Impact of Disease Duration on Coronary Calcification in Patients with Acromegaly

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Key words
- acromegaly
- coronary calcification
- disease duration

Abstract

It is well established, that the increased mortality in patients with acromegaly is due to cardiac diseases. Cardiomyopathy is the predominant cardiac alteration in patients with acromegaly. There are less data about coronary heart disease or coronary calcifications. Electron beam computed tomography (EBCT) is the standard imaging modality for identification of coronary artery calcifications (CAC) and can determine the extent and severity of coronary atherosclerosis. Coronary risk was evaluated by the Framingham risk score (FRS). The prospective study included 30 patients with acromegaly (mean age 53±14 year; 16 females, 14 males; BMI 28.1±3.6 kg/m^2; mean±SD), 12 patients had active disease (IGF-1 751±338 µg/L; GH 25.6±36.4 µg/L), 9 were well-controlled (IGF-1 157±58 µg/L; GH 1.8±1.1 µg/L) under somatostatin analogue octreotide (n=5), dopamine agonists (n=2), and the GH receptor antagonist pegvisomant (n=2; GH levels were not determined in this subgroup) and 9 were cured IGF-1 (148±57 µg/L; GH 0.5±0.2 µg/L). Increased left ventricular muscle mass index (LVMI >132 g/m^2) was focused in 53%, hypercholesterinemia in 63%, hypertension in 43%, diabetes mellitus/impaired glucose tolerance in 27%, and smokers in 53% (pack per year 9±15 yr). For quantification of CAC the EBCT was used and the Agatston calcium score was determined. Results were composed to established age and sex adjusted percentile distribution of CAC. CAC was present in 53%, high CAC score (75th percentile) in 37% and were categorized as cardiovascular high risk patients. FRS was related to the CAC score (p=0.008, r^2=0.22) and the disease duration (p=0.002, r^2=0.29). The CAC score correlated with LVMI (p=0.02, r^2=0.17), the disease duration of acromegaly (p=0.004, r^2=0.36), and the FRS (p=0.008, r^2=0.22). Patients with a high CAC score had a longer disease duration of 9.6±4.7 versus 5.4±2.8 years with CAC<75th percentile (p=0.02). In summary, the disease duration and consequently the accompanying metabolic disorders appear to influence the degree of CAC in patients with acromegaly. The observations underline the importance of early and sufficient treatment of acromegaly in high risk patients.

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Introduction

Acromegaly is a rare disease and due to chronic GH/IGF-1 excess almost of a GH-secreting pituitary adenoma [1]. Patients with acromegaly predominantly have a high prevalence of metabolic and cardio-vascular complications, such as hypertension, dyslipoproteinemia, diabetes mellitus/impaired glucose tolerance, which are associated with coronary atherosclerosis [2,3]. Cardiomegaly, cardiomyopathy, sleep apnoea syndrome as well as cerebrovascular diseases are complications, representing the first cause of death in acromegalics [4].

It has been shown, that the prevalence of myocardial infarction is similar to that observed in the general population, whereas arrhythmias are frequent in patients with acromegaly and may be due to cardiomegaly [4,5]. Autoptic studies demonstrated that severe coronary atherosclerosis are detectable only in patients with long-term acromegaly [6]. Disease control seems to influence alterations of arteries, regarding the observations that intima-media thickness of the carotid arteries were increased in about 50% of patients and normalized after cure or disease control [7].

Electron-beam CT (EBCT) enables the quantitative evaluation of calcified coronary atheroscle-

rosis [8–10]. Coronary risk is currently calculated by algorithms, i.e. the Framingham risk score (FRS), that based on the analysis of conventional risk factors, such as age, sex, smoking habit, diabetes mellitus, hypertension, and hypercholesterinemia [11].
The aim of our study was to investigate whether patients with acromegaly are at risk for coronary disease and to evaluate the influence of accompanying metabolic complications and the impact of disease duration.

