

# Diabetes mellitus induced by somatostatin analogue therapy is not permanent in acromegalic patients

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## Summary

**Context:** Therapy with somatostatin analogues (SSAs) may have deleterious effects on glucose metabolism in patients with acromegaly, often leading to the development of diabetes mellitus (DM).

**Aim:** The aim of the study was to evaluate whether DM, developed during therapy with SSAs, may revert after drug withdrawal and cure of acromegaly with pituitary adenectomy.

**Design:** Retrospective cohort study, in a tertiary referral centre.

**Patients:** Eighteen acromegalic patients without DM at the diagnosis of acromegaly treated with SSAs as a primary therapy, and then cured by pituitary adenectomy.

**Methods:** Endocrine status and glucose homeostasis were evaluated at diagnosis of acromegaly and at least every 6 months during SSA therapy. At each visit, patients were classified into one of the following classes: normal glucose tolerance, prediabetes, overt diabetes.

**Results:** Median follow-up after starting SSAs therapy was 69 months (IQR 54.75–132.25). During SSA therapy, all patients had controlled acromegaly defined by normal serum IGF1 concentrations for the age. Of the 13 euglycaemic patients at diagnosis, three developed prediabetes and three diabetes, whereas, of the five prediabetic patients at diagnosis, two worsened to overt diabetes and three remained in the prediabetic range ( $P = 0.04$ ). After curing acromegaly with pituitary adenectomy and subsequent SSA withdrawal, prediabetes reverted in five of six patients, and diabetes in all five patients (three reverted to euglycaemia, while two reverted to prediabetes) ( $P = 0.01$ ).

**Conclusions:** In acromegalic patients with controlled disease, changes in glycaemic status induced by SSAs are not permanent.

## KEYWORDS

acromegaly, diabetes mellitus, drug-induced diabetes mellitus, growth hormone-secreting pituitary adenoma, somatostatin analogues

## 1 | INTRODUCTION

Acromegaly is a rare disease characterized by an uncontrolled growth hormone (GH) secretion which leads to typical somatic changes and to an increased prevalence of comorbidities, including diabetes mellitus, arterial hypertension, cardiomyopathy, abnormality of respiratory function and neoplasms.<sup>1,2</sup> Systemic complications of acromegaly are the main determinants of the increased mortality rate of these patients compared to the general population.<sup>3-5</sup>

Transsphenoidal pituitary adenectomy is the first-line treatment for acromegalic patients.<sup>6</sup> Medical therapies with somatostatin analogues (SSAs), dopamine-agonists and pegvisomant are considered as second-line therapies for patients with persistent disease following surgery. A course of preoperative treatment with SSAs has been suggested by some but not all authors.<sup>6,7</sup> Alternatively, medical therapy with SSAs can be used as a first-line treatment for patients who cannot be cured by pituitary adenectomy, or who have contraindications, or refuse surgery.<sup>8</sup>

First-generation long-acting SSAs, which include octreotide long-acting release and lanreotide autogel, inhibit GH secretion preferentially binding somatostatin receptor subtype 2 (SSTR2). Pasireotide long-acting release is a second-generation SSA which acts by binding SSTR1, SSTR2, SSTR3 and SSTR5.<sup>9</sup>

The effect of SSAs on glucose metabolism is complex.<sup>8,10-13</sup> On the one hand, GH-IGF1 secretion is reduced by SSAs, theoretically leading to an improvement in insulin sensitivity. On the other, SSAs act on pancreatic alpha- and beta-cells, impairing both insulin and glucagon secretion. Despite many studies demonstrating that SSA administration can worsen glucose homeostasis, others have concluded that the effect on glucose metabolism is not statistically significant.<sup>10,14,15</sup> However, it is unknown whether changes in glucose metabolism occurring during SSA therapy are permanent after drug discontinuation.

## 2 | SUBJECTS AND METHODS

We performed a retrospective cohort study in order to evaluate changes in glucose homeostasis in patients treated with somatostatin analogues after the diagnosis of acromegaly. The aim was to identify the changes in glucose metabolism that occurred during therapy with SSAs and then after the withdrawal of the drug following surgical cure of acromegaly.

### 2.1 | Patients and study design

Eighteen naive acromegalic patients were enrolled in this study.

Acromegalic patients were evaluated on the basis of a standardized protocol, which has been used by our department for several years. Data are collected at diagnosis of acromegaly and then every 6 months for the entire follow-up period. Therapy for acromegaly is modified during each visit as appropriate, based on clinical and biochemical grounds.

