

Endothelial Dysfunction in Patients with Acromegaly

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It has been shown that Growth hormone (GH) and insulin like growth factor 1 (IGF-1) has important effects on heart and vascular system. However, little is known about endothelial function in acromegaly. The aim of this study was to determine endothelial function in patients with acromegaly.

Endothelial function was evaluated in 10 patients with active acromegaly (eight men, two women) and in 11 age, sex and weight matched control (eight men, two women) using a flow mediated dilatation (FMD) technique in the brachial artery.

In acromegalic patients mean FMD was 8.3 ± 3.5 % and significantly lower than that of control group ($p=.023$). However, there were no significant correlations between GH, IGF-1 levels and percentage of FMD.

These findings suggest that endothelial function impaired in patients with acromegaly.

Keywords: Acromegaly, Endothelial dysfunction, Growth hormone

Introduction

Acromegaly is associated with a two-threefold increase in cardiovascular mortality compared to the normal population (1). Before the introduction of modern, effective therapeutic modalities, about 80% of these patients died before the age of 60 from cardiovascular disease (2). It is usually explained by the high prevalence of risk factors leading to atherosclerosis, such as hypertension, type 2 diabetes mellitus, dyslipidemia which are more frequent in acromegalic patients (3-4). In spite of this background, little attention has been given to the direct role of excess GH and IGF-1 secretion in endothelial dysfunction which is triggering event in the development of atherosclerosis.

Endothelial cells are one of the major cell type that contributes atherosclerosis. These cells are

metabolically highly active and play a key role in vascular homeostasis through the release of a variety of autocrine and paracrine substances. Assessment of endothelial functions by different methods has emerged as a tool for detection of presence of preclinical CVD (5). The assessment of flow mediated dilatation (FMD) of brachial artery has been widely used as a simple, non-invasive method of endothelial function evaluation (6,7).

Studies on endothelial functions in acromegaly are rare and very little is known about effects of acromegaly on vascular function (8,9) To assess whether GH excess is associated with endothelial dysfunction or not, we measured brachial artery FMD in patients with active acromegaly. More importantly, control group were selected from subjects that each matched to an acromegalic patient for age, sex, smoking habit. Numbers of diabetic and hypertensive patients were also matched to evaluate direct role of disease itself.

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Materials and Methods

We studied 10 patients with active acromegaly (either newly diagnosed or unsuccessfully treated)

and 11 age, sex, BMI, smoking habit, diabetes mellitus, hypertension and hiperlipidemia matched subjects as control group. Acromegaly diagnosed on basis of high levels of fasting serum GH, not suppressible GH levels below 2 ng/mL after 100 g oral glucose loading and high IGF-1 levels for age. Informed consent was obtained from all individuals.

Blood sampling was performed to measure serum GH and IGF-1 levels, lipid profile and other biochemical parameters in the morning of examination after at least 8-h overnight fasting. GH and IGF levels assayed by Chemiluminescent and Immune Radiometric Assay Methods, respectively.

To measure flow-mediated dilatation, brachial artery ultrasonography was performed using a standard technique (6,7). All measurements were carried out in a quiet laboratory at the stable temperature of 21-23 C. All subjects were asked to give up alcohol or caffeine-containing beverages for at least 12 h before the study. Aspirin and other NSAID drugs were stopped at least 5 days prior to study. Measurements were performed after an overnight fasting. All subjects rested in supine position for 15 min before and during study procedure. A high-resolution Doppler ultrasound system (HDI-5000; ATL, Bortel, Washington, USA) equipped with a 12MHz linear-array transducer was used to measure the diameter and flow velocity of brachial artery. A non-tortuous segment of the brachial artery was scanned longitudinally 4-5 cm above the elbow at which clearest image was determined, the skin was marked and the arm kept in a constant position throughout the study. A pneumatic tourniquet was placed around the forearm distal to the target artery, inflated to a pressure of 250 mmHg and pressure was held for 5 min. The diameter of brachial artery was measured from the anterior to the posterior interface between the media and adventia at the end of diastole, incident with R wave on a continuously recorded electrocardiogram at baseline and second scans was performed to determine endothelium-dependent vasodilation. The percentage of FMD was defined as maximum vessel diameter change (10)

Statistical analysis was performed with SPSS for Windows version 11.0(SPSS Inc., Chicago, Illinois, USA). Data are presented as mean \pm SD. Mann-Whitney test was used to compare continuous

variables and X2-test was used to compare categorical variables. The levels of $p < 0.05$ was considered statistically significant.