Patients and Methods

Patients

Thirty patients (16 females, 14 males) with a mean age 53±14 (mean±SD) years (range 30–81) with acromegaly were included in the study. They were recruited from the Department of Endocrinology, University of Duisburg-Essen in Germany. The diagnosis of acromegaly was made on the basis of physical examination, IGF-1 and GH levels after an oral glucose load (75 g) [12,13]. 67% (20/30) were previously surgically treated, 13% (4/30) underwent radiotherapy (which was ã-knife in all cases). 27% (8/30) of the patients were treated with the somatostatin analogue (SSA) octreotide acetate (Sandostatin LAR® 20 or 30 mg every 4 weeks, Novartis Pharma GmbH, Basel, Switzerland) and 7% (2/30) with pegvisomant (Pfizer GmbH, Karlsruhe, Germany) 15 mg s.c. daily. 7% (2/30) were treated with dopamin agonists (bromocriptine 5 mg daily and cabergoline 1 mg twice weekly).
The disease duration was estimated from the lag time between the onset of symptoms and signs of disease and the date when the treatment was proven to be effective (group of well controlled patients) or the data of enrolment in this study (group of active patients). Body mass index (BMI), systolic and diastolic blood pressure, plasma glucose at 0 and 120 min during the oGTT, total cholesterol, HDL cholesterol, LDL cholesterol, triglyceride levels and smoking habit (pack per year) were evaluated in each patient. The risk of cardiovascular events within the next 10 years were determined according the Framingham risk scoring (FRS) (age, sex, plasma blood glucose, smoking habit, systolic and diastolic blood pressure, LDL and HDL) [11].

Echocardiographic examination

Images were recorded with patients in the left lateral decubitus position with a 3.75-MHz. sector probe using a Toshiba SSA 380 A Power Vision or a Hewlett Packard Sonos 1500 machine (both commercially available). For each patient, an electrocardiogram was simultaneously recorded. The echocardiographic examination was performed by an investigator who had no knowledge of the clinical or angiographic data of the patients. Standard views were recorded according to the guidelines of the American Society of Echocardiograp [14]. For recordings of the mitral inflow velocity pattern, the sample volume (size 2 mm) of the pulsed Doppler was placed between the tips of the mitral leaflets in the apical 4-chamber-view. Left ventricular outflow velocity was recorded from the apical long-axis view with the sample volume of the pulsed Doppler positioned just below the aortic annulus. Two-dimensional and Doppler tracings were recorded over 5 cardiac cycles at a sweep speed of 50 or 100 mm/s and stored on videotape for later playback and analysis.

Electron-beam computed tomography

Non-enhanced EBCT scans were performed with a Siemens Evolution scanner (GE Imatron, South San Francisco). The scanner was operated in the single slice mode with an image acquisition time of 100 milliseconds and a section thickness of 3 mm as described previously [15,16]. A 26 cm^2 field of view was used. Contiguous slices down to the apex of the heart were obtained (○ **Fig. 1**).

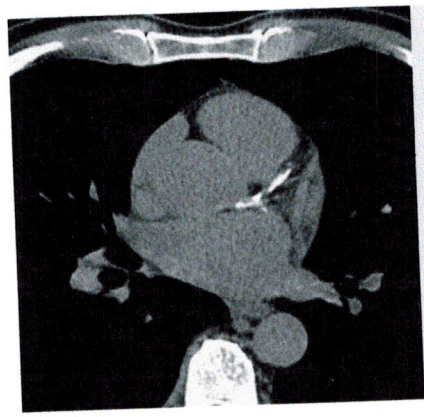

Fig. 1 EBCT scan imaging shows diffuse calcified plaques of the left anterior descendent artery (LAD) in a 55 year old female with active acromegaly.

