Somatostatin Analogs and Glucose Metabolism in Acromegaly: A Meta-Analysis of Prospective Interventional Studies

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Context: Somatostatin analogs (SSAs) effectively control growth hormone secretion in first- and second-line treatment of acromegaly. Their effect on glucose metabolism is still debated.

Objective: To address the following questions: (1) Do SSAs affect fasting plasma glucose (FPG), fasting plasma insulin, glycosylated hemoglobin (HbA1c), glucose load (glucose levels after 2-hour oral glucose tolerance test), homeostatic model assessment of insulin resistance (HOMA-I), homeostatic model assessment of pancreatic β-cell function (HOMA-β), triglycerides, weight, or body mass index? (2) Do lanreotide and octreotide affect metabolism differently? (3) Does their effect depend on disease control?

Design: We performed a meta-analysis of prospective interventional trials treating acromegaly with SSAs. Inclusion criteria: all studies reporting glycometabolic outcomes before and after SSAs with a minimum 6-month follow-up.

Results: The inclusion criteria were met by 47 studies treating 1297 subjects (631 females). SSA treatment effectively lowered fasting plasma insulin [effect size (ES), −6.67 mU/L; 95% confidence interval (CI), −8.38 to −4.95 mU/L; $P < 0.001$], HOMA-I (ES, −1.57; CI, −2.42 to −0.72; $P < 0.001$), HOMA-β (ES, −47.45; CI, −73.15 to −21.76; $P < 0.001$), and triglycerides (ES, −0.37 mmol/L; CI, −0.47 to −0.27 mmol/L; $P < 0.001$). SSAs worsened glucose levels after a 2-hour oral glucose tolerance test (ES, 0.59 mmol/L; CI, 0.05 to 1.13 mmol/L; $P = 0.032$), but not FPG. A mild but significant increase in HbA1c (ES, 0.12%; CI, 0.00% to 0.25%; $P = 0.044$) was found in subjects treated with octreotide.

Conclusions: SSA treatment in acromegaly patients, while improving disease control, reduces insulin levels, increases after-load glucose, and, ultimately, increases HbA1c levels without affecting FPG. The findings suggest that clinicians treating acromegaly with SSAs should consider targeting postprandial glucose. **(*J Clin Endocrinol Metab* 103: 2089–2099, 2018)**

Impaired glucose metabolism, from impaired glucose tolerance to severe diabetes mellitus (DM), is a hallmark of acromegaly (1) and may contribute to the increased cardiovascular morbidity and mortality associated with the disease (2–4). The prevalence of DM in acromegaly differs significantly among studies, ranging

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Abbreviations: 2h-OGTT, 2-hour oral glucose tolerance test; BMI, body mass index; CI, confidence interval; DM, diabetes mellitus; ES, effect size; FPI, fasting plasma insulin; FPG, fasting plasma glucose; GH, growth hormone; HbA1c, glycosylated hemoglobin; HOMA-I, homeostatic model assessment of insulin resistance; HOMA-β, homeostatic model assessment of pancreatic β-cell function; IGF-1, insulin-like growth factor-1; LAN, lanreotide; LAR, long-acting release; MD, mean difference; OCT, octreotide; OGTT, oral glucose tolerance test; RCT, randomized controlled trial; SD, standard deviation; SE, standard error; SSA, somatostatin analog; SSTR, somatostatin receptor subtype; TGD, triglyceride.

from 19% to 56%. This high variability reflects the heterogeneity in baseline study population characteristics, but also the different criteria used to diagnose glucose metabolism disorders (2, 3).

Insulin resistance is a key contributor to the development of DM in acromegaly. Excess growth hormone (GH) hampers insulin signaling and diminishes glucose uptake, favoring lipolysis, free fatty acid release, and hepatic glucose production (2, 3, 5). Excess GH also alters insulin sensitivity through indirect mechanisms, including adipokine dysregulation, causing local and systemic inflammation (5). Pancreatic β-cell dysfunction has also been described (3, 6), predicting glucose homeostasis after curing the acromegaly (3, 7).

Long-acting somatostatin analogs (SSAs) are widely used as both first- and second-line treatment when neurosurgical removal is not appropriate or curative (8, 9), achieving biochemical control in about half of acromegaly patients. Both the antisecretory and antiproliferative effects of SSAs are mediated by somatostatin receptor subtype (SSTR)-2 and to a lesser extent by SSTR-5 (10). SSTR-5 is highly expressed in pancreatic β-cells and is involved in modulating insulin secretion, whereas SSTR-2 is mainly involved in glucagon regulation (11). Finally, incretins are also modulated by SSAs (12). All of these pathways contribute to raising or lowering blood sugar levels, highlighting the need for a better understanding of the net effect of SSAs on glucose metabolism. Because most acromegaly patients are treated for years with SSAs, and each of the currently available diabetes drugs targets a different pathway, identification of the mechanisms most relevant to metabolic control will help physicians to tailor these medications more appropriately.

A previous meta-analysis of 31 studies including 619 acromegaly patients investigated glucose metabolism during octreotide (OCT) and lanreotide (LAN) treatment; however, the authors concluded that the impact of first-generation SSAs was marginal (13). The effect of SSAs on glucose metabolism, as well as how to counteract their potentially negative side effects in acromegaly, remains open.

The aim of this meta-analysis was to address the following questions: (1) Do SSAs affect fasting plasma glucose (FPG), fasting plasma insulin (FPI), glycosylated hemoglobin (HbA1c), glucose load [glucose levels after a 2-hour oral glucose tolerance test (2h-OGTT)], homeostatic model assessment of insulin resistance (HOMA-I), homeostatic model assessment of pancreatic β-cell function (HOMA-β), triglycerides (TGDs), weight, or body mass index (BMI)? (2) Do LAN and OCT long-acting release (LAR) affect metabolism differently? (3) Does their effect depend on disease control?

Methods

This study was performed in line with the Cochrane Collaboration and PRISMA statement (14).

Search strategy

From March 2016 to August 2016 we searched for English language articles published after 1990 in Medline, Embase, Cochrane Library, and Scopus databases. Search key words were "acromegaly AND diabetes," "acromegaly AND medical treatment," and "acromegaly treatment." We updated the search in January 2017, but no further studies were included.

