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Echocardiography

Evaluation of the Impact of Treatment on Endothelial Function and Cardiac Performance in Acromegaly

Ebru Akgul, M.D.,* S. Lale Tokgozoglu, M.D.,† Tomris Erbas, M.D.,‡ Giray Kabakci, M.D.,† Kudret Aytemir, M.D.,† Ibrahim Haznedaroglu, M.D.,§ Ali Oto, M.D.,† and S. Sirri Kes, M.D.†

*Department of Cardiology, Ufuk University School of Medicine, Ankara, Turkey; Departments of †Cardiology, ‡Endocrinology, and §Hematology, Hacettepe University School of Medicine, Ankara, Turkey

Objective: To evaluate the effects of treatment on left ventricular (LV) performance and endothelial function in patients with acromegaly. Method: Nineteen patients with active acromegaly (AA), 18 patients with cured/well-controlled acromegaly (CA), and 25 healthy control subjects were studied. LV performance was evaluated by two-dimensional/Doppler echocardiography and Doppler tissue imaging (TDI). Flow-mediated dilatation (FMD) was measured by B-mode ultrasound. Endothelial cell markers; thrombomodulin (TM), and P-selectin were also measured. Results: Tei index was higher than the control subjects in both acromegaly groups. The ratio of early and late diastolic annular velocities (Em′/Am′) was significantly lower in the AA group than the other groups ($P < 0.05$). FMD in both acromegaly groups was significantly lower than the controls ($P < 0.001$) but difference between acromegaly groups was not significant ($P > 0.05$). In the CA group, P-selectin was higher than the controls and was even higher in the AA ($P < 0.05$). TM was significantly higher in the active group ($P < 0.05$) and not different than the controls in the CA group. Conclusion: TDI determine LV performance changes in acromegaly earlier than conventional echocardiographic methods. Endothelial function both in the form of FMD and endothelial cell markers is impaired in acromegaly. While in cured acromegaly endothelial cell injury, as evidenced by TM levels, is decreased, endothelial dysfunction still persists. (Echocardiography 2010;27:990-996)

Key words: acromegaly, cardiac performance, endothelial dysfunction, flow-mediated dilatation, P-selectin, thrombomodulin

Even with modern treatment, overall standardized mortality ratio of patients with acromegaly is found to be 1.48.[1] The duration of disease and serum growth hormone (GH) level are independent predictors of overall mortality and there is good evidence that serum GH seems to not only a good tumor marker identifying persistent disease but also predicts long-term outcome.[2,3] However, we also know that there is an increased prevalence of cardiovascular mortality risk factors in acromegaly such as hypertension, diabetes mellitus, dyslipidemia, abdominal obesity, and insulin resistance. What is more interesting is that a specific cardiomyopathy has been postulated even in the absence of predisposing factors.[4]

Though we know much about structural cardiac abnormalities in acromegaly, functional data on cardiac performance are not sufficient. Most echocardiographic studies show normal left ventricular (LV) systolic function but impaired diastolic function as an early finding in acromegalic cardiomyopathy leading to impaired LV filling. As a new echocardiographic method, tissue Doppler imaging (TDI) complements the conventional methods in evaluation of systolic and diastolic LV performance.[5–8] The Tei index was introduced by Tei and is defined as the sum of isovolumic contraction time (ICT) and isovolumic relaxation time (IRT) divided by the ejection time (ET).[9] It provides useful information in many disease states before routine echocardiographic methods detect any problem.

