ENDOTHELIAL DYSFUNCTION IN ACROMEGALIC PATIENTS: A CASE-CONTROL STUDY

S. Ghiorghe^{1,*}, A. Dragomir², D. Bartos³

¹“Policlinico di Monza” Medical Center, Dept. of Cardiology, ²“C.I. Parhon” National Institute of Endocrinology, ³Clinical Emergency Hospital, Dept. of Internal Medicine, Bucharest, Romania

Abstract

Purpose. Assessing cardiovascular risk in patients with acromegaly using traditional cardiovascular risk factors is inadequate. Endothelial dysfunction seems to be a much better indicator for assessing cardiovascular risk in acromegaly. The study aims to compare from this point of view two groups of patients, with hypertension and with acromegaly.

Methods. The first group consists of 54 patients with acromegaly and the second group of 64 hypertensive patients. Endothelial dysfunction was evaluated by the FMD method. The relationship between endothelial dysfunction, specific humoral markers of acromegaly and traditional cardiovascular risk factors was analysed in both groups.

Results. Although the presence of cardiovascular risk factors was statistically significantly higher in the group of hypertensives (the most important were age, blood pressure, glycemia, hypertriglyceridemia and SCORE), the presence of endothelial dysfunction was higher in the acromegaly group (61.10% vs. 32.10%, $p=0.02$). The best correlation with endothelial dysfunction in acromegaly group was the level of GH (28.9 ± 28 vs. 11.7 ± 10.3 , $p=0.003$).

Conclusions. The presence of endothelial dysfunction in patients with acromegaly is highly dependent on the level of GH and traditional cardiovascular risk factors are less important. In these patients the cardiovascular risk should not be evaluated in the same way as in normal population.

Key words: Acromegaly, endothelial dysfunction, cardiovascular risk factors.

INTRODUCTION

Cardiovascular diseases are currently considered to be among the most common causes of mortality and morbidity in developed countries and therefore consuming a significant amount of health system resources. Over time, various systems of cardiovascular risk assessment have been developed, most of them having the traditional risk factors (hypertension, dyslipidemia, smoking,

diabetes, obesity, gender, age) as the input variables. Endothelial dysfunction (ED) is another cardiovascular risk factor that has been increasingly studied in recent years. Considered as the initial change in the atherogenesis process (1), it has been studied in detail in its relationship with other risk factors / morbidity: smoking, high blood pressure (HBP), dyslipidemia, diabetes, etc. Although some of the endocrine disorders are recognized as pathologies that considerably increase the cardiovascular risk, their relationship to endothelial dysfunction has been relatively poorly studied.

Acromegaly is one of the endocrine disorders with a higher morbidity and mortality than general population (2), especially related to cardiovascular pathology. The cause seems to be an increase in the incidence of HBP, dyslipidemia and diabetes in these patients. Another cause may be endothelial dysfunction induced by excess GH and IGF1 present in acromegaly (3). Consequently, the aim of the present study is to assess the relationship between the presence of various risk factors and endothelial dysfunction in acromegaly patients as compared to patients with primary HBP.

PATIENTS AND METHODS

The study was carried out during 2007-2017 on 54 patients with acromegaly, which is considered to be a rare disease (4-6/1 mil. individuals) (4), with an important impact on the survival of the affected individuals, especially in relationship with the associated cardiovascular disease. The patients were recruited in the National Institute of Endocrinology “C.I. Parhon”, Bucharest, Romania. All cases were informed about the study protocol and signed the informed consent. The study was in agreement with the Helsinki declaration of human rights and fulfilled the requirements of the Institutional Ethics Committee. The study design is cross sectional, every individual was assessed once, at presentation for follow-up of acromegaly status.

