Cardiovascular Risk Factors in Patients with Uncontrolled and Long-Term Acromegaly: Comparison with Matched Data from the General Population and the Effect of Disease Control

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Context: Data on cardiovascular risk in acromegaly are scanty and lack a clear correlation to epidemiological data.

Objective: Our aim was an evaluation of cardiovascular risk factors in patients with active acromegaly, a calculation of the Framingham risk score (FRS) compared with age- and gender-matched controls of the general population, and an evaluation of the effect of IGF-I normalization.

Design and Setting: We conducted a retrospective, comparative study at a university referral center.

Patients: A total of 133 patients with acromegaly (65 men, aged 45–74 yr) from the German Pegvisomant Observational Study were matched to 665 controls from the general population.

Main Outcome Measures: Risk factors were measured at baseline and after 12 months of treatment with pegvisomant (n = 62).

Results: Patients with acromegaly had increased prevalence of hypertension, mean systolic and diastolic blood pressure (BP), history of diabetes mellitus and glycosylated hemoglobin (all $P < 0.001$) and decreased high-density lipoprotein, low-density lipoprotein, and total cholesterol (all $P < 0.001$). FRS was significantly higher in patients with acromegaly compared with controls ($P < 0.001$). At 12 months, systolic BP ($P = 0.04$) and glycosylated hemoglobin ($P = 0.02$) as well as FRS ($P = 0.005$) decreased significantly. IGF-I was normalized in 62% (41 of 62). In these patients, glucose and systolic and diastolic BP was significantly lower than in partially controlled patients.

Summary: We found an increased prevalence of cardiovascular risk factors in acromegalic patients compared with controls. Control of acromegaly led to a significant decrease of FRS, implying a reduced risk for coronary heart disease. This was most significant in those patients who completely normalized their IGF-I levels.

Conclusion: Disease control is important to reduce the likelihood for development of coronary heart disease. **(*J Clin Endocrinol Metab* 95: 3648–3656, 2010)**

Acromegaly is characterized by chronic GH and IGF-I excess and is associated with increased morbidity and mortality, mainly due to cardiovascular and cerebrovascular diseases (1, 2). The well established negative effects of GH/IGF-I excess on cardiac structure and function are often further aggravated by comorbidities like obesity, hypertension, impaired glucose homeostasis, or dyslipidemia, all contributing to a high-risk cardiovascular profile in acromegalic pa-

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Abbreviations: BMI, Body mass index; BP, blood pressure; CHD, coronary heart disease; FPG, fasting plasma glucose; FRS, Framingham risk score; GPOS, German Pegvisomant Observational Study; HbA1c, glycosylated hemoglobin; HDL, high-density lipoprotein; HNR, Heinz Nixdorf Recall; LDL, low-density lipoprotein; ULN, upper limit of normal.

tients (3, 4). Despite this unfavorable cardiovascular risk profile, it is unclear whether and to what extent acromegalic patients are at risk for coronary heart disease (CHD). So far, the existing data on cardiovascular risk and CHD in patients with acromegaly mainly refer to heterogeneous cohorts and to pathological examination of old series of patients (5–8). Autoptic studies revealed that atherosclerotic alterations of the coronary arteries are detectable in patients with long-term acromegaly (8). In a study by Courville and Mason (5), among patients with acromegaly submitted to necropsy, 24% had atherosclerosis of the aorta, 11% had coronary artery disease, and 15% had evidence of old myocardial infarction. Some studies have also found evidence of premature atherosclerosis of carotid arteries with increased intima-media thickness detected by ultrasonographic evaluation in 50% of acromegalic patients, followed by normalization after disease control (9). The Framingham risk score (FRS) is the best validated algorithm to calculate cardiovascular risk in the general population based on the analysis of conventional risk factors, such as sex, age, left ventricular mass, hypertension, smoking habit, diabetes mellitus, and lipid status (10). Recently, CHD risk in patients with acromegaly was evaluated through the calculation of the FRS and detection of coronary artery calcification score by computed tomography (11). The authors found that 40% of patients were at risk for coronary atherosclerosis. In contrast, CHD risk in acromegalic patients, predicted by FRS, was reported to be low in another study (12). However, both studies included heterogeneous groups of uncontrolled and controlled acromegalic patients and lack a clear correlation to data from the general population with respect to gender- and age-specific cardiovascular risk distribution. The aim of the study was to evaluate the prevalence of cardiovascular risk factors and the FRS in patients with active acromegaly in comparison with age- and gender-matched controls from the population-based Heinz Nixdorf Recall (HNR) Study and to evaluate the longitudinal effect of disease control on CHD risk factors in acromegaly.