Endothelial cell dysfunction is the initiating event in the development of atherosclerosis and assessment of endothelial function by different methods has emerged as a tool for detection of evidence of preclinical cardiovascular disease.[10,11] The reduction in endothelium-dependent flow-mediated dilatation (FMD) is a marker of endothelial dysfunction and is found not only in the brachial artery of patients with coronary and peripheral arterial disease, but also of those with cardiovascular risk factors but without angiographically apparent disease.[12–14] Although there are several reports of hemodynamic abnormalities and disordered cardiovascular function in acromegaly, we have little information about endothelial function in acromegaly and the contribution of the risk factors and the effect of GH/IGF-I on endothelial function. To the best of

Address for correspondence and reprint requests: Ebru Akgul, M.D., Ufuk University School of Medicine, Department of Cardiology, Balgat Ankara, Turkey. Fax: +90-312-467-94-20; E-mail: eakgul2004@yahoo.com

our knowledge, there are no studies on soluble endothelial cell markers in acromegaly.

The aim of this study was to assess endothelial function and global LV performance in patients with active acromegaly (AA) and cured/well-controlled acromegaly (CA). We used TDI analysis and Tei index measurement as well as conventional echocardiographic methods. Finally, we aimed to elucidate the impact of treatment on endothelial function and global LV performance in acromegaly.

Subjects and Methods:

Patients:

We studied 37 patients (17 female and 20 male) with acromegaly. The diagnosis of acromegaly was based on the presence of classical clinical features, elevated age-adjusted serum IGF-I concentration, and confirmed by insufficient suppression of GH concentration during a glucose tolerance test and the presence of pituitary adenoma on radiological imaging.

The duration of disease was defined by careful comparison of old photographs and by the onset of clinical symptoms related to GH excess. All patients with acromegaly had previously undergone transsphenoidal surgery. Of the 37 patients, 19 had received conventional radiotherapy or stereotactic radiosurgery. We divided the study population into two groups; AA or CA according to consensus criteria for cure of acromegaly.[15] Acromegaly was considered cured when fasting or glucose-suppressed GH levels were below 2.5 μg/L and 1 μg/L, respectively, and with normal IGF-I levels for age. Patients who were treated with somatostatin analogues were defined as having well-controlled state in the presence of an age-adjusted normal range of IGF-I level. According to these criteria, 18 patients were considered as CA and formed the CA group (9 female and 9 male, aged 41 $\pm$ 8 years, mean IGF-I level, 295 $\pm$ 116 ng/mL, mean GH level 2.3 $\pm$ 2.0 ng/mL). Nineteen patients were found to have active disease and formed the AA group (8 female and 11 male, aged 40 $\pm$ 7 years, mean IGF-I level, 731 $\pm$ 214 ng/mL, mean GH level, 6.6 $\pm$ 9.0 ng/mL). Fourteen patients in AA group and 11 patients in CA group were treated with depot octreotide acetate. All patients with acromegaly who had partial or complete anterior pituitary insufficiency were receiving adequate substitution therapy all through the study period. None of the patients had symptoms related to coronary artery disease, cerebrovascular disease or peripheral arterial disease. Both of the acromegaly groups were appropriately matched according to the number of patients affected by diabetes and systemic hypertension. The hypertension and diabetes control was achieved at the time of the study. None of the patients was on lipid-lowering therapy and was smoking.

The control group consisted of 25 asymptomatic subjects (13 female and 12 male, aged 40 $\pm$ 6 years) without history of systemic hypertension, diabetes mellitus, or coronary artery disease and no evidence of heart disease. None of them were smoking, consumed drugs, or were affected by conditions known to alter endothelial function. All the participants were given informed consent to participate in the study.

Biochemistry:

