Endocrine (2015) 50:749–755
DOI 10.1007/s12020-015-0628-4

ORIGINAL ARTICLE

Low risk of coronary artery disease in patients with acromegaly

Cintia Marques dos Santos Silva[1] · G. A. B. Lima[2] · I. C. M. Volschan[3] · I. Gottlieb[4] · L. Kasuki[1,5] · L. Vieira Neto[1,6] · M. R. Gadelha[1]

Received: 17 February 2015 / Accepted: 5 May 2015 / Published online: 17 May 2015

Abstract The aims of this study are to determine the prevalence of coronary atherosclerosis in acromegalic patients and to investigate the relationship between the coronary artery calcium score (CS) and acromegaly status and clinical parameters [Framingham risk score (FRS)]. Fifty-six acromegalic patients and paired non-acromegalic volunteers were stratified according to the FRS into low-, intermediate-, and high-risk groups. CS was assessed using multidetector computed tomography. The patients were considered to have controlled or active acromegaly at the time they were submitted to evaluation. Sixty-six percent of acromegalic patients exhibited arterial hypertension, 36 % had diabetes mellitus, and 34 % had hypercholesterolemia. The median FRS and the median risk for cardiovascular event within the next 10 years were similar in the acromegalics and the controls. The median total CS and CS >75th percentile didn't differ significantly between these groups. In patients with controlled acromegaly, a low, intermediate, or high FRS risk was observed in 86, 14, and 0 %, respectively. In patients with active disease, a low, intermediate, or high FRS risk was verified in 94, 3, and 3 %, respectively, and differences between the controlled and active groups were not significant. Seventy-two percent of the patients had total CS = 0, and there were no differences between the controlled and active groups. The risk of coronary artery disease in acromegalic patients, determined according to FRS and CS, is low despite the high prevalence of metabolic abnormalities.

Keywords Acromegaly · Cardiac disease · Framingham risk score · Coronary artery calcium score

Introduction

Acromegaly is a rare disease that is typically caused by a growth hormone (GH)-secreting pituitary adenoma [1] and is characterized by increased serum GH and insulin-like growth factor type I (IGF-I) levels. Acromegaly may cause

Cintia Marques dos Santos Silva and G. A. B. Lima have equally contributed to the development of the research and this paper.

Electronic supplementary material The online version of this article (doi:10.1007/s12020-015-0628-4) contains supplementary material, which is available to authorized users.

✉ Cintia Marques dos Santos Silva
cintiasilva.marques@bol.com.br

M. R. Gadelha
mgadelha@hucff.ufrj.br

[1] Neuroendocrinology Research Center/Endocrinology Section, Medical School and Hospital Universitário Clementino Fraga Filho – Universidade Federal do Rio de Janeiro, Rua Prof. Rodolpho Paulo Rocco, 255, 9th floor, Ilha do Fundão, Rio de Janeiro 21941-913, Brazil

[2] Endocrinology Section, Medical School and Hospital Universitário Antônio Pedro – Universidade Federal Fluminense, Niterói, Brazil

[3] Cardiology Section, Medical School and Hospital Universitário Clementino Fraga Filho – Universidade Federal do Rio de Janeiro, Rio de Janeiro, Brazil

[4] Clínica de Diagnóstico por Imagem/Multi-Imagem, Rio de Janeiro, Brazil

[5] Endocrinology Section, Hospital Federal de Bonsucesso, Rio de Janeiro, Brazil

[6] Endocrinology Section, Hospital Federal da Lagoa, Rio de Janeiro, Brazil

disorders of the cardiovascular system, resulting from the chronic exposure to high levels of GH/IGF-I. Cardiovascular disease has been purported to be one of the most severe complications of acromegaly, contributing significantly to mortality in this disease [2, 3].

Many patients with acromegaly are exposed to coronary risk factors, such as arterial hypertension, diabetes mellitus (DM), or hypertriglyceridemia, which confer an increased risk for atherosclerosis [4]. Furthermore, the excess of GH and IGF-I may directly cause cardiac abnormalities [1, 4, 5]. Some reports have suggested that acromegaly can cause a typical cardiomyopathy characterized by a concentric ventricular hypertrophy, impairment of diastolic function, and additionally, a progressive impairment of systolic performance [6–8].

