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ORIGINAL ARTICLE

Changes in metabolic parameters and cardiovascular risk factors after therapeutic control of acromegaly vary with the treatment modality. Data from the Bicêtre cohort, and review of the literature

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Summary

Context Untreated acromegaly is associated with increased morbidity and mortality due to malignant, cardiovascular, and cerebrovascular disorders. Effective treatment of acromegaly reduces excess mortality, but its impact on cardiovascular risk factors and metabolic parameters are poorly documented.

Aim We analyzed changes in cardiovascular risk factors and metabolic parameters in patients receiving various treatment modalities.

Patients and methods We retrospectively studied 96 patients with acromegaly, both at diagnosis and after IGF-I normalization following surgery alone ($n = 51$) or medical therapy with first generation somatostatin analogues (SSA, $n = 23$), or pegvisomant ($n = 22$). Duration of follow-up was 77 (42–161) months, 75 (42–112) months, and 62 (31–93) months, in patients treated with surgery alone, SSA, and pegvisomant, respectively. In all the cases except four, patients treated medically had underwent previous unsuccessful surgery.

Results IGF-I normalization was associated with increased body weight, decreased systolic blood pressure (SBP) in hypertensive patients, decreased fasting plasma glucose (FPG) and HOMA-IR and HOMA-B levels, increased HDL cholesterol (HDLc); whereas, LDL cholesterol (LDLc) was not significantly different. Plasma PCSK9 levels were unchanged in patients with available values. Cardiovascular and metabolic changes varied with the treatment modality: surgery, but not pegvisomant, had a beneficial effect on SBP; FPG decreased after surgery but increased after SSA; the decline in HOMA-IR was only significant after surgery; pegvisomant significantly increased LDLc and total cholesterol; whereas SA increased HDLc and had no effect on LDLc levels.

Conclusion Treatments used to normalize IGF-I levels in patients with acromegaly could have differential effects on cardiovascular risk factors and metabolic parameters.

Keywords Acromegaly · Cardiovascular risk factors · Metabolic parameters · HDLc · LDLc · Total cholesterol · PCSK9

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Introduction

Acromegaly is characterized by a chronic GH/IGF-I excess [1, 2], leading to increased morbidity and mortality, particularly from cardiovascular and cerebrovascular disorders [3, 4]. Patients with acromegaly have a clinical and biological atherogenic profile, including a higher prevalence of hypertension, altered glucose metabolism, and lipid abnormalities [3, 5, 6]. However, studies based on the Framingham risk score or the Agatston coronary artery calcium score have given discordant results: some suggest that the cardiovascular risk is often elevated [5, 7, 8], whereas others suggest that this risk is low [9].

Despite their possible unfavorable cardiovascular risk profile, coronary events do not appear to be more frequent in acromegalic patients [7, 9–13], and recent epidemiological studies suggest that cancer is now responsible for more deaths than cardiovascular (or cerebrovascular) disease [14, 15].

Effective treatment of acromegaly reduces the excess mortality [16, 17], but its benefit on cardiovascular mortality and morbidity is less clearcut. Moreover, acromegalic cardiomyopathy must be distinguished from "usual" coronary heart disease (CHD). Effective treatment of acromegaly clearly improves acromegalic cardiomyopathy, reducing left ventricular (LV) hypertrophy and improving both diastolic function and the LV ejection fraction [18], but its impact on coronary events has not been really established. Normalization of GH/IGF-I levels in this setting has controversial effects on CV risk factors, and particularly on the lipid profile [5, 9, 11, 19–51]. This may be related, at least in part, to the use of different therapeutic modalities. We therefore conducted a longitudinal study of metabolic profiles in a large cohort of acromegalic patients studied both at diagnosis and on IGF-I normalization by surgery alone or by single-agent medical therapy with first generation somatostatin analogues (SSA) or pegvisomant. We also studied plasma proprotein convertase subtilisin kexin type 9 (PCSK9), which influences plasma LDL cholesterol (LDLc) levels by triggering the degradation of LDL receptors [52], as circulating PCSK9 levels are reduced by GH [53, 54].