Pituitary adenectomy is the first-line therapy for patients affected by acromegaly. Upon the evaluation of systemic complications, pituitary adenectomy is usually proposed. For patients who fail surgery or for those who refuse surgery or for whom the operation is contraindicated, therapy with first-generation SSA is usually proposed as a second-line therapy and the dose is titrated every 6 months up to 30 mg Octreotide LAR or up to 120 mg Lanreotide Autogel every 28 days. In cases where the disease is not fully under control during SSAs therapy, other therapeutic options are considered, as appropriate.

For the purposes of the study, we analysed the clinical records of the entire population of acromegalic patients referred to the Endocrinology Unit of the Department of Clinical and Experimental Medicine at the University of Pisa up to December 2016 ( $n = 312$ ), not taking into account those patients whose clinical records were incomplete for our analysis ( $n = 67$ ).

We considered only patients treated with first-generation SSAs as first-line therapy for at least 12 months, who were not affected by diabetes mellitus at diagnosis of acromegaly ( $n = 79$ ). We excluded patients for whom biochemical control of the disease was not reached (as defined below) during SSAs therapy and who were then switched to another therapeutic regimen ( $n = 38$ ).

Twenty-seven patients with biochemical control of disease with SSAs, underwent pituitary adenectomy. The reasons for this were as follows: some patients experienced side effects or did not tolerate SSA therapy ( $n = 9$ ), some patients came to our attention after a course of SSAs performed at different centres and were then offered surgical intervention for the first time ( $n = 12$ ), some patients decided to switch to surgery for personal reasons ( $n = 6$ ).

We included in this study only acromegalic patients cured by pituitary adenectomy, after a long course of effective treatment with SSAs ( $n = 18$ ); as a consequence, SSA therapy was completely withdrawn in these patients. The reason was to avoid the effect of acromegaly activity on glucose metabolism.

### 2.2 | Diagnosis of acromegaly and definition of the disease control

Acromegaly was diagnosed taking into account clinical and biochemical features.<sup>3,16,17</sup>

The estimated duration of disease consisted in the length of time between the onset of symptoms suggestive of acromegaly and diagnosis. It is our practice to perform regular follow-up visits on a six monthly basis after acromegaly diagnosis.

Acromegaly was defined as controlled during SSA therapy by an age-normalized IGF1 level<sup>6,18</sup> (IGF1 index  $\leq 1$ ; see section "Assays" for details) confirmed during the next 12 months in the follow-up evaluations. Surgical intervention is considered effective and consequently acromegaly is considered cured if biochemical control of the disease is achieved in the patient, as defined by a normal IGF1 for the age. This judgement is finally given at least 12 months after pituitary adenectomy. It is our practice to perform a first postsurgical evaluation between 3 and 6 months after pituitary adenectomy and a second visit 6 months later.

## 2.3 | Evaluation of glucose metabolism

An oral glucose tolerance test (OGTT) for glucose, insulin and GH was used to confirm the diagnosis of acromegaly and to gain information on glucose homeostasis at the time of the acromegaly diagnosis and at the first visit after surgery. After the baseline evaluation, glucose metabolism was assessed at every follow-up visit, on average every 6 months. It is our practice to test glucose metabolism in the follow-up visits using fasting plasma glucose and glycated haemoglobin levels and to refer the patient to an OGTT when one of these indexes is reported abnormal. Patients diagnosed with prediabetes were advised to modify their diet and increase physical activity. Patients diagnosed with overt DM were advised to begin antidiabetic treatment if this status was confirmed after at least two different evaluations. Antidiabetic treatment was re-evaluated at every check-up.

We classified patients into one of the following three categories, adopting the 2014 ADA Standards of Medical Care in Diabetes<sup>19</sup>:

1. Euglycaemic patients (normal glucose tolerance—NGT)
2. Patients affected by prediabetes (PD)
3. Patients affected by diabetes mellitus (DM)

We decided to retrospectively include a patient in one of the three categories only if the alteration was confirmed by repeated testing (at least in two different consecutive determinations, ie, on average 12 months after the first report of variation in glycaemic homeostasis) in order to avoid short-course transient variations in glycaemic status. Whenever fasting plasma glucose concentrations, glycated haemoglobin and glucose levels at 120' after OGTT were not concordant, the test result that was above the diagnostic cut-off was taken into account for the inclusion in one of the three above-mentioned categories.

Glycaemic status was defined as worsened when a progression from NGT to PD or overt DM was demonstrated, or a progression from PD to DM. Glycaemic status was defined as improved when a regression from DM to PD or to NGT, or a regression from PD to NGT was demonstrated.

