

Increased Risk of Persistent Glucose Disorders After Control of Acromegaly

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Purpose: Combining surgery and medical treatments allows the control of growth hormone hypersecretion in 80% of cases. Our objective was to determine the rate of acromegaly comorbidities once hypersecretion of growth hormone is controlled.

Methods: Our retrospective monocentric study was based on 130 patients followed on a regular basis, with acromegaly controlled by medical treatments or cured by surgery or radiation technique. Our main outcome measures were the prevalence of major metabolic complications of acromegaly (diabetes, hypertension, low-density lipoprotein cholesterol, triglycerides) at diagnosis and last follow-up in comparison with French epidemiological data.

Results: As expected, controlling hypersecretion significantly improved the metabolic complications of acromegaly. However, the proportion of patients having at least one metabolic complication of acromegaly at last follow-up (mean, 72 months after remission) was 27% for altered glucose tolerance or diabetes, 39% for hypertension, 34.3% for hypercholesterolemia, and 13.3% for hypertriglyceridemia. Interestingly, our data showed that diabetes was the only comorbidity different with a higher prevalence in patients in remission versus a general population of a similar median age (21.6% vs 6.9%, respectively).

Conclusions: The follow-up of glucose disorders needs to be maintained on a long-term basis in patients controlled for acromegaly.

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Acromegaly is a rare disease generally due to a growth hormone (GH)–secreting pituitary adenoma [1]. Although the prevalence is estimated to be between 40 and 70 cases per million, it is probably underestimated owing to the slow appearance of clinical signs [1]. The overall diagnosis delay is usually 5 to 10 years, which allows for the installation of a number of comorbidities. As a rule, these are already present at the time acromegaly is diagnosed.

The longstanding increase of GH and insulin-like growth factor (IGF)-1 levels is responsible for polymorphic metabolic complications. For instance, the increase of GH levels is responsible for insulin resistance in the liver and other peripheral tissues, leading to impaired glucose tolerance or overt diabetes mellitus [2, 3]. GH excess may also alter the lipid profile,

Abbreviations: BMI, body mass index; ENNS, French Nutrition and Health Survey; GH, growth hormone; IGF, insulin-like growth factor; LDL, low-density lipoprotein, OGTT, oral glucose tolerance test.

with increased triglyceride and low-density lipoprotein (LDL) cholesterol levels [4, 5]. This metabolic profile, together with arterial hypertension, induces an increased overall risk of cardiovascular morbidity and mortality in acromegalic patients [6]. Additionally, cardiovascular dysfunction may be linked to a specific cardiomyopathy with initial left ventricular hypertrophy, evolving to a dilated cardiomyopathy [1]. Of note, patients with acromegaly also frequently develop respiratory disorders such as sleep apnea, which may worsen the metabolic and cardiovascular complications [1, 7, 8]. Diagnosis and management of such complications are crucial, as acromegaly is progressively becoming a chronic disease, with <50% of all cases of acromegaly cured at last follow-up, but almost 80% to 90% controlled by multimodal treatments including antiseecretory drugs [9, 10].

The comorbidities associated with acromegaly are known to lead to an impaired quality of life and an average 10-year reduction in life expectancy in untreated patients compared with the general population, mainly due to cardiovascular disease [11]. A still debated question is the persistence of such comorbidities on a long-term basis once the control of hypersecretion is obtained. The aim of our study was to try to give insights on this point, based on 130 patients with acromegaly in remission or controlled and followed in a single French center, in comparison with French epidemiological data.

