Impairment in insulin secretion without changes in insulin resistance explains hyperglycemia in patients with acromegaly treated with pasireotide LAR

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Abstract

Objective: Pasireotide is a second-generation somatostatin receptor ligand (SRL) used for treating acromegaly. Its clinical use is limited by adverse effects on glucose homeostasis. The aim of this study was to evaluate longitudinal changes in beta-cell function and insulin sensitivity associated with pasireotide in patients not controlled by first-generation SRLs.

Design: We performed a retrospective study.

Methods: The efficacy (growth hormone (GH)/insulin-like growth factor (IGF-1) concentrations; tumor size) and effect on glucose homeostasis were analyzed in 33 patients. Longitudinal data on oral glucose tolerance tests were available before, shortly (mean ± s.d., 6.1 ± 3.8 months) and long term (24.4 ± 11.1 months) after initiation of pasireotide in 14 patients. Insulin secretion (insulinogenic index; disposition index) and insulin sensitivity were calculated by validated indices.

Results: Pasireotide-induced diabetes occurred in 12 patients (36%). It was mediated by impaired insulin secretion, which occurred shortly after initiation of treatment and then remained stable on long term (insulinogenic index, median (min; max), 80 (12; 542) vs 16 (6.4; 101) vs 25 (3.7; 396) pmol/mmol, respectively; P = 0.028; disposition index, 1.45 (0.42; 4.88) vs 0.53 (0.17; 2.63) vs 0.60 (0.22; 1.71), respectively; P = 0.024). No significant changes in insulin sensitivity were observed, despite a marked reduction of GH/IGF-1 concentrations. Older age and a worse glycemic control at baseline were the strongest predictors for hyperglycemia and the need for antidiabetic treatment.

Conclusion: Worsening of glycemic control during pasireotide therapy is caused by an impaired insulin secretion, whereas insulin sensitivity is not affected. These findings might be important for the choice of antidiabetic treatment for pasireotide-induced hyperglycemia.

Significance statement: Pasireotide, a second-generation SRL used for treating acromegaly, may be associated with glucose metabolism impairment. In a retrospective study of 33 patients, we observed that treatment with pasireotide was associated with normalization of serum IGF-1 in almost 60% of patients, but one-third of patients developed diabetes. In the patients who stopped pasireotide because of hyperglycemia, HbA1c promptly decreased. Longitudinal data in 14 patients show that diabetes is

Key Words
- acromegaly
- growth hormone
- insulin resistance
- somatostatin receptor ligand
mediated by impaired insulin secretion, which occurred shortly and then remained stable on long term, while no significant changes in insulin sensitivity were observed, despite a marked reduction of GH/IGF-1 concentrations. Older age and a worse glycemic control at baseline were the strongest predictors for hyperglycemia.

**Introduction**

Acromegaly results in a clinical syndrome following increased serum concentrations of growth hormone (GH) and insulin-like growth factor-1 (IGF-1). If not adequately treated, GH excess is associated with increased morbidity and mortality, mainly because of cardio-metabolic complications (1, 2, 3).

Impaired glucose metabolism is frequently observed in acromegaly. It is mainly caused by the insulin-antagonizing effects of GH-inducing hepatic and peripheral insulin resistance (4). Glycemic control is associated with disease activity (5), but the effects of GH-lowering therapy on glucose metabolism depend on the chosen therapeutic modality. Whereas pituitary surgery and treatment with the GH receptor antagonist pegvisomant both improve insulin sensitivity (6), glucose metabolism may improve or worsen when patients are treated with first-generation somatostatin receptor ligands (SRLs), octreotide and lanreotide (7, 8, 9, 10).

Pasireotide is a somatostatin multireceptor ligand of somatostatin receptor (SSTR) subtypes 1, 2, 3 and 5 (11). It is recommended as second-line therapy for patients with acromegaly uncontrolled by surgery or first-generation SRLs in the presence of a clinically relevant residual tumor (1). In addition to its GH-lowering efficacy (12, 13), wide clinical use is limited due to frequently observed side effects on glycemic control, especially in patients with preexisting impaired glucose metabolism (14, 15).