As a consequence, patients were included in the three categories for the first time at diagnosis of acromegaly, then after at least 12 months of disease control during SSA therapy, and finally at least 12 months after effective pituitary adenectomy and SSA withdrawal.

**TABLE 1** Clinical parameters at diagnosis of acromegaly

Sex: female	10 (55.6%)
Pituitary macroadenoma	13 (72.2%)
Age at diagnosis (y)	44.5 (37-55.3)
Estimated delay in diagnosis (mo)	60 (57.5-111)
Family history for diabetes mellitus	2 (11.1%)
BMI (kg/m <sup>2</sup> )	27.3 (24.9-29.8)

BMI, body mass index.

Data are expressed as number (%) for categorical variables and as median (IQR) for continuous variables.

When a modification of glycaemic status was confirmed, the time of occurrence was calculated as the length of time between the last therapeutic switch and the first report of such a modification.

## 2.4 | Assays

The patients included in the study received an acromegaly diagnosis from 1993 to 2012. Over the 20-year study period, the hormonal assays for GH and IGF1 changed, as expected. Until 2006 GH was measured using the HGH kit (Nichols Institute Diagnostic, San Juan Capistrano, CA, USA); from 2006 GH was measured using an automated Advantage Chemiluminescent GH Assay (DiaSorin S.p.A., Saluggia, Italy). Until 2006, IGF1 was measured by the automated Advantage chemiluminescent IGF1 assay (Nichols Diagnostics, Bad Nauheim, Germany); from 2006, IGF1 was measured by an automated RIA (DIASource ImmunoAssays S.A., Nivelles, Belgium), which included ethanol extraction. Even though it is our practice to measure GH both for the diagnosis of acromegaly (both as random GH and during a oral glucose load) and during the follow-up (as random GH measurement), for the purposes of this study, disease activity was assessed by serum IGF1 concentrations. To compare serum IGF1 concentrations over the study period, we adopted the IGF1-index (the ratio between the IGF1 measured and the upper limit of the normal range for age), as previously reported.<sup>3,16,17,20</sup> Remission or controlled disease was defined when the IGF1 index was  $\leq 1$ . On the other hand, uncontrolled disease was defined when the IGF1 index was  $>1$ .

## 2.5 | Statistical analysis

Data were expressed as median and interquartile range for continuous variables, and as frequency and percentage for categorical variables.

Patients were divided into the three glycaemic status groups (NGT, normal glucose tolerance; PD, prediabetes; DM, diabetes mellitus) and modifications in the glycaemic status over time were compared using Bowker's discordance test. In order to assess the concordance of the different tests used for the inclusion in the glycaemic status categories, a concordance study was performed. The degree of agreement between the different methods was tested using the Cohen's Kappa measure. A *P* value of  $<0.05$  was considered as significant.

All computations were performed using the spss statistical package (SPSS, Chicago, IL, USA).

## 3 | RESULTS

A GH-secreting pituitary adenoma was responsible for acromegaly in all the 18 patients considered in this study. Specifically, acromegaly was caused by macroadenoma in thirteen (72.2%) and by microadenoma in five (27.8%) cases. No mixed secreting adenomas were found in this cohort of patients. No patient suffered from

	Diagnosis of acromegaly	SSAs therapy	Pituitary adenectomy and SSAs withdrawal
IGF1 (ng/mL)	767 (592.5-1003.5)	250 (176.5-371.4)	211.5 (185.75-278.75)
IGF1 index	1.93 (1.26-2.68)	0.66 (0.55-0.81)	0.57 (0.49-0.71)
FPG (mg/dL)	89 (81-95)	96 (83.7-109.25)	80 (77-90.75)
Glucose at 120' after OGTT	125.5 (105.25-144.25)	164 (124.75-193.25)	126.5 (102-132.5)
HbA1c (mmol/mol/L)	38.5 (33.25-39)	44.5 (38-49)	37 (33.5-38.75)

FPG, fasting plasma glucose; OGTT, oral glucose tolerance test; SSAs, somatostatin analogues.