Data in the literature about coronary artery disease (CAD) in patients with acromegaly is limited and controversial [9, 10]. The coronary risk can be calculated using algorithms, such as the Framingham risk score (FRS), that are based on the analysis of conventional risk factors, such as sex, age, arterial hypertension, smoking habit, DM, and lipid status [11]. One suggested approach to improve cardiovascular risk prediction over the FRS is the quantification of the coronary artery calcium score (CS), most commonly using multidetector computed tomography (MDCT) [12]. Computed tomography allows a noninvasive and quantitative detection of CS. There is evidence of an association between CS and the risk of cardiovascular events, and the assessment of calcium deposition in coronary arteries has been shown to be a useful tool in cardiovascular risk stratification [13–15].

Initially, the prevalence of CAD has been investigated in patients with acromegaly in autopsy study. Lie et al. [16] reported that 11 % of the acromegaly patients had CAD; this diagnosis was confirmed in older patients and 15 % had evidence of previous myocardial infarction.

More recently, some studies have evaluated the risk of CAD in patients with acromegaly using FRS and CS. Cannavo et al. [9] reported that 41 % of acromegaly patients were at risk for atherosclerosis. Bogazzi et al. [10] demonstrated that the risk of cardiovascular events in these patients was low, and they did not evidence a major cardiac event during the 5-year study period. In addition, Akutsu et al. [17] reported a low risk of cardiovascular events in newly diagnosed patients with acromegaly. The authors also reported that in the majority of patients, CAD remained stable after successful treatment. Herrmann et al. [18] demonstrated that CS >0 was present in 53 % of the patients and was correlated with the disease duration and metabolic disorders. Ragonese et al. [19] reported lethal ischemic cardiovascular events in 9.6 % of the patients with acromegaly during the 5-year study period. Also, they demonstrated that CS >400 is associated with the increased risk of lethal ischemic cardiovascular events, while FRS is associated with a decreased life expectancy, regardless of disease control. Furthermore, other studies, using different methods of evaluation, have suggested an antiatherogenic effect of GH and IGF-I excess [16, 20]. Otsuki et al. [20] observed that acromegalic patients with atherosclerosis exhibited lower concentrations of plasma IGF-I than those without CAD.

The aim of this study was to determine the prevalence of coronary atherosclerosis in patients with acromegaly using the CS, comparing with a matched control group. Furthermore, we investigated the relationship between CS and acromegaly control, disease duration and clinical parameters (FRS).

Patients and methods

Study population

This was a cross-sectional study. Patients with acromegaly were recruited from the Endocrinology outpatient's clinic of the Hospital Universitário Clementino Fraga Filho/Universidade Federal do Rio de Janeiro (HUCFF/UFRJ) from March 2012 until July 2014. The inclusion criteria were as follows: patients older than 18 years, with the diagnosis of acromegaly, according to clinical and laboratory features, including increased serum IGF-I levels for age and lack of GH suppression to <1 ng/mL during 75 g oral glucose tolerance test (OGTT). Acromegaly was considered controlled, with basal GH <1 ng/mL and normal IGF-I for age. The presumed duration of acromegaly was assessed by comparing photographs taken over a period of 05–20 years and by interviews.

Non-acromegaly volunteers (matched for sex, age, smoking habit, and the presence of arterial hypertension, DM, and hypercholesterolemia) were also included. These non-acromegaly volunteers were selected from a database of the Clínica de Diagnóstico por Imagem/Multi-Imagem. The reasons for ineligibility in both groups included patients with clinical history of CAD and women at childbearing age not practicing a medically accepted contraception method.

The study was approved by the Ethics Committee of HUCFF/UFRJ and all patients signed informed consent before entering the study. This study was conducted according to the principles expressed in the Declaration of Helsinki.

Hormone assays

Plasma GH levels were measured using a chemiluminescence assay kit (IMMULITE 2000; DPC—Diagnostic Products Corp., Inc., Los Angeles, CA, USA). The inter- and intra-assay coefficients of variation (CV) were 6.0 and 5.8 %, respectively. The international reference preparation (IRP) for GH was the 98/574. Plasma IGF-I levels were measured using a chemiluminescence assay kit (IMMULITE 2000; DPC). The inter- and intra-assay CV were 3.6 and 6.6 %, respectively. The IRP for IGF-I was

87/518. IGF-I level was expressed as the percentage of the upper limit of normal range (ULNR).