Study selection

Eligibility criteria for study selection included: (1) randomized controlled trials (RCTs) and nonrandomized prospective interventional trials; (2) acromegaly patient population; (3) long-acting SSA treatment with a minimum follow-up of 6 months; (4) assessment of glucose metabolism outcomes (as primary or secondary endpoints) before and after treatment with SSAs.

We excluded reviews, animal studies, retrospective studies, nonoriginal articles, and studies in which SSAs were combined with other medical therapies (*e.g.*, dopamine agonists, pegvisomant).

Three independent reviewers screened all identified titles and abstracts, and full-text reports were evaluated for articles considered potentially eligible. When full-text reports were not available, the corresponding authors were contacted but no further articles were obtained. Interobserver agreement was high (96%: 130 of 135 studies selected for full-text relevance assessment). Any disagreement was resolved by unanimous decision after open discussion. Figure 1 shows the literature eligibility assessment process.

Data extraction and quality assessment

Two independent reviewers (A.C. and T.F.) extracted data on study design (RCTs, prospective interventional study), sample population (age, sex, previous treatments), treatment characteristics (active compound: LAN slow release or Autogel, OCT LAR, or generic SSAs, dosage and follow-up), and disease control. Response to treatment was assessed by means of GH and insulin-like growth factor-1 (IGF-1) levels before and after therapy, as well as the percentage of patients matching the remission criteria adopted by each study, including mean GH $<$2.5 ng/mL (adopted in most studies), GH $<$5 ng/mL in five cases (15–19), GH $<$5 mU/L (20), GH $<$2 ng/mL (21–23), GH $<$1.9 ng/mL (24), GH $<$1 ng/mL after oral glucose tolerance test (OGTT) (25), and/or safe GH levels with normal IGF-1 levels adjusted for age and sex (17, 19, 23–34).

The third investigator (E.G.) performed quality control checks on extracted data. Risk of bias for all trials was assessed by the investigators independently, using the Cochrane risk-of-bias algorithm modified for non-RCTs by removing inapplicable criteria (35) (Supplemental Table 1).

Outcomes

We selected studies reporting at least one of the following parameters before and after SSAs administration: FPG, HbA1c, FPI, 2h-OGTT, TGDs, HOMA-I, HOMA-β, weight, and BMI. We excluded interim data and only the last follow-up assessment

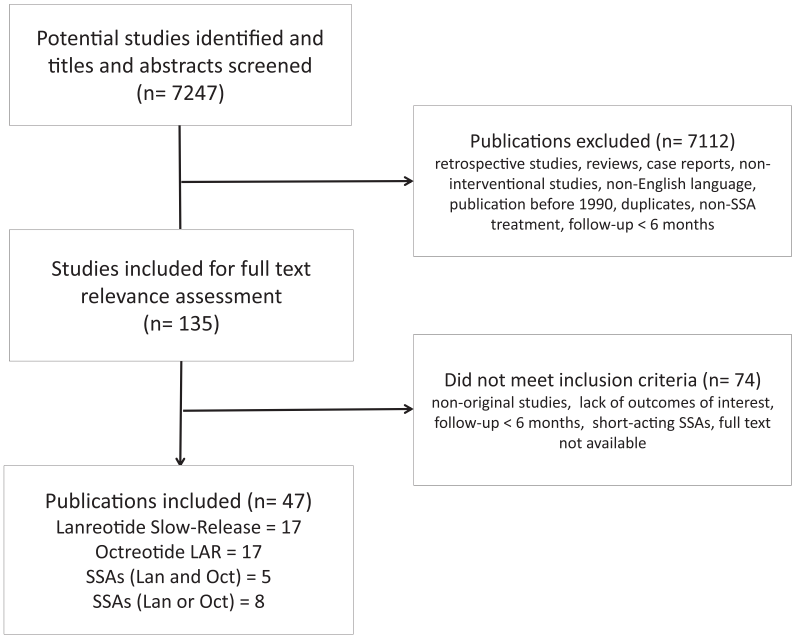

Figure 1. Flowchart of literature eligibility assessment process.

was considered. To avoid duplication, for papers involving the same populations, only those with the most complete and recent data were included.

Data synthesis and statistical analysis

Quantitative data reported as mean ± standard deviation (SD) or median and range at baseline and after SSA treatment were extracted from the full-text reports for all of the above outcomes. If reported, difference from baseline and/or percentage of change were also extracted. When the summary statistics reported standard error (SE), the corresponding SD was calculated. When data (SD or pretreatment or posttreatment values) were missing, we contacted the authors to obtain the necessary information. Units of measurements were converted in line with the International System of Units when necessary.

To explore whether different SSAs affect glucose metabolism outcomes differently, all studies were divided by active compound: LAN slow release or Autogel and OCT LAR. Then they were analyzed by monthly dosage (LAN ≥90 mg; LAN <90 mg; OCT ≥30 mg; OCT <30 mg) and by previous treatments (if SSAs were used as first- or second-line treatment). Finally, they were categorized by the percentage of patients with safe GH and/or normal IGF-1, arbitrarily divided in three groups (≤50%, between 50% and 70%, or ≥70% of patients at target) according to the criteria adopted by each study, to establish whether the effect of SSAs on glucose metabolism correlates with disease control.