Patients and Methods

Patients with acromegaly

The acromegalic study population was recruited from the German Pegvisomant Observational Study (GPOS). GPOS is an observational, multicenter, surveillance study to monitor safety and efficacy of pegvisomant, which comprises noninterventional data collection in accordance with the standard management of patients with acromegaly in everyday practice and in the respective sites. It includes patients eligible for treatment with pegvisomant, *i.e.* patients with active acromegaly resistant to other treatment modalities and also collects follow-up data during pegvisomant-induced disease control. Details of the study have been reported recently (13). The study has been approved by the Independent Ethics Committee of the Charité Universitätsmedizin, Berlin, Germany, and all patients gave their written informed consent. Data of the sixth interim analysis of GPOS (data close July 15, 2007) were evaluated for this study.

Cross-sectional study

A total of 133 acromegalic patients (65 men) aged 45–74 yr (mean 58.8 ± 13.4 yr) from 30 participating centers from GPOS fulfilling the following criteria were included in the cross-sectional study: 1) active acromegaly at baseline with elevated IGF-I levels, 2) complete risk factor assessment available (see below) at baseline, 3) no clinical evidence of ischemic heart disease (history, symptoms, and resting electrocardiogram), and 4) age from 45–74 yr. At time of data close, a total number of 152 GPOS patients were in the age range 45–74 yr. Nineteen of them did not fulfill the other inclusion criteria and were excluded. Baseline characteristics (gender, duration of disease, and IGF-I level) of these 19 patients were not different from the 133 patients included in the cross-sectional study.

In these 133 patients, mean disease duration was 15.1 ± 7.8 yr, and mean IGF-I levels at baseline were 1.74 ± 0.72-fold upper limit of normal (ULN) (range 1.34–3.21 ULN). Treatments before pegvisomant were in 55% of patients one surgical intervention followed by a medical therapy with somatostatin analogs (octreotide long-acting release 20 or 30 mg or lanreotide 60 or 120 mg, im every 28 d), in 20% one surgical intervention followed by irradiation and medical therapy, in 10% two surgical interventions followed by irradiation and medical therapy, in 1% three surgical interventions followed by irradiation and medical therapy, and in 3% three surgical interventions and medical therapy, and 5% were not operated and only medically pretreated.

Forty-one percent of the patients had LH/FSH deficiency, 39% had TSH deficiency, 34% had ACTH deficiency, and 5% had diabetes insipidus as reported by the local investigators. Patients were on stable conventional replacement therapy for at least 12 months.

Longitudinal study

Sixty-two of the 133 patients (31 men) with data available also from a 12-month follow-up visit were included in the longitudinal study investigating the influence of disease control on cardiovascular risk factors. Patients were treated with pegvisomant as monotherapy for acromegaly. IGF-I was normalized in 42 patients (62%, controlled patients) and was reduced but not normalized in 20 patients (38%, partially controlled patients). In controlled patients, mean IGF-I at the 12-month visit was significantly lower compared with baseline [1.6 ± 0.7 (1.2–3.2) ULN *vs.* 0.7 ± 0.2 (0.5–0.9) ULN, $P < 0.0001$]. In partially

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controlled patients, IGF-I decreased from 2.0 ± 1.1 (1.4–2.9) ULN to 1.4 ± 0.4 (1.1–1.8) ULN ($P = 0.21$). Mean pegvisomant dose at the 12-month visit was 16.8 ± 6.7 mg/d (controlled patients 17.9 ± 1.1 mg/d, partially controlled patients 14.8 ± 1.3 mg/d, $P = 0.09$).

Control population

Data of 133 acromegalic patients were matched to 665 controls (ratio 1:5) from the HNR Study. The patients and controls were matched for age and gender. The HNR Study is an ongoing study designed to assess the prognostic value of modern risk stratification methods and is conducted in the German Ruhr area, recruiting a large unselected cohort of 4814 men and women, aged 45–74 yr, from the general population (14, 15).