All plasma samples were collected in the early morning after an 8-hour fasting period.

Determination of the Framingham risk score at 10 years

Age, sex, smoking habit, systolic blood pressure (BP), use of antihypertensives, total cholesterol, and high-density lipoprotein cholesterol (HDLc) were evaluated in all patients and controls to calculate the risk for a cardiovascular event within the next 10 years, according to FRS. On the basis of this score, patients were stratified into low- (<10 %), intermediate- (10–20 %), and high-risk (≥20 %) groups.

The participants were classified as cigarette smokers (individuals who smokes at least one cigarette per day for not <6 months) or non-smokers (individuals who quit smoking at least 6 months ago) [21].

Total cholesterol and HDLc were determined using automatic standard routine enzymatic methods.

Other evaluations

Arterial hypertension was defined as systolic BP ≥140 mmHg and/or diastolic BP ≥90 mmHg or treatment of previously diagnosed arterial hypertension.

Body mass index (BMI) was calculated in all patients and controls using the formula [weight (kg) divided by height squared (m^2)] [22].

Family history of coronary heart disease was obtained by asking the participants whether any member of their first-grade relatives had a fatal or nonfatal myocardial infarction, coronary angioplasty, or coronary artery bypass surgery [14]. All patients were asymptomatic for CAD.

Plasma glucose was measured using a hexokinase method (Dimension; Dade Behring, Newark, DE). Triglycerides (TG) were determined using automatic standard routine enzymatic methods. DM was diagnosed when fasting plasma glucose levels were ≥126 mg/dL at two consecutive measurements or when the 2-h post-OGTT glucose level was ≥200 mg/dL or if the patient was currently being treated for previously diagnosed DM. Hypercholesterolemia was defined as a total cholesterol level ≥200 mg/dL, according to the National Cholesterol Education Program Adult Treatment Panel III guidelines or in patients using drugs to treat dyslipidemia [23].

Cardiac computed tomography (CT) scan and coronary calcium content

Patients were imaged on a 256-slice CT scanner (Brilliance iCT, Philips, Best, The Netherlands) using standard techniques: axial acquisition with collimation 32 × 3 mm and no gap, and reconstruction with a standard (B) filter at 75 % of the cardiac cycle. Tube voltage was 120 kVp and amperage was adjusted according to body habitus.

The Agatston CS was calculated in an offline remote workstation (Philips Portal) at the level of left main artery (LMA), left anterior descendent (LAD) artery, left circumflex artery (LCA), and right coronary artery (RCA) [24]. Moreover, we calculated the total CS as the sum of the CS of the coronaries above. We used two different cut-off points of the total CS to define increased cardiac risk: (a) for all individuals—total CS >0 [25], and (b) for individuals ≥60 years—total CS >300 [24]. In addition, the total CS was adjusted for age, gender, and ethnicity, and patients in the >75th percentile were identified as high-risk individuals [26].

Statistical analysis

The statistical analysis was performed using SPSS version 20.0 for MacOS (SPSS Inc., Chicago, IL). In the descriptive analysis, categorical variables are expressed as the percentage and frequency, and numerical variables are expressed as the median (minimum and maximum). The Mann–Whitney test was performed to compare the numerical variables between the two groups. Correlations between the numerical variables were analyzed using Spearman's correlation test. The χ^2 test and Fisher's exact test were applied to compare categorical variables. p values <0.05 were considered statistically significant.

Results

Patients characteristics

From a total of 98 patients seen at our center in the study period, we studied the first 56 patients with acromegaly that agreed to participate [32 women, median age 49 years (20–76)]. The median GH and IGF-I levels at the time that the patients were submitted to MDTC, were 2.4 ng/mL (0.2–25.9 ng/mL) and 160 % ULNR (40–520 % ULNR), respectively. Thirty-four (61 %) patients had a macroadenoma. Forty-two (75 %) patients were previously surgically treated. Acromegaly was considered controlled in 21/56 patients (38 %; 17 women and 4 men) and uncontrolled in the remaining 35 patients (62 %; 16 women and 19 men). Among patients with controlled disease, two patients had been cured after transsphenoidal surgery, and 19 patients had controlled disease under medical treatment. Women were more frequent in the controlled acromegaly group than men ($p = 0.006$). Among patients with active acromegaly, 24 patients were receiving specific medical

treatment for acromegaly, and 11 patients had just been diagnosed. In the whole group, six patients underwent radiotherapy.