Total serum cholesterol, triglyceride, lipoproteins (including lipoprotein (a)), Apo A-I, and Apo B were measured by commercially available kits. Serum GH level was determined with chemiluminescence enzyme immunometric assay (Immulite Growth Hormone, Diagnostic Products Corp., Los Angeles, CA, USA; normal ranges were 0.06–5.0 ng/mL; detection limit of assay was 0.01 ng/mL; interassay coefficients of variation (CVs) at 3.0 ng/mL and 18 ng/mL were 5.7% and 6.1%, respectively). Plasma IGF-I was measured using a highly sensitive and specific immunoradiometric assay that uses modified form of the standard acid-etonol extraction procedure (Diagnostic System Laboratories, Webster, TX, USA DSL-5600 ACTIVE; normal ranges were 0–363 ng/mL; detection limit of assay was 0.80 ng/mL; interassay CV's at 10.41 ng/mL and 255.9 ng/mL were 8.2% and 3.7%, respectively). Plasma thrombomodulin was determined by a two-side ELISA with two monoclonal anti-human thrombomodulin antibodies (ELISA, Asserachrom Thrombomodulin, Diagnostica Stago, Asnières-sur-Seine, France) and concentration of soluble P-selectin was measured with ELISA kits (R&D System, Abington, United Kingdom). The ranges of intra- and interassay CV were 5.3–7.8%, and 6.4–9.1%, respectively.

Echocardiographic Examination:

Echocardiographic images were obtained using a 3.75 MHz standard probe (General Electric, Vingmed) according to the guidelines of the American Society of Echocardiography.[16] Peak velocity of early (E) and late (A) filling, deceleration time, and IRT were measured from Doppler scan of the mitral inflow and the aortic outflow. Tei index was calculated as mentioned before. Pulsed-wave TDI was performed by using TDI function of the same machine. From the apical four-chamber view, peak systolic myocardial velocity (S′), early diastolic (E′), and late diastolic velocity (A′) were measured at the septal side of the mitral annulus. E′/A′ ratio was calculated thereafter.

Endothelial Function Study:
FMD was measured by a validated, reproducible technique.[17] First of all, brachial artery diameter was measured from B-mode ultrasound images with a 7.5 MHz linear array transducer (General Electric, Vingmed, System-Five). Flow velocity was measured with a pulsed-Doppler signal at a 70° angle to the vessel. Then the brachial artery was recorded in a suitable transducer position and the arm remained in the same position all through the study. The blood pressure cuff was applied to the proximal portion of the arm and inflated to 250 mmHg for 5 minutes. After deflation of the cuff, artery diameter was again measured after 60 seconds of reactive hyperemia. FMD was then calculated as the change in the diameter of the brachial artery. All images were recorded on VHS videotape for subsequent analysis. Anatomical markers were determined in order to standardize diameter measurements taken at end of diastole, at the same time with the R-wave on a continuously recorded electrocardiogram. The average of four cardiac cycle measurements was used as the final diameter. FMD was calculated as the percent ratio of the baseline diameter to the diameter reached after reactive hyperemia. Each study was performed by the same experienced operator with an intraobserver variability for repeated measurements of 0.01 ± 0.02 mm.

Study Procedure:
The subjects were told not to drink/eat caffeine containing food or beverage for at least 12 hours before the study. Studies were performed in a quiet room at room temperature. All drugs were stopped for at least 18 hours before the study. Echocardiographic and endothelial function studies were carried out after at least 15 minutes of rest.

Statistical Analysis:
Data are expressed as the mean ± standard deviation. Comparison of ratios between groups was done by chi-square test. For distribution of continuous variables between groups, Kolmogorov-Smirnov test was used. Mean values in different groups were compared with either Student's *t*-test or Mann-Whitney U test. Continuous variables between groups were analyzed with either one-way analysis of variance (ANOVA) or Kruskal-Wallis one-way analysis. The variables that show significant difference after one-way variance analysis were then compared by using multiple comparison procedures (Tukey's HSD). A difference was considered significant at a P value of < 0.05. SPSS for Windows Version 10.0 program (SPSS Inc., Chicago, IL, USA) was used for the statistical analysis.

Results:
Both of the acromegaly groups and the control group did not show any difference with respect to heart rate, systolic and diastolic blood pressure. Body mass index (BMI) and mean age of the acromegalic patients were found to be increased than the control subjects (AA:29 ± 4, CA:28 ± 5, C:23 ± 3 kg/m^2 and AA: 40 ± 7, CA: 41 ± 8 C:35 ± 6 year, respectively, $P < 0.05$). The disease duration did not differ between the acromegaly groups (AA: 4.7 ± 3.9, CA: 7.5 ± 5.7).

