Glucose Tolerance and Somatostatin Analog Treatment in Acromegaly: A 12-Month Study

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Objective: The objective of the study was to investigate the impact of first-line somatostatin analogs (SSAs) on glucose tolerance (GT) in acromegaly.

Design: The design was open and prospective.

Patients: One hundred twelve patients (63 with normal GT (56.2%), 24 with impaired GT (21.4%), and 25 with diabetes (22.3%)) were treated with depot SSAs for 12 months: 54 patients (48.2%) achieved mean fasting GH levels less than 2.5 μg/liter in presence of normal IGF-I levels (controlled) during SSA.

Primary Outcome Measures: Fasting glucose and glycosylated hemoglobin levels were measured.

Results: At study end, 57 patients had normal GT (50.1% vs. baseline; \( P = 0.55 \)), 30 had impaired fasting glucose or impaired GT (26.8%, \( P = 0.43 \)) and 25 had diabetes (22.3%, \( P = 1.0 \)). Twenty-eight patients (25.0%), modified their GT [11 improved (9.8%), 17 worsened (15.2%)]: 90% of the patients with GT improvement achieved control of acromegaly and 89% of those having GT worsening did not (\( P < 0.0001 \)). The major predictors of GT changing were disease control (\( t = 4.99; \ P = 0.0001 \)), baseline GT (\( t = -2.84; \ P = 0.0054 \)), and GH levels (\( t = 2.70; \ P = 0.008 \)). Fasting glucose levels were predicted by patients’ age (\( t = 2.74; \ P = 0.0071 \)) and IGF-I levels (\( t = 2.14; \ P = 0.035 \)). Glycosylated hemoglobin levels were predicted by disease duration (\( t = 3.53; \ P = 0.0006 \)), GH levels (\( t = 2.70; \ P = 0.0071 \)), and IGF-I levels (\( t = 2.11; \ P = 0.037 \)).

Conclusions: This study showed a similar prevalence of deterioration and improvement of GT 12 months after first-line SSA treatment. Uncontrolled acromegaly during SSA treatment and abnormal GT at baseline were associated with GT worsening.

Different treatments of acromegaly display diverse effects on glucose tolerance (6). Reportedly surgery and the GH receptor antagonist pegvisomant improve glucose levels (7–10), and somatostatin analogs (SSAs) have variable effects on glucose levels because of GH and insulin suppression (11, 12). SSA, either octreotide-long-acting release (LAR) or lanreotide (LAN), currently represent the most widely used treatment of acromegaly. They induce control of GH and IGF-I excess in approximately 60% of patients after 12 months of treatment, either applied after unsuccessful surgery or as first-line in newly diagnosed pa-

Abbreviations: BMI, Body mass index; CI, confidence interval; FG, fasting glucose; GT, glucose tolerance; HbA\(_{1c}\), glycosylated hemoglobin; IFG, impaired fasting glucose; IGT, impaired glucose tolerance; IRS, insulin resistance syndrome; LAN, lanreotide; LAR, octreotide-long-acting release; NGT, normal glucose tolerance; oGTT, oral glucose tolerance test; q, every; SSA, somatostatin analog. ULN, upper limit of normal.
tients (13–16). We recently demonstrated that after 1 yr of cure, glucose levels were lower in patients treated with surgery than with SSAs (8) in analogy with a 5-yr retrospective study by Ronchi et al. (7). However, after 5 yr of cure with either SSA or surgery, we did not find any difference in glucose levels and glucose status between the two groups (5). The major predictor of deterioration of glucose tolerance after 5 yr of treatment was increase in body mass index (BMI), whereas the type of treatment was not relevant on glucose status (5).

Data on glucose tolerance in patients undergoing first-line therapy with SSAs are still very limited. These data are clinically relevant as first-line therapy with SSAs is becoming currently more frequent (17), and potential negative effects on glucose tolerance should be weighed against the beneficial effects on GH and IGF-I levels and tumor shrinkage.