Preclinical studies and studies in healthy volunteers have shown that pasireotide was associated with a decrease in insulin secretion (16, 17). However, evidence on detailed changes in beta-cell function and insulin sensitivity in patients with acromegaly is missing. Given the strong impact of GH levels per se on glucose metabolism, improvement of insulin resistance by controlling GH excess might counteract the diabetogenic effects of pasireotide. In addition, a better understanding of the pathophysiological background of the development of hyperglycemia might be important for the choice of antidiabetic treatment. The aim of this study was therefore to evaluate longitudinal changes in glucose homeostasis in detail in a real-life cohort of patients with acromegaly treated with pasireotide.

**Methods**

**Study oversight**

We performed a retrospective single-center study at the Department of Endocrinology and Reproductive Diseases, Bicêtre Hospital, France. The study protocol was approved by the local ethical committee of the University Paris Saclay (n°2020-052). Medical records of patients with acromegaly in routine clinical care between January 2010 and May 2021 were analyzed.

**Included patients**

Acromegaly was defined according to clinical practice guidelines as an IGF-1 above the sex- and age-specific reference range and/or an insufficient suppression of GH under 0.4 μg/L during an oral glucose tolerance test (2). All patients > 18 years who fulfilled the diagnostic criteria and in whom treatment with pasireotide was started were included. Anterior pituitary insufficiency was registered based on the history of patients’ charts and concomitant hormone substitution therapy.

**Outcome parameters**

The efficacy and safety of pasireotide were analyzed in all patients. Therefore, information on patients’ history and the individual therapeutic indication for the initiation of pasireotide, biochemical changes in disease activity (IGF-1 and GH) and changes in tumor size (largest diameter in mm) was included. Side effects were recorded based on the history of patients’ charts. In addition, changes in fasting plasma glucose and HbA1c were analyzed.

Prediabetes was defined as either an HbA1c between 5.7 and 6.4% (39 and 46 mmol/mol) or an impaired fasting plasma glucose (between 5.6 and 6.9 mmol/L), or an impaired glucose tolerance (between 7.8 and 11 mmol/L). Diabetes was defined as an HbA1c ≥ 6.5% (48 mmol/mol) or a fasting plasma glucose concentration above 7.0 mmol/L (18).

In a subgroup of patients, data on blood glucose, insulin and GH at 0, 30, 60, 90 and 120 min during oral
glucose tolerance tests (OGTTs) before and after initiation of pasireotide were available. Based on dynamic changes in glucose and insulin concentrations during the test, indices for insulin secretion and insulin sensitivity were calculated. The mean values of the latest two OGTTs before initiation of pasireotide were used as baseline values.

IGF-1 is given as % above the assay-specific upper limit of normal of the age- and sex-specific reference range (ULN). Blood glucose, HbA1c, insulin, GH and IGF-1 were measured with routine laboratory methods (19).

Indices of insulin sensitivity, such as the HOMA-IR, the MATSUDA index for baseline glucose and insulin values, and the oral glucose insulin sensitivity (OGIS) index for dynamic changes during the OGTT, were calculated as previously described (20, 21). As a surrogate, the insulin secretion index (ISI) was calculated as the ratio of insulin after 30 min minus fasting concentrations to glucose after 30 min minus fasting concentrations (insulin$_{30}$−insulin$_{0}$)/(glucose$_{30}$−glucose$_{0}$). The disposition index, which reflects insulin secretion adjusted for insulin sensitivity, was calculated as reported (22). Area under the curve (AUC) of concentrations of glucose, insulin and GH during the OGTT were calculated using the trapezoidal rule.

**Statistical analysis**

Exploratory statistical analysis was performed by using SPSS (IBM, version 26) and GraphPad Prism 8. Data were given as the mean ± s.d. or median (minimum; maximum) depending on their normal distribution. Treatment-induced changes were expressed as baseline-adjusted changes from baseline (pretreatment value minus posttreatment value/pretreatment value × 100%).

Comparison of longitudinal changes was performed by using Kruskal–Wallis tests with Dunn’s correction for multiple testing. The chi-square test was used to analyze discrete variables. Multiple stepwise backward regression analysis was performed (one independent variable for ten subjects) to identify predictors of the development of diabetes in the whole cohort. The statistical significance level was set at $P < 0.05$.