Data were entered into Stata 10.1. The meta-analysis was performed using a random effects model to obtain summary statistics for the overall difference. We computed the mean difference (MD) between postvalues and prevalues; negative values indicate prevalues higher than postvalues. We evaluated heterogeneity via χ^2 and the I^2 test. The latter describes the rate of variation across studies due to heterogeneity rather than chance, ranging from 0 (no heterogeneity) to 100 (maximal heterogeneity). This index was interpreted using the classification proposed by Higgins *et al.* (36): I^2 0%, no heterogeneity; I^2 25%, low heterogeneity; I^2 50%, moderate heterogeneity; and I^2 75%, high heterogeneity. This was further investigated through subgroup analyses considering treatment (LAN and OCT), previous treatment (naive patients, previously treated), or percentage of patients under disease control (≤50%, 50% to 70%, ≥70%) as group factors. Meta-regression analysis was then applied with the following independent variables: posttreatment/pretreatment difference in GH values; posttreatment/pretreatment difference in IGF-1 values; difference in sex distribution; number of patients with posttreatment safe GH; number of patients with normal posttreatment IGF-1; number of patients with posttreatment safe GH and normal IGF-1. When reported for a sufficient number of studies, we also considered the posttreatment/pretreatment differences in the number of patients with diabetes, the number of patients with impaired fasting glucose, and the number of patients with impaired glucose tolerance. Cumulative meta-analysis was applied to evaluate the temporal effect. The studies were accumulated from the earliest to the latest, where each successive study included a summary of all previous experiments. Publication year was also included in a meta-regression analysis. Publication bias was investigated by funnel plot, the interpretation of which was aided by contour-enhanced funnel plot, which also includes contours of statistical significance. If studies appear to be missing in areas of low statistical significance, then the asymmetry could be due to publication bias. Missing studies in areas of high statistical significance are less likely to be caused by publication bias. Egger's test was then used to provide statistical evidence for funnel plot symmetry, and the Duval and Tweedie nonparametric "trim and fill" method of accounting for publication bias was performed.

Sensitivity analysis was performed excluding studies with low or fair quality. The estimated effect size (ES) was reported as mean difference and 95% confidence interval (CI). Statistical significance was defined as a $P < 0.05$.

Results

Study selection

Figure 1 shows the literature eligibility assessment process in Medline, Embase, Cochrane, and Scopus databases (from March 2016 to August 2016 and updated in January 2017). We found 7247 potentially relevant studies. Of these, 7112 were excluded on the basis of title and abstract screening, and 88 were excluded after full-text analysis. The main reasons for exclusion were not in English, not in humans, not interventional prospective studies, no relevant outcomes, short-acting SSAs, or combination therapy and short follow-up (<6 months). The remaining 47 studies were eligible.

Study characteristics

The effects of long-acting SSAs in acromegaly patients on glucose metabolism parameters were analyzed as

primary or secondary endpoints. Overall, 17 articles investigated LAN-treated subjects (15–19, 24, 26, 27, 32, 34, 37–43), with 2 including two different treatment arms (26, 43); and 17 investigated OCT-treated subjects (20, 22, 23, 25, 28–31, 44–52), with 2 including two different treatment arms (23, 30) and 1 three arms (29). Thirteen articles investigated both LAN and OCT: five (33, 53–56) described the two arms separately, eight reported the overall effect of the two SSAs (21, 57–63), and one reported data from two different populations (21). In all, the 47 articles provided data from 59 distinct populations for a total of 1297 treated subjects (per protocol analysis) treated with SSAs (417 with LAN; 566 with OCT; 314 with a nonspecified SSA that was either LAN or OCT). Table 1 summarizes the characteristics of the included studies.

Variables encountered comprised (1) daily dose: LAN from 30 mg every 7/14 days to 120 mg every 21/28 days, OCT from 10 to 40 mg every 21/28 days; (2) mean follow-up: from 6 to 60 months; (3) previous treatment: neurosurgery/radiotherapy/medical therapy (SSAs and/or dopamine agonists). SSAs were used as first-line therapy in eight studies (21, 24, 31, 32, 46, 52, 54, 60). All studies enrolled both male and female patients, with a mean age of 50 years (range 20 to 82 years). All studies were interventional prospective and five were RCTs (23, 34, 53, 58, 62). Seventeen trials were funded by pharmaceutical companies (15, 21, 23, 26, 33, 34, 37–39, 41, 42, 45, 46, 50, 52, 53, 62).

Glucose metabolism outcomes

Supplemental Table 2 summarizes the results for both the main and subgroup analyses for SSA type, first- *vs* second-line treatment, and disease control. Subgroup analysis by monthly dosage did not show significant differences compared with the main analysis.

FPG

Thirty-four studies, including 42 populations, investigated the effect of SSAs (LAN or OCT) on FPG (1042 patients). A marginal nonsignificant FPG increase was found (ES, 0.06 mmol/L; 95% CI, −0.06 to 0.18 mmol/L; $P = 0.354$). Heterogeneity was high ($I^2 = 80.4\%$; $P < 0.001$), and subgroup analysis revealed no influence of different SSAs. Fourteen studies, including 16 populations, evaluated the effect of LAN on FPG (275 patients), yielding similar nonsignificant results (ES, 0.09 mmol/L; 95% CI, −0.10 to 0.27 mmol/L; $P = 0.353$) (15, 18, 19, 24, 26, 27, 32, 37, 39, 41–43, 56, 60). Heterogeneity was moderate ($I^2 = 49.3\%$; $P = 0.013$). Fifteen studies, including 19 populations, evaluated the effect of OCT on FPG (463 patients), with no significant effects (ES, 0.05 mmol/L; 95% CI, −0.13 to 0.22 mmol/L; $P = 0.605$) (20, 23, 25, 28–31, 44, 45, 48, 49, 51, 52, 56, 60). Heterogeneity was high ($I^2 = 88.5\%$; $P < 0.001$). A statistically significant difference was observed only in the subgroup (715 patients) in which SSAs were used as second-line therapy (ES, 0.14 mmol/L; 95% CI, 0.01 to 0.27 mmol/L; $P = 0.037$), although with high heterogeneity ($I^2 = 78.6\%$; $P < 0.001$).

HbA1c

HbA1c analysis was possible in 31 study populations (810 patients) and revealed a significant increase over time (ES, 0.12%; 95% CI, 0.04% to 0.21%; $P = 0.003$). Heterogeneity was extremely high ($I^2 = 94.5\%$; $P < 0.001$). Subgroup analyses revealed a significant ES only in OCT-treated subjects (12 studies, 14 populations, 334 patients) (ES, 0.12%; 95% CI, 0.00% to 0.25%; $P = 0.044$) (22, 23, 25, 28, 30, 31, 45, 48, 49, 51, 52, 55), but with heterogeneity remaining high ($I^2 = 96.2\%$; $P < 0.001$). Eleven studies, including 13 populations, investigated HbA1c in LAN-treated patients (234), with no significant change over time (ES, 0.09%; 95% CI, −0.04% to 0.23%; $P = 0.179$) (16, 17, 19, 26, 27, 34, 39–43). Heterogeneity was high ($I^2 = 91.8\%$; $P < 0.001$). The effect of SSAs on HbA1c was significant either when they were used as first-line (124 patients; ES, 0.21%; 95% CI, 0.04% to 0.37%; $P = 0.013$) or second-line treatment (630 patients; ES, 0.11%; 95% CI, 0.02% to 0.20%, $P = 0.017$). Figure 2 shows the results of main analysis on HbA1c.