Risk factor assessment

GPOS

Cardiovascular risk factors were assessed by personal interviews and direct laboratory measurements. Cardiovascular medication use (antihypertensive, lipid-lowering, and antidiabetic medication) was noted. All subjects were free from clinical evidence of ischemic heart disease (history, symptoms, and resting electrocardiogram). At baseline, 48% (64 of 133) of acromegalic patients were on lipid-lowering medication, 61% (81 of 133) were on antihypertensive medication, and 38% (51 of 133) were on antidiabetic medication. At 12 months follow-up, lipid-lowering medication was unchanged. For antihypertensive and antidiabetic medication, there was no documented increase in dose or medication, but the number of patients on antihypertensive and antidiabetic medication at 12 months decreased to 58% (77 of 133) and 37% (49 of 133), respectively. A dose reduction of antihypertensive or antidiabetic medication was documented in 22% (17 of 77) and 17% (eight of 49) of these patients, respectively. Systolic and diastolic blood pressure (BP) was measured in supine position. BP was measured manually according to the Riva-Rocci method. Diabetes mellitus was defined as self-reported diabetes or taking an antidiabetic drug or a nonfasting serum glucose higher than 200 mg/dl or a fasting plasma glucose (FPG) higher than 126 mg/dl on two occasions. Hypercholesterolemia was defined as total cholesterol levels that were 200 mg/dl or greater, according to the National Cholesterol Education Program Adult Treatment Panel III guidelines, or when taking medication for hypercholesterolemia (16).

HNR Study

BP was measured in sitting position with an automatic oscillometric BP device (Omron HEM-705CP, Omron, Mannheim, Germany), and the mean value of the second and third of three measurements taken at least 3 min apart was recorded. Fourteen percent of the HNR subjects were on lipid-lowering medication, and 21% were on antihypertensive medication. Other risk factors were assessed using the same criteria as described above for GPOS.

Cardiac evaluation and determination of the FRS at 10 yr

The 10-yr likelihood for development of cardiovascular events was estimated for each subject using the multivariate scoring system of the Framingham Heart Study (17). It calculates the risk from age, sex, systolic blood pressure, the ratio of total to high-density lipoprotein (HDL) cholesterol, smoking habit, and presence of diabetes in subjects between the ages of 45 and 75 yr. Patients at risk to undergo myocardial infarction within the next 10 yr, according to the FRS were stratified into low (<10%), intermediate (10–20%), and high (>20%) midterm risk groups.

Assays

Samples of blood were taken after an overnight fast. Serum IGF-I levels were measured in the local laboratories and interpreted according to the local, age-dependent reference ranges. Results were given as total IGF-I levels and, to have a better comparability, as x-fold of the individual age-related ULN. Standard enzymatic methods were used to measure HDL and low-density lipoprotein (LDL) and total cholesterol (milligrams per deciliter). Current smoking was defined as a history of smoking during past years. Glucose, cholesterol, and triglyceride analyses were carried out on an automated analyzer using commercial reagents, and HDL cholesterol was measured without a precipitation step. The level of LDL cholesterol was calculated using the Friedewald formula (18).

Statistical analysis

Descriptive statistics were used to summarize the subject characteristics. Results are presented as mean ± SD for approximately normally distributed and as median (interquartile range) for nonnormally distributed variables. For IGF-I values, mean ± SD and range are given. Frequencies are given as percentages.

Cross-sectional study

In the cross-sectional phase, groups were compared by one-way ANOVA, Mann-Whitney *U* test. or χ^2 test, as appropriate. Accounting for the individually 1:5 matched design (with respect to age and gender), univariate and multivariable conditional logistic regression models were calculated to identify associations between risk factors and acromegaly. Results are given as odds ratios with their 95% confidence intervals. Two-sided *P* values < 0.05 were considered significant.

Longitudinal study

Development from baseline was evaluated using Wilcoxon sign-rank test and McNemar statistics as appropriate. Two-sided *P* values <0.05 were considered significant.

Results

Cross-sectional study

Clinical and biochemical results of the study groups are given in Table 1.

Hypertension

Acromegalic men and women had increased prevalence of hypertension compared with matched controls (men 63 *vs.* 42%, $P = 0.001$; women 71 *vs.* 42%, $P = 0.001$). Acromegalic women had both increased systolic and diastolic BP (140 ± 23 *vs.* 126 ± 21 mm Hg, $P < 0.0001$; and 86 ± 14 *vs.* 78 ± 11 mm Hg, $P < 0.0001$), whereas acromegalic men had increased diastolic BP only (88 ± 11

TABLE 1. Risk factors and calculated FRS in 133 acromegalic patients and 665 controls, matched for age and gender from the general population (HNR Study) and *P* values (Mann-Whitney *U* test or χ^2 test)