**Results**

**Patient characteristics**

This study included 33 patients (20 women). Their mean age was 46 ± 13 years and mean BMI was 27 ± 6 kg/m². Mean acromegaly duration was 5.1 ± 5 years. Twenty-nine patients underwent pituitary surgery. Before initiating pasireotide, acromegaly had been treated with cabergoline, first-generation SRLs, pegvisomant or a combination therapy of first-generation SRL and pegvisomant in 1, 27, 3 and 2 patients, respectively. Patients had corticotropic, thyrotropic, gonadotropic deficiency in 3, 3 and 9 cases, respectively. Adequate hormonal substitution was not modified during treatment with pasireotide. The therapeutic indication for the initiation of pasireotide was resistance to first-generation SRLs in 25 out of 33 patients (76%) or side effects of pegvisomant in 4 out of 33 patients (12%). In 4 out of 33 patients (12%), pasireotide was started because of severe headache, which has been previously pointed out in a case report (23). Two patients (6%) were biochemically controlled with their IGF-1 serum levels within their age- and sex-specific reference range before the initiation of pasireotide and were switched to pasireotide because of side effects of the ongoing treatment or severe headache. The other patients were resistant to first-generation SRLs. Prediabetes or diabetes was present in 13 out of 33 patients (40%) before pasireotide initiation, 11 and 2 patients being at that time under first-generation SRL or under pegvisomant, respectively.

Longitudinal results of the OGTT before and after the initiation of pasireotide were available in 14 patients.

**Whole cohort**

Treatment with pasireotide was associated with a significant reduction in serum IGF-1 levels, which normalized in 20 (58.8%) patients after a mean follow-up period of 19 ± 17 months (Fig. 1A). Among the 25 patients resistant to first-generation SRLs, 16 (64%) normalized their IGF-1 levels under pasireotide.

Longitudinal data on tumor size were available for 20 patients. Tumor size was reduced by more than 20% in two patients (10%), increased by more than 20% in one patient (5%) and remained stable in the others. The mean size remained stable during the observation period.

With regard to glucose metabolism, the mean HbA1c increased significantly (Table 1). Twelve patients (33%) developed diabetes under pasireotide treatment. Medical antidiabetic treatment was initiated in 14 patients (47%) during follow-up, and pasireotide was stopped because of the development of hyperglycemia in 8 patients (23.5%). In two patients (14%), diabetes was treated by a s.c. injection of glucagon-like-peptide-1 (GLP-1) analog, and three patients (21%) received insulin. All other patients were treated by oral antidiabetic medication (metformin monotherapy (six patients (42%)) or in combination with...
Figure 1
(A) Longitudinal changes in IGF-1 (given as % of ULN) in all patients; patients who had normalized IGF-1 levels according to the age- and sex-specific reference range are marked by *; patients in whom a medical treatment for diabetes was started are shown in gray; (B) Longitudinal changes in HbA1c following the initiation of pasireotide in patients WITHOUT (left) and WITH (right) antidiabetic treatment during the observation period; different colors highlight different antidiabetic therapies; ▼ indicates a stop of pasireotide because of hyperglycemia.
dipeptidyl peptidase-4 (DPP-4) inhibitors or sulfonylurea (three patients (21%)).

Glucose homeostasis worsened mainly until the first months (8 ± 5 and 7 ± 5 months after the initiation of treatment; Fig. 1B). In the subgroup of patients who required antidiabetic medication during the follow-up period, 12 (86%) patients already had prediabetes or diabetes before the initiation of pasireotide. Worsening of glucose homeostasis had no effects on the clinical efficacy of pasireotide to normalize IGF-1 levels (Fig. 1A).

In the subgroup of patients who stopped pasireotide because of hyperglycemia, the mean HbA1c promptly decreased from 8.45 ± 2.9% (69 ± 23 mmol/mmol) to 6.59 ± 1.3% (49 ± 10 mmol/mmol) after 5 ± 5 months of follow-up without intensification of antidiabetic treatment.

All data on longitudinal changes during pasireotide therapy are reported in detail in Table 1.