Patients and methods

Patients

Between 1981 and 2013, 365 patients with acromegaly were regularly monitored in our institution (Bicêtre Hospital). Acromegaly was diagnosed on the basis of clinical findings and elevated levels of insulin-like growth factor 1 (IGF-I) and serum growth hormone (mean GH serum profile and/or nadir above 1 µg/L after an oral glucose load) [55–57]. Patients with pituitary deficiency received replacement therapy. We excluded 249 patients from the study, because of incomplete disease control in 92 cases, previous radiotherapy in 52 cases, no baseline evaluation in our institution in 80 cases, acromegaly secondary to ectopic GHRH secretion in 2 cases, plurihormonal pituitary adenoma in one case (GH and prolactin) and combination therapy or different drug classes in 22 cases. Among the remaining 116 patients, 20 patients received a statin at diagnosis or during follow-up and were thus excluded from the lipid study. The longitudinal study population thus consisted of 96 patients. PCSK9 was measured in a subgroup of 24 patients with available values both at baseline and after IGF-I normalization. Normalization of sex- and age-adjusted IGF-I levels was the sole criterion for disease control.

Respectively 22 of 23 (96%) and 19 of 22 (86%) patients treated with SSA and pegvisomant had undergone unsuccessful surgery.

All the patients gave their written informed consent to study participation.

Assays

The following immunoassays were used for GH measurement: Nichols Advantage® GH assay until 2006 (WHO IS 80/505 GH standard), intra- and inter-assay coefficients of variation were 2.8% and 5.7%, respectively, for the 0–30 mUI/L concentration range and 2.5% and 5%, respectively for the >30 mUI/L concentration range; and Siemens Immulite® assay after 2006 (WHO IS 98/574 GH standard), intra- and inter-assay coefficients of variation were 3.7% and 5.5%, respectively, for the 0–30 mUI/L concentration range and 3.6% and 4.2%, respectively for the >30 mUI/L concentration range [58, 59].

The following immunoassays were used for IGF-I measurement: Immunotech, Beckman Coulter Company until 2007 (WHO 1st IRR 87/518 IGF-I standard) with intra- and inter-assay coefficients of variation were 6.3% and 6.8%, respectively, for >300 ng/mL concentration range, and Siemens Immulite® assay after 2007 (WHO 1st IRR 87/518 IGF-I standard) with intra- and inter-assay coefficients of variation of 3% and 7.7%, respectively for a concentration of 77 ng/mL and 2.9% et 7.4%, respectively, for a concentration of 380 ng/mL.

Age-adjusted IGF-I values were calculated with age-specific reference ranges for our IGF-I assay (IGF-I% = patient's IGF-I/age-specific upper limit × 100, the age-specific upper limit being the normal mean IGF-I level for age and sex + 2 SD).

Glucose, total cholesterol (TC), HDL cholesterol (HDLc), and triglyceride (TG) levels were measured locally with standard techniques. LDL cholesterol (LDLc) levels were calculated with Friedewald's formula. Insulin sensitivity and secretion were evaluated with the homeostasis

Table 1 Clinical and biological characteristics of patients at diagnosis

	Surgery	SSA	Pegvisomant	*P*-value
Number of patients	51	23	22	
Age (years)	49 (39–57)	44 (31–59)	37 (28–46)	$P = 0.006$*
Gender (M/F)	26/25	12/11	11/11	NS
Follow-up (months)	77 (42–161)	75 (42–112)	62 (31–93)	NS
Hormonal parameters at diagnosis				
IGF-I, (%ULN)	252 (190–360)	222 (139–299)	258 (215–356)	NS
Nadir GH (mUI/l)	18 (6–32)	23 (11–40)	37 (17–69)	$P = 0.04$*
Medical history at diagnosis				
Diabetes	2	1	3	
Hypertension	12	3	6	
BMI (kg/m^2)	25.6 (22.8–27.4)	25.6 (22.8–27.6)	25.9 (24.7–31.1)	NS
Systolic BP (mmHg)	130 (120–140)	120 (114–130)	120 (110–136)	NS
Diastolic BP (mmHg)	80 (70–83)	70 (69–80)	70 (69–80)	NS
Metabolic parameters at diagnosis				
FPG (mmol/l)	5.5 (5.2–6.0)	5.3 (4.8–6.0)	5.5 (4.8–6.3)	NS
TC (mmol/l)	5.4 (4.7–6.1)	4.9 (4.4–5.5)	4.9 (4.3–5.7)	NS
HDLc (mmol/l)	1.3 (1.1–1.7)	1.6 (1.0–2.0)	1.2 (1.0–1.5)	NS
LDLc (mmol/l)	3.4 (2.8–4.1)	3.0 (2.6–3.6)	2.9 (2.6–3.5)	NS
TG (mmol/l)	1.0 (0.7–1.2)	1.0 (0.6–1.4)	1.1 (0.8–1.6)	NS
Pituitary deficiencies at diagnosis				
ACTH	0	0	0	
TSH	4	2	4	
LH/FSH	2	4	11	

Data are expressed as median (IQR)

SSA somatostatin analogues, *ULN* upper limit of normal, *BMI* body mass index, *BP* blood pressure, *FPG* fasting plasma glucose, *TC* total cholesterol, *HDLc* HDL cholesterol, *LDLc* LDL cholesterol, *TG* triglyceride

*Comparison between surgery and pegvisomant groups

model assessment (HOMA-IR and HOMA-B) [60], applied to single measurements of fasting glucose and insulin. Insulin was measured with the Diasorin Liaison® assay.