In the acromegaly group, 37 patients (66 %) had arterial hypertension, 20 (36 %) had DM, 19 (34 %) had hypercholesterolemia, and 9 (16 %) were current smokers. The median BMI was 30 kg/m^2 (22.4–45.2). The median BMI differed between the acromegaly group and the control group ($p = 0.01$). These data are depicted in Table 1. This group was not different in terms of cardiovascular risk factors from those patients from our center not included in this study (Supplementary Table 1).

The main characteristics of the acromegaly patients (controlled vs. active disease) are presented in Table 2.

Cardiovascular findings

Framingham risk score

The median FRS did not differ between acromegaly patients and the control group ($p = 0.17$).

In patients with disease control, a low, intermediate, or high FRS was demonstrated in 18 (86 %), 3 (14 %), and zero patients, respectively. In the active acromegaly group a low, intermediate, or high FRS risk was verified in 33 (94 %), 1 (3 %), and 1 (3 %) patients, respectively. The median FRS did not significantly differ between patients with controlled versus active disease ($p = 0.89$).

The median risk for a cardiovascular event within the next 10 years according to FRS was 2 % (0–20 %). The median risk for a cardiovascular event within the next 10 years according to FRS did not differ between the acromegaly patients versus control group ($p = 0.23$). In addition, the median risk for a cardiovascular event within the next 10 years according to FRS also did not differ between patients with controlled disease versus active disease ($p = 0.14$).

Measure of the coronary artery calcium score

There were no differences in the median CS of the LMA ($p = 0.94$), LAD ($p = 0.17$), LCA ($p = 0.91$), and RCA ($p = 0.95$) between patients with acromegaly and the control group. Furthermore, there were no differences in the median CS of the LMA ($p = 0.88$), LAD ($p = 0.27$), LCA ($p = 0.20$), and RCA ($p = 0.44$) between patients with active and controlled disease.

There were no differences in the total CS >0 ($p = 0.42$) and total CS >300 (≥60 years) ($p = 0.62$) between patients with acromegaly and the control group. In the total patient group, 40 patients (72 %) had total CS = 0, and 16 patients had total CS >0 (28 %). Three patients (5 %) had total CS >300 (≥60 years). There were no differences between the active and controlled acromegaly groups with respect to the presence of total CS >0 ($p = 0.61$) and there were no differences in the total CS >0 between women and men ($p = 0.22$). The three patients with total CS >300 were part of the controlled acromegaly patients group. A total of 9 (16 %) patients with acromegaly had CS above the 75th percentile (seven women). The number of patients with CS >75th percentile did not differ between patients with acromegaly and the control group ($p = 0.17$). In addition, the number of patients with CS >75th percentile did not differ between individuals with controlled or active acromegaly ($p = 1.00$). These data are described in Tables 3 and 4.

Correlation between FRS, risk for a cardiovascular event within the next 10 years according to FRS, coronary artery CS, GH, IGF-I, and the estimated disease duration

In patients with acromegaly, the FRS and risk of cardiovascular event within the next 10 years according to FRS were not associated with plasma GH, IGF-I ULNR, or the estimated disease duration.

Among patients with FRS <10 % (low risk), 39 patients had a total CS = 0 and 12 had a total CS >0. Among

Table 1 Clinical features of patients with acromegaly versus control group

	Acromegaly group ($n = 56$)	Control group ($n = 56$)	p value
Age (years)	49 (20–76)	50 (26–56)	0.44
Sex (female/male, *n*)	32/24	32/24	1.00
BMI (kg/m^2)	30 (22.4–45.2)	27 (19.4–42.2)	0.01
Arterial hypertension (%)	66	64	0.843
Diabetes mellitus (%)	36	34	0.843
Hypercholesterolemia (%)	34	36	0.843
Smoking habit (%)	16	9	0.253
Familial history of coronary artery disease (%)	21	59	0.0001

BMI body mass index

Table 2 Clinical and biochemical characteristics of acromegaly patients (controlled vs. active)