For each study, a calcium score was determined using the methods of Agatston et al. calcified lesions were encircled manually by a physician and included in the analysis only if strictly in the trajectory of the coronary arteries [16]. Percentile values of the CAC were calculated on the basis of EBCT coronary calcium scans in 1346 men and 643 women with no indication of ischemic heart disease who had been scanned at our institutions [15,17]. On the basis of the coronary segmental classification proposed by the American Heart Association, the calcium score was calculated for each of 11 major coronary segments [18]. For convenience, these segments can be assumed to correspond largely to the proximal, mid, and distal portions of the right coronary artery (segments 1–3 according to the American Heart Association), the left main stem (segment 5), the proximal, mid, and distal left anterior descending coronary artery and the first diagonal branch (segments 6–9), and the proximal and mid left circumflex coronary artery as well as the obtuse marginal branch (segments 11–13).

Hormone assays

Serum GH levels were determined by a chemiluminescence immunometric assay (Nichols Institute Diagnostics GmbH, Bad Nauheim, Germany). The assay was calibrated against the WHO 1st international standard (80/505) for human GH. Normal range was ≤5 µg/l. Intra- and interassay coefficients of variation (CVs) for a low point of the standard curve were 5.4% and 7.9%, respectively. Plasma IGF-I concentrations were measured by an immunoradiometric assay (Nichols Institute Diagnostics GmbH, Bad Nauheim, Germany). The assay was calibrated against the WHO 1st International Reference Reagent 87/518. Intra- and interassay CVs for low IGF-I concentrations were 2.4% and 5.2%, respectively. Normal range of IGF-1 levels: 182–780 µg/L (16–24 years), 114–492 µg/L (25–39 years), 90–360 µg/L (40–54 years) und 71–290 µg/L (>54 years).

Statistical analyses

The data, if not marked otherwise, represent the mean±standard deviation. In case of skewed distribution the median was also determined. Comparisons of dichotomous variables were done by Fisher's exact test. Continuous data were tested statistically by the U-test according to Wilcoxon, Mann and Whitney on differences between the groups. All tests were done two-tailed,

p-values < 0.05 were considered statistically significant. Correlation of calcification (Agatston calcium score) to various variables were analyzed with Pearson's test. Statistical analyses were perfomed using GraphPad InStat version 3.02 (GraphPad Software, San Diego, California USA). Differences were considered statistically significant at $p < 0.05$. (**Table 1**)

Results

The GH and IGF-1 levels in the included 30 patients with acromegaly were 406 ± 357 µg/L and 11. 6 ± 26.3 µg/L, respectively. 12 patients had active disease (IGF-1 751 ± 338 µg/L; GH 25.6 ± 36.4 µg/L), 9 were well-controlled (IGF-1 157 ± 58 µg/L; GH 1.8 ± 1.1 µg/L) under somatostatin analogue octreotide (n = 5), dopamine agonists (DA) (n = 2) and the GH-receptor antagonist pegvisomant (n = 2; GH levels were not determined in this subgroup) and 9 were cured IGF-1 (148 ± 57 µg/L; GH 0.5 ± 0.2 µg/L). Baseline serum GH and IGF-1 levels were significantly lower in patients with well controlled and cured acromegaly (**Table 2**). There were no statistical differences concerning smoking habit, hypercholesterolemia, hypertension, diabetes mellitus/impaired glucose tolerance (IGT), and the Framingham risk score. No patient suffered myocardial infarction or a coronary angioplasty.

53% (16/30) had an increased left ventricular muscle mass index, but the prevalence of cardiomegaly did not differ between the 3 groups. All other echocardiographic parameters (IVSD: intraventricular septum diameter; LVEDD: left ventricular end-diastolic diameter; FS: fractional shortening; EF: ejection fraction; LVMI left ventricular muscle mass index) were also similar in the three groups (**Table 3**).

CAC was focused in 16 (53%) of patients. The total EBCT scores ranged from 0–4390. The median was 1.5, the 25th percentile 0, and the 75th percentile 123; 37% had a high CAC score (75th percentile) and were categorized as cardiovascular high risk patients, 47% were below the 25th percentile, 13% below the 50th percentile, and 3% below the 75th percentile. Less than 50% of patients in all groups (◦ **Fig. 2**) had an increased FRS evaluated by determination of the 75th percentile of the coronary Agatston calcium score (CAC score) by electron beam computed tomography (EBCT).