FPI

SSAs significantly decreased FPI levels in the main analysis including 33 study populations and 772 patients. The ES was −6.66 mU/L (95% CI, −8.38 to −4.95 mU/L; $P < 0.001$), but with high heterogeneity ($I^2 = 96.5\%$; $P < 0.001$). In subgroup analysis, both LAN and OCT reduced FPI significantly. Ten studies (131 patients) evaluated the effect of LAN on FPI, finding a significant posttreatment decrease (ES, −8.32 mU/L, 95% CI, −10.44 to −6.20 mU/L; $P < 0.001$) (15, 18, 19, 32, 33, 37, 41, 55, 56, 60). Heterogeneity was lower, but still fairly high ($I^2 = 71.8\%$; $P < 0.001$). FPI also dropped significantly (ES, −6.50 mU/L; 95% CI, −8.63 to −4.36 mU/L; $P < 0.001$) in the 18 study populations (393 patients) taking OCT, albeit with higher heterogeneity ($I^2 = 97.3\%$; $P < 0.001$) (23, 25, 29, 30, 33, 44, 45, 47–51, 54, 56). The effect of SSAs in lowering insulin was confirmed in all the other subgroup analyses. Figure 3 shows the results of main analysis on FPI.

Glucose levels after 2h-OGTT

In the nine study populations (344 patients) in the main analysis, 2h-OGTT levels significantly increased against the baseline (ES, 0.59 mmol/L; 95% CI, 0.05 to 1.13 mmol/L; $P = 0.032$) with nonsignificant

heterogeneity (I^2 = 42.3%; P = 0.085). Only one study evaluated the effect of LAN on 2h-OGTT (15). Four studies (120 patients) were included in the OCT subgroup analysis, confirming the significant increase (ES, 0.60 mmol/L; 95% CI, 0.07 to 1.12 mmol/L; P = 0.025; I^2 = 0.0%) (31, 51, 52, 55). Figure 2 shows the results of main analysis on 2h-OGTT.

HOMA-I

Fifteen study populations (279 patients) showed a significant decrease in HOMA-I (ES, −1.57; 95% CI, −2.42 to −0.72; $P < 0.001$) after administration of SSAs. Heterogeneity was high (I^2 = 82.5%; $P < 0.001$). Subgroup analysis of the four studies using LAN (55 patients) revealed a significant decrease in HOMA-I (ES, −2.11; 95% CI, −3.54 to -0.69; P = 0.004), without significant heterogeneity (I^2 = 38.8%; P = 0.179) (32, 54–56). The OCT subgroup analysis included nine study populations (138 patients) and confirmed the decrease in HOMA-I, with ES of −1.43 (95% CI, −2.51 to −0.34; P = 0.010), but higher heterogeneity (I^2 = 88.2%; $P < 0.001$) (29, 45, 46, 49, 51, 54, 56). The effect of SSAs in lowering HOMA-I was confirmed in all other subgroup analyses. Figure 3 shows the results of main analysis on HOMA-I.

HOMA-β

Main analysis of HOMA-β was possible in nine study populations (286 patients), revealing a significant drop (ES, −47.45; 95% CI, −73.15 to −21.76; $P < 0.001$). Heterogeneity was high (I^2 = 92.7%; $P < 0.001$). Only one study evaluated the effect of LAN on HOMA-β (54). Six study populations (112 patients) were included in the OCT subgroup analysis, revealing a significant drop in HOMA-β over time (ES, −36.65; 95% CI, −63.21 to −10.08; P = 0.007), but with a very high heterogeneity (I^2 = 94.5%; $P < 0.001$) (29, 49, 51, 54). This result was confirmed in the subgroup for SSAs used as first- and second-line treatment and in the subgroup for ≥70% disease control.

TGDs

Thirteen study populations (305 patients) were included in the main TGD analysis, revealing a significant drop after treatment with an ES of −0.37 mmol/L (95% CI, −0.47 to −0.27 mmol/L; $P < 0.001$). Heterogeneity was high (I^2 = 94.4%; $P < 0.001$). Subgroup analysis revealed a significant ES (ES, −0.41 mmol/L; 95% CI, −0.52 to −0.29 mmol/L; $P < 0.001$) only in the six study populations (152 patients) treated with OCT (25, 30, 31, 45, 54). Heterogeneity remained high (I^2 = 94.3%; $P < 0.001$). Four studies (73 patients) were included in LAN subgroup analysis, with no change in TGD (ES, −0.27 mmol/L; 95% CI, −0.57 to 0.03 mmol/L; P = 0.083) (27, 40, 41, 54). Heterogeneity was high (I^2 = 95.0%; $P < 0.001$). SSAs were found to affect TDG in all other subgroups.

Weight

Weight did not change (ES, −0.36 kg; 95% CI, −2.51 to 1.80 kg; P = 0.744) in the main analysis of seven study populations (174 patients) (25, 38, 39, 53, 57, 62). Subgroup analysis was not performed because of the nonsignificant heterogeneity (I^2 = 0.0%; P = 0.998).

BMI

Main analysis of BMI (ES, −0.01 kg/m^2; 95% CI, −0.40 to 0.38 kg/m^2; P = 0.962) was possible in nine studies (207 patients), showing no significant change (25, 40, 41, 45, 55, 57–59, 63). Heterogeneity was high (I^2 = 85.4%; $P < 0.001$). Subgroup analysis revealed no significant change in BMI (ES, −0.44 kg/m^2; 95% CI, −0.95 to 0.06 kg/m^2; P = 0.086) in the three LAN studies (45 patients), with nonsignificant heterogeneity (I^2 = 50.2%; P = 0.134) (40, 41, 55).