*Correspondence to: Silviu Ghiorghe MD, “Policlinico di Monza” Medical Center, Dept. of Cardiology, 27th Tony Bulandra, 2nd District, Bucharest, 021967, Romania, E-mail: gsilviu2002@yahoo.com

Table 1. Comparison of two groups

Risk factors	Acromegaly	Control	P
Age (years)	50.2±13.5	59.4±11.2	<0.001
Smokers(%)	13.0%	17.2%	0.525
SBP (mmHg)	128.9±21.8	149.9±26.1	<0.001
DBP (mmHg)	80.0±12.9	85.6±12.8	0.023
Diabetes mellitus(%)	16.7%	28.1%	0.140
Glycemia (mg/dL)	99±17.0	110.9±33.9	0.015
Cholesterol (mg/dL)	202.6±34.4	192.4±52.1	0.204
Triglycerides (mg/dL)	106.6±48.9	143.4±91.7	0.006
SCORE	2.1±3.1	7.6±8.9	<0.001
%FMD	6.2±14.8	7.8±8.5	0.469
ED(%)	61.1%	39.1%	0.017

SCORE= risk score calculation; FMD, flux mediated dilation; ED= endothelial dysfunction.

Table 2. Comparison between patients with ED in the two groups

Risk factors	Acromegaly	Control	P
Age (years)	49.3±12.1	63.8±9.2	<0.0001
Smokers(%)	15.2%	36.0%	0.066
SBP (mmHg)	131.9±23.3	158.4±27.0	<0.0001
DBP (mmHg)	82.4±14.4	88.0±14.1	0.126
Diabetes mellitus(%)	15.2%	48.0%	0.006
Glycemia (mg/dL)	100.7±16.5	123.6±46.6	0.027
Cholesterol (mg/dL)	195.3±29.5	205.8±40.8	0.284
Triglycerides (mg/dL)	111.3±56.5	178.8±108.4	0.008
SCORE	2.07±2.8	12.5±11.8	<0.0001

SBP= systolic blood pressure; DBP = diastolic blood pressure; SCORE= risk score calculation.

All acromegaly patients had active disease when they were enrolled in the study. The vast majority were treated patients (surgical / radiotherapy / medical therapy), only 15 of them being newly diagnosed, without treatment at the time of evaluation. This group of patients was compared to another group of 64 non-acromegaly, hypertensive patients, enrolled in the order of their presentation at the Cardiology Department of “Policlinico di Monza” Medical Center, Bucharest, Romania. All hypertensive patients received treatment for their cardiovascular disorders. Comparison included the analysis of the main cardiovascular risk factors (sex, age, BP, dyslipidemia, diabetes mellitus, smoking) and risk score calculation (SCORE), all related to the presence of ED in these patients. SCORE was calculated according to the formula specific of high cardiovascular risk populations (5).

Determination of endothelial dysfunction

Assessment of ED was performed by the ultrasonographic method for evaluation of the flux-mediated and endothelium-dependent dilatation response (FMD) in the brachial artery (6,7). The procedure consists in measuring the initial diameter of the brachial artery and subsequent induction of ischemia in its territory by inflating a pneumatic

tourniquet to reach a pressure 50 mm Hg higher than the systolic pressure in the upper half of brachial artery and complete the artery occlusion for 5 minutes. The brachial artery was scanned longitudinally at 2 to 10 cm above the elbow with a 10 MHz linear array transducer and with a GE ultrasound system. The second measurement was performed between 30 and 120 seconds after disinflation of pneumatic tourniquet. Upon the release of the occlusion, an increase in shear stress results in an endothelial-dependent, NO-driven, FMD of the brachial artery. The diameter of artery is assessed before and after occlusion with results being reported as a percent change from baseline. The measurements are made at the end of diastole (R-wave on ECG). ED is defined as a lack of increase of the brachial artery diameter by 10% (8).

Statistical methods

The SPSS version 19.0 for Windows was used for statistical analysis. Normal variables were expressed as mean ± standard and nominal variables as percent. We performed Spearman, means correlations and chi square test. The level of significance as $p < 0.05$ was used to determination if there is a relationship between the variables.