Patients and Methods

The results reported in the current study have been collected in the context of a larger, prospective study to investigate the effect of first-line surgery or medical therapy (with somatostatin analogs and/or dopamine/agonists) on GH, IGF-I, tumor mass, cardiovascular risk markers, cardiomyopathy, hypertension, metabolic profile, and prostate diseases in all the patients coming for a diagnosis of acromegaly in our department and approved by our ethical committee [the 14/10/97 (no. 60/97)]. All patients signed an informed consent for the scientific use of their data.

Inclusion criteria

These included patients treated with first-line depot SSA treatment for at least 12 months, achieving or not control of the disease. Our routine procedure considers a first-line treatment with SSAs for 6–12 months, unless the tumors are clearly noninvasive on magnetic resonance imaging and/or the patients do not present any surgical or anesthesiological risk (17).

Exclusion criteria

These included patients treated with first-line surgery, requiring dopamine-agonists with SSAs because of a mixed GH/prolactin-secreting tumor, receiving the sc octreotide for longer than 2 wk, or requiring surgery or SSAs as second-line treatment before the completion of the 12 months or with a follow-up shorter than 12 months.

Cure criteria

In line with Giustina et al. (18), acromegaly was considered to be controlled if mean fasting GH levels were 2.5 \(\mu\)g/liter or less (5 \(\mu\)U/liter) in presence of normal IGF-I levels for sex and age. In the patients with discrepancy between GH and IGF-I levels (n = 9; 8.0%), disease control was based on IGF-I levels.

Patients

From January 1, 1997, to June 30, 2007, of 245 patients treated, 158 received first-line SSAs, 32 patients were excluded because they received a combined treatment with SSAs and cabergoline, 14 because of long-term use of sc octreotide, and two were lost at follow-up. Therefore, in this study were included data of 112 patients, 75 treated with octreotide-LAR, 22 treated with lanreotide-slow release, and 15 treated with lanreotide-Autogel (supplemental figure, published as supplemental data on The Endocrine Society’s Journals Online Web site at http://csem.endojournals.org).

Study protocol

As for our routine procedure, at diagnosis all patients underwent a complete metabolic and endocrine screening. After an overnight fasting, serum IGF-I levels were assayed twice in a single sample at the time 0 of the GH profile; GH levels were calculated as the mean value of five or fewer samples drawn every 30 min over a period of 2 h, and the average value was considered for the statistical analysis; fasting glucose and insulin levels were also measured at the time 0 of the GH profile. At diagnosis and 12 months after SSA, in the nondiabetic patients the oral glucose tolerance test (OGTT) was performed by measuring GH, glucose, and insulin levels every 30 min for 2 h after the oral administration of 250 ml water solution of 75 g glucose. Diabetes was diagnosed according with modern guidelines (19) based on fasting glucose 126 mg/dl or greater (6.99 mmol/liter) or 2 h glucose after OGTT 200 mg/dl or greater (11.1 mmol/liter) or because of ongoing treatment with glucose-lowering drugs. Glucose tolerance was normal (NGT) when glucose levels were less than 100 mg/dl (equal to 5.6 mmol/liter) at fasting and less than 140 mg/dl (7.8 mmol/liter) 2 h after OGTT. IFG was diagnosed when fasting glucose levels were 100–126 mg/dl (5.6–6.99 mmol/liter) and IGT was diagnosed when glucose levels 2 h after OGTT were greater than 140 and less than 200 mg/dl (7.8–11.1 mmol/liter). The conversion factor from milligrams per deciliter to millimoles per liter for glucose is 0.05551. Glycosylated hemoglobin levels (HbA\(_1c\)) were measured at baseline and after 3 and 12 months.

Study design

This was an open, prospective study to evaluate the effect of SSA treatment on glucose tolerance. Primary outcome measures were fasting glucose (FG) and HbA\(_1c\) levels. Secondary outcome measures were glucose levels 2 h after glucose load and insulin levels. Data were analyzed according with baseline glucose tolerance and disease control. In this study we included the results recorded at diagnosis and after 1, 3, and 12 months after SSA treatment. In all patients, GH and IGF-I levels and glucose profile were collected the day before the next drug injection.