Meta-regression and sensitivity analysis

A significant effect of publication year was observed only for blood glucose: more recent studies produced smaller posttreatment/pretreatment MD estimates (β = –0.026, SE = 0.012; P = 0.039), suggesting improved attention toward glycemic control.

There was a significant effect of post/pre GH MD on the pooled estimate: the greater the reduction in GH levels, the greater the drop in insulin levels (β = 0.17, SE = 0.05; P = 0.001). Similar results were also seen for post/pre MD in IGF-1 values (β = 0.02, SE = 0.00; $P < 0.001$). Combining these differences in a multivariable meta-regression model revealed that their effects were significant: the pooled MD in insulin dropped by 0.14 U for each 1 U drop in post/pre GH difference while holding the IGF-1 difference constant (95% CI, 0.00 to 0.28; P = 0.044); holding the GH difference constant, the pooled MD in insulin dropped by 0.02 U for each 1 U drop in IGF-1 (95% CI, 0.00 to 0.03; P = 0.012). Supplemental Fig. 1 shows the results of meta-regression.

Finally, for HOMA-I a significant effect was also found with the post/pre difference in IGF-1 values (0.01; 95% CI, 0.00 to 0.01; P = 0.030).

A sensitivity analysis considering only studies with good or excellent quality found no differences in size and direction of investigated effect, except for 2h-OGTT (0.57 mmol/L; 95% CI, −0.82 to 1.96 mmol/L; P = 0.422) (but only including three studies), and BMI (0.15 kg/m^2; 95% CI, −0.59 to 0.89 kg/m^2; P = 0.694).

Risk of bias

Most of the studies had low risk of attrition and reporting bias; 11 had high risk of attrition bias and 10 of