### Table 1 Information on changes in disease activity, tumor size and clinical parameters in all patients treated with pasireotide at baseline and at last follow-up.

|                                | Baseline | Last follow-up | P value |
|--------------------------------|----------|----------------|---------|
| n (F/M)                        | 33 (20/13)| 20 ± 17        |         |
| Follow-up (months)             |          |                |         |
| IGF-1 (% of ULN)               | 155 ± 51 | 106 ± 9        | <0.001  |
| GH (mg/dL)                     | 7.8 ± 7.8| 3.5 ± 3.4      | 0.011   |
| Tumor size (mm)                | 14.7 ± 7.5| 14.5 ± 9.4     | 0.74    |
| ≥20% reduction (n(%))          | (2)      | 17 (85)        |         |
| Stable (n(%))                  |          |                |         |
| ≥20% increase (n(%))           | (1)      |                |         |
| Systolic BP (mmHg)             | 120 ± 19 | 130 ± 19       | 0.53    |
| Diastolic BP (mmHg)            | 77 ± 11  | 80 ± 11        | 0.35    |
| Prediabetes (n (%))            | 13 (39)  | 18 (53)        | 0.206   |
| Diabetes (n(%))                | 2 (6)    | 12 (35)        | 0.002   |
| HbA1c (%/mmol/mmol)            | 5.8 ± 0.4/40 ± 2.7 | 6.8 ± 1.7/51 ± 12.7 | 0.001   |
| Diabetes treatment (n(%))      | 2 (6)    | 14 (42)        | <0.001  |

### Pasireotide-induced changes in glucose tolerance and insulin secretion

Longitudinal data on changes in glucose metabolism were available in a subgroup of 14 patients (8 women) who underwent an evaluation before pasireotide initiation, after 6.1 ± 3.8 months (early evaluation) and in the long term (24.4 ± 11.1 months) (Table 2). Five patients were on oral antidiabetic treatment during follow-up: three patients were treated by metformin alone, one patient was treated by metformin and a DPP-4 inhibitor and one patient was treated by a combination therapy of metformin, DPP-4 inhibitor and sulfonylurea. An impaired glucose tolerance was present in two patients at baseline and in five patients at the last follow-up.

Initiation of pasireotide resulted in marked reduction of GH and IGF-1 concentrations (GH baseline vs follow-up: 7.8 ± 7.8 vs 3.5 ± 3.4 ng/mL; P = 0.011; IGF-1 baseline vs...

### Table 2 Longitudinal changes in insulin secretion and insulin sensitivity following the introduction of pasireotide treatment in 14 patients; data are given as the mean ± s.d. or median (minimum; maximum) depending on their normal distribution.

| Follow-up (months) | Baseline | First follow-up | Last follow-up | P value |
|--------------------|----------|----------------|---------------|---------|
| OGTT area under the curve |                  |                |               |         |
| AUC<sub>Gh</sub> (mIU/L × min) | 988 (75; 6062) | 295 (45; 1441) | 196 (74; 1168) | 0.028   |
| AUC<sub>Glucose</sub> (mmol/L × min) | 860 (764; 1176) | 1008 (633; 1577) | 1110 (756; 1644) | 0.034   |
| AUC<sub>Insulin</sub> (mmol/L × min) | 32451 (11251; 145940) | 21616 (3042; 112926) | 20418 (9897; 248770) | 0.34    |
| Indices of insulin secretion |          |                |               |         |
| IGI (pmol/mmol) | 80 (12; 542) | 16 (6.4; 101) | 25 (3.7; 396) | 0.028   |
| Disposition index | 1.45 (0.42; 4.88) | 0.53 (0.17; 2.63) | 0.60 (0.22; 1.71) | 0.024   |
| Indices of insulin resistance |          |                |               |         |
| HOMA IR | 1.68 (0.46; 4.13) | 1.28 (0.26; 6.31) | 1.36 (0.37; 5.07) | 0.54    |
| Matsuda index | 3.49 (0.95; 14.42) | 5.06 (0.87; 17.65) | 3.60 (0.73; 12.37) | 0.44    |
| OGIS (mL/min × m²) | 418 (204; 465) | 361 (220; 484) | 370 (224; 462) | 0.09    |