The disease duration had the major impact of coronary calcification. Patients (n = 11) above the 75th percentile of the coronary Agatston calcium score (◦ **Fig. 3**) had a significantly longer disease duration than patients below the 75th percentile (9.6 ± 4.7 versus 5.4 ± 2.8 years; p = 0.02). The CAC score correlated with the disease duration of acromegaly (p = 0.004, $r^2 = 0.36$; ◦ **Fig. 4**)

Table 1 Treatment of 30 patients with active, well controlled and cured acromegaly.

Previous treatments	active	well controlled	cured
none	6		
surgery	2		7
SSA	3	1	
surgery + SSA		4	4
surgery + DA		1	1
surgery + Rx	1		2
surgery + Rx + DA		1	
surgery + PEG		2	2
total	12	9	9

Table 2 Clinical data of 30 patients with acromegaly; IGF: impaired glucose tolerance.

	Total	active	well controlled	cured
number	30	12	9	9
female (%)	53	50	66	44
male (%)	47	50	33	55
age (years)	53 ± 14	48 ± 15	54 ± 14	59 ± 12
BMI (kg/m²)	28.1 ± 3.6	27.8 ± 3.2	28.5 ± 4.2	27.9 ± 3.8
disease duration (years)	7 ± 4	7 ± 3	9 ± 6	5 ± 2
GH (µg/L)	11.6 ± 26.3	25.6 ± 36.4†	1.8 ± 1.1††	0.5 ± 0.2
IGF-I (µg/L)	406 ± 357	751 ± 338[a]	157 ± 58	148 ± 57
smoking (%)	53	50	55	33
pack per year	9 ± 15	8 ± 12	14 ± 17	5 ± 11
hypercholesterolemia (%)	63	50	56	89
hypertension (%)	43	33	55	44
diabetes mellitus/IGF (%)	27	42	22	11
Framingham risk score	10.3 ± 8.4	6.3 ± 6.0	12.0 ± 10.8	13.9 ± 6.8

†p < 0.05 active vs. well controlled and active vs. cured

††p < 0.05 well controlled vs. cured

[a]p < 0.001 active vs. well controlled and active vs. cured

Table 3 Echocardiographic parameters of 30 patients with acromegaly.

	Total	active	well controlled	cured
IVSD (cm)	1.18 ± 0.21	1.16 ± 0.22	1.11 ± 0.23	1.22 ± 0.17
posterior wall sickness (cm)	1.16 ± 0.22	1.21 ± 0.23	1.16 ± 0.28	1.16 ± 0.17
LVEDD (cm)	4.99 ± 0.68	5.28 ± 0.46	4.53 ± 0.56	5.05 ± 0.82
FS (%)	38.2 ± 6.2	37.2 ± 5.1	37.8 ± 6.6	39.9 ± 7.4
EF (%)	58 ± 9.3	55.6 ± 11.7	60.2 ± 5.2	59.0 ± 8.9
LVMI (g/m²)	137.3 ± 46	153.8 ± 48.7	112.2 ± 50.6	140.4 ± 27.0

IVSD: intraventricular septum diameter; LVEDD: left ventricular end-diastolic diameter; FS: fractional shortening; EF: ejection fraction; LVMI (left ventricular muscle mass index)