"Diagnosis of acromegaly" refers to the data collected when acromegaly was diagnosed. "SSAs therapy" refers to the data collected when the glycaemic status changed during SSAs therapy and at least 6 mo after the control of acromegaly was achieved, or at the last follow-up visit before surgery, if no change in glycaemic status occurred. "Pituitary adenectomy and SSAs withdrawal" refers to the data collected when the glycaemic status changed 1 y after the pituitary adenectomy and SSAs withdrawal, or at last the follow-up visit if no change in glycaemic status occurred. Data are expressed as median (IQR).

hypopituitarism at diagnosis of acromegaly or after surgical intervention. Table 1 summarizes the clinical and biochemical findings of the patients at diagnosis of acromegaly.

Median follow-up time was 69 months (IQR 54.75-132.25).

During SSA therapy, all patients had a controlled disease defined by a serum IGF1 concentration within the normal range for age. The IGF1 index decreased from 1.93 (1.26-2.68) at baseline evaluation to 0.66 (0.55-0.81) after gaining biochemical control of the disease during SSA therapy. Normalization of the IGF1 index was obtained after a median time of 7 (4-14.25) months of SSA therapy.

After biochemical control of the disease, patients experienced a deterioration in glucose homeostasis during SSA therapy, as reported in Tables 2 and 3.

At baseline evaluation, 13 patients had normal glucose tolerance and five had prediabetes (see Tables 3 and S1 and Figure 1).

Of the 13 euglycaemic patients at the baseline evaluation, during SSA therapy seven remained euglycaemic and six had a deterioration in their glycaemic homeostasis (three were classified in the prediabetic range, and three in the diabetic range); of the five prediabetic patients at diagnosis, three remained in the prediabetic group, while two became overtly diabetic during SSA therapy ( $P = 0.04$ ).

Changes in glycaemic status occurred after 12.5 (10.5-25) months of SSA therapy, and after 5.5 (1.75-18.5) months after gaining biochemical control of the disease with SSA treatment.

The patients included in this study underwent pituitary adenectomy after a median time of 26 months (IQR 17.75-57.5) after starting SSA therapy.

After undergoing successful pituitary adenectomy, SSA therapy was withdrawn in all patients: as expected the IGF1 levels remained in the normal reference range for age (median 0.57 [0.49-0.71] after pituitary adenectomy vs 0.66 [0.55-0.81] during SSAs).

After SSAs withdrawal, despite there being no significant difference in the biochemical control of the disease, many patients underwent an improvement in glucose homeostasis, as reported in Table 3, Table S1 and in Figure 1. After curing acromegaly and

**TABLE 2** Median hormonal and metabolic parameters over the study period

**TABLE 3** Variations in glycaemic status related to SSAs therapy

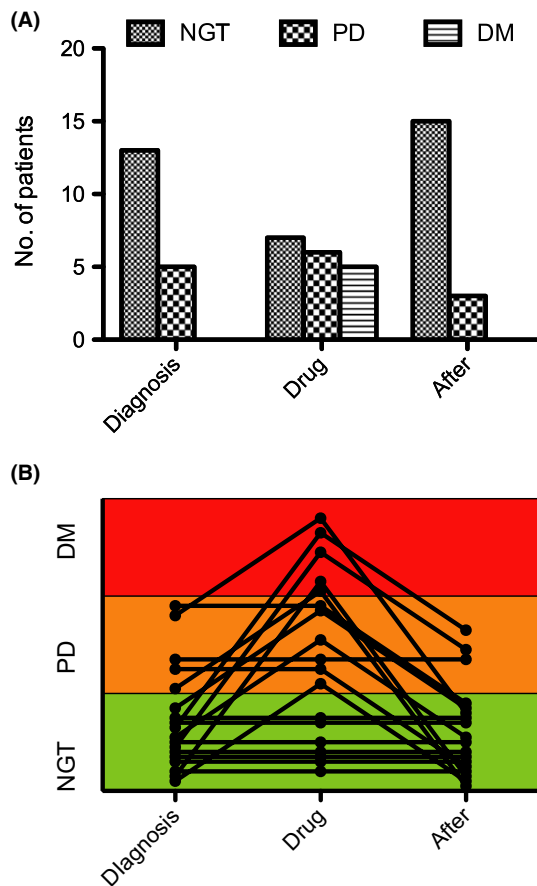
Panel A			
	During SSA therapy		
	NGT	PD	DM
Baseline			
NGT (13)	7	3	3
PD (5)	0	3	2
Panel B			
	After SSA withdrawal		
	NGT	PD	
During SSAs therapy			
NGT (7)	7	0	
PD (6)	5	1	
DM (5)	3	2	

DM, diabetes mellitus; NGT, normal glucose tolerance; PD, prediabetes; SSAs, therapy with somatostatin analogues.