AUC, area under the curve; HOMA IR, homeostatic model assessment for insulin resistance; IGI, insulinogenic index; OGIS, oral glucose insulin sensitivity index; OGTT, oral glucose tolerance test.
follow-up: 155 ± 51 vs 106 ± 9 % of ULN; \(P < 0.001\). Eight patients normalized their IGF-1 levels during treatment. During the OGTT performed at the initial visit and during follow-up, glucose concentrations increased, while insulin concentrations decreased not significantly. Nonetheless, worsening of glycemic control was mainly due to impaired insulin secretion, as indicated by the significant reduction in the insulinogenic index and the disposition index compared to baseline (Table 2). These changes remained stable at the long-term follow-up visit. Insulin sensitivity did not change significantly throughout the observation period. Of note, also in the subgroup of patients who normalized their IGF-I levels under pasireotide, no improvements in insulin sensitivity could be observed (OGIS_{baseline} vs OGIS_{first follow up} vs OGIS_{last follow up}: 396 (204; 483) vs 351 (220; 484) vs 341 (199; 538); \(P=0.4557\)).

Longitudinal data on changes in glucose metabolism are illustrated in Fig. 2.

Predictors of the onset of diabetes mellitus and pasireotide interruption in the whole cohort

In multiple regression analysis, age (\(b=0.025\); \(P<0.001\); \(r=0.770\)) and HOMA-IR (\(b=0.115\); \(P<0.001\); \(r=0.770\)) at

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**Figure 2**

Longitudinal changes in glucose concentrations (A), insulin concentrations (B) and growth hormone concentrations (C), as well as in insulin sensitivity (OGIS) (D), insulin secretion (insulinogenic index) (E) and insulin secretion adapted for insulin sensitivity (disposition index) (F) following the initiation of pasireotide; AUC, area under the curve; OGIS, oral glucose insulin sensitivity index; *\(P<0.05\) for overall differences between the groups.
baseline were the strongest predictors for the initiation of antidiabetic treatment during treatment with pasireotide. HbA1c at baseline ($b=0.464; P=0.036; r=0.440$) was the strongest predictor for the interruption of pasireotide treatment because of hyperglycemia.

**Discussion**

Our study indicates that worsening of glycemic control during treatment with pasireotide results from a significant reduction in insulin secretion. The impairment of beta-cell function occurs shortly after the introduction of the therapy and then remains stable during long-term follow-up. This explains the development of hyperglycemia in patients with acromegaly treated with pasireotide, despite the improved control of GH excess (and the higher number of patients normalizing their IGF-1 level).

Impaired glucose metabolism is frequently observed in patients with acromegaly. GH counteracts the suppressive effects of insulin on gluconeogenesis and stimulates endogenous glucose production (24, 25). Furthermore, GH strongly stimulates lipolysis in adipose tissue, which results in increased concentrations of circulating nonesterified fatty acids and is followed by lipid-induced peripheral insulin resistance and impaired glucose disposal in skeletal muscle (26). One might have therefore assumed that the normalization of GH excess would have beneficial effects on insulin sensitivity and could partly counteract the pro-diabetogenic potential of pasireotide, as is generally observed under first-generation SRLs. However, in a detailed longitudinal assessment of glucose metabolism in our patients, impairment of insulin secretion played the most important role, while no relevant changes in insulin sensitivity over time could be observed, including in patients who normalized their IGF-1 levels under pasireotide (Fig. 2).

Our findings in patients with acromegaly are in line with previous mechanistic studies in healthy volunteers (17) and in patients with Cushing’s syndrome (27). The development of diabetes and the impact on insulin secretion during pasireotide therapy can be explained by its binding affinity. Insulin-producing pancreatic beta-cells express SSTR subtypes 2 and 5, whereas glucagon-producing pancreatic alpha cells mainly express SSTR2 (11). The strong binding affinity of pasireotide to SSTR5 might result in an unbalanced glucagon/insulin ratio and impaired insulin secretion (28). Furthermore, lower postprandial incretin levels might play a role, as concentrations of GLP-1 and glucose-dependent insulinotropic polypeptide (GIP) were reported to decline after administration of pasireotide for one week in healthy males (17).