Risk factor	Acromegalics	Controls	*P* value
Age (yr)	59 ± 8	59 ± 8	0.35
Males (%)	49	49	
Smokers (%)	17.3	22.7	<0.001
History of hypertension (%)	63.0	41.1	<0.001
Systolic BP (mm Hg)	140 ± 22	131 ± 21	<0.001
Diastolic BP (mm Hg)	87 ± 13	81 ± 11	<0.001
History of diabetes mellitus (%)	37.6	6.9	<0.001
Glucose (mg/dl)	113.1 ± 42.4	110.7 ± 26.9	0.16
HbA1c (%)	6.2 ± 0.9	5.5 ± 0.8	<0.001
History of hyperlipidemia (%)	57.9	80.6	<0.001
Total cholesterol (mg/dl)	194 ± 63	231 ± 38	<0.001
LDL cholesterol (mg/dl)	121 ± 46	147 ± 36	<0.001
HDL cholesterol (mg/dl)	48 ± 17	58 ± 17	<0.001
Triglycerides (mg/dl)	148 ± 97	146 ± 84	0.76
FRS	13.6 ± 7.9	10.6 ± 7.7	<0.001
Low risk (%)	38.4	57.4	<0.0001
Intermediate risk (%)	49.6	31.7	<0.0001
High risk (%)	12.0	10.8	<0.0001

vs. 84 ± 10 mm Hg, $P = 0.014$). Percentage of acromegalic patients with hypertension grade I (systolic BP 140–159 mm Hg or diastolic BP 90–99 mm Hg) was 1.3-fold higher compared with matched controls (28 *vs.* 21%, $P < 0.001$) and with hypertension grade II (systolic BP ≥ 160 mm Hg or diastolic BP ≥ 110 mm Hg) was 2.3-fold higher compared with matched controls (27 *vs.* 12%, $P < 0.001$).

Diabetes mellitus

Prevalence of diabetes mellitus was significantly higher in acromegalic patients than in matched controls (men 30.8 *vs.* 16.6%, $P = 0.008$; women 44.1 *vs.* 9.1%, $P < 0.0001$). FPG was 113 ± 42 mg/dl in acromegalic patients *vs.* 111 ± 27 mg/dl in controls ($P = 0.16$). Glycosylated hemoglobin (HbA1c) levels were significantly higher in acromegalic patients than in matched controls (6.2 ± 0.9% compared with 5.5 ± 0.8%, $P < 0.001$). Of the acromegalic patients, 73.7, 18.2, and 8.1% of patients had HbA1c of less than 6.5%, more than 6.5% to less than 7.5%, and more than 7.5% compared with 93.3, 3.9, and 2.7%, respectively, of matched controls (for all, $P < 0.0001$).

Lipid status

Prevalence of hyperlipidemia was lower in acromegalic patients than in matched controls (57.3 *vs.* 80.6%, $P < 0.001$). Total cholesterol, HDL, and LDL levels were decreased in patients with acromegaly compared with matched controls (Table 1).

FRS

Calculated FRS was higher in acromegalic patients compared with matched subjects of the general population (13.6 ± 7.9 *vs.* 10.6 ± 7.7%, $P < 0.001$) with a gender-specific difference (men 15.2 ± 9.3 *vs.* 14.3 ± 8.5%, $P = 0.37$; women 12.6 ± 6.1 *vs.* 7.1 ± 4.7%, $P = 0.002$) (Fig. 1). Disease duration at baseline ($P = 0.03$) but not IGF-I ($P = 0.45$) correlated positively with calculated FRS.

Matched analysis

Odds ratios by univariate conditional logistic regression were 1.08 (1.05–1.12) per 1 kg/m^2 body mass index (BMI) increase, 1.26 (1.15–1.39) for systolic and 1.28 (1.17–1.40) for diastolic BP (each per 10 mm Hg increase), 4.23 (2.7–6.54) for history of diabetes, 0.84 (0.80–0.88) for total cholesterol, 0.83 (0.79–0.88) for LDL cholesterol (each per 10 mg/dl increase), 0.79 (0.74–0.85) for HDL cholesterol (per 5 mg/dl increase), and 1.07 (1.04–1.11) for FRS (all $P < 0.001$) (Table 2). Results for multivariable logistic regression are also given in Table 2. When adjusted for BMI, the odds ratio by multivariate

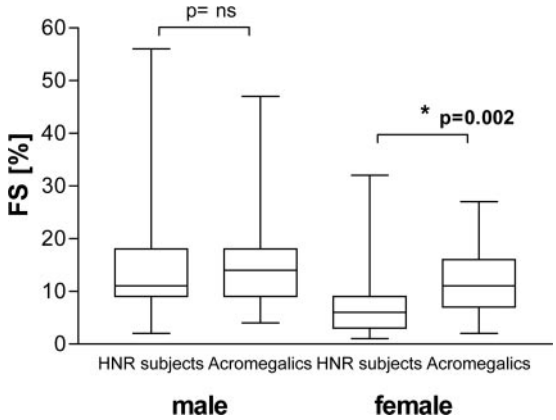

FIG. 1. FRS (FS) in male (n = 65) and female (n = 68) acromegalic patients in comparison with age- and gender-matched male (n = 325) and female (n = 340) HNR Study subjects of the general population. ns, Not significant.