	Controlled acromegaly (21/56)	Active acromegaly (35/56)	*p* value
Age (years)	49 (29–74)	49 (20–76)	0.43
Sex (male/female)	4/17	20/15	0.006
BMI (kg/m^2)	31 (23–45)	30 (22–38)	0.80
GH (ng/mL)	1.0 (0.2–5.9)	3.7 (0.2–26)	<0.0001
IGF-I (ULNR)	90 (40–120)	270 (140–520)	<0.0001
Disease duration (years)	10 (2–16)	10 (2–22)	0.89
Arterial hypertension (%)	62	68	0.61
Diabetes mellitus (%)	24	42	0.15
Total cholesterol (mg/dL)	180 (126–239)	180 (89–292)	0.80
HDLc (mg/dL)	54 (33–75)	46 (29–88)	0.26
LDLc (mg/dL)	93 (47–174)	102 (42–180)	0.35
Triglycerides (mg/dL)	142 (54–339)	100 (34–338)	0.017
Hypercholesterolemia (%)	33	43	0.94
Smoking habit (%)	14	17	1.00
Familial history of coronary artery disease (%)	0	34	0.02

BMI body mass index, *HDLc* high-density lipoprotein cholesterol, *LDLc* low-density lipoprotein cholesterol

Table 3 Cardiac evaluation of patients with acromegaly versus control group

	Acromegaly group ($n = 56$)	Control group ($n = 56$)	*p* value
CS > 0	16	20	0.42
CS > 300 (≥60 years)	3	1	#
CS > 75th percentile	9	15	0.17

CS coronary artery calcium score

[#] Statistical analysis for these parameters was not performed due to small sample size

Table 4 Cardiac evaluation of acromegalic patients (controlled acromegaly vs. active acromegaly)

	Controlled acromegaly (21/56)	Active acromegaly (35/56)	*p* value
CS > 0	6	10	0.61
CS > 300 (≥60 years)	3	0	#
CS > 75th percentile	3	6	1.00

CS coronary artery calcium score

[#] Statistical analysis for these parameters was not performed due to small sample size

patients with FRS from 10 to 20 % (intermediate risk), one patient had a total CS = 72, and three patients a total CS >300. The patient who was classified as high risk (FRS more than 20 %) had a total CS = 0.

The coronary artery total CS was positivity correlated with age, FRS, risk of a cardiovascular event within the next 10 years according to FRS and CS >75th percentile. Total CS was not correlated with plasma GH, IGF-I ULNR, or the estimated duration of disease. Plasma GH, IGF-I % ULNR, or duration of disease were not different in those who had or not CS >75th percentile. The CS of the LCA was negatively correlated with IGF-I ($p = 0.019$; $r = -0.313$).

Discussion

The association between atherosclerosis and GH/IGF-I excess is controversial in the literature [9, 10, 20, 27]. To aid in the clarification of this issue, we studied the CS in 56 patients with acromegaly (to the best of our knowledge, the largest series in the literature to date). We did not detect an increased prevalence of CS compared with a matched control group. We demonstrated that 72 % of our patients had a total CS = 0 and were considered at low cardiac risk. Those patients also had, in the majority of the cases (91 %), a low risk of CAD after calculating the FRS.

Acromegaly is frequently associated with metabolic abnormalities, which increase the atherosclerotic risk [7, 28]. In our group, the metabolic alterations were very common. Sixty-six percent of patients had arterial hypertension, 36 % DM, and 34 % hypercholesterolemia. Some studies suggest that GH influences the endothelium either directly via endothelial IGF-I synthesis or indirectly through hypertension, abnormalities of body composition, and lipid metabolism [7]. Acromegaly often affects young individuals. The median age of our patients was 49 years old. In our study, the patients and the control group were matched with respect to sex, age, smoking, and the presence of arterial hypertension, DM and dyslipidemia. As expected, the median BMI was greater in acromegaly patients. It has previously been demonstrated that GH excess is associated with alterations in body composition, including an increase in lean body mass and a reduction in body fat [29].

We evaluated the risk of ischemic events using the FRS and coronary calcium deposits measured using CS. The majority of our patients were classified as low risk (91 %) based on the FRS consensus stratification [11], 9 % were classified as intermediate risk, and only one patient was classified as high risk. In contrast, Cannavo et al. [9] demonstrated that 41 % of their study's acromegaly patients were classified as intermediate risk. Nevertheless, these authors used a different cut-off for the FRS stratification.

In our study, the three patients who were classified as intermediate risk according to FRS had total CS >300 and could be reclassified as high risk.