With regard to the treatment of pasireotide-induced hyperglycemia, our findings suggest against the use of metformin as a first-line monotherapy, since improvement of insulin sensitivity appears to be of less importance (29). This is in line with a recent clinical practice recommendation by Coopmans et al. (30) but in contrast to others (31, 32). A study in healthy volunteers showed a better efficacy for DPP-4 inhibitors and GLP-1 analogs than metformin (33). Of note, treatment with GLP-1 analogs might be superior, as incretin secretion is suppressed by pasireotide, which might limit the effectiveness of DPP-4 inhibitors (34). However, due to the limited number of patients treated with different antidiabetic drugs in the whole cohort, no conclusions on the ideal choice of treatment can be drawn based on the results of our study.

In the whole cohort, approximately 90% of patients were defined as prediabetic or diabetic at the time of last follow-up after 20 ± 18 months of treatment. Half of them required an antidiabetic treatment, whereas the other half was on dietary regimen only. These findings extend recently published observations from real-life clinical settings in short- (35) and long-term follow-up (36). In approximately one-quarter of our patients, treatment with pasireotide was stopped due to worsening of glycemic control, which is markedly higher than the dropout rates in prospective clinical trials (12, 14, 37). Of note, HbA1c was higher than 7.5% (58 mmol/mol) in only half of these patients, which suggests that an increased awareness of the diabetogenic potential of pasireotide might have led to an early switch to other drug classes. Following the interruption of pasireotide, glucose homeostasis quickly improved in all patients.

Older age and worse glycemic control at baseline were the strongest predictors for the development of hyperglycemia and the need for antidiabetic treatment, which is in line with previously published studies (14, 38). Therefore, especially in patients with impaired glucose tolerance or diabetes, blood glucose should be monitored closely by self-monitoring of fasting and postprandial glucose levels, as well as regular HbA1c measurements during the first months of pasireotide treatment (30). Of note, similar to previous reports (14, 15, 38), impairment of glucose metabolism occurred shortly after the initiation of treatment with pasireotide but then remained stable in most of the patients (Fig. 1B).

With regard to clinical efficacy, pasireotide was effective in the biochemical control of acromegaly in
our cohort of patients that was mainly resistant to first-generation SRLs. IGF-1 concentrations significantly decreased during the study and normalized in 58% of the included patients. Furthermore, the positive effects on tumor size (12, 39) could be confirmed, as an increase of more than 20% in tumor size was observed only in a single patient.

The major limitation of our study is its retrospective nature. This explains why concentrations of GIP and GLP-1 during OGTT were not available, as they were not measured during routine clinical care. The higher prevalence of pasireotide withdrawal in our cohort compared to clinical studies might be biased by an increased awareness of the treating physician for potential hyperglycemic side effects. Detailed assessment of beta-cell function and insulin sensitivity could be performed only in a subgroup of patients who underwent longitudinal OGTTs. Furthermore, the use of a mixed meal test might be more physiological than the OGTT to evaluate postprandial changes in glycemic control. However, despite the limited sample size, we were able to demonstrate the detrimental effects of pasireotide on insulin secretion.

In conclusion, this is the first study to investigate longitudinal changes in beta-cell function and insulin sensitivity in patients with acromegaly during treatment with pasireotide, the second-generation SRL. Our data show that the worsening of glucose homeostasis is mainly related to a decrease in insulin secretion, whereas insulin sensitivity is not affected. These findings might be of importance for treatment strategies for pasireotide-induced hyperglycemia.

Declaration of interest
P C has received unrestricted research and educational grants from Ipsen, Novartis, Novo-Nordisk, and Pfizer as Head of the Department of Endocrinology and Reproductive Diseases, Assistance Publique-Hôpitaux de Paris-Université Paris-Saclay. P C has served as an investigator (principal or coordinator) for clinical trials funded by Novartis, Pfizer, Ipsen, Italfarmaco, Antisense, and Cinetics. P C is member of Advisory Boards from Ipsen, Novartis, Pfizer, Cinetics, Recordati. P C gave lectures for Ipsen, Novartis, Recordati and Pfizer. J Y has served as an investigator (principal) for clinical trials funded by Novartis, Cinetics and Recordati. J Y is member of an Advisory Board from Recordati. All the fees and honoraria received by P C and J Y are paid to their Institution or Research Association. P K has received speakers honoraria from Ipsen and Pfizer and congress invitations from Sandoz, Ipsen and Pfizer. The other authors have no conflicts of interest to declare.