Panel A: Changes in glycaemic status at baseline and during therapy with SSAs. Panel B: Changes in glycaemic status at baseline and after withdrawal of therapy with SSAs. Patients in each category are shown in brackets. See text for details.

withdrawing the SSAs therapy, seven euglycaemic patients remained euglycaemic; of the six prediabetic patients, five reverted to euglycaemia, while one remained in the same category; of the five overtly diabetic patients, three reverted to euglycaemia, while two reverted to prediabetes. Glycaemic status did not deteriorate in any patient after stopping SSA therapy (Bowker test,  $P = 0.01$ ).

The median time from SSA withdrawal to the improvement in glycaemic status was 5.5 months (IQR 3.75-7). For those patients whose glycaemic status ameliorated after pituitary adenectomy, the follow-up lasted for a median time of 25.5 months (IQR 12.75-34.5). During this period, there were no variations in glycaemic status.



**FIGURE 1** Panel A, Variations in glycaemic status groups during the study period. Panel B, Individual changes in glycaemic status during and after somatostatin analogue (SSA) therapy. DM, diabetes mellitus; NGT, normal glucose tolerance; PD, prediabetes. “Diagnosis” refers to the classification performed at the time of diagnosis of acromegaly. “Drug” refers to the classification performed after at least 6 mo of acromegaly control during SSA therapy. “After” refers to the classification performed at least 12 mo after pituitary adenomectomy and SSA withdrawal

The concordance between the different tests used for the inclusion in the glycaemic status categories was analysed: when comparing glycated haemoglobin levels and glucose concentrations at 120’ during OGTT, the results were concordant in 21/25 tests (Table S1), with a Cohen’s Kappa of 0.693, a result that denotes a good quality of agreement.<sup>21</sup>

Eight patients considered in this study were treated with Octreotide LAR, and 10 were treated with Lanreotide Autogel. No difference was observed in the baseline characteristics and outcomes in relation to the specific drug used.

## 4 | DISCUSSION

The results of this study show that the glycaemic alterations induced by first-generation somatostatin analogues are transient. Acromegaly can affect the glucose metabolism, either through GH,

which leads to a worsening in glycaemic indexes, or through IGF1, which, conversely, improves the glycaemic profile. In fact, GH acts on glucose homeostasis mainly by inducing insulin resistance. Tissues acutely or chronically exposed to GH have been found to show a decreased glucose uptake and disposal,<sup>22,23</sup> decreased glucose oxidation (together with a proportionate increase in nonoxidative glucose use),<sup>24</sup> and increased neoglucogenesis.<sup>25</sup>

Most alterations are due to the lipolytic effect of GH and subsequent glucose-fatty acid substrate competition.<sup>26</sup> In contrast, IGF1 improves insulin sensitivity, by promoting glucose uptake and by suppressing liver neoglucogenesis.<sup>27,28</sup> In line with these observations, the exogenous administration of IGF1 reduced glucose levels both in healthy volunteers and diabetic patients.<sup>29</sup> Insulin, GH and IGF1 are also linked through IGF binding proteins (IGFBPs). For example, an elevated insulin level acts on the liver leading to an increase in IGFBP-1 production. Consequently IGF1 increases, which in turn acts as a negative feedback by lowering GH levels, with a positive overall effect on the glucose metabolism.<sup>30</sup>

Somatostatin analogues intervene in this complex equilibrium by exerting an ambivalent function.<sup>31</sup> On the one hand, these drugs act by lowering GH secretion, thus leading to a normalization both in GH and IGF1 levels. On the other, they act on pancreatic alpha- and beta-cells, reducing both insulin and glucagon secretion.<sup>32,33</sup> Conversely, somatostatin reduces the clearance of insulin<sup>34</sup> and directly improves glucose uptake from the muscle,<sup>35</sup> and the same is performed by its analogues. As a consequence, in clinical terms, SSAs have different effects on glucose homeostasis. According to many studies, SSAs have a significant detrimental effect on glycaemic indexes both in acromegalic<sup>14-17,36</sup> and nonacromegalic patients.<sup>37</sup>

Even though some studies performed on first-generation SSAs did not lead to significant results,<sup>13</sup> therapy with Pasireotide-LAR seems associated with a significant detrimental effect on glucose homeostasis,<sup>38,39</sup> especially when compared to first-generation SSAs.<sup>40</sup>

In this study, we only included patients in whom a complete biochemical control of the disease had been gained both during therapy with first-generation SSAs and after SSAs withdrawal due to pituitary adenomectomy. We thus eliminated the effect of uncontrolled acromegaly in order to directly evaluate the effect of SSAs on glucose metabolism.