1. Subjects and Methods

Data on patients followed regularly in the Department of Endocrinology, La Timone Hospital (Marseille, France) and then La Conception Hospital (Marseille, France) were retrieved through the last 15 years. The diagnosis of acromegaly was based on unsuppressed GH level after OGTT (>1.2 mUI/L) and increased IGF-1 value for age and sex. Patients were included at the first time they had both suppressed GH after OGTT (<1.2 mUI/L) or a mean of GH values (every 15 minutes during 2 hours) < 1 ng/mL (in patients with diabetes) and normal IGF-1 for age and sex (after surgery or radiation techniques, or normal IGF-1 while on medical treatments), and if they had at least one evaluation of the complications before and after hypersecretion control. Each patient gave informed consent for the collection and analysis of individual data. Recorded data at initial diagnosis included sex, age at diagnosis, body mass index (BMI), pituitary adenoma size (microadenoma or macroadenoma), GH and IGF-1, treatment modalities and time to obtain normal hormone levels, and pituitary deficiencies. The results of hormonal evaluations performed every 3 to 12 months during follow-up were also noted.

The aim of the study was to evaluate the prevalence of acromegaly metabolic and cardiovascular complications at diagnosis of acromegaly, and after long-term remission. During follow-up, several complications were thus regularly evaluated and data were retrieved from medical files: (1) Metabolic complications included BMI, fasting blood glucose level and after OGTT, LDL cholesterol, and triglycerides. Diabetes mellitus was defined as fasting glucose level ≥ 1.26 g/L or ≥ 2 g/L after an OGTT. High fasting blood glucose level was defined as fasting glucose level between 1.1 and 1.26 g/L and impaired glucose tolerance as glucose level between 1.4 and 2 g/L after OGTT. At each time point, the modalities of treatments given to control blood glucose were also noted. Hypercholesterolemia was defined as fasting LDL ≥ 1.6 g/L, and hypertriglyceridemia as fasting triglyceride level ≥ 1.5 g/L. (2) Cardiovascular complications included high blood pressure levels and myocardial hypertrophy as determined by echocardiography. High blood pressure was defined as blood pressure $\geq 140/90$ mmHg. At each time point, the modalities of treatments given to control blood pressure were also noted. Myocardial hypertrophy was defined as a left ventricular wall thickness >13 mm. Data on myocardial infarction and cerebrovascular disease were also noted.

As a comparison, we used the publicly available data of two large French epidemiological studies. The French Nutrition and Health Survey (ENNS) was designed to describe dietary intakes, nutritional status, and physical activity in the French population, including 3- to 17-year-old children and 18- to 74-year-old adults. In adults, health examinations that included anthropometry and blood pressure measurements and blood, urine, and hair samples were

performed using standardized procedures that took place at either a French Social Security Health Examination Center or at the subject's home (nurse visit). A total of 3115 adults were included in this study [12–14]. The Mona Lisa study was an epidemiological multicenter cross-sectional population-based study aimed at assessing the prevalence and treatments of cardiovascular risk factors. The data of a total of 4609 inhabitants randomly included from three French areas, aged 35 to 74 years, were analyzed in this study [15].

A. Statistical Analysis

Quantitative data are presented as the median (minimum, maximum). Categorical data are summarized as the count and percentage in each category. Univariate comparisons between groups were made by a two-tailed Student unpaired *t* test or analysis of variance for continuous variables (variance equality was verified by the Levene test and Welch correction was applied when necessary). A two-tailed Pearson χ^2 or Fisher's exact test were used for comparison of qualitative data. Variables with a *P* value < 0.25 were selected for the multivariate analysis as well as interactions between covariates. Forward stepwise logistic regression analysis was used for multivariate studies, with selection based on likelihood ratio. The remaining covariates were considered significant when the *P* value was < 0.05. All statistical tests were performed with XLSTAT version 2013.4.05 (Addinsoft, Paris, France).

2. Results

A. General Characteristics of the Population

Out of 218 patients' files evaluated, 38 patients (17.5%) were not included, as they were still uncontrolled at last follow-up. Seven patients (3.2%) were not included, as they presented a mixed GH–adrenocorticotrophic hormone or GH–thyrotropin adenoma, or McCune–Albright or Carney syndrome–associated acromegaly. At last follow-up, 173 patients (79.3%) were in remission: 43 of them were not included due to missing presurgical complications data. A total of 130 patients, 75 females (57.7%) and 55 males (42.3%), were thus included in this retrospective study. Remission was obtained by surgery in 73 patients (56.1%) and only by medical treatments in 34 patients (26.2%). Radiation therapy was performed in 23 patients (17.7%). Mean time to obtain remission was 18 ± 19 months. Mean follow-up after remission was 72 ± 58 months. A flowchart of the study is depicted in Fig. 1. General characteristics of this cohort are given in Table 1.