Results

All subjects tolerated the study well. Study population consisted of 10 patients (8 male, 2 female) and 11 (8 male, 3 female) controls. The study and the control groups were well matched for BMI and age. The numbers of diabetic and hypertensive patients were similar in the study (one diabetic, three hypertensive) and control (one diabetic, two hypertensive) groups. The smoking status was also similar in the study (4 smokers, 6 non-smokers) and in the control (4 smokers, 7 non-smokers) groups. The study group had significantly lower mean FMD than the control group. However, in correlation analysis there was no significant correlation between mean FMD and GH levels or IGF-1. Table 1 summarizes baseline characteristics in the 10 acromegalic and in 11 control subjects.

Table 1. Baseline characteristic of the study and the control groups

	Acromegalics	Controls	P
Age (years)	48.0 \pm 9.8	51.1 \pm 6.7	NS
BMI(kg/m ²)	28.5 \pm 4.1	27.2 \pm 4.0	NS
Systolic BP (mm Hg)	123.2 \pm 12.1	117.3 \pm 14.2	NS
Diastolic BP(mm Hg)	75.0 \pm 9.4	75.5 \pm 9.1	NS
Total cholesterol (mg/dl)	194.1 \pm 33.7	185.0 \pm 12.7	NS
Triglyceride (mg/dl)	200.4 \pm 78.3	147.1 \pm 34.4	0.033

NS: not significant

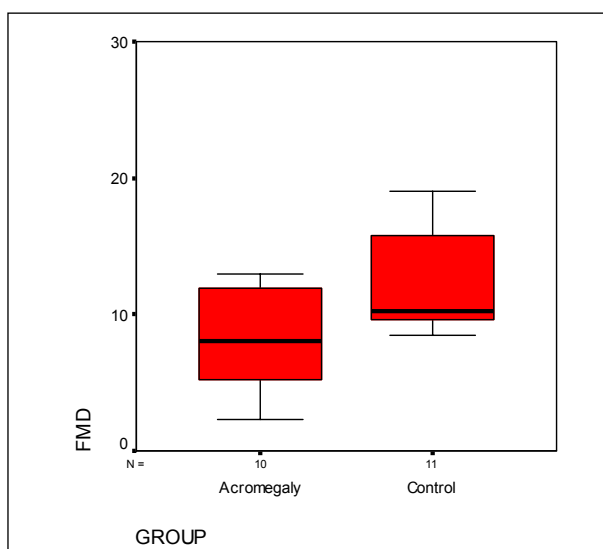


Figure 1. Flow mediated dilatation in patients with acromegaly and in controls

Discussion

The endothelium is metabolically highly active and plays a key role in vascular hemostasis through the release of a variety of autocrine and paracrine substance. The healthy endothelium, particularly endothelium derived nitric oxide, modulates the tone of underlying vascular smooth muscle and inhibits several preatherogenic effects. Several disorders like DM, insulin resistance, obesity, PCOS, hypopituitarism, Cushing's disease, hypothyroidism are known to be associated with endothelial dysfunction (11). However, studies on endothelial function in acromegaly are rare, although there are several reports of haemodynamic abnormalities and impaired cardiovascular function in acromegaly.

Chanson et al. (9) demonstrated the reduced brachial artery blood flow with significantly higher forearm vascular resistance in acromegalic patients. This is in contrast to the previously reported increased renal blood flow, glomerular hyperfiltration (12) and functional liver plasma flow (13). Maison et al. (8) reported impaired endothelium-dependent vasodilatation and increased sympathetic system mediated vasoconstrictor response in acromegalic patients. Bereveti et al. (14) demonstrated that patients with active acromegaly have functional and morphological vascular alterations using FMD method and measuring intima-media thickness of carotid artery, and suggested that the decreased FMD may be attributable, at least in part, to abnormal GH and IGF-1 secretion itself (14). It has been shown that IGFs are potent mitogens for vascular smooth muscle cells (15), and constant infusion of IGF-1 further stimulates vascular smooth muscle cell proliferation in rat aorta after balloon catheter injury (16). Furthermore, treatment with IGF-1 increases the transcription of intercellular adhesion molecules that is a typical feature of endothelial dysfunction (17). On the other hand, IGF-1 increases the nitric oxide production from endothelium (18), treatment with GH improves endothelial functions in hypothyroid patients.

We have demonstrated that mean FMD was significantly low in acromegaly compared with matched healthy control. Since the impaired FMD represent the earliest functional change in atherogenesis, these patients may be at high risk to develop cardiovascular diseases. The mechanism

by which acromegaly leads to the endothelial dysfunction remains to be elucidated. Acromegaly is associated with a cluster of risk factors (19), each of them may induce the vascular damage. In our study, the control group is consisted of the subjects who are similar to acromegalic patients as regards to cardiovascular risk factors. Age, sex, smoking habit, mean systolic and diastolic blood pressure, and number of diabetic patients were similar in both group.

In conclusion: These findings suggest that disease itself (abnormal GH and IGF-1 secretion) may play a role in generating endothelial dysfunction beside the accompanying risk factors.

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