Table 3. Acromegaly group. Analysis by sex

	Women	Men	P
Age (years)	53.5±11.1	44.2±15.6	0.015
Smokers (%)	11.4%	15.8%	0.64
HBP (%)	51.4%	57.9%	0.64
SBP (mmHg)	126.3±19.2	133.7±25.9	0.23
DBP (mmHg)	78±12.8	83.9±12.6	0.1
Diabetes (%)	14.3%	21.1%	0.52
Dislipidemia (%)	82.9%	68.4%	0.22
Cholesterol (mg/dL)	213.5±30.3	182.6±33.1	0.001
Triglycerides (mg/dL)	104.2±46.8	109.4±53.6	0.71
HOMA	4.9±9.7	4.7±6.1	0.94
Duration of acromegaly (years)	9.9±5.9	7.8±6.6	0.24
ED (%)	51.4%	78.9%	0.048
SCORE	1.8±2.7	2.7±3.7	0.323

HBP= high blood pressure; SBP= systolic blood pressure; DBP = diastolic blood pressure; ED = endothelial dysfunction; HOMA = Homeostasis Model Assessment; SCORE= risk score calculation.

Table 4. Correlation of risk factors with endothelial dysfunction in acromegaly group

ED	YES	NO	P	Spearman
Age (years)	49.3±12.1	51.6±15.6	0.53	0.13
Smokers (%)	15.2%	9.5%	0.54	
HBP (%)	54.5%	52.4%	0.87	
SBP (mmHg)	131.9±23.3	124±18.7	0.19	0.08
DBP (mmHg)	82.4±13.4	76.4±11.5	0.09	0.01
Diabetes (%)	15.2%	19.0%	0.7	
Dislipidemia (%)	24.0%	18.0%	0.26	
Cholesterol (mg/dL)	195.3±29.5	214.2±38.9	0.049	0.02
Triglycerides (mg/dL)	111.3±56.5	97.7±33.2	0.32	0.47
HOMA	4.82±10	4.93±5.7	0.96	0.3
Duration of acromegaly (years)	8.6±6.5	10.2±5.6	0.37	0.02
GH (ng/mL)	28.9±28	11.7±10.3	0.003	<0.0001
SCORE	2.1±2.8	2.3±3.5	0.86	0.779

RESULTS

The direct comparison of the two groups revealed that the presence of cardiovascular risk factors was higher in the control group, which was confirmed by the obviously higher SCORE value in this group, but the presence of ED was statistically higher in the acromegaly group, only 25 patients with hypertension had ED vs. 33 patients with acromegaly (Table 1). Furthermore, the analysis of the ED subgroups in both groups showed a significantly higher prevalence of risk factors in hypertensive patients than in those with acromegaly (Table 2).

The analysis of the acromegaly group based on sex showed that ED was significantly higher in males, although older age and hypercholesterolemia were more prevalent in women (Table 3).

Of the risk factors that correlated with the presence of ED in the acromegaly group, the most powerful was the GH level. Statistically significant were also the cholesterol level, DBP values and

duration of acromegaly (Table 4).

The control group was homogenous concerning the presence of risk factors in the analysis by sex, without any statistical difference (Table 5). A significant difference was found between the ED group and non -ED group. All risk factors, except DBP and level of cholesterol, were more prevalent in patients with ED. It is noted that SCORE (a composite of risk factors) was much higher in the group with ED, with a very high significance ($p<0.001$) (Table 6).