Fasting plasma PCSK9 was measured with an enzyme-linked immunosorbent assay (Circulex CY-8079, CycLex Co, Nagano, Japan) [61].

Statistical analysis

Results are reported as median and interquartile range (IQR). Groups were compared with Mann and Whitney test, and the Wilcoxon test was used for longitudinal comparisons between baseline and IGF-I normalization.

Results

Baseline characteristics

Ninety-six acromegalic patients (47 females) were included in this analysis. Their median age was 56 years (range, 24–87). Baseline clinical and biological parameters did not differ according to the treatment modality, except for age which was younger in the group secondarily controlled by pegvisomant than in the group secondarily controlled by surgery. If baseline IGF-I was not different between the three groups, baseline nadir of GH after OGTT was significantly higher in the group controlled by pegvisomant than in the group secondarily controlled by surgery (Table 1).

Characteristics of the patients at time of disease control

Follow-up duration was very variable but was not significantly different from one group to the other [77 (42–161) months, 75 (42–112) months, and 62 (31–93) months, in patients treated with surgery alone, SSA, and pegvisomant, respectively]. At time of disease control, median (IQR) age was younger in patients treated with pegvisomant [42.5 (35–53) years] compared with those cured by surgery alone [57 (49–63) years, $p = 0.001$] or

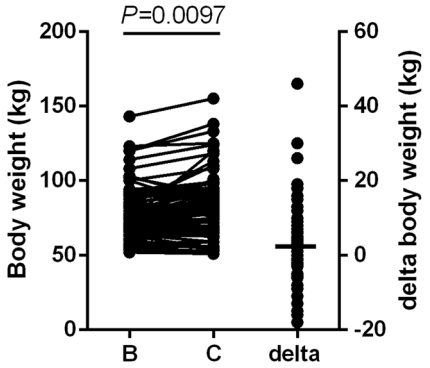

Fig. 1 Changes in body weight between diagnosis (B) and control of acromegaly (C) in 96 patients receiving various treatments

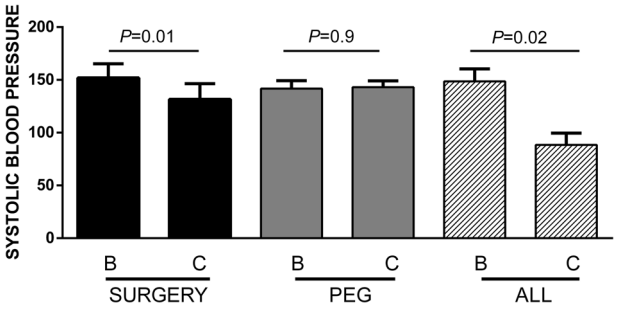

Fig. 2 Blood pressure changes between diagnosis (B) and control of acromegaly (C), both overall (ALL) and after surgery and PEG) in acromegalic patients with systolic blood pressure >140 mmHg or receiving treatment for hypertension (patients whose antihypertensive treatment was modified were excluded from this analysis). As all patients of the SSA group modified their antihypertensive treatment, BP could not be compared in this treatment group

those treated with SSA [57 (50–68) years, $p = 0.004$]. BMI was not different between the four groups at the time of disease control [26 (23, 29) kg/m^2, 25 (23, 28) kg/m^2, and 27 (24, 33) kg/m^2] in the patients treated with surgery alone, SSA, or pegvisomant, respectively.

Body weight changes

Between baseline and control of acromegaly, body weight increased significantly, with a median (IQR) gain of 1 kg (−2, + 6) ($p = 0.01$) (Fig. 1). The increase in body weight was statistically significant in female patients [+3 (−2, +6) kg, $p = 0.048$] but not in males [+1 (−2, +6) kg, $p = 0.08$]. Median weight gain was statistically significant in the patients cured by surgery [+1.5 (−1.7, +6) kg ($p = 0.02$)], although there was only a trend with the medical treatment modalities [+2.5 (−5.7, +10.5) kg ($p = 0.1$), and +0.78 (−5, +6) kg ($p = 0.7$) under pegvisomant, or SSA, respectively]. There was no statistical difference in terms of weight gain between SSA and pegvisomant groups. When the time interval between baseline and time of disease control was taken into account (follow-up ranged from 6 to 270 months), median weight gains were not statistically different between groups [+0.14 (−0.26, +0.1) kg/year, +0.8 (−0.65, +2.37) kg/year, and +0.1 (−1, +0.66) kg/year, in the patients treated with surgery alone, pegvisomant and SSA, respectively]. An analysis based on the body mass index (BMI) gave similar results.