Treatment protocol

According with previous studies (20–24), LAR treatment was started at a dose of 20 mg every (q) 28 d for 3 months and then up-titrated to 30 mg q28 d in the patients who did not normalize GH and IGF-I levels (n = 45) or down-titrated to 10 mg q28 d in the patients who suppressed GH levels less than 1 \(\mu\)g/liter (n = 4). Treatment with LAN-SR was started at a dose of 60 mg q28 d for 3 months and then up-titrated to 90 and 120 mg q28 d (n = 14) in the patients who did normalize GH and IGF-I levels. Treatment with lanreotide autogel was started at a dose of 120 mg q28 d, and after 3 months the interval between injections was delayed to 42 or 56 d if GH and IGF-I levels were normalized (n = 11).

According with modern guidelines treatment for diabetes (19), metformin treatment was given as first option to all patients with a diagnosis of diabetes up to a maximal dosage of 2500 mg/d. In patients not achieving FG levels according with the criteria above, treatment was changed into insulin. Starting from 2004, treatment with metformin was also given to patients with insulin resistance syndrome (IRS) (25) based on at least two criteria of the following: triglyceride levels 1.7 mmol/liter or greater, high-density lipoprotein cholesterol levels 1.0 mmol/liter or less, blood pressure above 130/85 mm Hg, fasting glucose between 6.1 and 7 mmol/liter, or 2 h after OGTT between 7.7 and 11.1 mmol/liter. IRS was found in 64 of 87 patients without overt diabetes (73.6%) and in all patients with diabetes: of these, 37 were treated with metformin during the study. In all patients receiving metformin at study end and showing a normal HbA\(_1c\) level (<6.5%), fasting glucose levels were reevaluated after 3–5 d of treatment withdrawal. Glucose load was performed after metformin withdrawal in all patients except from those with fasting glucose above 7 mmol/liter.

Assays

GH levels were assayed by immunoradiometric assays (Radim, Po- mezia, Italy) or more recently, Immulite (Diagnostic Products Corp.,
Llamberis, UK). Different GH assay kits were used during the study, and both calibration of standard curve and assays sensitivity changed accordingly (from 0.05 to 0.01 μg/liter). Conversion factors from milligrams to international units were 2.0 IU or 2.6 IU or 3.3 IU (from older to modern assays). Serum IGF-I was measured by immunoradiometric assay after ethanol extraction using Diagnostic System Laboratories Inc. (Webster, TX) or more recently, Immulite (Diagnostic Products). The sensitivity of the assays were 0.8 and 0.2 μg/liter. Data are shown as upper limit of normal range (ULN) normal = ±1. The acid/ethanol extraction method was reported to have limited value in patients with diabetes (26). Nevertheless, in the current series, control of acromegaly was based on both GH and IGF-I levels so that the IGF-I assay limitation in patients with diabetes did not have influence the classification of our patients.

Statistical analysis

Results were expressed as mean ± SD unless otherwise specified. The statistical analysis was performed by MedCalc Software for Windows (MedCalc, Mariakerke, Belgium) package using nonparametric tests. The comparison among baseline, 1, 3, and 12 months post-treatment results in all patients and separately in patients with NGT, IGT, and diabetes mellitus was performed by the Dunn’s test among NGT, IGT, and diabetes mellitus groups; c P < 0.05 in the univariate analysis.

Results

Baseline characteristics (Table 1)

At diagnosis, diabetes was diagnosed in 25 patients (22.3%): seven were receiving treatment with insulin and 11 with metformin. Of the 18 patients already receiving treatment with glucose-lowering drugs, 14 had with fasting glucose levels 5.55 mmol/liter or greater; HbA1c levels ranged from 4.4 to 8.3%. Another 24 patients (21.4%) had IFG or IGT, whereas 63 patients (56.3%) had NGT.

The patients with diabetes mellitus were older and had a longer disease duration and higher BMI than those with NGT. The patients with IGT had a higher BMI than those with NGT and diabetes mellitus but were younger and had a shorter disease duration than those with diabetes.