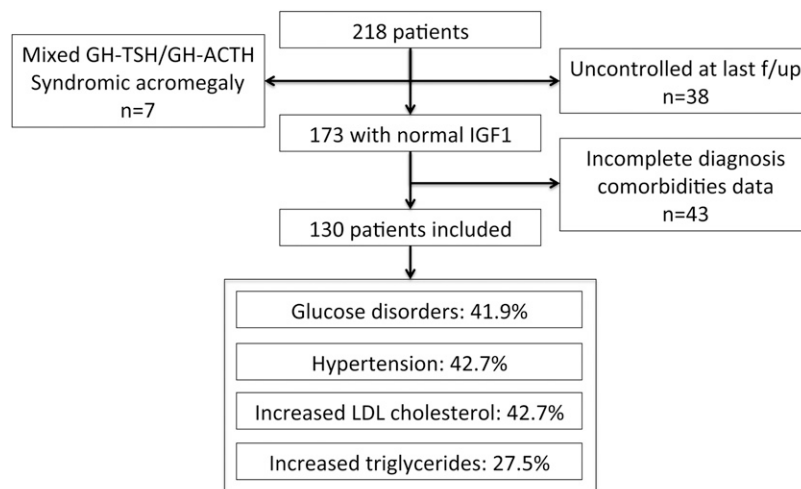


Figure 1. Flowchart of the study. Glucose disorders, hypertension, triglycerides, LDL: percentage of patients with the complication at the diagnosis of acromegaly.

Table 1. Initial Characteristics of the Population

Number of Patients	130
Sex ratio (F/M)	75/55 (57.7%/42.3%)
Microadenoma/macroadenoma	30/100 (23%/77%)
Time to remission, mo (mean \pm SD)	18 \pm 19
Time between remission and last follow up (mean \pm SD months)	72 \pm 58
Secretory characteristics	
Pure GH adenoma	95
Mixed GH-prolactin adenoma	35
Pituitary deficiency at remission	
Adrenocorticotrophic hormone	7
LH/follicle-stimulating hormone	12
Thyrotropin	33

Note that data on initial pituitary evaluation could not be retrieved for 11 patients. Abbreviations: M, male; F, female; SD, standard deviation.

B. Metabolic and Cardiovascular Comorbidities

In the whole cohort, three patients (2.3%) aged 58, 63, and 70 years at diagnosis, suffered from a myocardial infarction, and five (3.8%) aged 51, 52, 60, 61, and 63 years presented a stroke. Among these eight patients, three presented the cardiovascular event before remission (mean, 14.7 months) and five after remission (mean, 49.8 months). Overall, 40 patients (30.8%) could be considered at high cardiovascular risk at diagnosis as they presented at least two metabolic disorders; the rate (28.5%) was slightly decreased at last follow-up ($P = 0.67$).

As shown in [Table 2](#), there was no statistical difference between the metabolic profiles of patients who presented at least one pituitary deficiency vs patients with normal pituitary function at last follow-up.

B-1. Glucose disorders

At diagnosis, 24 of 112 patients (21.4%) had glucose intolerance or high fasting blood glucose level, and 23 (20.5%) had diabetes. Comparison between patients with or without normal blood glucose level found a significant difference in terms of age (48.1 ± 14.8 years vs 43.2 ± 13 years in both groups, respectively; $P = 0.048$), IGF-1 (3.6 ± 1.4 -fold vs 3.1 ± 1 -fold upper normal value, $P = 0.045$) but not in sex ratio ($P = 0.86$) or in BMI (26.9 ± 3.7 vs 26.7 ± 5.3 , $P = 0.86$). Comparison of glucose status with French epidemiological data ([Table 3](#), ENNS study, comparable mean age and sex ratio) showed a much higher prevalence of diabetes (20.5% vs 5.1%) in our cohort at diagnosis.