Changes in blood pressure

Blood pressure tended to decline after treatment, but this was not significant and correlated with IGF-I changes. At baseline, 75 patients had a systolic blood pressure (SBP) below 140 mmHg, and 15 patients were treated for hypertension (including five with SBP <140 mmHg). Antihypertensive treatment was introduced during follow-up in 25 patients (seven in the SSA group, seven in the pegvisomant group, and 12 in the surgery group). Antihypertensive treatment was increased in six patients (two in the surgery group, three in SSA group and one in the pegvisomant group), and reduced in three patients (two in the surgery group and one in the pegvisomant group) during the follow-up.

Among the 11 patients who were hypertensive at diagnosis (SBP >140 mmHg, or <140 mmHg on antihypertensive treatment) and whose antihypertensive treatment was not modified, median SBP fell significantly after control of acromegaly [from 150 (140, 158) to 130 (117, 150) mmHg; $p = 0.019$]. Surgery was associated with a significant reduction in SBP, whereas this was not the case with pegvisomant. As all patients of the SSA group modified their antihypertensive treatment, BP could not be compared. These differences were not correlated to IGF-I changes (Fig. 2).

Changes in fasting blood glucose and HOMA

Overall, fasting plasma glucose (FPG) fell significantly from 5.4 (4.9, 6.1) to 5.2 (4.7, 5.8) mmol/l, ($p = 0.026$) (Fig. 3a). FPG fell significantly after surgery, but increased after SAA (Fig. 3a). FPG changes were correlated to IGF-I decrease for all patients ($r = 0.048$; $p = 0.005$) and in the SSA group ($r = 0.25$; $p = 0.02$). FPG levels were not significantly altered with pegvisomant.

HOMA-IR and HOMA-B levels also fell significantly, from 2.25 (1.0–3.5) to 0.88 (0.7–1.3) ($p = 0.040$), and from 115 (50–172) to 40 (32–101) ($p = 0.02$), respectively, clearly indicating improved insulin resistance and insulin secretion (Fig. 3b, c). These changes were not correlated to IGF-I changes. HOMA-IR and HOMA-B decreases were

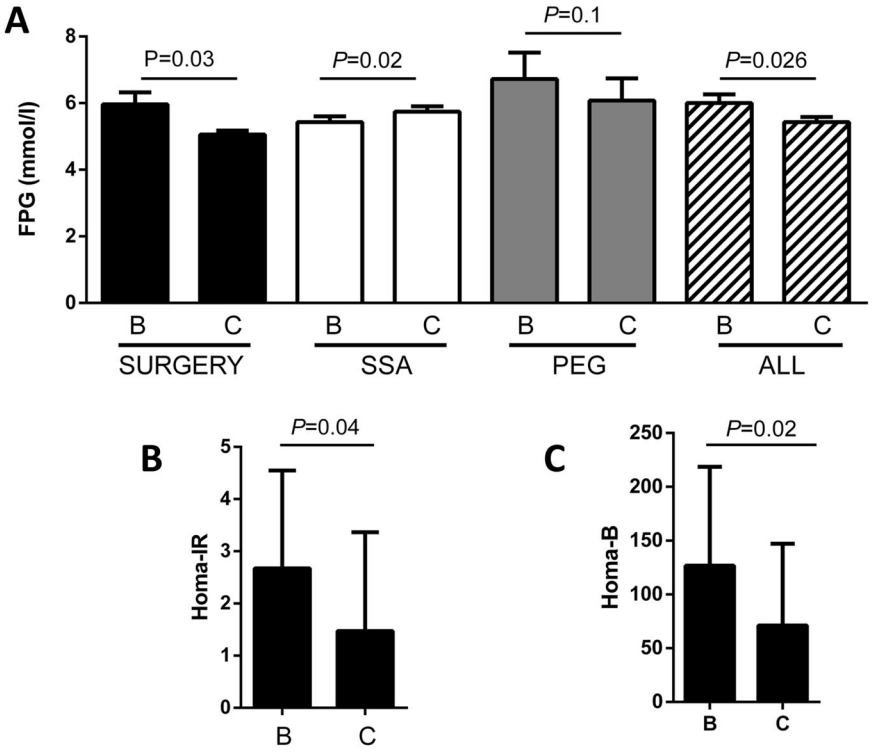

Fig. 3 **a** Changes in fasting plasma glucose (FPG), both overall (ALL) and after each treatment modality. **b** Overall changes in HOMA-IR between diagnosis (B) and control of acromegaly (C). **c** Overall changes in HOMA-B between diagnosis (**B**) and control of acromegaly (**C**)

observed in each treatment group, but were only significant for HOMA-IR after surgery ($p = 0.0002$) (data not shown).

