artery stiffness decreased partially with active disease with pharmacologic treatment. Dassie et al. (35) emphasized that ambulatory arterial stifness index may have an important role in predicting cardiovascular risk independent of increased blood pressure in acromegaly. Paisley et al. (36) found a significant increase in PWV as an indicator of arterial stiffness in patients with acromegaly without a change in carotid intima-media thickness. They suggested that premature cardiovascular disease in patients with acromegaly was related to pressure-related arterial stiffness and left ventricular stiffness rather than atherosclerosis. On the contrary, Matsuda et al. (13) have demonstrated reduced arterial stiffness in patients with acromegaly using the cardio-ankle vascular index. In this study the cardio-ankle vascular index showed a significant negative correlation with the serum IGF-1 level.

In our study, a significant difference was found between patients with active acromegaly and the healthy control group in terms of PWV. PWV was markedly increased in the hypertensive group with acromegaly. However, no significant difference was noted between the patients with acromegaly and the healthy control group in terms of augmentation index ($p>0.05$). Increased PWV in patients with acromegaly suggests the presence of an increased risk of cardiovascular disease in the early period.

Circulating platelets are heterogeneous in size, density and reactivity. Increased platelet reactivity results in increased platelet volume (37). The ability to measure the size of different cells by electronic cell counters makes it possible for clinicians and researchers to evaluate MPV (38, 39). Mean platelet volume is a recent risk indicator for atherothrombosis. Increased platelet volumes have been described in acute myocardial infarctions, acute cerebral ischemia and transient ischemic attacks (17-19). A relation was found between MPV and microalbuminuria which is an indicator of microangiopathy in patients with 2 DM (40). In the general population, a significant relationship was found between MPV and coronary artery calcification, which is a risk factor for coronary vascular events and mortality (15, 41). Özlü et al. (42) showed that increased MPV was established as an independent predictor of non-ST-segment elevation acute coronary syndromes (NSTE-ACS). Martin et al. (43) showed that MPV was an independent risk factor for recurrent myocardial infaction. Han et al. (44) showed that MPV was a predictive marker for coronary artery disease and stroke in patients with 2 DM. Increased MPVs in patients with 2 DM compared to the normal population have been reported in several studies (39, 40). In our study, 60.7% of the patients with acromegaly had DM and 14.3% had impaired glucose tolerance. Therefore, patients with acromegaly were compared with the control group with type 2 DM along with the healthy control group in terms of MPV. No study on MPV in patients with acromegaly has been previously published in the literature. In our study, MPV was found to be significantly higher in patients with active acromegaly compared to both the healthy control group and the type 2 DM control group. Increased MPV in patients with acromegaly suggests that MPV can be a marker of atherosclerotic disease in these patients.

Study limitations

There are some limitations, because this study was conducted with a small group. Therefore, further prospective studies that include larger series with long-term follow-up evaluation are necessary to clarify the clinical significance of MPV and PWV in patients with acromegaly.

Conclusion

Although it is proposed that there is an increased risk of cardiovascular disease in patients with acromegaly, cardiac screening is still not recommended (45). We determined an increase in aortic PWV and MPV in patients with acromegaly. Our study revealed a positive association between indicators of active disease and MPV in patients with acromegaly. In conclusion, evaluation of MPV and arterial stiffness in future studies could be beneficial in determining the risks for cardiovascular disease in patients with acromegaly.

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