At last follow-up, 4 of 74 patients (5.4%) had glucose intolerance or high fasting blood glucose level, and 16 of 74 (21.6%) had diabetes ($P < 0.0001$ vs diagnosis for all types of glucose disorders). Of note, 28.6% of the patients who presented persistent glucose disorders after remission needed to increase their dose of antidiabetic treatment during follow-up after remission. Comparison of glucose status with French epidemiological data ([Table 3](#), Mona

Table 2. Comparison of Metabolic Data in Patients With or Without Pituitary Deficiency

	At Least One Pituitary Deficiency	No Pituitary Deficiency
Glucose disorders	40% (14/35)	42.9% (33/77)
Hypertension	33.3% (12/36)	47.3% (35/74)
Hypercholesterolemia	38.2% (13/34)	37.1% (23/62)
Hypertriglyceridemia	37.5% (12/32)	22% (13/59)

No significant differences were observed.

Table 3. Comparison of Metabolic Data in Our Study and in the Two Main French Sets of Epidemiological Data

	ENNS (2006)	Current Study: Diagnosis	Mona Lisa (2007)	Current Study: Last Follow-up
Mean age, y	44 (18–74)	45.7 (13–81)	55 (35–74)	51.8 (20–82)
Sex ratio, % female/male	63/37	58/42	50/50	58/42
Number of people/patients	3115	130	4609	130
Overweight or obesity	47.1%	58%	NA	NA
Hypertension	31%	42.7%	49.9%	39%
Mean systolic blood pressure, mmHg \pm SD	124 \pm 10	131 \pm 19	134 \pm 21	123 \pm 13
Mean diastolic blood pressure, mmHg \pm SD	78 \pm 9	77 \pm 12	81 \pm 11	74 \pm 9
Hypercholesterolemia	29.7%	37.5%	31.3%	34.3%
Mean LDL level, g/L \pm SD	1.27 \pm 0.3	1.3 \pm 0.3	1.4 \pm 0.35	1.2 \pm 0.3
Hypertriglyceridemia	NA	27.5%	22.3%	13.3%
Mean triglyceride level, g/L \pm SD		1.2 \pm 0.7	1 \pm 0.6	1 \pm 0.6
Diabetes	5.1%	20.5%	6.9%	21.6%

Abbreviations: NA, not available; SD, standard deviation.

Lisa study, comparable mean age with the one of our cohort) showed a much higher prevalence of diabetes (21.6% vs 6.9%) in our cohort.

Of note, at last follow-up, after excluding patients who had been controlled by radiation techniques, 41.2% of patients (7 of 17) who were controlled by somatostatin analogs had blood glucose disorders. In contrast, only 20.5% of patients (9 of 44) cured by surgery presented with glucose disorders ($P = 0.23$).

B-2. Blood pressure levels and left ventricular hypertrophy

At diagnosis, 47 of 110 patients (42.7%) had hypertension. Comparison between patients with and without hypertension did not find any significant difference in terms of sex ratio ($P = 0.37$), IGF-1 (3.1 \pm 1.2-fold vs 3.3 \pm 1.1-fold upper normal value, $P = 0.36$) or BMI (26.8 \pm 5.9 vs 26.8 \pm 3.9, $P = 0.96$). Patients with hypertension were significantly older (mean, 53.5 \pm 12.4 vs 41.2 \pm 13 years, $P < 0.001$). Of note, 23% presented left ventricular hypertrophy and 55% of them had hypertension. Comparison of hypertension status with French epidemiological data (Table 3, ENNS study) showed a higher prevalence of hypertension (42.7% vs 31%) in our cohort at diagnosis.