TABLE 2. Univariate and multivariate conditional logistic regression matched for age and gender of risk factors accounting for the individually 1:5 matched design

Risk factor	Odds ratio	95% confidence interval	*P* value
Univariate			
Systolic BP (10 mm Hg)	1.262	1.148–1.387	<0.0001
Diastolic BP (10 mm Hg)	1.281	1.173–1.398	<0.0001
Total cholesterol (10 mg/dl)	0.838	0.800–0.877	<0.0001
HDL (5 mg/dl)	0.790	0.735–0.850	<0.0001
LDL (10 mg/dl)	0.831	0.787–0.877	<0.0001
Triglycerides (20 mg/dl)	1.004	0.961–1.050	0.8457
History of diabetes	4.233	2.742–6.535	<0.0001
Current smoker	0.456	0.272–0.765	0.0029
FRS	1.074	1.044–1.106	<0.0001
Multivariate			
Systolic BP (per 10 mm Hg)	1.266	1.125–1.425	<0.0001
HDL (per 5 mg/dl)	0.814	0.748–0.887	<0.0001
LDL (per 10 mg/dl)	0.849	0.798–0.903	<0.0001
History of diabetes	3.212	1.887–5.469	<0.0001
Current smoker	0.452	0.247–0.827	0.0099

conditional logistic regression for FRS was 1.068 (1.036–1.100) ($P < 0.001$).

Longitudinal study

Overall changes

Data of overall changes during follow-up for BMI, hypertension, diabetes mellitus, lipid status, and FRS (Fig. 2) after 12 months of treatment are summarized in Table 3.

Changes during follow-up for controlled and partially controlled patients

Hypertension. After 12 months, systolic BP was significantly lower in controlled than in partially controlled patients (132 ± 14 *vs.*141 ± 4 mm Hg, $P = 0.04$) (Fig. 3A). Moreover, systolic BP decreased significantly during treatment in controlled patients (142 ± 25 *vs.* 132 ± 14 mm Hg, $P = 0.03$) but not in partially controlled patients

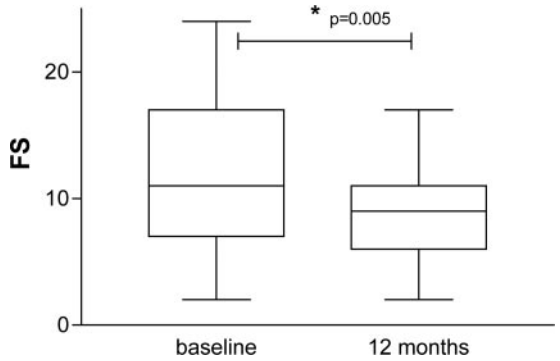

FIG. 2. FRS (FS) in 62 acromegalic patients at baseline and after 12 months of treatment.

TABLE 3. Risk factors and calculated FRS in 62 acromegalic patients at baseline and after 12 months of treatment and *P* values (Wilcoxon sign rank test or McNemar statistics)

Risk factor	Baseline	12 months follow-up	*P* value
IGF-I (ULN)	1.7 ± 0.7	0.9 ± 0.6	<0.0001
BMI (kg/m^2)	30.2 ± 1.2	30.9 ± 1.9	0.74
Systolic BP (mm Hg)	141 ± 27	135 ± 17	0.03
Glucose (mg/dl)	119 ± 50	107 ± 14	0.23
HbA1c (%)	6.3 ± 1.0	6.0 ± 1.0	0.02
Total cholesterol (mg/dl)	196 ± 60	203 ± 63	0.51
LDL cholesterol (mg/dl)	119 ± 43	123 ± 50	0.33
HDL cholesterol (mg/dl)	52 ± 19	51 ± 17	0.44
FRS	13.9 ± 7.9	11.3 ± 5.9	0.005
Low risk (%)	38.7	50.0	<0.0001
Intermediate risk (%)	40.3	38.7	
High risk (%)	21.0	11.3	