Funding
Peter Wolf was supported by a research fellowship of the Endocrinology section of the UEMS and the FDIME internal medicine research grant.
14 Fleseriu M, Rusch E, Geer EB & ACCESS Study Investigators. Safety and tolerability of pasireotide long-acting release in acromegaly—results from the acromegaly, open-label, multicenter, safety monitoring program for treating patients who have a need to receive medical therapy (ACCESS) study. Endocrine 2017 55 247–255. (https://doi.org/10.1007/s12020-016-1182-4)

15 Schmid HA, Brue TC, Colao A, Gadela MR, Shimon I, Kapur K, Petroncelli AM & Fleseriu M. Effect of pasireotide on glucose- and growth hormone-related biomarkers in patients with inadequately controlled acromegaly. Endocrine 2016 53 210–219. (https://doi.org/10.1007/s12020-016-0895-8)

16 Hauge-Evans AC, King AJ, Carmignac D, Richardson CC, Robinson IC, Low MJ, Christie MR, Persaud SJJ & Jones PM. Somatostatin secreted by islet delta-cells fulfills multiple roles as a paracrine regulator of islet function. Diabetes 2009 58 403–411. (https://doi.org/10.2373/dobp-0792)

17 Henry RR, CiaraLDi TP, Armstrong D, Burke P, Liguero-Saylan M & Muddaliar S. Hyperglycemia associated with pasireotide: results from a mechanistic study in healthy volunteers. Journal of Clinical Endocrinology and Metabolism 2013 98 3446–3453. (https://doi.org/10.1210/jc.2013-1771)

18 Cosentino E, Grant PJ, Aboyan V, Bailey CJ, Ceriello A, Delgado V, Federici M, Filippatos G, Grobbee DE, Hansen TB, et al. 2019 ESC guidelines on diabetes, pre-diabetes, and cardiovascular diseases developed in collaboration with the EASD. European Heart Journal 2020 41 255–323. (https://doi.org/10.1093/eurheartj/ehz486)

19 Kuhn E, Maione L, Bouchachi A, Roziere M, Salenave S, Brallty-Tabard S, Young J, Kamenicky P, Assayag P & Chanson P. Long-term effects of pasireotide on comorbidities in patients with acromegaly: a retrospective single-center study. European Journal of Endocrinology 2015 174 693–702. (https://doi.org/10.1530/EJE-15-0500)

20 Anderwald CH, Tura A, Gessl A, Luger A, Pacini G & Krebs M. Adequately adapted insulin secretion and decreased hepatic insulin extraction cause elevated insulin concentrations in insulin resistant non-diabetic adrenal incidentaloma patients. PLoS ONE 2013 8 e73726. (https://doi.org/10.1371/journal.pone.0073726)

21 Wolf P, Krssek M, Winihof Y, Anderwald CH, Zweitler E, Just Kukurua I, Gessl A, Trattnig S, Luger A, Baumgartner-Parzer S, et al. Cardiometabolic phenotyping of patients with familial hypocalcuric hypercalciemia. Journal of Clinical Endocrinology and Metabolism 2014 99 E1721–E1726. (https://doi.org/10.1210/jc.2014-1541)

22 Utzschneider KM, Pringle RL, Faulenbach MV, Tong J, Carr DB, Boyko EJ, Leonetti DL, McNeely MJ, Fujimoto WY & Kahn SE. Oral glycemic control in patients with resistant acromegaly in real-world clinical settings. Endocrine 2016 54 1–2. (https://doi.org/10.1007/s12020-016-1029-2)

23 Gardela MR, Gu F, Bronstein MD, Brue TC, Fleseriu M, Shimon I, van der Lely AJ, Ravichandran S, Kandra A, Pedroncelli AM, et al. Risk factors and management of pasireotide-associated hyperglycemia in acromegaly. Endocrorine Connections 2020 9 1178–1190. (https://doi.org/10.1530/EC-2 0-0361)

24 Breitschat A, Hu K, Hermosillo Resendiz K, Darstein C & Golor G. Management of hyperglycemia associated with pasireotide (SOM230): a healthy volunteer study. Diabetes Research and Clinical Practice 2014 103 458–465. (https://doi.org/10.1016/j.diabres.2013.12.001)