Changes in the lipid profile

Overall, LDLc and total cholesterol levels tended to rise; HDLc rose significantly [from 1.27 (1.1–1.7) to 1.45 (1.2–1.8) mmol/l, $p = 0.005$] with no change in plasma triglyceride levels. LDLc rose significantly in patients treated with pegvisomant [from 2.87 (2.6–3.5) to 3.6 (2.9–4.3) mmol/l ($p = 0.0007$)], whereas HDLc rose significantly ($p = 0.04$) and LDLc tended to decline in patients treated with SSA (Fig. 4). Surgery was not associated with any significant variation in CT, TG, LDLc, and HDLc (Fig. 4). These changes in lipid parameters were not correlated to IGF-I changes.

Changes in PCSK9 levels

In the subgroup of 24 patients with available values, control of acromegaly did not modify median plasma PCSK9 levels [448 (357–549) vs 440 (332–534) ng/mL, $p = 0.93$] (Fig. 5). Median PCSK9 levels tended to decline in the groups treated with surgery [519 (470–590) vs 444 (382–520) ng/mL, $p = 0.1$]. In contrast, plasma PCSK9 concentrations tended to increase on pegvisomant [from 338 (312–445) to 369 (219–709) ng/mL, $p = 0.3$] and SSA [from 437 (300–528) to 460 (341–552) ng/mL, $p = 0.6$].

Discussion

The main finding of this study is that the different treatments used to control acromegaly are associated with different changes in metabolic parameters and cardiovascular risk factors. Indeed, while HDLc increased in the overall population, LDLc increase only with pegvisomant treatment. The amplitude and sometimes the direction of change varied with the treatment modality. Overall, body weight increased whatever the treatment modality, and FPG declined except in the group treated with SSA. Insulin resistance, assessed in terms of HOMA-IR, also declined significantly, whereas SBP declined in hypertensive patients.

Acromegaly is characterized by GH/IGF-I hypersecretion, which leads to bone overgrowth and soft-tissue infiltration due to its anabolic, lipolytic, and sodium-retaining effects [1–3]. At diagnosis, patients with acromegaly have an altered body composition, with elevated body water and total body weight, and below-normal body fat [62–65]. Surgical control of acromegaly reduces body water and fat free mass, leading to rapid weight loss, but body fat subsequently increases (particularly visceral fat) [29, 44, 48, 66–72].

We found that body weight increased after effective treatment of acromegaly, but the change was only statistically significant after surgery. Elsewhere, intra-abdominal fat was found to increase while total body weight did not