(141 ± 20 *vs.* 139 ± 20 mm Hg, $P = 0.7$). After 12 months, diastolic BP was significantly lower in controlled than in partially controlled patients (84 ± 2 *vs.* 89 ± 3 mm Hg, $P = 0.002$). There were no significant changes in each group compared with baseline (controlled patients 88 ± 15 mm Hg at baseline compared with 84 ± 11 mm Hg at 12 months, $P = 0.34$; partially controlled patients 88 ± 10

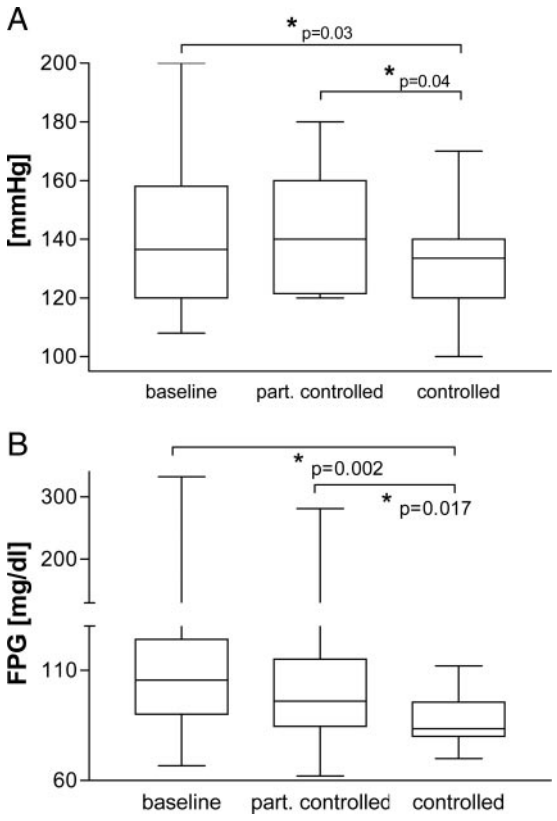

FIG. 3. Systolic BP (A) and FPG (B) in controlled and partially (part.) controlled acromegalic patients at baseline and after 12 months of treatment.

mm Hg at baseline compared with 91 ± 14 mm Hg at 12 months, $P = 0.7$).

Diabetes mellitus. After 12 months, FPG was significantly lower in controlled than in partially controlled patients (88 ± 2 *vs.* 109 ± 12 mg/dl, $P = 0.017$) (Fig. 3B). In the controlled group, there was compared with baseline a significant decrease of FPG (123 ± 56 *vs.* 88 ± 11 mg/dl, $P = 0.002$) but not in partially controlled patients (109 ± 47 *vs.* 114 ± 34 mg/dl, $P = 0.30$). HbA1c levels were 5.9 ± 0.2% in the controlled group and 6.2 ± 0.3% in the partially controlled group ($P = 0.42$).

Lipid status. Total cholesterol ($P = 0.51$), LDL cholesterol ($P = 0.33$), and HDL cholesterol ($P = 0.44$) did not change during treatment (Table 3). At 12 months, there was no significant difference between controlled and partially controlled patients in total cholesterol (200 ± 11 *vs.* 210 ± 12 mg/dl, $P = 0.53$), HDL cholesterol (53 ± 3 *vs.* 47 ± 3 mg/dl, $P = 0.14$), or LDL cholesterol (126 ± 8 *vs.* 114 ± 11 mg/dl, $P = 0.39$).

FRS. Overall, after 12 months of treatment with pegvisomant, FRS in acromegalic patients decreased significantly from 13.9 ± 7.9 to 11.3 ± 5.9% ($P = 0.005$) (Fig. 2) with controlled patients decreasing from 14.3 ± 7.2 to 10.8 ± 0.9% ($P = 0.19$) and partially controlled patients decreasing from 13.1 ± 8.3 to 12.6 ± 1.3% ($P = 0.62$). FRS at 12 months was not significantly different between controlled and partially controlled patients (10.8 ± 0.9 *vs.* 12.6 ± 1.3%, $P = 0.31$). Overall, percentage of acromegalic patients after 12 months of treatment with intermediate or high 10-yr likelihood for development of CHD decreased from 61.3% (n = 38) at baseline to 50% (n = 31) increase after 12 months of treatment with pegvisomant ($P < 0.001$), whereas the number of patients with low risk increased from 38.7% (n = 24) to 50.0% (n = 31) ($P < 0.001$).