25 Luger A. Hyperglycemia in pasireotide-treated patients with acromegaly and its treatment. Endocrine 2014 48 0792–0800. (https://doi.org/10.1007/s12020-016-0895-8)

26 Neggers SJCMM. How to position pasireotide LAR treatment in acromegaly. Journal of Clinical Endocrinology and Metabolism 2019 104 1978–1988. (https://doi.org/10.1210/jc.2018-01979)

27 Colao A, De Block C, Gazzambide MS, Kumar S, Seufert J & Casanueva FF. Managing hyperglycemia in patients with Cushings’s disease treated with pasireotide: medical expert recommendations. Pituitary 2014 17 180–186. (https://doi.org/10.1007/s11102-013-0483-3)

28 Schmid HA & Brueggen J. Effects of somatostatin analogs on glucose homeostasis in rats. Journal of Endocrinology 2012 212 49–60. (https://doi.org/10.1530/JEO-11-0224)

29 Samson SL, Gu F, Feldt-Rasmussen U, Zhang S, Yu Y, Witek P, Kalra P, Aboyans V, Bailey C, Ceriello A, Delgado V, Hauge-Evans AC, King AJ, Carmignac D, Richardson CC, Robinson IC, Low MJ, Christie MR, Persaud SJJ & Jones PM. Somatostatin secreted by islet delta-cells fulfills multiple roles as a paracrine regulator of islet function. Diabetes 2009 58 403–411. (https://doi.org/10.2373/dobp-0792)

30 Fleseriu M, Regazzo D, Mondin A, Zilio M, Lizzul L, Zaninotto M, Plebani M, Arnaldi G, Ceccato F & Scaroni C. Is pasireotide-induced diabetes mellitus predictable? a pilot study on the effect of a single dose of pasireotide on glucose homeostasis. Pituitary 2020 23 534–542. (https://doi.org/10.1007/s11120-020-01083-x)

31 Shimon I, Kapur K, Akirov A, Gorshtein A, Dotan I, Khazen NS, Pauker Y, Gershinsky M, Sheppard M, Bronstein MD, Boyko EJ, Leonetti DL, McNeely MJ, Fujimoto WY & Kahn SE. Oral glycemic control in patients with resistant acromegaly in real-world clinical settings. Frontiers in Endocrinology 2021 12 633944. (https://doi.org/10.3389/fendo.2021.633944)

32 Akirov A, Gorshtein A, Dotan I, Khazen NS, Pauker Y, Gershinsky M & Shimon I. Long-term safety and efficacy of long-acting pasireotide in acromegaly. Endocrine 2021 74 396–403. (https://doi.org/10.1007/s12020-021-0272-2)

33 Sheppard M, Bronstein MD, Freda P, Serri O, De Marinis L, Naves L, Rohzihnska I, Hermosillo Resendiz K, Ruffin M, Chen Y, et al. Pasireotide LAR maintains inhibition of GH and IGF-1 in patients with acromegaly for up to 25 months: results from the blinded extension phase of a randomized, double-blind, multicenter, phase III study. Pituitary 2018 21 385–394. (https://doi.org/10.1007/s11120-014-0385-6)

34 Muhammad A, Coopmans EC, Delhanty PJ, Dallenga AHG, Haitsma IK, Jansen JAMJL, van der Lely AJ & Neggers SJCM. Efficacy and safety of switching to pasireotide in acromegaly patients controlled with pegvisomant and somatostatin analogues: PAP extension study. European Journal of Endocrinology 2018 179 269–277. (https://doi.org/10.1530/EJE-18-0353)

35 Mondin A, Manara R, Volta G, Tizianel J, Denaro L, Ferrari M, Barbot M, Scaroni C & Ceccato F. Pasireotide-induced shrinkage in GH and ACTH secreting pituitary adenoma: a systematic review and meta-analysis. Frontiers in Endocrinology 2022 13 935759. (https://doi.org/10.3389/fendo.2022.935759)

Received in final form 22 September 2022
Accepted 21 October 2022
Accepted Manuscript published online 21 October 2022