The most important predictors of baseline fasting glucose levels were baseline IGF-I levels measured as micrograms per liter (t = −3.56; P = 0.0005), followed by disease duration (t = 2.54; P = 0.012). The most important predictors of HbA1c were disease duration (t = 2.79; P = 0.0061) and patients’ age (t = 2.77; P = 0.0065). The most important predictors of glucose levels 2 h after glucose were BMI (t = 3.87; P = 0.0002), followed by GH levels (t = 3.84; P = 0.0002) and age (t = 3.59; P = 0.0006). The most important predictors of fasting insulin levels was male gender (t = 3.38; P = 0.0001) followed by BMI (t = 2.81; P =

### TABLE 1. Patients’ profile at diagnosis according to glucose tolerance status

<table>
<thead>
<tr>
<th></th>
<th>All patients</th>
<th>NGT</th>
<th>IFG/IGT</th>
<th>Diabetes mellitus*</th>
<th>p&lt;0.0001</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>112</td>
<td>63</td>
<td>24</td>
<td>25</td>
<td></td>
</tr>
<tr>
<td>Women/men</td>
<td>61/51</td>
<td>36/27</td>
<td>12/12</td>
<td>13/12</td>
<td>0.0004</td>
</tr>
<tr>
<td>Age (yr)</td>
<td>46.5 ± 16.8</td>
<td>39.2 ± 12.4*</td>
<td>47.7 ± 16.6*</td>
<td>63.8 ± 14.0</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Disease duration (months)</td>
<td>112 ± 83</td>
<td>80 ± 55*</td>
<td>102 ± 72*</td>
<td>176 ± 105</td>
<td></td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>24.8 ± 2.8</td>
<td>23.2 ± 2.8*</td>
<td>26.4 ± 2.3*</td>
<td>24.5 ± 2.0</td>
<td>0.0007</td>
</tr>
<tr>
<td>GH levels (μg/liter)</td>
<td>46.5 ± 34.6</td>
<td>47.3 ± 31.4</td>
<td>51.6 ± 30.6</td>
<td>48.8 ± 45.2</td>
<td>0.32</td>
</tr>
<tr>
<td>IGF-I levels (μg/liter)</td>
<td>772.3 ± 252.3</td>
<td>863.1 ± 226.8*</td>
<td>733.4 ± 269.2</td>
<td>581.0 ± 175.6</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Tumor volume (cm³)</td>
<td>1.66 ± 1.49</td>
<td>1.78 ± 1.56</td>
<td>1.46 ± 1.54</td>
<td>1.56 ± 1.29</td>
<td>0.073</td>
</tr>
<tr>
<td>Glycated hemoglobin levels (%)</td>
<td>5.0 ± 0.9</td>
<td>4.5 ± 0.5*</td>
<td>5.3 ± 0.6</td>
<td>6.0 ± 1.2</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Fasting glucose levels (mmol/liter)</td>
<td>5.46 ± 0.97</td>
<td>4.86 ± 0.39*</td>
<td>5.86 ± 0.37*</td>
<td>6.61 ± 1.15</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Fasting insulin levels (μU/liter)</td>
<td>16.5 ± 8.9</td>
<td>17.3 ± 7.6*</td>
<td>25.7 ± 9.7*</td>
<td>25.7 ± 3.5</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

* Seven of 32 patients were receiving insulin treatment at diagnosis of acromegaly and their insulin data were thus not calculated; b P values refer to Kruskal-Wallis followed by the Dunn’s test among NGT, IGT, and diabetes mellitus groups; c P < 0.001 vs. diabetes mellitus; d P < 0.01 vs. IGF/IGT; e P < 0.05 vs. IGF/IGT.
TABLE 2. Effect of first-line SSA therapy on fasting glucose and glycated hemoglobin levels in the patients grouped according to baseline glucose tolerance status and achievement or not of disease control after 12 months