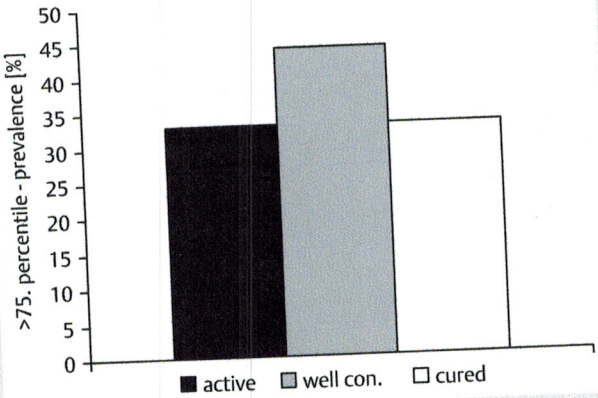

Fig. 2 Prevalence [%] of the coronary Agatston calcium score (CAC score) >75th percentile computed by electron beam computed tomography (EBCT) in 30 patients with acromegaly. 33% (4/12) had active disease, 44% (4/9) were well controlled and 33% (3/9) were cured. There was no statistical differences between the three groups (n=n.s.).

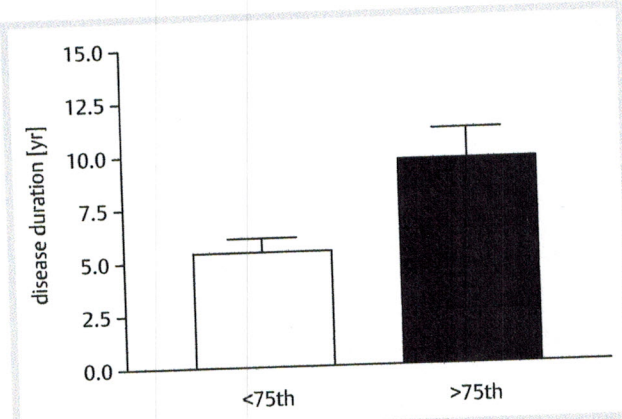

Fig. 3 Disease duration of 30 patients with acromegaly below and above the 75th percentile of the coronary Agatston calcium score (CAC score) by electron beam computed tomography (EBCT). Patients (n=11) above the 75th percentile had a significant longer disease duration than patients below the 75th percentile (9.6±4.7 versus 5.4±2.8 years; p=0.02).

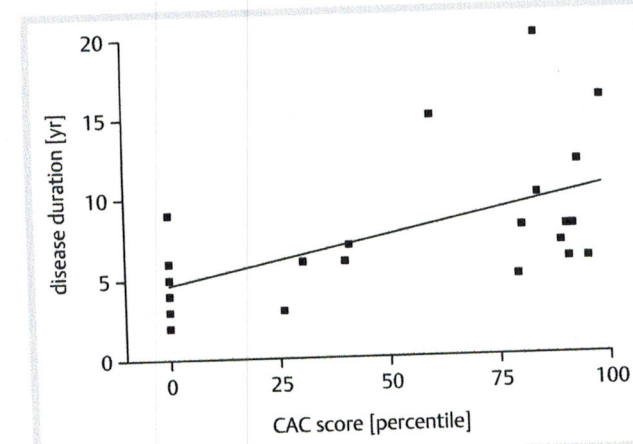

Fig. 4 Correlation between disease duration and the percentile of the coronary Agatston calcium score (CAC score) of 30 patients with acromegaly ($r^2=0.36$; p=0.004).

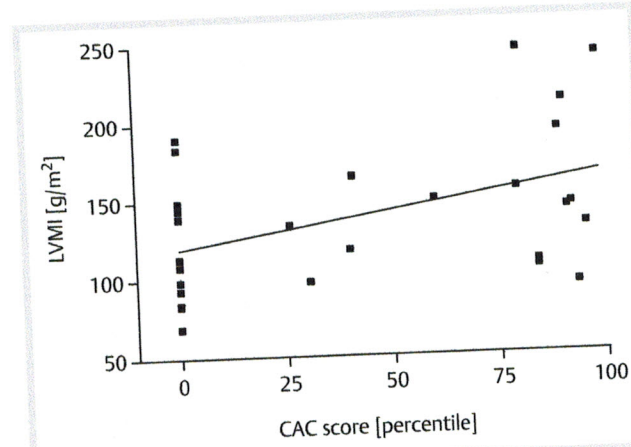

Fig. 5 Correlation between LVMI (left ventricular muscle mass index) and the percentile of the coronary Agatston calcium score (CAC score) of 30 patients with acromegaly ($r^2=0.17$; p=0.02).