Discussion

Cardiovascular risk in acromegaly has been poorly investigated until now, and the relationship between CHD and GH/IGF-I excess is a matter of argument. Until now, many studies lack homogeneous and large cohorts of acromegalic patients, and furthermore, a clear age- and gender-matched correlation to epidemiological data is missing.

This is the largest study to date measuring classical cardiovascular risk factors in patients at a resistant end of the disease spectrum with long-term and active acromegaly and comparing them cross-sectionally with a matched control population from the general population. In addition, risk factors were evaluated in a longitudinal study before and during control of disease.

The results of the cross-sectional study show that the prevalence of hypertension in active acromegaly is 1.5-fold higher compared with age- and gender-matched controls of the general population and that the prevalence of diabetes is even 2.9-fold higher. The analysis of lipid levels showed that HDL and LDL cholesterol were significantly lower in the acromegalic population, whereas triglyceride levels were comparable to the general population. In consequence, when calculating the FRS, the overall percentage of acromegalic patients with intermediate or high 10-yr likelihood for development of CHD was 1.5-fold increased compared with the risk existing in the general population. However, a remarkable finding was a strong gender difference with only females showing a significantly increased FRS risk.

Acromegalic patients were recruited from the GPOS, and baseline data from this study were used for the comparison of CHD risk between acromegalic patients and the general population. The GPOS comprises a study population with refractory disease and usually a long history of acromegaly (13). Although it offers a very large and homogeneous study population of patients with active acromegaly, the severity and duration of disease in these patients at the more resistant end of the disease spectrum may not be fully representative for all patients with active acromegaly. In a recent study, CHD risk in a more mixed group of acromegalic patients was not significantly elevated (12). In addition, a negative influence of previous or ongoing treatments such as somatostatin analogs on risk factors cannot fully be excluded (19). Because somatostatin analogs affect glucose metabolism by inhibiting insulin secretion, an influence on calculated cardiovascular risk at the time of inclusion in GPOS cannot be excluded. Moreover, the long history of acromegaly has to be taken into account because it is known that a longer disease duration correlates with a higher degree of coronary artery calcifications (20). Pituitary irradiation may result in visual loss or deterioration, brain necrosis, secondary tumor formation, or hypopituitarism (21). The preexisting hypopituitarism relating to irradiation, the pituitary mass itself, or previous surgery is associated with increased mortality rates (22), although whether this is because of GH deficiency, which is unusual in patients with acromegaly, is controversial (23), and all our patients were on a stable hormonal replacement therapy.

However, the study population well reflects the group of acromegalic patients not controlled by surgery and/or radiotherapy, in whom chronic medical treatment and the control of comorbidities and improvement of long-term outcome is the most prominent clinical issue.

The patients were matched to participants from the HNR Study, an ongoing German epidemiological study designed to assess the prognostic value of modern risk stratification methods, conducted in the German Ruhr area, recruiting a large unselected cohort from the general population (14, 15). Because this study includes only controls aged 45–74 yr, the inclusion of acromegalic patients was restricted to this age group as well. Epidemiological data of the HNR study showed a strong gender difference of cardiovascular risk in the general population (14). For correct interpretation, matching for age and gender is an important aspect when comparing cardiovascular risks, which was achieved in this study by an individually 1:5 age- and gender-matched design. Due to the given study design of the HNR Study, we used manually measured BP values in sitting position of the acromegalic patients for comparability. However, 24-h BP monitoring would allow a better evaluation of BP independent of intermittent influence but due to the noninterventional study design, data of 24-h BP procedures were unavailable or available at the discretion of the responsible physicians.

Epidemiological studies reported that cardiovascular and cerebrovascular events are the main cause of death in patients with acromegaly, relating this to the GH/IGF-I excess (3, 24, 25) or previous radiation therapy (24). However, it is unclear whether and to what extent acromegalic patients are at risk for CHD nowadays. So far, the existing data on cardiovascular risk and CHD in patients with acromegaly mainly refer to heterogeneous cohorts and to pathological examination of old series of patients (5–9). Cardiac complications like hypertrophy and fibrosis are the most frequent abnormalities in patients with acromegaly (26–29); in contrast, data on CHD are conflicting (11, 12). Autoptic studies have found myocardial fibrosis in 50–75% and myocardial hypertrophy in 90% of acromegalic patients (5–8). In a pathological series of acromegalic hearts by Lie (8), approximately one third of patients had wall thickness of coronary arteries and their small intramural branches, and an additional 15% of patients had gross evidence of myocardial infarction. Moreover, Courville and Mason (5) found atherosclerosis of the aorta in 50% of patients. Furthermore, there is evidence of premature atherosclerosis of carotid arteries with increased intima-media thickness in 50% of acromegalic patients, followed by normalization after disease control (9, 30).