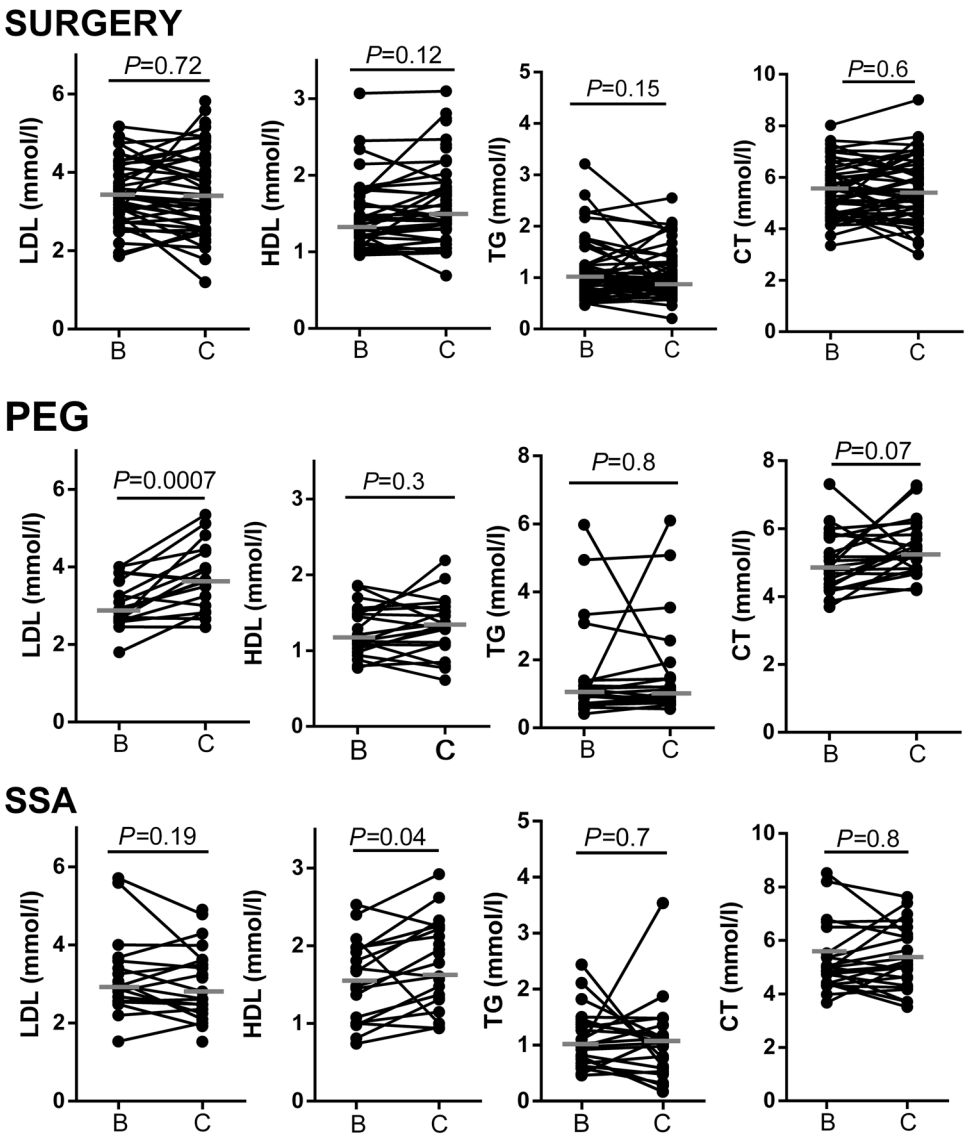

Fig. 4 Changes in lipid levels between diagnosis (B) and control of acromegaly (C), both overall (ALL) and after each treatment modality. The gray lines represent the mean values

change after treatment with pegvisomant, somatostatin analogues or surgery [19, 23, 68, 69, 71–74]. Freda et al. [64] found a negative correlation between visceral fat and IGF-I levels. We found that median weight gain was significant in women but not in men. The effect on fat mass is reported to be similar whatever the treatment [75], as would be expected from the lipolytic effect of GH. A summary of published data on fat mass and body weight during treatment of acromegaly is provided in Suppl Table 1.

We found that SBP and DBP tended to decline after control of acromegaly. The elevated extracellular (EC) volume observed in active acromegaly, due to the anti-natriuretic effect of GH/IGF-I [76], may contribute to hypertension. The decrease in EC water following a therapeutic reduction in GH/IGF-I levels would improve blood pressure. However, while some studies suggest that control of acromegaly leads to a decline in BP, particularly in case of pre-existing hypertension [77, 78], others show no such effect [9, 11, 20, 29, 37, 47, 50, 79–86] (Suppl. Table 2). Moreover, control of acromegaly did not have the same effect on SBP and DBP in some studies [29, 45, 87, 88]. We found a significant decrease in SBP in hypertensive patients but not in patients with normal BP at diagnosis. A review of published studies shows a negative relationship between BP and IGF-I in conditions of low IGF-I levels, and a positive relationship in case of markedly elevated IGF-I levels [89]. We found no differential effect of the treatment modality on BP, as in previous studies comparing surgery and SSA [87, 90]. Thus, control of acromegaly is generally associated with a positive or neutral effect on SBP, although an increase in SBP during treatment was observed in two studies [35, 91]. Control of acromegaly is associated with decrease in the heart rate, whatever the treatment modality [11, 35, 37, 77, 79, 80, 84, 87, 91–93].