Coronary artery calcium directly measures the volume of calcium deposits in the coronary arteries. Thus, coronary artery calcium could be considered an index of coronary artery atherosclerosis. Our data indicated that 28 % of our patients had total CS >0 and could be considered at increased cardiac risk. CS >75th percentile was present in 16 % of the patients. These results suggest a low risk of CAD in acromegaly, which is consistent with Bogazzi et al. [10], who reported a low risk of CAD in these patients.

Some studies suggest a protective effect of IGF-I levels on CS [20, 30]. In our group, we observed that the three patients ≥60 years old who had total CS >300 were part of the group of patients with controlled disease, despite the familiar history of CAD being more common in the active group. However, we cannot reach any conclusion from these results because of the low number of patients in this group. Therefore, a statistical analysis was not performed. Interestingly, Otsuki et al. [20] proposed that high IGF-I is protective against atherosclerotic process in some patients with acromegaly; the underlying mechanism might be the regulation of local blood flow through an IGF-I-mediated vascular production of endothelial nitric oxide [31]. However, direct support for this hypothesis has not yet been established. In addition, Juul et al. [32] demonstrated that low IGF-I levels are correlated with increased risk of ischemic heart disease in the general population. However, GH could decrease insulin sensitivity, causing hyperinsulinemia and exerting proatherogenic actions [33].

We observed a low risk of CAD after calculating the FRS and CS in patients with acromegaly. These results did not demonstrate a difference between patients and control individuals. However, we observed a more prevalent familiar history of CAD in the control group. Our control group was selected from a database of a private clinic. A possible explanation for the low CAD in the acromegaly group is that the median age of our patients, 49 years, matched that of the control. In this age group, less atherosclerosis would be normally expected.

Additionally, FRS and CS were not influenced by acromegaly activity. Our data are consistent with Cannavo et al. [9], who also failed to observe an effect of disease activity. However, the results contradict those of Herrmann et al. [18], who demonstrated the influence of disease duration and consequently the accompanying metabolic disorders on the degree of CS in acromegaly patients.

We observed a negative correlation between the CS of the LCA and IGF-I. Additionally, in this series, total CS was positivity correlated with FRS and CS >75th percentile.

This study is the largest in the literature to use the FRS and CS in patients with acromegaly. We have demonstrated that the risk of CAD in these patients, determined according to FRS and CS, is low despite the high prevalence of metabolic abnormalities. However, further studies are required to confirm these data.

Conflict of interest The authors declare that they have no conflict of interest.

References

1. A. Colao, D. Ferone, P. Marzullo, G. Lombardi, Systemic complications of acromegaly: epidemiology, pathogenesis, and management. Endocr. Rev. **25**(1), 102–152 (2004). doi:10.1210/er.2002-0022
2. I.M. Holdaway, M.J. Bolland, G.D. Gamble, A meta-analysis of the effect of lowering serum levels of GH and IGF-I on mortality in acromegaly. Eur. J. Endocrinol. **159**(2), 89–95 (2008). doi:10.1530/EJE-08-0267
3. O.M. Dekkers, N.R. Biermasz, A.M. Pereira, J.A. Romijn, J.P. Vandenbroucke, Mortality in acromegaly: a metaanalysis. J. Clin. Endocrinol. Metab. **93**(1), 61–67 (2008). doi:10.1210/jc.2007-1191
4. G. Brevetti, P. Marzullo, A. Silvestro, R. Pivonello, G. Oliva, C. di Somma, G. Lombardi, A. Colao, Early vascular alterations in acromegaly. J. Clin. Endocrinol. Metab. **87**(7), 3174–3179 (2002). doi:10.1210/jcem.87.7.8643