Guidelines on prevention of CHD use predicted 10-yr risk of coronary events to identify candidates for risk factor modification (31). Ideally, a predictor of the overall risk of clinical events should be based on a multifactorial model (26). Published primary prevention risk-scoring methods use equations derived from large cohort studies, such as the U.S. Framingham Heart and Offspring Studies (32–34). There is a positive linear relation between the estimated risk of clinical events derived from established risk scores like the FRS and the extent of plaque progression (32, 33). In the absence of a validated risk score for secondary prevention in acromegaly, we used this established primary-event risk score like in the study by Cannavo *et al.* (11) and Bogazzi *et al.* (12) to assess the relationship between the estimated FRS risk and IGF-I status in acromegalic patients. FRS stratification was based on a consensus stratification, identifying those having FRS less than 10% as low-risk subjects, those having FRS between 10% or greater and less than 20% as intermediate risk, and those having FRS 20% or greater as high risk.

However, there might be discrepancy between calculated coronary risk and true coronary calcifications. Therefore, an exercise stress test would be useful to exclude ischemic heart disease, but due to the noninterventional study design, such tests were at the discretion of the responsible physicians and were not available in our patients. Furthermore, measurement of coronary calcification might be of incremental value (11) because it measures the amount of calcification deposits in the coronary arteries. A recent study using FRS and coronary calcification reported that 41% of acromegalic patients were at risk for CHD, half of them having coronary artery calcifications (11).

Our study is the first that describes that active acromegaly in women is accompanied by increased CHD risk and that this risk can be reduced by disease control for both men and women. This effect might be observational due to selection of a group of active and long-term acromegalic patients, a fact that in previous studies has been rarely investigated. The fact that acromegalic women have a more increased CHD risk may be due to the fact that gender-specific differences in CHD risk are covered by the effect of the disease on CHD risk. It is also known that premature menopause is associated with an increased risk of CHD. Forty-two percent of the female patients in this study were gonadotrope insufficient, with 46% of postmenopausal women not receiving hormonal replacement therapy. However, there is no clear-cut relationship between gonadotrope deficiency and CHD risk, so more studies are needed to further investigate the gender differences in CHD risk in acromegaly.

Evaluation of the effect of successful IGF-I normalization was possible in 62% of patients where IGF-I was completely normalized after 12 months of treatment. This IGF-I control rate is lower than expected, possibly due to an inadequate dose titration; possible reasons have been evaluated by Schreiber *et al.* (13). Because GPOS is a surveillance study using the field conditions of clinical prac-

tice, dose titration of pegvisomant treatment, in contrast to controlled clinical trials, did not follow a preassigned dosing algorithm and was not finalized in a significant number of patients. After 12 months of treatment, a relevant proportion of the patients with elevated IGF-I levels still had daily pegvisomant doses of 10 or 15 mg, *i.e.* had not yet reached the maximum dose.

Sixty-one percent of acromegalic patients have intermediate (40%) or high (21%) risk for developing CHD when included in GPOS. We found that IGF-I normalization results in a reduction of severity of comorbidities, *e.g.* degree of hypertension or diabetes mellitus, that lowers predicted CHD risk. This observation is independent from antihypertensive, antidiabetic, and lipid-lowering medication because their dose has not been increased during the treatment period. This is in contrast to previous studies that showed no influence of IGF-I normalization on CHD risk (11, 12). However, the limited study groups of the previous studies might have underestimated the effects of acromegaly on CHD risk.

In conclusion, this study showed a significantly increased prevalence of hypertension and diabetes in a large cohort of patients with active acromegaly compared with age- and gender-matched controls. In addition, acromegalic patients had lower HDL and LDL cholesterol levels, whereas triglyceride levels were not different from the normal population. When calculating the FRS as an estimate for the likelihood to develop CHD, acromegaly was found to be associated with increased risk of coronary artery disease. However, only female patients with acromegaly showed a significantly increased score compared with controls. Control of acromegaly led to a significant improvement of cardiovascular risk factors and to a reduction of the FRS in both males and females, implying a reduced risk for CHD. This was most significant in those patients who completely normalized their IGF-I levels. Our data clearly suggest that beside treatment of comorbidities, effective control of acromegaly is important to reduce the likelihood for development of CHD.

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