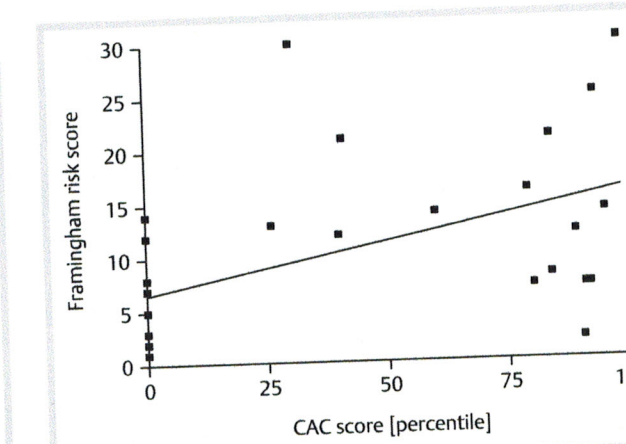

Fig. 6 Correlation between Framingham risk score and the percentile of the coronary Agatston calcium score (CAC score) of 30 patients with acromegaly ($r^2=0.22$; p=0.008).

and the LVMI (p=0.02, $r^2=0.17$; ○ **Fig. 5**). FRS was related to the CAC score (p=0.008, $r^2=0.22$; ○ **Fig. 6**) and the disease duration (p=0.002, $r^2=0.29$; ○ **Fig. 7**). 56% of patients had a low risk (10/12 in the active group; 5/9 in the well controlled group; 2/9 in the cured group), 27% had an intermediate risk (1/12 in the active group; 1/9 in the well controlled group; 6/9 in the cured group) and 17% had a high risk (1/12 in the active group; 3/9 in the well controlled group; 1/9 in the cured group) for developing CHD. No correlation were found between CAC score and influence of radiation.

Discussion

In the present study, we have demonstrated that the coronary calcification score (Agatston CAC score) is related to the disease duration of patients with acromegaly and to the Framingham risk score for stratification of coronary heart disease (CHD) risk. Moreover, the CAC score correlated with the left ventricular muscle mass index (LVMI). This observation of the impact of disease duration as the major factor of systemic complication in acromegaly has been shown in previous studies [4,19].

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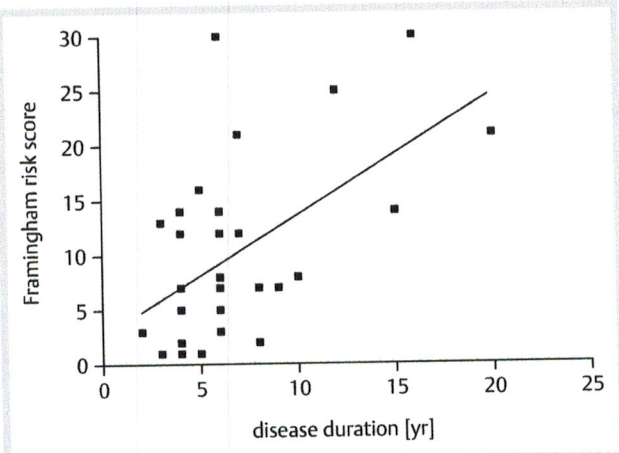

Fig. 7 Correlation between Framingham risk score and the disease duration of 30 patients with acromegaly ($r^2 = 0.29$; $p = 0.002$).

The development of cardiomegaly and cardiomyopathy as well as sleep apnoea syndrome, thyroid volume and the prevalence of thyroid nodules are related to the estimated disease duration (2, 4, 19-21). It is obvious, that the current disease activity is not related to the systemic complication, considering the fact that the cure of a patient with acromegaly, after recently successful resection of the GH-producing pituitary adenoma, may not influence systemic complications, when long-term GH-excess occur several years before.