DISCUSSION

Acromegaly is a condition in which mortality is predominantly due to cardiovascular complications. It appears to increase the incidence of cardiovascular risk factors (HBP, dyslipidemia, insulin resistance) (9). However, studies conducted so far suggest that the main mechanism by which acromegaly causes cardiovascular pathology is not only the increased incidence of risk factors but also the direct action of

Table 5. Characterization of the control group by sex

	Men	Women	P
Age (years)	59.7±10.4	59.1±12.3	0.844
SBP (mmHg)	149.4±21.1	150.5±30.4	0.864
DBP (mmHg)	84.7±8.7	86.4±16.0	0.597
Cholesterol (mg/dL)	188.1±55.6	196.6±48.9	0.516
Triglycerides (mg/dL)	157.2±102.9	129.7±78.2	0.235
Glycemia (mg/dL)	117.1±41.7	104.8±22.9	0.150
Diabetes (%)	18.8%	9.4%	0.095
Smokers (%)	10.9%	6.3%	0.320
ED (%)	37.5%	40.6%	0.789
SCORE	10.2±8.9	4.9±8.2	0.018

Table 6. Characterization of the control group, correlation of risk factors with the presence of

ED	YES	NO	P
Age (years)	63.8±9.2	56.6±11.6	0.012
SBP (mmHg)	158.5±27.0	144.4±24.1	0.035
DBP (mmHg)	88.0±14.1	83.9±11.8	0.215
Cholesterol (mg/dL)	205.8±40.9	183.7±57.0	0.099
Triglycerides (mg/dL)	178.8±108.4	120.7±72.0	0.023
Glycemia (mg/dL)	123.6±46.6	102.8±19.1	0.043
Diabetes (%)	77.8%	22.2%	0.003
Smokers (%)	48.0%	15.4%	0.005
SCORE	12.5±11.8	4.4±4.2	<0.001

GH on the endothelium (10). It appears that the action of GH and IGF-1 is potentially mitogenes on smooth muscle cells in vascular vessels (3), and IGF-1 increases the synthesis of adhesion molecules, a modification described in the context of endothelial dysfunction (11). So, controlling plasma levels of GH and IGF1 is very important in these patients (12).

Vascular endothelium is a highly complex, multi-function metabolic tissue, modulated by endocrine, paracrine and autocrine intercourses. Evaluation of endothelial dysfunction can be performed by multiple methods - evaluating its reactivity to various triggers, evaluating structural imaging, or measuring various humoral markers. The most commonly used method is the assessment of FMD response in the brachial artery and the presence of endothelial dysfunction in acromegaly patients could be highlighted by this method (13).

The vast majority of studies published assess endothelial dysfunction in acromegalic patients and normal individuals or patients with matched cardiovascular risk factors. In our study we included non-acromegaly, hypertensive patients as the inclusion criteria, but with an incidence of risk factors higher than those of the acromegalic patients. A peculiarity of the study was that hypertensive, non-acromegaly patients were already diagnosed and treated patients. All other studies used a small number of patients, at the limit of using statistical methods, acromegaly being a

very rare condition. In our study we included a total of 54 acromegaly patients, the largest group of literature on this subject being 39 patients (14). The results of our study are in concordance to other studies on this topic. Endothelial dysfunction in acromegaly patients does not correlate with cardiovascular risk factors but especially with GH levels and duration of acromegaly. Comparing the two groups we show a prevalence of endothelial dysfunction in the acromegaly population superior to the control group, although the risk factors in these control patients were statistically significantly higher.

In conclusion, traditional cardiovascular risk factors are not as representative for acromegaly patients. If the cardiovascular risk factors in the control group have a clear statistical correlation with the presence of endothelial dysfunction, SCORE (cumulative of these factors) revealed a strong association, the same is not the case with the group of acromegalics. In patients with acromegaly, both the traditional risk factors taken individually, and also the SCORE value, did not correlate with the presence of endothelial dysfunction. The only one who had a statistically strong association was the plasma level of GH. In other words, the main promoter of endothelial dysfunction in acromegaly patients is the plasma GH level, apparently not by accentuating traditional cardiovascular risk factors but by other mechanisms independent of hypertension, dyslipidemia, diabetes or smoking.

Conflict of interest

The authors declare that they have no conflict of interest.

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