Table 1. Details of Selected Studies

Author, Year, Reference	No. of Patients (Male/Female)	Age (y) (Mean ± SD or Range)	Dosage (Mean or Range)	Mean Follow-up (mo)	SSAs First-Line (Yes/No)	Disease Control (%)
LAN						
Heron *et al.*, 1993 (37)	14 (5/9)	27–69	30 mg/14 d	6	No	100 (IGF-1)
Marek *et al.*, 1994 (18)	13 (8/5)	23–64	30 mg/14 d	19	No	23 (GH*); 23 (IGF-1)
Al-Maskari *et al.*, 1996 (15)	10 (5/5)	27–70	30 mg/14–21 d	6	No	60 (GH*); 50 (IGF-1)
Caron *et al.*, 1997 (16)	22 (9/13)	51 ± 3	30 mg/14 d	36	No	13.6 (GH*)
Kendall-Taylor *et al.*, 2000 (33)	5	34–68	30 mg/14 d	6	No	80 (GH); 100 (IGF-1); 80 (GH + IGF-1)
Chanson *et al.*, 2000 (38)	116	—	30 mg/14 d	12	No	41 (GH); 41 (IGF-1)
Verhelst *et al.*, 2000 (39)	66 (37/29)	49.6 ± 24.4	30 mg/7–14 d	12	No	45 (GH); 44 (IGF-1)
Díez *et al.*, 2001 (17)	10 (3/7)	53.5 ± 12	30 mg/14 d	36	No	70 (GH*); 70 (IGF-1); 70 (GH + IGF-1)
Colao *et al.*, 2002 (41)	24 (12/12)	20–58	60–90 mg/28 d	6	No	75 (GH); 62.5 (IGF-1)
Ronchi *et al.*, 2002 (55)	10 (6/4)	46 ± 16	30 mg/14 d	19	No	40 (GH); 10 (IGF-1)
Ambrosio *et al.*, 2002 (43)	10 (7/3)	57.1 ± 11.5	60 mg/28 d	8	No	90 (GH); 40 (IGF-1)
Ambrosio *et al.*, 2002 (2) (43)	10 (3/7)	58.3 ± 14.4	60 mg/21 d	8	No	40 (GH); 30 (IGF-1)
Ronchi *et al.*, 2003 (56)	15 (5/10)	—	30–60 mg/7–28 d	6	No	33.3 (IGF-1)
Alexopoulou *et al.*, 2004 (42)	25 (13/12)	51 ± 12	108 mg/28 d	6	No	48 (GH); 52 (IGF-)
Gutt *et al.*, 2005 (40)	11 (8/3)	47–79	109 mg/28 d	48	No	54.5 (IGF-1)
Abrams *et al.*, 2007 (26)	9 (5/4)	54.6 ± 13.1	30 mg/7 d	9	No	100 (GH); 100 (IGF-1)
Abrams *et al.*, 2007 (2) (26)	12 (6/6)	49.2 ± 16.2	40 mg/7 d	9	No	25 (GH); 16.7 (IGF-1); 8 (GH + IGF-1)
Attanasio *et al.*, 2008 (27)	27 (12/15)	49.2 ± 19.9	60–120 mg/28 d	12	No	40 (GH); 51.8 (IGF-1); 37 (GH + IGF-1)
Andries *et al.*, 2008 (53)	5 (3/2)	40.2 ± 20.4	—	6	No	—
Colao *et al.*, 2009 (54)	17	59.3 ± 16.6	60–120 mg/21–28 d	60	Yes	100 (GH)
Colao *et al.*, 2009 (24)	26 (9/17)	54.3 ± 10.4	120 mg/28 d	12	Yes	57.7 (GH[†]); 58.2 (IGF-1); 53.8 (GH + IGF-1)
Kelly *et al.*, 2010 (19)	13 (6/7)	52.6 ± 12.1	60–120 mg/28 d	12	No	78 (GH*); 44 (IGF-1); 44 (GH + IGF-1)
Gasco *et al.*, 2012 (32)	13 (4/9)	50.8 ± 11.4	60 mg/28 d	6	Yes	46.1 (GH + IGF-1)
Shimatsu *et al.*, 2013 (34)	32	47 ± 13.4	90 mg/28 d	12	No	46.9 (GH); 53.1 (IGF-1); 40.6 (GH + IGF-1)
OCT						
Flogstad *et al.*, 1997 (22)	14 (6/8)	49.4 ± 12.4	20–40 mg/28 d	18	No	64.3 (GH[§]); 64.3 (IGF-1)
Davies *et al.*, 1998 (20)	13 (5/8)	48 ± 10.9	20–40 mg/28–42 d	36	No	50 (GH[˚]); 75 (IGF-1)
Kendall-Taylor *et al.*, 2000 (2) (33)	5	34–68	20 mg/28 d	6	No	80 (GH); 100 (IGF-1); 80 (GH + IGF-1)
Colao *et al.*, 2001 (44)	36 (15/21)	52.7 ± 13.7	27 mg/28 d	22	No	71.4 (GH); 67.8 (IGF-1)
Colao *et al.*, 2002 (30)	15	—	20–40 mg/28 d	6	Yes	53.3 (GH + IGF-1)
Colao *et al.*, 2002 (2) (30)	10	—	20–40 mg/28 d	6	Yes	50 (GH + IGF-1)
Ronchi *et al.*, 2002 (2) (55)	10 (6/4)	46 ± 16	20 mg/28 d	21	No	50 (GH); 20 (IGF-1)
Ronchi *et al.*, 2003 (2) (56)	12 (6/6)	—	20–30 mg/28 d	6	No	41.7 (IGF-1)
Tan *et al.*, 2003 (45)	14 (11/3)	41.5 ± 8.1	10–30 mg/28 d	6	No	100 (IGF-1)
Frajese *et al.*, 2003 (46)	6 (4/2)	42–70	20–30 mg/28 d	6	No	50 (GH); 50 (IGF-1)
Freda *et al.*, 2003 (47)	10 (4/6)	43.2 ± 12.1	10–30 mg/28–42 d	11.2	No	80 (IGF-1)
Jallad *et al.*, 2005 (48)	80 (34/46)	43 ± 12.9	—	16.6	No	74 (GH); 41 (IGF-1)
Cozzi *et al.*, 2006 (31)	67 (31/36)	54.9 ± 14.2	20–30 mg/28 d	48 (median)	Yes	68.7 (GH); 60.1 (IGF-1); 56.7 (GH + IGF-1)
Colao *et al.*, 2007 (29)	24 (14/10)	53 ± 17	20 mg/28 d	24	No	100 (GH); 100 (IGF-1); 100 (GH + IGF-1)
Colao *et al.*, 2007 (2) (29)	15 (8/7)	37 ± 15	30 mg/28 d	24	No	100 (GH); 100 (IGF-1); 100 (GH + IGF-1)
Colao *et al.*, 2007 (3) (29)	17 (8/9)	40 ± 13	40 mg/28 d	24	No	35.3 (GH); 29.4 (IGF-1)
De Marinis *et al.*, 2007 (49)	10 (5/5)	45.8 ± 8.1	40 mg/28 d	34 (median)	No	O (IGF-1)
Andries *et al.*, 2008 (2) (53)	5 (2/3)	56.2 ± 16.7	—	6	No	—
Delaroudis *et al.*, 2008 (25)	18 (8/10)	48 ± 3.4	—	6	No	0 (GH[#]); 0 (IGF-1); 0 (GH + IGF-1)
Colao *et al.*, 2009 (2) (54)	28	52.8 ± 18.9	30–40 mg/28 d	60	Yes	100 (GH)
Ghigo *et al.*, 2009 (50)	56 (28/28)	49.8 ± 13.8	30–40 mg/28 d	12	No	34 (IGF-1)
Mazziotti *et al.*, 2011 (23)	11 (7/4)	49.4 ± 13.8	60 mg/28 d	6	No	27.2 (GH[§]); 36 (IGF-1); 18 (GH + IGF-1)
Mazziotti *et al.*, 2011 (2) (23)	15 (5/10)	52.3 ± 11.9	30 mg/21 d	6	No	0 (GH[§]); 0 (IGF-1); 0 (GH + IGF-1)
Chen *et al.*, 2011 (51)	18 (6/12)	47.5 ± 16.3	20–40 mg/28 d	12	No	89 (GH); 61 (IGF-1)
Chieffo *et al.*, 2013 (28)	41 (14/27)	51.3 ± 11.9	10–40 mg/28 d	6	No	84 (GH + IGF-1)
Helseth *et al.*, 2016 (52)	32 (21/11)	47 ± 14	20 mg/28 d	6	Yes	26.9 (IGF-1); 19.2 (GH + IGF-1)
SSA (LAN or OCT)						
Ayuk *et al.*, 2002 (21)	22 (6/16)	28–69	OCT: 20–30 mg/28–42 d; LAN: 30 mg/10–14 d	41	No	36 (GH[§]); 67 (IGF-1)
Ayuk *et al.*, 2002 (2) (21)	10 (2/8)	45–69	OCT: 20–30 mg/28–42 d; LAN: 30 mg/10–14 d	41	Yes	40 (GH[§]); 60 (IGF-1)

(*Continued*)

Table 1. Details of Selected Studies (Continued)

Author, Year, Reference	No. of Patients (Male/Female)	Age (y) (Mean ± SD or Range)	Dosage (Mean or Range)	Mean Follow-up (mo)	SSAs First-Line (Yes/No)	Disease Control (%)
Baldelli *et al.*, 2003 (58)	24 (11/13)	50.7 ± 12.7	OCT: 27 mg/28 d; LAN: 30 mg/12 d	6	No	62 (GH); 30 (IGF-1)
Baldelli *et al.*, 2003 (59)	20 (9/11)	48.2 ± 14.2	OCT: 20–30 mg/28 d; LAN: 30 mg/10–14 d	6	No	—
Colao *et al.*, 2009 (24)	112 (51/61)	46.5 ± 16.8	OCT: 10–30 mg/28 d; LAN: 60–120 mg/28 d	12	Yes	48.2 (GH + IGF-1)
Colao *et al.*, 2009 (60)	34 (19/15)	55 ± 17	OCT: 10-40 mg/28 d; LAN: 60–120 mg/28 d	60	Yes	100 (GH); 97.8 (IGF-1)
Madsen *et al.*, 2011 (62)	6 (1/5)	52 ± 16.2	OCT: 10–30 mg/28 d; LAN: 80 mg/28 d	6	No	—
Urbani *et al.*, 2013 (63)	50 (23/27)	47.8 ± 12.4	OCT: 30 mg/28 d; LAN: 120 mg/28 d	12	No	38 (IGF-1)
Auriemma *et al.*, 2017 (57)	36 (14/22)	52.3 ± 10.2	OCT: 34 mg/28 d; LAN: 130 mg/28 d	36 (median)	No	13.9 (GH); 0 (IGF-1)