Aging and long duration of GH/IGF-1 excess are the main determinants of cardiac derangements; results collected in vivo and post-mortem showed a prevalence of cardiac hypertrophy higher than 90% in patients with long disease duration [6].

Several echocardiographic studies have demonstrated morphological alterations such as LV hypertrophy and functional abnormalities (diastolic dysfunction), followed by systolic dysfunction in patients with active acromegaly [22–25]. Doppler echo measurements showed an abnormal LV filling, indicating impairment of diastolic function in patients with elevated muscle mass index of the left ventricle (LVMI) in comparison with healthy controls [23]. Furthermore, electrocardiography studies including ventricular late potentials as well as Holter recordings have documented abnormalities of cardiac rhythm [5, 26].

The sum of different cardio-vascular risk factors, which can be observed in patients with long-term GH-excess, determines the category of the Framingham risk score (FRS). A consensus stratification of CHD risk based on FRS identifies those having FRS less 10% as low risk subjects, those having FRS between 10% or greater and less than 20% as intermediate-risk, and those having 20% or greater as high risk [11]. A recent study from Cannavó et al., reported that 41% of patients with acromegaly were at risk for CHD, half of them having coronary calcifications [27].

Atherosclerosis in patients with acromegaly has been poorly investigated [27,28]. Intima-media thickness of the carotid arteries is a surrogate parameter of atherosclerosis and cardiovascular complications and is increased in 50% patients with active acromegaly [7,29]. Atherosclerosis results in the deposition of calcium within the walls of arteries. Over the past years, CT technology has advanced to the point that detection of minimal calcium deposits can be accomplished quite easily. Non-invasive assessment of coronary calcium by electron-beam computed tomography has been suggested to identify patients at increased risk of myocardial infarction, because it provides an estimate of overall coronary plaque burden [8,10,30,31]. For quantification of coronary calcification Agatston calcium score (CAC score) was computed (EBCT) with 53% of patients who had coronary calcifications. 37% had a high CAC score (75th percentile) and were categorized as cardiovascular high risk patients.

In our present study, it could be demonstrated that coronary calcification is related to the disease duration and consequently to sum of the accompanying metabolic disorders, which defined the FRS. Beside the sex, age and smoking habit, hypertension, dyslipoproteinemia and blood glucose as well-known systemic complication in acromegaly have major impact of the FRS and the risk of coronary calcifications. Therefore, coronary calcification is essentially influenced by long-term disease duration and not by the current disease activity. We have seen that 44% were at risk for CHD according to the FRS, similar to the observation of Cannavó (41%) [27]. 5 patients with acromegaly in our study had a high risk for CHD. These 5 patients were distributed in all three groups (1/12 in the active, 3/9 in the well controlled and 1/9 in the cured group).

To date, it is not obvious whether coronary calcification reflects exactly the risk of CHD in patients with acromegaly. Perfusion abnormalities in acromegaly, verified by myocardial scintigraphy with SPECT using thallium, may precede angiographic stenosis, indicating that development of calcification and perfusion defects has a different sequence than in non-acromegalics [32]. Another study has shown that coronary artery disease in patients with acromegaly was detected in 20% of cases, examined by myocardial perfusion scintigraphy [33].

The coexistence of additional risk factors may accelerate the progression of events leading to cardiomyopathy. Hypertension, arrhythmias, and metabolic complications as well as common cardiovascular risk factors such as smoking, hereditary disorders, dyslipoproteinemia, and fibrinogen have all been associated with increased cardio-vascular morbidity. Untreated acromegaly is also exposed to elevated levels of triglycerides, apolipoproteine A-I and Apo E, fibrinogen, and plasminogen activator inhibitor [4]. The role of this multifactorial mosaic should be considered to define the progression of cardiovascular complications and their potential reversibility in individual patients with acromegaly.

In summary, we have demonstrated that 37% of patients with acromegaly were at risk for cardio-vascular disease and that coronary calcification is influenced by disease duration and the sum of cardio-vascular risk factors, determining the Framingham risk score.

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