<table>
<thead>
<tr>
<th>Glucose levels</th>
<th>Fasting levels (mmol/liter)</th>
<th>Change vs. baseline (%)</th>
<th>Glycated hemoglobin (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Controlled</td>
<td>Uncontrolled</td>
<td>P</td>
</tr>
<tr>
<td>NGT</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pretreatment</td>
<td>26</td>
<td>37</td>
<td>1.0</td>
</tr>
<tr>
<td>1 month</td>
<td>5.27 ± 0.46*</td>
<td>5.25 ± 0.55*</td>
<td>0.49</td>
</tr>
<tr>
<td>3 months</td>
<td>4.68 ± 0.28*b</td>
<td>4.93 ± 0.33*b</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>12 months</td>
<td>4.94 ± 0.49*d</td>
<td>5.42 ± 0.69*d</td>
<td>0.003</td>
</tr>
<tr>
<td>P values</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
<td></td>
</tr>
<tr>
<td>IFG or IGT</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pretreatment</td>
<td>14</td>
<td>10</td>
<td>0.53</td>
</tr>
<tr>
<td>1 month</td>
<td>5.97 ± 0.61</td>
<td>6.50 ± 0.82*</td>
<td>0.082</td>
</tr>
<tr>
<td>3 months</td>
<td>5.03 ± 0.38*b</td>
<td>5.37 ± 0.34*b</td>
<td>0.023</td>
</tr>
<tr>
<td>12 months</td>
<td>5.25 ± 0.74*b</td>
<td>5.46 ± 0.39*b</td>
<td>0.42</td>
</tr>
<tr>
<td>P values</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
<td></td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pretreatment</td>
<td>14</td>
<td>11</td>
<td>0.75</td>
</tr>
<tr>
<td>1 month</td>
<td>5.94 ± 0.98*</td>
<td>5.81 ± 0.86*</td>
<td>0.97</td>
</tr>
<tr>
<td>3 months</td>
<td>5.15 ± 0.34*a</td>
<td>5.38 ± 0.51*a</td>
<td>0.066</td>
</tr>
<tr>
<td>12 months</td>
<td>5.44 ± 0.65*</td>
<td>5.23 ± 0.28*a</td>
<td>0.33</td>
</tr>
<tr>
<td>P values</td>
<td>&lt;0.0001</td>
<td>0.0015</td>
<td></td>
</tr>
</tbody>
</table>

The comparison between controlled and noncontrolled patients was performed by the Mann-Whitney U test. The comparison among different time points was performed by the Kruskal-Wallis test. Superscript letters indicate statistical significance among different time points within the same group after applying the Dunn’s multiple comparison test: *P < 0.01 vs. baseline; aP < 0.05 vs. 1 month; bP < 0.05 vs. baseline; cP < 0.01 vs. 3 months; dP < 0.05 vs. 3 months.

0.006). The results of linear correlation analysis are shown in the supplemental table.

Effect of 12 months SSA treatment

Patients with NGT (Table 2 and Fig. 1)

Forty-one of 63 patients with NGT (65.1%) had IRS; 25 of them received treatment with metformin at doses of 1–1.5 mg/d before or during the first weeks of SSA treatment. After the first month of SSA treatment, FG levels significantly increased (P < 0.0001) by 8.5 ± 9.7% [95% confidence interval (CI) 6.1–11.0%] and insulin levels decreased (P < 0.0001) by 46.3 ± 19.0% (95% CI 41.5–51.1%) after 3 months FG levels were similar to baseline (P = 0.71). After 12 months, metformin treatment was withdrawn, FG levels were significantly increased by 8.1 ± 15.0% (95% CI 4.3–11.8%) compared with baseline (5.22 ± 0.65 vs. 4.86 ± 0.89; P < 0.0001) as well as glucose levels 2 h after glucose load (5.86 ± 1.35 vs. 5.42 ± 0.76 mmol/liter, P = 0.023). Insulin levels remained stable after 3 months (9.1 ± 3.6 mIU/liter) and 12 months (6.8 ± 1.3 mIU/liter) compared with 1 month and overall decreased by 55.2 ± 11.5% (95% CI 51.3–59.1%). Of the 63 patients, 26 (41.3%) achieved GH and IGF-I control. Controlled patients had lower FG levels after 12 months than the 37 uncontrolled with no change of glucose levels 2 h after oGTT (5.56 ± 1.46 vs. 5.31 ± 0.85 mmol/liter, P = 0.86 and 5.74 ± 1.02 vs. 5.50 ± 0.70 mmol/liter, P = 0.10, respectively) and no difference between them. HbA1c levels did not significantly change in controlled patients whereas slightly but significantly increased in the uncontrolled ones (Table 2). At study end, after metformin treatment withdrawal, one controlled and 13 noncontrolled patients had IFG or IGT (22.2%) and one uncontrolled patient developed diabetes (1.6%).
Patients with IFG or IGT (Table 2 and Fig. 2)