Both of the acromegaly groups were homogenous in respect to the routine biochemical and lipid parameters. High density lipoprotein (HDL) however was found to be significantly lower in the AA group than the control subjects (AA:46 ± 13 mg/dL, CA:50 ± 11 mg/dL, C:57 ± 15 mg/dL, $P < 0,05$). Fasting blood glucose, total cholesterol, low density lipoprotein (LDL), Lp(a), Apo B, and fibrinogen levels were significantly higher in both of the acromegaly groups than the control group (Table I). C-reactive protein (CRP) did not differ between the groups. GH were significantly higher in the AA group (AA:6.6 ± 9.0 ng/mL, CA:2.3 ± 2.0 ng/mL, $P < 0,05$) as it was for IGF-I levels (AA:731 ± 214 ng/mL, CA:295 ± 116 ng/mL, $P < 0,05$)

TABLE I

Clinical and Biochemical Parameters

	Control (n = 25)	AA (n = 19)	CA (n = 18)
Age (year)	35 ± 6*	40 ± 7	41 ± 8
Disease duration (year)	–	4.7 ± 3.9	7.5 ± 5.7
BMI (kg/m^2)	23 ± 3*	29 ± 4	28 ± 5
SBP (mmHg)	116 ± 12	127 ± 12	122 ± 8
DBP (mmHg)	74 ± 7	79 ± 7	77 ± 6
Heart rate (min)	73 ± 12	76 ± 10	74 ± 9
Glucose (mg/dL)	83 ± 9*	110 ± 18	111 ± 27
HbA_1C (%)	–	5.9 ± 2	5.3 ± 1
Total Cholesterol (mg/dL)	169 ± 29*	199 ± 47	203 ± 36
Triglyceride (mg/dL)	117 ± 52	155 ± 65	130 ± 64
LDL (mg/dL)	83 ± 29*	122 ± 32	125 ± 34
HDL (mg/dL)	57 ± 15†	46 ± 13	50 ± 11
VLDL (mg/dL)	25 ± 12	32 ± 13	28 ± 18
Lp (a) (mg/dL)	13 ± 11*	33 ± 27	42 ± 27
Apo AI (mg/dL)	136 ± 28	128 ± 32	139 ± 23
Apo B (mg/dL)	73 ± 17*	111 ± 27	115 ± 22
CRP (mg/dL)	0.37 ± 0.1	0.30 ± 0.2	0.37 ± 0.2
Fibrinogen	285 ± 43*	359 ± 55	349 ± 59

*Control versus other groups, $P < 0.05$.
†Control versus CA group, $P < 0.05$.
SBP = Systolic blood pressure; DBP = Diastolic blood pressure; BMI = Body mass index; VLDL = very low density lipoprotein.

TABLE II

Hormonal Parameters

	AA	CA
IGF-1 (ng/mL)	731 ± 214	295 ± 116
GH (ng/mL)	6.6 ± 9.0	2.3 ± 2.0

(Table II). Prolactin, T_3, T_4, and TSH did not show any difference between the AA and CA groups.

TM was significantly higher in the active disease state and found not to show any difference from the controls in the CA group (AA:23.88 ± 11.9, CA:19.23 ± 9.0, C:14.1 ± 8.4 ng/mL, P < 0,05). P-selectin, however, was strikingly higher in both of the acromegaly groups than the control group and found to be significantly increased in the AA group than the CA group as well (AA:266.6 ± 156, CA:177.4 ± 98, C:108.8 ± 5 pg/mL, P < 0,05) (Table III).