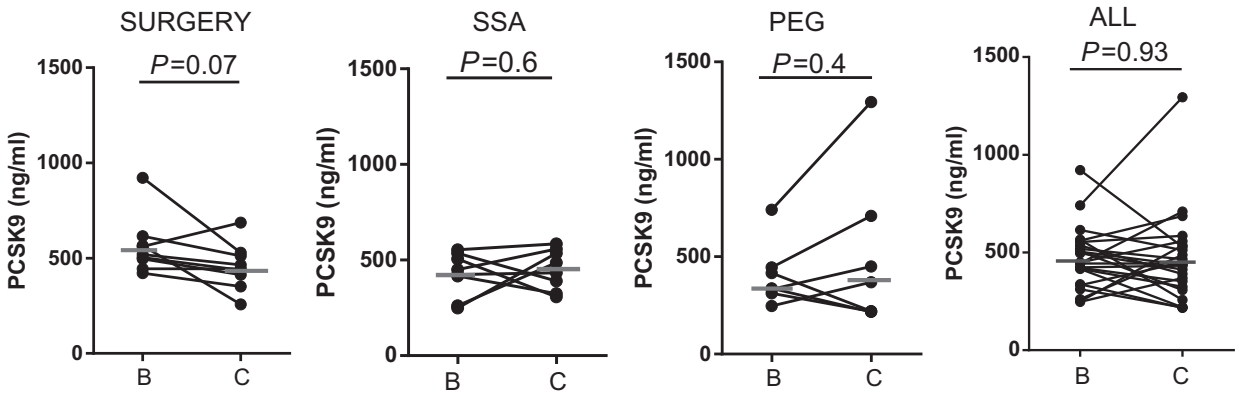

Fig. 5 Changes in PCSK9 between diagnosis (B) and control of acromegaly (C), both overall (ALL, $n = 24$) and after each treatment modality, i.e. surgery ($n = 9$), somatostatin analogue (SSA, $n = 8$), pegvisomant (PEG, $n = 7$). The gray lines represent the mean values

We found that control of acromegaly was associated with a significant improvement in glucose metabolism in the whole population. However, FPG rose in patients treated with SSA, confirming previous reports [75, 94, 95]. Indeed, many studies have shown that SSA can have a negative impact on beta cells, impairing insulin secretion and FPG, whereas pegvisomant (which has no effect on insulin secretion) improves these parameters [5, 20, 21, 50, 75, 96–102]. However, a meta-analysis of studies examining changes in glucose metabolism during SSA therapy showed no significant change in FPG but modest and significant glucose intolerance during the OGTT [103, 104]. We confirm that insulin sensitivity improves under treatment, whatever the modality [19, 28, 29, 44, 47, 50, 68, 77, 85, 86, 95, 105–110] (Suppl. Table 3).

The impact of effective treatment of acromegaly on the lipid profile is somewhat controversial (Suppl. Table 3). In the present study, LDLc tended to decrease and total cholesterol tended to increase, whereas HDLc increased significantly in the whole population. LDLc and total cholesterol increased during pegvisomant treatment, confirming some previous reports [22, 24, 45], but not others [5, 23]. Such an increase in LDLc after correction of the GH excess may be related to the stimulatory effect of GH on LDL receptor expression [111]. In addition, pegvisomant also tended to raise PCSK9 levels in the small number of subjects with available data (Fig. 5). This effect could mediate the cholesterol-raising action of pegvisomant, and it would be interesting to verify these data in a larger cohort. SSA treatment was associated with an increase in HDLc, as previously reported [26, 27, 36, 85, 94, 112]. HDLc is regulated by lipoprotein lipase, and GH has an inhibitory effect on lipoprotein lipase in adipose tissue. This may explain the increase in HDLc observed after control of acromegaly. The differential effect on HDLc may be due to different effects on the secretion of insulin, which activates lipoprotein lipase. Moreover, GH excess has an inhibitory effect on LCAT (lecithin:cholesterol acyl transferase), CETP (cholesteryl ester transfer protein) and PLTP (phospholipid transfer protein), which esterify free cholesterol in HDL and transfer it to VLDL and LDL. This may explain the low HDLc and high LDLc levels observed in patients with acromegaly [113], and also the opposite effects observed during effective treatment.

In view of a previous study of healthy volunteers, in whom GH treatment was associated with a decrease in plasma PCSK9 concentrations [54], we expected that circulating PCSK9 levels would be low in patients with active acromegaly and be increased by effective treatment. Our results are not very clearcut, however. Indeed, PCSK9 levels tended to increase with pegvisomant and SSA but to decrease with surgery. PCSK9 is very sensitive to many hormonal parameters. For instance, thyroid hormones and estrogen lower plasma PCSK9, while insulin increases PCSK9 expression [114–116]. In addition, diets [117] as well as inflammatory status [118] modulate PCSK9 expression and circulating levels. Although our treatment groups were comparable at baseline for these parameters, this may have introduced a source of confusion [53, 119].