The percentage of disease control is expressed using the following criteria: for GH, (GH) indicates <2.5 ng/mL; (GH*), <5 ng/mL; (GH$^{\circ}$), <5 mUI/L; (GH†), <1.9 ng/mL; (GH$^{\#}$), <1 ng/mL after OGTT; (GH§), <2 ng/mL. (IGF-1) indicates normal IGF-1 levels adjusted for age and gender; (GH + IGF-1) indicates both safe GH and normal IGF-1 levels. The number "2" in parentheses refers to studies in which two groups of patients were analyzed separately. The number "3" in parentheses refers to studies in which three groups of patients were analyzed separately.

reporting bias (Supplemental Table 1). The funnel plots did not show major asymmetries. A significant publication bias was excluded for all of the outcomes analyzed except for HOMA-I and HOMA-β. Whenever appropriate (>10 to 20 studies and low between-study heterogeneity), we assessed publication bias using the Egger regression asymmetry test and visual inspection of funnel plots.

Discussion

This meta-analysis reveals that LAN and OCT as first- or second-line therapies for acromegaly do not have a neutral effect on metabolism. SSAs increase HbA1c (especially OCT) and lower insulin levels to an extent proportional to their efficacy in reducing GH levels. The clinical implication of these findings is that the physician should expect some metabolic worsening when treating acromegaly with SSAs, but that this appear marginal compared with the effects of disease control, and that greater attention should be paid to avoiding postprandial hyperglycemia in these patients.

Impaired glucose homeostasis, from impaired glucose tolerance to severe DM, is a hallmark of acromegaly (1–4). Insulin resistance is a key contributor to the development of DM in acromegaly. Excess GH induces insulin resistance by impairing the ability of insulin to suppress glucose production and stimulate its use (2, 3).

SSA treatment can affect insulin and, to a lesser extent, glucagon secretion in acromegaly patients through binding to SSTR-5, which is highly expressed in pancreatic β-cells and is involved in insulin secretion modulation (10, 64).

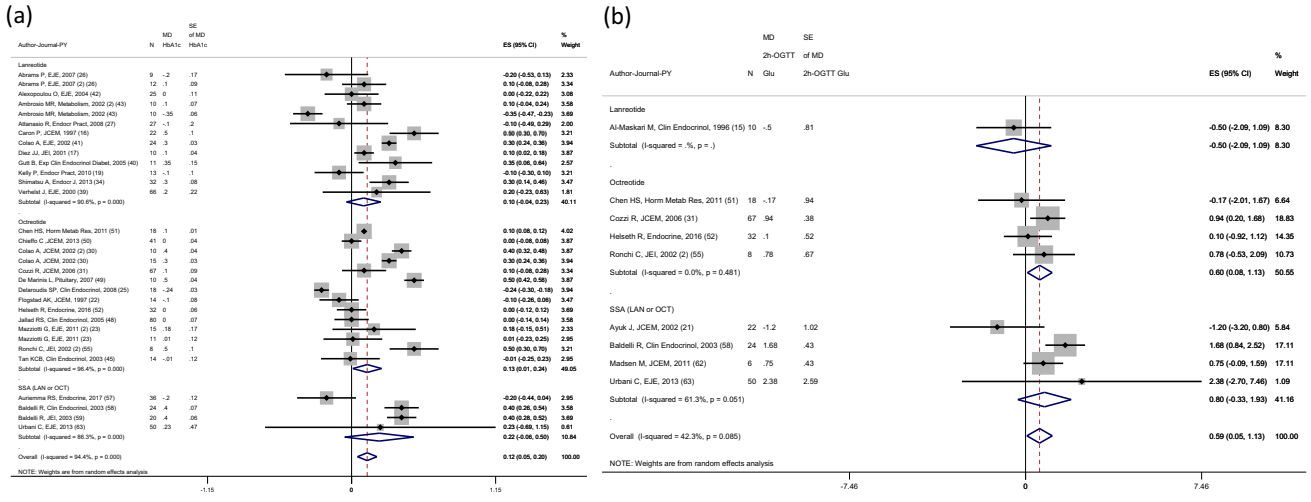

Figure 2. (a) Results of main analysis of SSA effects on HbA1c in acromegaly. (b) Results of main analysis of SSA effects on 2h-OGTT glucose in acromegaly. Single studies are identified by first authors and publication year. The number "2" in parentheses refers to studies in which two groups of patients were analyzed separately.