Two-dimensional (2D) and Doppler Echocardiographic Parameters:

The three study groups did not show a significant difference with respect to conventional systolic performance parameters. LV end diastolic and end systolic diameter measurements in the AA group were significantly higher than the controls, but they did not differ between the CA group and the controls. LV mass was found to be significantly increased in both of the disease groups. Mitral inflow Doppler parameters; peak E velocity, and E/A ratio did not differ between the acromegaly groups but was lower than the controls. Peak A velocity was found to be higher in the AA group than the control group. Tei index did not show a significant difference between the acromegaly groups, but was found to be markedly increased in AA and CA groups than the controls (Table IV).

TDI Analysis:

We did not find a significant difference between the groups with respect to myocardial systolic (S′) mitral annular velocity. Early diastolic myocardial velocity (E′) was found to be decreased in both of the acromegaly groups. E′/A′ ratio in the AA group, however, was significantly reduced when compared with the controls. E′/A′ ratio in CA group did not differ from the control group (Table V).

TABLE III

Endothelial Cell Markers

	Control	AA	CA
Thrombomodulin (ng/mL)	14.1 ± 8.4	23.8 ± 11.9*	19.2 ± 9.0
P-selectin (pg/mL)	108.8 ± 51	266.6 ± 156†	177.4 ± 98

*AA versus controls, P < 0.05.
†AA versus other groups, P < 0.05.

TABLE IV

2D Doppler Echocardiography Parameters

	Control (n = 25)	AA (n = 19)	CA (n = 18)
LVEDD (cm)	4.9 ± 0.5†	5.2 ± 0.5	5 ± 0.4
LVESD (cm)	3 ± 0.4†	3.3 ± 0.5	3.3 ± 0.3
EF (%)	68 ± 5	67 ± 7	65 ± 4
FS (%)	38 ± 4	37 ± 5	36 ± 4
Septum (mm)	0.8 ± 0.1*	1 ± 0.2	1 ± 0.1
Post. Wall (mm)	0.9 ± 0.1*	1 ± 0.2	1 ± 0.1
LVM (g)	139 ± 33*	217 ± 75	189 ± 39
E (m/sec)	0.8 ± 0.2*	0.7 ± 0.2	0.7 ± 0.1
A (m/sec)	0.5 ± 0.1†	0.6 ± 0.1	0.5 ± 0.1
E/A ratio	1.6 ± 0.4*	1.3 ± 0.3	1.3 ± 0.4
DT (msec)	203 ± 54	205 ± 78	223 ± 80
ICT (msec)	45 ± 7*	65 ± 13	62 ± 10
ET (msec)	331 ± 9*	314 ± 10	317 ± 14
IRT (msec)	85 ± 9*	90 ± 16	99 ± 11
Tei index	0.38 ± 0.2*	0.55 ± 0.2	0.53 ± 0.2

*Control versus other groups, P < 0.05.
†Control versus. AA group, P < 0.05.

Brachial Artery FMD:

The three study groups did not differ significantly with respect to baseline brachial artery diameter (AA:3.5 ± 0.7 mm, CA:3.4 ± 0.7 mm, C:3.2 ± 0.5 mm). FMD was significantly lower in both of the acromegaly groups than in the controls (AA: 8 ± 4.0%, CA:10 ± 4.7%, C:17 ± 3.0%, P < 0,001).Though FMD in AA group was lower than in CA group, we did not find a statistically significant difference between acromegaly groups (Fig. 1).

Discussion:

In acromegaly, the symptoms of heart failure may develop even in the absence of

TABLE V

TDI Analysis Parameters (Mitral Annulus)

	Control (n = 25)	AA (n = 19)	CA (n = 18)
E′m (cm/sec)	12 ± 2*	9 ± 3	10 ± 2
A′m (cm/sec)	7 ± 2†	9 ± 2	8 ± 2
Sm (cm/sec)	8 ± 0.8	7 ± 1	8 ± 1
E′/A′ (cm/sec)	1.7 ± 0.5†	1.1 ± 0.5	1.3 ± 0.6

*Control vs. other groups, P < 0.05.
†Control vs. AA group, P < 0.05.