5. I. Kartal, H. Oflaz, B. Pamukcu, M. Meric, F. Aral, N. Ozbey, F. Alagol, Investigation of early atherosclerotic changes in acromegalic patients. Int. J. Clin. Pract. **64**(1), 39–44 (2010). doi:10.1111/j.1742-1241.2008.01750.x
6. L. Sacca, A. Cittadini, S. Fazio, Growth hormone and the heart. Endocr. Rev. **15**(5), 555–573 (1994). doi:10.1210/edrv-15-5-555
7. R.N. Clayton, Cardiovascular function in acromegaly. Endocr. Rev. **24**(3), 272–277 (2003). doi:10.1210/er.2003-0009
8. A.F. Casini, P.B. Araujo, R. Fontes, S.S. Xavier, M.R. Gadelha, Cardiac morphology and performance alterations and analysis of determinant factors of left ventricular hypertrophy in 40 patients with acromegaly. Arq. Bras. Endocrinol. Metabol. **50**(1), 82–90 (2006). doi:10.1590/S0004-27302006000100012
9. S. Cannavo, B. Almoto, G. Cavalli, S. Squadrito, G. Romanello, M.T. Vigo, F. Fiumara, S. Benvenga, F. Trimarchi, Acromegaly and coronary disease: an integrated evaluation of conventional coronary risk factors and coronary calcifications detected by computed tomography. J. Clin. Endocrinol. Metab. **91**(10), 3766–3772 (2006). doi:10.1210/jc.2005-2857
10. F. Bogazzi, L. Battolla, C. Spinelli, G. Rossi, S. Gavioli, V. Di Bello, C. Cosci, C. Sardella, D. Volterrani, E. Talini, P. Pepe, F. Falaschi, G. Mariani, E. Martino, Risk factors for development of coronary heart disease in patients with acromegaly: a five-year prospective study. J. Clin. Endocrinol. Metab. **92**(11), 4271–4277 (2007). doi:10.1210/jc.2007-1213
11. R.B. D'Agostino Sr, S. Grundy, L.M. Sullivan, P. Wilson, C.H.D.R.P. Group, Validation of the Framingham coronary heart disease prediction scores: results of a multiple ethnic groups investigation. JAMA **286**(2), 180–187 (2001)
12. P. Greenland, L. LaBree, S.P. Azen, T.M. Doherty, R.C. Detrano, Coronary artery calcium score combined with Framingham score for risk prediction in asymptomatic individuals. JAMA **291**(2), 210–215 (2004). doi:10.1001/jama.291.2.210
13. M.J. Budoff, K. Nasir, R.L. McClelland, R. Detrano, N. Wong, R.S. Blumenthal, G. Kondos, R.A. Kronmal, Coronary calcium predicts events better with absolute calcium scores than age-sex-race/ethnicity percentiles: MESA (multi-ethnic study of atherosclerosis). J. Am. Coll. Cardiol. **53**(4), 345–352 (2009). doi:10.1016/j.jacc.2008.07.072
14. R. Detrano, A.D. Guerci, J.J. Carr, D.E. Bild, G. Burke, A.R. Folsom, K. Liu, S. Shea, M. Szklo, D.A. Bluemke, D.H. O'Leary, R. Tracy, K. Watson, N.D. Wong, R.A. Kronmal, Coronary calcium as a predictor of coronary events in four racial or ethnic groups. N. Engl. J. Med. **358**(13), 1336–1345 (2008). doi:10.1056/NEJMoa072100
15. A.J. Taylor, J. Bindeman, I. Feuerstein, F. Cao, M. Brazaitis, P.G. O'Malley, Coronary calcium independently predicts incident premature coronary heart disease over measured cardiovascular risk factors: mean three-year outcomes in the Prospective Army Coronary Calcium (PACC) project. J. Am. Coll. Cardiol. **46**(5), 807–814 (2005). doi:10.1016/j.jacc.2005.05.049
16. J.T. Lie, Pathology of the heart in acromegaly: anatomic findings in 27 autopsied patients. Am. Heart J. **100**(1), 41–52 (1980)
17. H. Akutsu, J. Kreutzer, G. Wasmeier, D. Ropers, C. Rost, M. Mohlig, H. Wallaschofski, M. Buchfelder, C. Schofl, Acromegaly per se does not increase the risk for coronary artery disease. Eur. J. Endocrinol. **162**(5), 879–886 (2010). doi:10.1530/EJE-09-0945
18. B.L. Herrmann, M. Severing, A. Schmermund, C. Berg, T. Budde, R. Erbel, K. Mann, Impact of disease duration on coronary calcification in patients with acromegaly. Exp. Clin. Endocrinol. Diabetes **117**(8), 417–422 (2009). doi:10.1055/s-0029-1214386