Our study, like others, [11, 39, 120, 121] shows that active acromegaly is not associated with a clear cardiovascular risk profile, and that control of acromegaly may worsen some classical cardiovascular risk factors. Indeed, SBP, FPG, insulin resistance, total cholesterol and HDLc improve, albeit moderately, while fat mass (particularly visceral fat) and LDLc and VLDL levels tend to increase. Elsewhere, fibrinogen, Lp(a), ApoB, free fatty acids, homocystein, and endothelin-1 levels have been reported to increase after effective treatment [34, 70, 122]. Adiponectin levels are low in patients with active acromegaly and also increase after effective treatment [121, 123–126].

Recent studies suggest that although patients with active acromegaly have risk factors for atherosclerosis, markers of inflammation and oxidative stress are limited or absent

[6, 20, 22, 30, 31, 46, 47, 70, 127, 128], and treatment of acromegaly is associated with an increase in hsCRP [30, 39, 46, 47, 128].

Data on early markers of atherosclerosis and arterial stiffness are also controversial in this setting. Indeed, at diagnosis, some studies have shown significantly low flow-mediated dilatation, increased carotid intima media and epicardial adipose tissue thickness, and increased carotid-femoral pulse wave velocity [31, 49, 107, 129, 130], whereas others showed no such changes [30, 131]. Improvements in FMD and/or endothelial function have been observed in some studies after surgery [33] and SSA therapy [132], but not in others [49].

Studies based on the Agatston score (AS) and the coronary artery calcium (CAC) score do not support an increased prevalence of atherosclerotic lesions in patients with active acromegaly. Indeed, the Agatston score was found to be lower in patients with active acromegaly than in controls, and was not modified by effective treatment [7, 9, 11, 133].

The differential effects of the three treatment modalities observed both here and elsewhere are difficult to explain. One possibility is that biochemical definitions of acromegaly control vary from one study to another. Indeed, differences in metabolic outcomes have been reported according to the timing and quality of acromegaly control, which may differ according to the treatment modality [75, 134]. Olarescu et al. found no difference in body-fat changes among patients treated with SSA, pegvisomant or surgery, but reported that blood glucose and insulin responded differently to SSA by comparison with the other treatments [75]. Berg et al. reported a cardiovascular risk profile in patients treated with SSA compared with those treated surgically [90]. Another possible explanation is a differential effect of available treatments on insulin secretion: indeed, SSA, surgery and pegvisomant are all able, by reducing GH levels, to improve insulin resistance secondary to the GH excess, but only SSA reduces insulin secretion [109].

The retrospective nature of our study is clearly one of its limitations. In addition, some cardiovascular risk markers were unavailable in our study, including hsCRP. Another important limitation of this study is the absence of a control group of healthy subjects in order to assess, in parallel, the effects of aging on cardiometabolic features, as follow-up duration was very variable from 1 to 20 years. Nevertheless, one can argue that, on average, the duration of follow-up was similar among the four groups and that the course of parameters such as blood pressure, LDLc, blood glucose, or HOMA under treatment in that study is not what is usually observed with aging. Acromegaly severity can also be a bias for this study, even if basal parameter were not different in terms of IGF-I or hormonal deficit. One can hypothesize that acromegaly is more severe when treated with pegvisomant (usually after SSA failure) than with SSA, and that acromegaly cured with surgery might be less severe, with less GH excess.

Conclusion

This study shows that therapeutic control of acromegaly is associated with weight gain and a decrease in systolic blood pressure, whatever the treatment modality. By contrast, changes in other cardiovascular risk markers (blood glucose, lipids, etc.) vary, albeit minimally, with the type of treatment. Whether this variability should be taken into account when evaluating the impact of acromegaly on cardiovascular morbidity and mortality will require further studies.

Compliance with ethical standards

Conflict of interest Disclosure of potential conflicts of interest: P.C. is a consultant for Novartis, Ipsen, and Pfizer. Honoraria and lecture fees from Novartis, Ipsen, and Pfizer have been paid to his institution. The Service d'Endocrinologie et des Maladies de la Reproduction, Hôpital de Bicêtre, has received educational and research grants from Novartis, Ipsen, and Pfizer. B.C. has received research funding from Pfizer and Sanofi-Regeneron, and honoraria from Amgen, AstraZeneca, Pierre Fabre, Janssen, Eli-Lilly, MSD Merck & Co., Novartis, Novo-Nordisk, Sanofi, and Takeda. All the remaining authors declare that they have no conflict of interest.

Ethical approval All procedures performed in this study involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all individual participants included in the study.

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