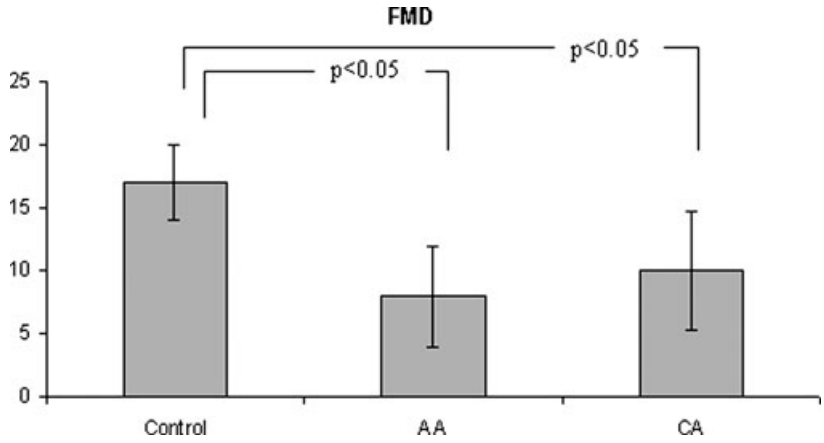

Figure 1. Flow-mediated dilatation (FMD) in acromegaly and control groups. AA = active acromegaly; CA = cared/well-controlled acromegaly.

predisposing risk factors such as systemic hypertension, diabetes mellitus, or coronary heart disease. It is well known that chronic GH and IGF-I excess lead to the development of an acromegalic cardiomyopathy characterized by interstitial fibrosis, lymphomononuclear infiltration, and areas of monocyte necrosis.[4,18,19] On the other hand, with conventional echocardiographic methods, we can only evaluate structural abnormalities. Subtle changes in the functional data, however, are difficult to obtain with routine echocardiographic examination. Most echocardiographic studies show normal LV systolic function but impaired diastolic function as an early sign of acromegalic cardiomyopathy.[5,20] In another study, the prevalence of diastolic dysfunction was found to be approximately 30% in untreated acromegaly with conventional methods.[21] Using more sensitive equilibrium radionuclide angiography, impairment of EF after exercise was observed in 73% of patients.[22] Therefore, it is clear that novel echocardiographic methods are needed to evaluate global cardiac performance in acromegaly.

In our study, cardiac performance was evaluated with TDI analysis of mitral annulus velocity and Tei-index measurement as well as conventional 2D Doppler scan measurements. E/A ratio was found to be lowered in both AA and CA groups. According to this Doppler parameter, it was difficult to differentiate active disease state from well-controlled/cured acromegaly. E′/A′ ratio, derived from TDI analysis of mitral annulus velocity, was significantly reduced in AA when compared with controls. It did not differ between CA group and control subjects. We defined this TDI derived parameter as a better correlate of disease activity. So conventional methods are insufficient for determination of early functional changes in acromegaly and the impact of appropriate treatment on cardiac performance can be detected accurately at an earlier stage with TDI analysis.

In our study, Tei index was significantly elevated in both of the acromegaly groups as a result of prolongation of IVC and shortening of ET. Tei index did not differ between the acromegaly groups and was incapable of determining the impact of treatment but as a novel marker of early impairment of systolic function, it has to be included in the routine echocardiographic evaluation of acromegalic patients in clinical practice.[9]

As a highly metabolically active organ, the endothelium plays an important role in vascular homeostasis. It exerts this function by releasing many autocrine and paracrine substances. Nitric oxide (NO), the major product of the healthy endothelium, modulates the tone of the underlying vascular smooth muscle. It also plays a major role in the inhibition of several proatherogenic processes such as monocyte and platelet adhesion, oxidation of LDL, synthesis of inflammatory cytokines, smooth muscle cell proliferation and migration, and platelet aggregation. The detection of preclinical cardiovascular disease is now possible via assessment of endothelial function by various methods.