At last follow-up, 27 of 69 (39%) presented hypertension ($P = 0.003$ vs diagnosis). Interestingly, therapeutic intensification was necessary in 15% of them during follow-up after remission. Of note, 17% had left ventricular hypertrophy and 73% of them had hypertension ($P < 0.001$ for diagnosis vs remission). Comparison of hypertension status with French epidemiological data (Table 3, Mona Lisa study) showed a lower prevalence (39% vs 49.9%) in our cohort than in the general population (note that sex ratio in the Mona Lisa study included a higher percentage of males (50% vs 42% in our cohort).

B-3. Cholesterol

At diagnosis, 36 of 96 patients (37.5%) had high LDL level. Sex ratio ($P = 0.82$), IGF-1 (2.9 \pm 1.1-fold vs 3.4 \pm 1.3-fold upper normal value, $P = 0.1$), and BMI (27.7 \pm 5.6 vs 26.4 \pm 4.2, $P = 0.25$) were not significantly different between patients with or without hypercholesterolemia. Patients with high LDL cholesterol were significantly older (50.8 \pm 13.9 years vs 43.7 \pm 13.7 years, $P = 0.009$). At last follow-up, 23 of 67 patients (34.3%) had a high cholesterol level ($P = 0.003$ vs diagnosis). Comparison with French epidemiological data showed a higher prevalence at diagnosis (37.5% vs 18.8%), but a similar prevalence at last follow-up (34.3% vs 31%) in our cohort (Table 3).

B-4. Triglycerides

At diagnosis, 25 of 91 patients (27.5%) had high triglyceride levels. IGF-1 (3.7 ± 1.3 -fold vs 3.1 ± 1.2 -fold upper normal value, $P = 0.03$) and BMI (30.4 ± 5.9 vs 25.9 ± 3.8 , $P = 0.0001$) were significantly increased in comparison with normotriglyceridemic patients. Age (49 ± 15.9 years vs 44.9 ± 13.6 years, $P = 0.13$) and sex ratio ($P = 0.66$) were not significantly different. At last follow-up, 9 of 60 patients (15%) had hypertriglyceridemia ($P = 0.0027$ vs diagnosis, $P = 0.58$ vs remission). Comparison with French epidemiological data showed a lower prevalence at last follow-up (13.3% vs 22.3%) in our cohort (which included more females than in the general population) (Table 3).

Of note, among 72 patients with optimal lipid profile at last follow-up, 10 (13.9%) were on medications for dyslipidemia.

3. Discussion

Acromegaly increases the risk of long-term diabetes whatever the final GH status. In our series, glucose disorder was indeed the only comorbidity that was more prevalent in patients in remission than in the general population. Whereas Carmichael *et al.* [16] had already shown that the risk of diabetes was higher in biochemically uncontrolled patients compared with their controlled counterparts, our data show that the risk of diabetes is higher in controlled or cured patients compared with the general population. Given the potential impact of the medical treatments of acromegaly on glucose metabolism, it is crucial for endocrinologists to better know the spontaneous outcome of diabetes in patients with acromegaly. Interestingly, although not significant, the rate of glucose disorders seemed higher in patients controlled with medical treatments than in patients cured by surgery (41.2% vs 20.5%, respectively; $P = 0.23$). Diabetes is one of the major comorbidities reported in patients with acromegaly: the association of the glycemetic effects of insulin resistance, hyperinsulinemia, and increased gluconeogenesis leads to the development of diabetes in subjects usually lean or mildly overweight (mean BMI, 26.5 kg/m^2 in our study) [17, 18]. At diagnosis, our prevalence data of glucose disorders is close to the ones reported by Dal *et al.* [19] (fourfold increased risk) and Dreval *et al.* [20] (3.5-fold increased risk) with a 4.5-fold increased risk compared with the French population. The rate of diabetes was even higher in the 38 patients with uncontrolled acromegaly at last follow-up, not included in the study (eightfold increased risk). Fieffe *et al.* [21] had previously reported based on the French Acromegaly registry that 22.3% of 519 patients with acromegaly had diabetes at diagnosis, and that this glycemetic status was correlated with age, BMI, and hypertension, but not with the level of GH and IGF-1. These results are in contrast with ours, as the glycemetic status of our patients was correlated with age and IGF-1, but not BMI. Contradictory data were also reported for IGF-1 as a predictor of glycemetic status [2, 3, 22]. Based on 148 patients with newly diagnosed acromegaly, Alexopoulou *et al.* [23] had shown that a family history of diabetes and IGF-1 was associated with hyperglycemia, whereas BMI and IGF-1 were associated with insulin resistance. This discrepancy probably suggests that other modifying factors modulate the overall risk of diabetes in patients with acromegaly. More interestingly, our data show that the increased risk of glucose disorders persists in patients with acromegaly despite long-term remission (mean, 72 months) when the prevalence data are compared with those of a population of a comparable age and from the same geographical area. Jonas *et al.* [24] had reported in 57 patients with acromegaly that at the last visit, >58% of patients had glucose disorders (in comparison with 50% at diagnosis), but the study included patients who were not controlled for acromegaly. Kinoshita *et al.* [25] had previously shown that the persistence of glucose disorders was due to an altered β -cell function at the time of diagnosis, concordant with the fact that older patients at diagnosis were at higher risk of persistent diabetes, as shown in our study. Glucose disorders should thus be monitored closely on a long-term basis after the control of GH hypersecretion.