19. M. Ragonese, A. Alibrandi, G. Di Bella, I. Salamone, S. Puglisi, O.R. Cotta, M.L. Torre, F. Ferrau, R.M. Ruggeri, F. Trimarchi, S. Cannavo, Cardiovascular events in acromegaly: distinct role of Agatston and Framingham score in the 5-year prediction. Endocrine **47**(1), 206–212 (2014). doi:10.1007/s12020-013-0115-8
20. M. Otsuki, S. Kasayama, H. Yamamoto, H. Saito, S. Sumitani, H. Kouhara, Y. Saitoh, T. Ohnishi, N. Arita, Characterization of premature atherosclerosis of carotid arteries in acromegalic patients. Clin. Endocrinol. **54**(6), 791–796 (2001)
21. World Health Organization, *Guidelines for the conduct of tobacco smoking among health professionals* (Report WHO Meeting, Winnipeg, Canadá, 1983)
22. World Health Organization, *Obesity: preventing and managing the global epidemic* (Report of a WHO Consultation, Geneva, 2000)
23. S.M. Grundy, J.I. Cleeman, C.N. Merz, H.B. Brewer Jr, L.T. Clark, D.B. Hunninghake, R.C. Pasternak, S.C. Smith Jr, N.J. Stone, National Heart, Lung and Blood Institute, American College of Cardiology Foundation, American Heart Association, Implications of recent clinical trials for the National Cholesterol Education Program Adult Treatment Panel III guidelines. Circulation **110**(2), 227–239 (2004). doi:10.1161/01.CIR.0000133317.49796.0E
24. A.S. Agatston, W.R. Janowitz, F.J. Hildner, N.R. Zusmer, M. Viamonte Jr, R. Detrano, Quantification of coronary artery calcium using ultrafast computed tomography. J. Am. Coll. Cardiol. **15**(4), 827–832 (1990)
25. I. Gottlieb, L. Sara, J.A. Brinker, J.A. Lima, C.E. Rochitte, CT coronary calcification: What does a score of "0" mean? Curr. Cardiol. Rep. **13**(1), 49–56 (2011). doi:10.1007/s11886-010-0151-4
26. R.L. McClelland, K. Nasir, M. Budoff, R.S. Blumenthal, R.A. Kronmal, Arterial age as a function of coronary artery calcium (from the Multi-Ethnic Study of Atherosclerosis [MESA]). Am. J. Cardiol. **103**(1), 59–63 (2009). doi:10.1016/j.amjcard.2008.08.031
27. M. Fleseriu, Insight into cardiovascular risk factors in patients with acromegaly. Endocrine **47**(1), 1–2 (2014). doi:10.1007/s12020-013-0157-y
28. C. Berg, S. Petersenn, H. Lahner, B.L. Herrmann, M. Buchfelder, M. Droste, G.K. Stalla, C.J. Strasburger, U. Roggenbuck, N. Lehmann, S. Moebus, K.H. Jockel, S. Mohlenkamp, R. Erbel, B. Saller, K. Mann, Investigative Group of the Heinz Nixdorf Recall Study and the German Pegvisomant Observational Study Board and Investigators, 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. J. Clin. Endocrinol. Metab. **95**(8), 3648–3656 (2010). doi:10.1210/jc.2009-2570
29. L. Katznelson, Alterations in body composition in acromegaly. Pituitary **12**(2), 136–142 (2009). doi:10.1007/s11102-008-0104-8
30. S. Cannavo, F. Marini, L. Curto, M.L. Torre, C. de Gregorio, I. Salamone, A. Alibrandi, F. Trimarchi, High prevalence of coronary calcifications and increased risk for coronary heart disease in adults with growth hormone deficiency. J. Endocrinol. Invest. **34**(1), 32–37 (2011). doi:10.3275/7076
31. P. Delafontaine, H. Lou, R.W. Alexander, Regulation of insulin-like growth factor I messenger RNA levels in vascular smooth muscle cells. Hypertension **18**(6), 742–747 (1991)
32. A. Juul, T. Scheike, M. Davidsen, J. Gyllenborg, T. Jorgensen, Low serum insulin-like growth factor I is associated with increased risk of ischemic heart disease: a population-based case-control study. Circulation **106**(8), 939–944 (2002)
33. E. Conti, C. Carrozza, E. Capoluongo, M. Volpe, F. Crea, C. Zuppi, F. Andreotti, Insulin-like growth factor-1 as a vascular protective factor. Circulation **110**(15), 2260–2265 (2004). doi:10.1161/01.CIR.0000144309.87183.FB