Acromegaly is associated with an increase in mortality, largely from cardiovascular disease, compared to the normal population. There is also a higher prevalence of hypertension, type 2 diabetes mellitus and insulin resistance. In spite of all these, endothelial function studies in acromegaly are scarce, though we have plenty of reports of hemodynamic abnormalities and disordered cardiovascular function. Chanson et al. showed that brachial artery blood flow was reduced with increased forearm vascular resistance in acromegaly patients when compared with matched controls.[23] Other reports, however, demonstrate increased renal blood flow and glomerular hyperfiltration and increased functional liver plasma flow.[24,25] As Evans et al. concluded, a heterogeneous distribution of cardiac output is the hemodynamic feature of acromegaly and endothelial

dysfunction may be the underlying mechanism of the defective brachial artery dilation in response to increased blood flow.[26]

Maison et al. showed that endothelium-dependent vasodilatation is defective in acromegalic patients and found an exaggerated sympathetic-mediated vasoconstrictor response. We studied endothelial function by two different methods.[27] We measured FMD with brachial Doppler ultrasound examination. Then, we complemented this study by measuring biochemical markers of endothelial activity. These are either secreted by the endothelium or shed from its surface in various disease states. TM and P-selectin are examples of these biochemical markers and can be measured in serum or plasma. TM, a cell-surface glycoprotein, exists in plasma as heterogenous fragments and appears to be derived from injured endothelial cells.[28,29] P-selectin, which belongs to a family of cell adhesion molecules called selectins, is an integral membrane glycoprotein localized to α-granules of platelets and Weibel-Palade bodies of endothelial cells. It mediates leukocyte rolling on the endothelium, a process that can precede firm attachment and extravasation during inflammation.[30] P-selectin is synthesized constitutively and stored intracellulary in both platelets and endothelial cells.[31,32] It has been shown that activation of endothelial cells and platelets via several mediators of inflammation induces quick surface expression of P-selectin.[30] A soluble form has been detected in the plasma of healthy subjects and elevated levels have been reported in a number of disease states.[33] Increased levels of P-selectin may reflect platelet and/or endothelial cell activation and be useful in monitoring disease activity.[34]

This study demonstrates that FMD, the earliest functional vascular change in atherogenesis, is reduced in both acromegaly groups and biochemical endothelial markers are found to be in inverse relation with FMD. Although FMD did not differ significantly between the two acromegaly groups, CA group still had lower FMD values when compared to healthy controls.

Impact of treatment is reflected as improvement in FMD in CA group and the active disease state may be accepted as the major factor that contributes to endothelial dysfunction as the two acromegaly groups were matched according to risk factors. P-selectin was increased in both of the acromegaly groups and significantly higher than the control subjects. TM, however, was found to be elevated only in the active disease state and did not differ between the CA group and the control group. In other words, endothelial cell activation that is reflected by high P-selectin levels is still present in CA but endothelial cell injury detected by measuring TM can be prevented by treatment in acromegaly. So endothelial cell injury in cured acromegaly, as evidenced by TM levels, is decreased, however endothelial dysfunction still persists.

This was a cross-sectional retrospective study. If the study was longitudinal and we could collect pre and post data from the same group of patients, the study would be much stronger. This can be regarded as a limitation of our study.

Tissue Doppler assessment is a useful additional tool to assess long-axis cardiac function in patients with acromegaly. Tei index and TDI analysis of mitral annulus velocity complement echocardiographic evaluation in acromegaly and should be a part of echocardiographic evaluation of patients with acromegaly. As well as these cardiac functional changes, endothelial function both in the form of FMD and endothelial cell markers is impaired in AA. We demonstrated that, as a marker of endothelial cell injury, TM measurement reflects the active disease state more specifically and endothelial injury is improved in acromegaly with appropriate treatment and control of disease activity.

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