During SSA therapy, an overall deterioration in the glycaemic profile was found in 44.4% of patients. This found percentage is in line with a study previously published by our group on a larger cohort of patients not affected by diabetes mellitus at diagnosis of acromegaly.<sup>16</sup> Changes in the metabolic status occurred despite the biochemical control of acromegaly due to the SSA therapy. These data are in keeping with previous studies<sup>12,41</sup> which reported that hyperglycaemia is a common side effect of SSAs.

After SSA withdrawal following effective pituitary adenomectomy and no change in the biochemical control of acromegaly, the patients underwent an overall improvement in their glycaemic indexes, so that a majority of patients (55.5%) reversed their glycaemic status, and none of the patients’ glycaemic index became worse.



Our data clearly show that SSAs-induced glycaemic alterations are transient. In addition, patients were followed for a median time of 34 (23–65) months after pituitary adenectomy. During this time, no deterioration in glycaemic status was recorded, which means that the reversal of glycaemic indexes after SSAs withdrawal is a stable phenomenon.

As glycaemic alterations were observed after gaining biochemical control of acromegaly due to SSA therapy, changes in glucose homeostasis cannot be considered to be related only to disease control. In fact, after SSA withdrawal, we observed a reversal in the baseline metabolic indexes for many patients.

For those patients who developed an overt diabetes mellitus, the median duration of this alteration was 18 (I.Q.R. 11–44.25) months. Note that during that time, no major acute cardiovascular event was recorded. Considering that diabetes mellitus takes many years before inducing major cardiovascular complications, we argue that the absence of any recorded acute events could be due to the relatively short duration of diabetes in our cohort of patients.

Considering that the glycaemic alterations induced by SSAs develop only in a subset of patients (about 50%), susceptibility factors may explain this phenomenon. We wonder whether factors such as family history for diabetes mellitus, high body mass index or an elevated waist-hips ratio could be predictors for the development of diabetes mellitus during SSAs therapy. Our group previously analysed the risk factors for the development of diabetes mellitus during SSAs therapy in a larger cohort of acromegalics, identifying age at diagnosis of acromegaly and the lack of biochemical control of disease during SSAs as the main predictors.<sup>16</sup> Unfortunately, the same multivariate analysis to identify predictors of development or reversal of glycaemic alterations could not be performed due to the small number of patients in this study and the consequent inappropriately low statistical power.

It is well-known that the concordance between different tests for the evaluation of glucose metabolism (ie, haemoglobin glycosylated vs glucose levels at 120 minutes during OGTT) is imperfect<sup>19</sup> due to the lower sensitivity of haemoglobin glycosylated compared to the other glycaemic indexes at the designated cut-off point for the diagnosis of diabetes mellitus.<sup>42</sup> Practically this means that it is not infrequent that the use of glucose levels during OGTT diagnoses glycaemic alterations more frequently compared to haemoglobin glycosylated levels.<sup>19</sup> As demonstrated by the good Cohen's Kappa value in the concordance study, in this small cohort of patients, the concordance between haemoglobin glycosylated concentrations and glucose levels at 120 minutes during OGTT was good.

The limitations of this study are due to the small number of patients enrolled (which is a consequence of the strict criteria used for selecting our cohort), and its retrospective nature. The strengths of this study are that this was a single-centre study, and that the data had been recorded prospectively.

It is worth-mentioning that the glycaemic alterations reported in this study developed in a cohort of patients treated with first-generation SSAs. Actually, we do not know whether the same results will be obtained for the second-generation SSA Pasireotide.

Glycaemic alterations occurring during SSA therapy have been previously reported. However, the reversibility of diabetes mellitus

after withdrawal of the drug and curing acromegaly by pituitary adenectomy has not been observed previously. This finding may be useful in the therapeutic decisions regarding acromegalic patients.

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## CONFLICT OF INTEREST

The authors have nothing to disclose.

## AUTHOR CONTRIBUTIONS

D.C., C.S. and F.B. designed the study. D.C., C.U., C.S., I.S., G.M., I.L., L.M. collected the data. D.C. and F.B. analyzed the data. D.C. drafted the manuscript. L.M., C.M. and F.B. revised the manuscript. All authors approved the final version of the manuscript.

## ETHICAL APPROVAL

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. The Ethical Committee of the University of Pisa approved this study (study no. 3916).

## INFORMED CONSENT

All patients gave their written informed consent for the scientific use of their data.

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## SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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