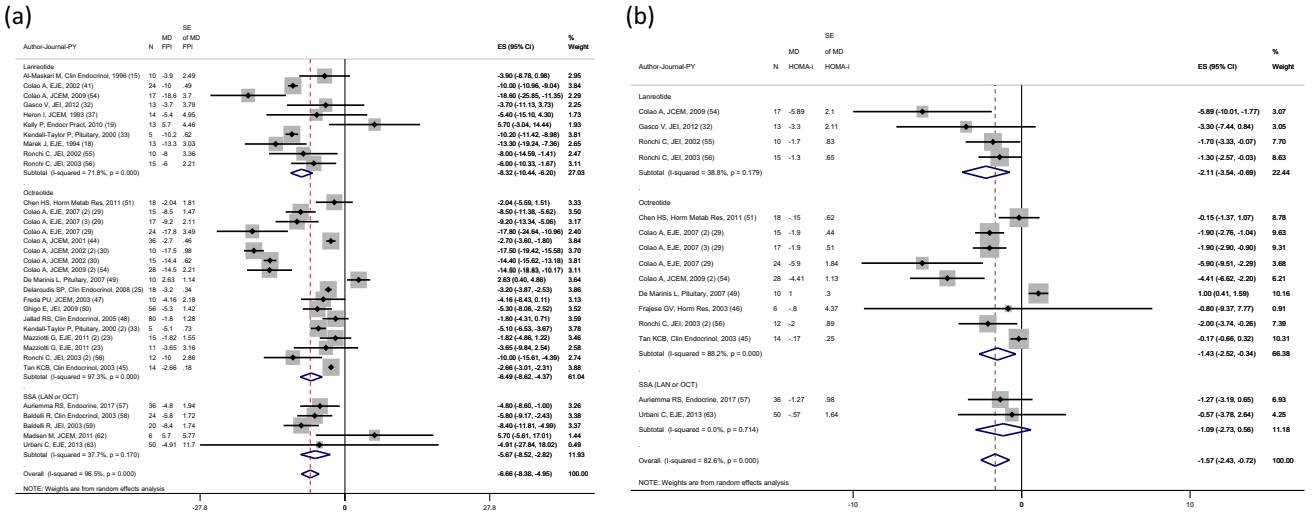

Figure 3. (a) Results of main analysis of SSA effects on FPI in acromegaly. (b) Results of main analysis of SSA effects on HOMA-I in acromegaly. Single studies are identified by first authors and publication year. The number "2" in parentheses refers to studies in which two groups of patients were analyzed separately. The number "3" in parentheses refers to studies in which three groups of patients were analyzed separately.

This is a possible mechanism through which SSA treatment might affect insulin secretion in acromegaly patients, especially in those with pre-existing impaired glucose metabolism (10, 64).

A previous meta-analysis of 31 studies including 619 acromegaly patients showed a decrease in plasma insulin levels during OCT or LAN treatment (13). The current meta-analysis evaluates a much larger number of studies (47) and patients (1297) and is updated to 2017. Moreover, to our knowledge, this is the first meta-analysis investigating the effect of SSAs on a complete panel of metabolic parameters, including not only fasting and postload blood glucose, HbA1c, and insulin but also HOMA-I, HOMA-β, TGD, weight, and BMI. To our knowledge, this is the first large analysis to compare the most frequently used SSAs (OCT and LAN) and their impact when used as first- or second-line treatment.

Our results show that SSAs significantly reduce insulin secretion, consistent with previous works (13), but they also suggest that this impairment is due to blunting of postload insulin elevation, with no major effect on fasting glucose. In contrast with the previous inadequately powered analysis (13), we demonstrated that postprandial hyperglycemia results in increased HbA1c after SSA treatment, as expected. Our results also showed a significant posttreatment drop in HOMA-I, HOMA-β, and TGD, confirming that the effect of SSAs on insulin secretion plays a major role to the metabolic impairment, the real novelty of the current study.

In the subgroup analysis by SSA type we observed some differences between LAN and OCT treatment: HbA1c and TGD only reached statistical significance in the OCT subgroup. This can be explained by the larger case load in the OCT subgroups (HbA1c OCT 334 *vs* LAN 234; TGD OCT 152 *vs* LAN 73), but may also be a consequence of different binding to SSTR-5 (65). Subgroup analysis by mean monthly dosage did not shown major differences compared with the main analysis. This was likely due to the paucity and homogeneity of studies reporting full details of the monthly dose regimen (with most studies reporting only the dose range), resulting in fewer studies included in each group.

An additional novelty is the subgroup analysis comparing first-line *vs* second-line treatment. The observation that blood glucose increases significantly only in second-line treatments suggests that more advanced disease, longer history of acromegaly, and, consequently, worse insulin resistance status are predictors of metabolic response to SSAs. This also carries clinical implications, as physicians should treat or prepare such patients more intensively prior to SSAs. In fact, compared with the overall group where the effects on FPG were neutral, in these patients the induced drop in insulin secretion also results in a worsening of FPG.

Conversely, the fact that SSAs affected insulin levels in all subgroups suggests it is more likely a drug-related rather than patient-dependent effect. This is further confirmed in the meta-regression analysis showing a mild correlation between reduced insulin and GH and IGF-1 reduction. The link between the effects of SSAs on insulin and on disease control is further supported by *in vitro* studies confirming an additive effect of insulin on IGF-1 generation in the liver (66). The reduction in insulin levels is therefore not necessarily detrimental but could reflect better disease control (greater sensitivity to SSAs) or reduction in a factor stimulating IGF-1 levels (67). The resulting improved disease control (whether through GH or IGF-1 reduction) also improves insulin sensitivity, as confirmed by our data on

HOMA-I and HOMA-β. SSAs reduce the insulin response to a meal or OGTT and, conversely, GH impairs insulin signaling. The net balance between the opposite effect of SSAs may vary among patients depending on their individual family history, predisposition to DM, BMI, and the presence of other known risk factors. The results of the current meta-analysis on acromegaly therefore have clinical implications. In patients with Cushing's disease receiving pasireotide, some authors suggested that a treatment or pretreatment with incretins might be necessary and speculated that this could also apply to acromegaly (68, 69). We provided data pointing toward the need for a tailored antidiabetic treatment specifically targeting postprandial glucose. We speculate that not only incretins, but also an individualized diet, acarbose, and possibly glycosuric drugs could be used in acromegaly patients treated with SSAs.

Our meta-analysis has some limitations. First, the great heterogeneity of the studies is a limitation, although this is partially reduced by subgroup and sensitivity analysis and partially explained by meta-regression. Second, missing glucose metabolism data in some publications represents a limitation, because negative results were not shown. Third, the lack of data on pasireotide, the new-generation multireceptor-targeted SSA that has a higher affinity for SSTR-5 than OCT and LAN and a potentially worse impact on glucose metabolism, is a limitation; the reported results were incomplete and meta-analyses of the available data were not possible.

In conclusion, this meta-analysis evaluated the effect of SSAs on a complete panel of glucose metabolism parameters, considering a large number of recent studies. It analyzed the effect of different types and doses of SSAs (OCT and LAN) and investigated any correlation between effects on glucose metabolism and effects on disease control. SSAs were found to affect glycemic status by reducing insulin, HOMA-I, HOMA-β, and TGD levels, with a slight but significant effect on HbA1c and glucose after OGTT. This suggests that SSAs mainly act on insulin secretion, which influences blood glucose levels in response to glucose loading, and hence HbA1c, without changes to fasting blood glucose. The net balance between the positive effects mediated by the drop in GH and IGF-1 and the negative effects on pancreatic β-cells could determine whether SSA treatment worsens glucose metabolism, depending on the patient's predisposition.

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