Twenty-three of 24 patients with IFG or IGT (95.8%) had IRS; 10 of these received treatment with metformin at doses of 1–1.5 mg/d before or during the first weeks of SSA treatment. After the first month of treatment, there was a slight significant increase of FG levels ($P = 0.041$) by 5.8 ± 11.6% (95% CI 0.9–10.7%). Metformin was started in another two patients because of diabetes (8.3%). After 3 months FG levels significantly decreased (5.18 ± 0.39 mmol/liter, $P < 0.0001$); in two patients metformin was withdrawn and in three others its dose was reduced. After 12 months of treatment, once metformin treatment was withdrawn in all but two patients, FG levels were lower than pretreatment (5.34 ± 0.62 mmol/liter, $P < 0.0001$) but glucose levels 2 h after oGTT did not change (7.47 ± 1.46 vs. 7.90 ± 0.99 mmol/liter, $P = 0.64$). The 14 patients with controlled disease after 12 months had significantly lower FG levels both after 3 months than the 10 uncontrolled. Glucose levels 2 h after glucose load did not significantly change both in controlled (6.89 ± 1.33 vs. 8.18 ± 0.94 mmol/liter, $P = 0.068$) and eight of 10 uncontrolled patients (8.28 ± 1.25 vs. 7.49 ± 0.95 mmol/liter, $P = 0.084$) but were significantly lower in the former than the latter ($P = 0.027$). HbA1c levels significantly decreased only in controlled patients (Table 2). After 12 months, of the 14 controlled patients, seven remained IGT and seven had NGT; of the 10 uncontrolled patients, seven remained IGT, two developed diabetes, and one had NGT without any treatment ($P = 0.58$).

Patients with diabetes mellitus (Table 2 and Fig. 3)

Before SSA treatment, metformin therapy was given to 18 patients, whereas in two of seven receiving insulin treatment, the insulin dosage was increased because of poor diabetes control. FG levels significantly decreased after 1 [from 6.61 ± 1.15 to 5.88 ± 0.91 mmol/liter, $P = 0.007$; by 9.5 ± 14.4% (95% CI 5.5–6.3%)] and 3 months of SSA treatment [5.25 ± 0.43 mmol/liter, $P = 0.007$ vs. 1 month; by 18.5 ± 13.8% (95% CI 12.8–24.5%) vs. baseline]. In three patients insulin replaced metformin, whereas in nine patients, insulin or metformin dosages were reduced. After 12 months, FG levels did not significantly change compared with 3 months (5.10 ± 0.29 mmol/liter, $P = 0.12$), being lower than baseline ($P < 0.0001$). Overall, FG decreased by 16.9 ± 15.4% (95% CI 10.5–23.3%). In three patients metformin was withdrawn, in two patients metformin replaced insulin, and in four others the dose of metformin was reduced.

FG levels after 1 and 3 months were similar in the 14 controlled and 11 uncontrolled patients, whereas after 12 months they were significantly lower in the former ($P = 0.007$). Glucose levels 2 h after oGTT were available in only two patients at baseline and four after treatment (all controlled patients); these data were thus not analyzed. HbA1c levels significantly decreased only in controlled patients (Table 2). Of the initial 25 patients, one achieved NGT and two had IGT (all controlled patients), whereas 22 remained diabetics (88%). In no patient HbA1c levels were higher than 6.5%.