Patients with controlled acromegaly remain at high cardiovascular risk factor. Apart from the glycemic status, dyslipidemia (34% and 13% of high cholesterol and triglyceride levels, respectively, at last follow-up) and hypertension (39% with hypertension at last follow-up) are indeed present in a large proportion of patients with controlled acromegaly, even if these comorbidities do not seem to be more prevalent than in the general population after long-term remission. Interestingly, our prevalence data were quite different from the ones reported by Petrossians *et al.* [26] in their large study on >3000 patients: they reported 27.5% diabetes (vs 20.5% in our study) and 28.8% (vs 42.7% in our study) hypertension. These differences could not be explained by the age at diagnosis (45.2 years vs 45.7 years), the sex ratio (54.5% vs 57.7% females), or the rate of macroadenoma (72% vs 77%) in the Liège Acromegaly Survey study vs ours, respectively. Differences could thus be explained by other factors of the metabolic profile (BMI for instance) or environmental factors that were not specifically evaluated in both studies. One fourth to one third of patients therefore still present cardiovascular risk factors despite remission of GH hypersecretion. Interestingly, the rate of patients with more than two cardiovascular risk factors is increased compared with the general population: 28.5% vs 20% in our study at last follow-up and in the Mona Lisa study, respectively. Of note, the prevalence of myocardial infarction was similar in our study and French epidemiological data (~2%), whereas the prevalence of stroke was much higher in our patients (3.8% vs 0.6%). Concordant with our results, dos Santos Silva *et al.* [27] had shown that patients with acromegaly were at low risk of coronary artery disease despite the high prevalence of metabolic abnormalities, whatever the phase (active or controlled) of the disease. This low number, in contrast to the data reported by Holdaway *et al.* [6], in which out of 72 patients, 50% of deaths were related to cardiovascular diseases and 8% to strokes, is probably explained by the fact that we only focused on controlled patients and not on the whole cohort of patients with acromegaly.

To conclude, although acromegaly has progressively become a chronic disease, the way patients should still be followed after cure or once control of hypersecretion is obtained has not been specifically evaluated in international guidelines. As the risk of recurrence can be considered very low, the major remaining issue is the extent to which complications might reverse. Our study clearly shows that despite a prolonged follow-up after remission, some of these complications will persist, emphasizing the need for a specific and regular follow-up of patients at high cardiovascular risk profile. The final prevalence of comorbidities does not seem higher than in the general population, except for glucose disorders, the main parameter that should be closely followed on a long-term basis after remission. This is a highly relevant issue, as about a fourth of the patients have been found to be lost to follow-up after control of hypersecretion [28].

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