Determinants of deterioration of glucose tolerance during SSA

At study end, 57 patients had NGT (50.1% vs. 56.2% in baseline; $P = 0.55$), 30 had IFG or IGT (26.8 vs. 21.4%; $P = 0.43$), and 25 had diabetes (22.3 vs. 22.3%; $P = 1.0$) (Fig. 4). Compared with baseline, 28 patients (25.0%) modified their glucose status, showing improvements in 11 (9.8%) or worsening in 17 patients (15.2%). Ninety percent of the patients with improvement in glucose status achieved control of acromegaly and 89% of those having worsening of glucose status did not ($P < 0.0001$). The major predictors of changing glucose status were disease control...
of these variables in determining glucose status is questionable. In contrast, control of acromegaly and baseline glucose tolerance status were major predictors of fasting and postglucose levels 12 months after SSA treatment.

GH excess has been shown to induce insulin resistance by impairing the ability of insulin to suppress glucose production and stimulate glucose use (1). Earlier studies suggested that impairment of glucose metabolism develops only in the so-called prediabetic patients, such as those with decreased insulin response to oGTT and thus unable to overcome the diabetogenic effect of GH by compensatory hyperinsulinism (27). Sonksen et al. (28) confirmed the presence of hyperinsulinism in a number of patients with acromegaly and suggested that diabetes in acromegaly develops from an initial hyperinsulinemic stage, characterized by NGT with a more rapid and higher insulin peak after oGTT returning back to normal later than controls, progresses into a stage characterized by a delayed insulin response to oGTT in presence of normal or slightly IGT, which is still likely reversible after adequate treatment, and ends when maximal pancreatic response is in the fasting state, with no further insulin rise after oGTT, a likely irreversible state after treatment. Based on this hypothesis, suppression of insulin levels by SSA can easily increase FG levels and worsen glucose tolerance at the beginning of treatment (5, 6). Indeed, in our series at diagnosis we found IRS according to criteria proposed by the American College of Endocrinology (25) in 41.1% of the patients with NGT, in all patients but one with IFG/IGT and in all with diabetes. This finding confirms that suppression of insulin levels by SSA is likely to be followed by significant increase in glucose levels in the patients with IRS. Nonetheless, control of GH and IGF-1 secretion should balance the negative effects of insulin suppression during SSA treatment continuation. Data on a strict follow-up of glucose tolerance during SSA treatment are still lacking, although glucose deterioration during treatment is clinically relevant because insulin resistance, IGT, and diabetes are assumed to play a pivotal role in determining the cardiovascular risk of acromegalic patients (29), as in the general population (30).

Early studies using sc octreotide therapy demonstrated that glucose tolerance and insulin resistance were only modestly altered, whereas improvement of insulin resistance by octreotide could likely counterbalance its inhibitory effect on insulin secretion (1). Verschoor et al. (31) found suppressed insulin secretion and slightly higher postprandial glucose levels, which did not further deteriorate during long-term treatment in 6 patients. Quabbe and Plockinger (32) also reported in the beginning of octreotide treatment decreased insulin levels that normalized after 12 months; besides, FG levels remained elevated in 12 patients. Ho et al. (33) found in seven patients normalization of glucose tolerance in four of five with previous IGT without significant changes in insulin levels. They also reported that improvement in glucose levels depended on baseline levels and concluded that octreotide improves whole-body insulin sensitivity by increased insulin ability to suppress hepatic glucose production (33). Breidert et al. (34) did not find any change in glucose disposal rate after 6 months in eight patients. In one of the largest cohort of 91 patients treated for 6 months, there was no change between mean daily blood glucose profiles at baseline or during

Discussion

This is the first study detailing changes of glucose tolerance after first-line SSA treatment in a large series of patients with acromegaly subjected to a strict follow-up. We confirm that in patients having NGT at diagnosis of acromegaly, there was an increase of FG levels, but this phenomenon was short lasting and was not present after 12 months in the patients who achieved disease control during SSA. In the patients with NGT at baseline who did not achieve disease control, there was a slight but significant increase, by 5.5% in median, of FG levels after 12 months of SSA treatment. In the patients having IGT or diabetes at diagnosis of acromegaly, FG levels decreased significantly, both because of optimization of treatment of diabetes or IRS using metformin together with SSA and because of reducing GH levels. Overall, at study end, final rate of glucose tolerance worsening was 15.2%, with a nonsignificant decrease in NGT and increase in IGF/IGT prevalence compared with baseline. We also found that fasting and 2 h after oGTT glucose and insulin levels were differentially predicted by patient’s gender, age, BMI, disease duration, and GH levels so that the predictive value of one

![FIG. 4. Prevalence of NGT, IFG or IGT and diabetes mellitus at baseline and at study end in the entire series of patients and according to acromegaly disease control.](image-url)
treatment (35). However, by oGTT during octreotide treatment, 20 and 29% of the patients with NGT at baseline developed IGT or diabetes, respectively, whereas three of the 11 patients who were diabetic at baseline normalized their glucose tolerance or developed IGT (35). Arosio et al. (36) also reported worsening of metabolic control in 25% of diabetic patients enrolled in a multicenter study including 68 patients with acromegaly who were treated with octreotide.

Overall, during sc octreotide treatment, the early insulin response to oGTT is reportedly reduced and is followed by a delayed normal increase, but due to concomitant GH suppression, peripheral insulin resistance is reduced and glucose tolerance remains generally normal in most patients (1).

Limited data exist on depot SSA, but, basically, all formulations are expected to decrease insulin levels and resistance in a similar extent. There is only one study by Ronchi et al. (37) reporting that octreotide-LAR was more detrimental to glucose metabolism than lanreotide-SR, despite being more effective in reducing GH and IGF-I levels. Steffin et al. (38) in a cross-sectional study with lanreotide-autogel did not find any difference between patients with active and inactive acromegaly. Baldelli et al. (39) reported a worsening of glucose uptake because of insulin resistance only in NGT patients but not in IGT or diabetes mellitus 6 months after LAR treatment. In an initial study, conducted in 36 patients treated with LAR, we already observed that the negative effect on insulin levels was noticeable at the beginning of treatment, whereas glucose tolerance improved after 12–24 months of treatment (21). Very recently a critical analysis of data of the literature confirmed a suppression of insulin levels with no significant changes of fasting glucose and HbaA1c during SSA treatment (40).

In the current study, which enrolled one of the largest cohort of patients with active acromegaly treated first line with depot SSA so far, we demonstrated that it is rather constant an increase in FG levels after 1 month of treatment because of rapid reduction in insulin levels. However, with the exception of one patient, those achieving disease control during the 12-month study period had unaffected or even improved glucose tolerance. At study end, the prevalence of NGT, IGT, or diabetes did not significantly change compared with baseline status, and only a minority of the patients received treatment because of new onset diabetes or increased dosage of previously treated diabetes [within 1 month of SSA beginning (22.3%)]. We confirmed in this study that changes in glucose tolerance were strongly correlated with achievement or not of disease control. In fact, 90% of the patients achieving improvement in glucose status also achieved control of acromegaly, whereas 89% of those having worsening of glucose status did not achieve control of acromegaly. We also confirmed that control of weight in patients with acromegaly as well as in the general population is mandatory because BMI remained one of the most important predictors of post-oGTT glucose levels in analogy with a previous study of our group (8). Because, however, it was reported that metformin effects could last more than 1 wk after drug withdrawal (41), it is possible that part of our results would have benefited from metformin, even if treatment was stopped before glucose tolerance assessment.

Conclusion

This open, prospective study conducted in a large series of newly diagnosed patients with acromegaly treated with depot SSA for 12 months demonstrated a similar rate of improvement and deterioration of glucose tolerance. Worsening of glucose control was more frequent at the beginning of SSA treatment in patients with diabetes or IGT at baseline. Adaptation of diabetes treatment is required during SSA treatment so that a careful follow-up is mandatory. Worsening of glucose tolerance after 12 months was associated with poor control of acromegaly. Whether treatment of IRS might prevent development of overt diabetes in patients with acromegaly undergoing SSA treatment should still be ruled out.

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