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Glycometabolic control in acromegalic patients with diabetes: A study of the effects of different treatments for growth hormone excess and for hyperglycemia

V.M. Cambuli[1], M. Galdiero[2], M. Mastinu[1], F. Pigliaru[1], R.S. Auriemma[2], A. Ciresi[3], R. Pivonello[2], M. Amato[3], C. Giordano[3], S. Mariotti[1], A. Colao[2], and M.G. Baroni[1]

[1]Endocrinology and Diabetes, Department of Medical Sciences, University of Cagliari, Cagliari; [2]Department of Molecular and Clinical Endocrinology and Oncology, Federico II University, Naples; [3]Section of Endocrinology, DOSAC (Dipartimento di Oncologia Sperimentale ed Applicazioni Cliniche), University of Palermo, Palermo, Italy

ABSTRACT. ***Background:*** **Diabetes mellitus is frequently observed in patients with acromegaly. Current therapies for acromegaly may impact glucose regulation, influencing insulin sensitivity and secretion. The question whether these therapies modify control and progression of diabetes once present is still open.** ***Aim:*** **Aim of our study is to analyze glucose control in acromegalic patients with diabetes, evaluating the relation with treatments for GH excess and for diabetes.** ***Methods:*** **Seventy patients with acromegaly and diabetes were studied. Duration and treatments of acromegaly and diabetes were recorded, together with clinical and metabolic parameters.** ***Results:*** **Most patients (92.8%) were treated with somatostatin analogs (SSA), either alone or in combination with dopamine-agonists (20%) or pegvisomant (15.7%); 7.1% of patients had been treated by surgery alone. Metformin (65.7%), alone or in combination with other hypoglycemic drugs, was the most frequent treatment for diabetes, followed by insulin (21.5%). Only 15.7% were treated with diet alone. The whole cohort showed a very good control of diabetes and acromegaly. Median glycated hemoglobin was 6.4% (5.9-7). IGF-I was within normal range for age in most patients. No relation was observed between duration of acromegaly or diabetes and metabolic control. SSA had a negative effect on insulin secretion, but these effects did not influence glucose control. Finally, we observed a low prevalence of nephropathy (6%) and retinopathy (20%).** ***Conclusions:*** **Our study shows that a good control of hyperglycemia can be obtained with success in the majority of acromegalic patients with diabetes, independently of the type of treatment for GH excess.**

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INTRODUCTION

Abnormal glucose tolerance and diabetes are frequently observed in patients with acromegaly (1). Impaired glucose metabolism develops in patients with acromegaly and concomitant β-cell insufficiency, and a proportion of patients (19-38%) develop overt diabetes mellitus (DM) (2). In acromegalic patients, the presence of diabetes has been observed to contribute to premature mortality (3), and impaired glucose tolerance has been found to correlate with the severity of acromegalic cardiomyopathy (4). GH opposes the effects of insulin on carbohydrate metabolism (5), increasing glucose production, primarily through its ability to stimulate lipolysis, and providing free fatty acids and glycerol as metabolic substrates. Additionally, GH inhibits insulin-induced suppression of hepatic gluconeogenesis (5). All these effects have clearly a negative impact on insulin action and are determinants of the reduced insulin sensitivity that is seen in acromegalic patients. This insulin resistance (IR) secondary to excessive GH secretion is generally compensated by hyperinsulinemia, but abnormal glucose tolerance and diabetes develops in patients when insulin secretion declines. The central role played by IR in the development of DM in acromegaly emerges clearly.

Treatments for acromegaly may also influence glucose metabolism. In alternative or addition to surgery, the most widely used drugs for the treatment of acromegaly are somatostatin analogs (SSA) (6). The use of pegvisomant is presently indicated to cases of intolerance or resistance to SSA (7). An open question regards the impact of these treatments on glucose metabolism: it is known that SSA affect insulin secretion, whereas pegvisomant appears to improve insulin secretion (8, 9). However, how much of the changes in glucose metabolism can be attributed to the various treatments for acromegaly is still a matter of debate. Conversely, it is also unclear whether the amelioration of GH excess *per se* can lead to improvement of glucose metabolism, aside from the mechanisms of action of the single drugs (10). Thus, although different therapeutic approaches for acromegaly may help to prevent the occurrence of glucose intolerance and diabetes (11), the question on how much the different therapies for GH excess influence the progression of diabetes and its complications, once present, is still open (12, 13). Moreover, which is the most effective treatment for diabetes in acromegalic patients is still unclear.

Aim of our study is therefore to analyze metabolic control in a large cohort of acromegalic patients with diabetes, evaluating in the clinical setting the relation between their

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Correspondence: M.G. Baroni, MD PhD, Department of Medical Sciences, Endocrinology and Diabetes, University of Cagliari, Policlinico Universitario, 09042, Monserrato (CA), Italy.

E-mail: marcobaroni@medicina.unica.it

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glucose control and their treatments for both GH excess and for diabetes, looking also at parameters of insulin sensitivity and secretion according to drug treatment.

SUBJECTS AND METHODS

Seventy patients with diagnosis of acromegaly, attending the Endocrine Units of the University of Cagliari, University Federico II of Napoli and University of Palermo, were selected for the study. All patients were affected by DM in the presence of acromegaly and, for these reasons, included in the analyses. Written consent for the analyses of the data was given by all patients.

For all participants duration and treatments of acromegaly and DM were recorded, together with the presence of major microvascular complications specific of DM (nephropathy and retinopathy). Nephropathy was defined by the presence of micro- or macro-albuminuria according to the American Diabetes Association guidelines (14). The diagnosis was given when 2 out of 3 positive samples were present. Retinopathy was detected by fundus examination, and classified as background, pre-proliferative, and proliferative (14).

Fasting glycemia, glycosylated hemoglobin (HbA_{1c}), insulin, GH, IGF-I, were measured in all subjects. Plasma glucose was determined by the glucose oxidase method (Autoanalyzer, Beckman Coulter, USA). Plasma insulin concentration was measured on frozen samples using a radio immunoassay (DLS-1600 Insulin Radioimmunoassay Kit, Diagnostic System Laboratories Inc., Webster, Texas, USA) with an intra-assay coefficient of variation (CV) between 4.7 and 12.2% and an inter-assay CV between 4.5 and 8.3%.

GH and IGF-I measurements were determined by a solid-phase, two site chemiluminescent immunometric assay (Immulite 2000, Siemens Helathcare Diagnostics, USA).

To estimate IR and insulin secretion in our population, the homeostasis model assessment for IR (HOMA-IR) and for β cells secretion (HOMA-B%) were used (15).

Statistical analysis

Data are expressed as medians±interquartile range. Categorical variables were analyzed by χ^2 or Fisher's exact tests. Differences between continuous variables were evaluated by a non-parametric test (Mann-Whitney U or Kruskal-Wallis). All statistical analyses were performed using the 15.0 version of SPSS/WIN package (SPSS, Chicago, IL).

RESULTS

Seventy patients (median age 63 years, range 52-72) affected by acromegaly and DM were studied. The median duration of acromegaly and DM were 10.5 years (interquartile range 7-16.2 years) and 9 years (interquartile range 6-13 years), respectively.

Treatment of acromegaly and diabetes

Most patients (92.8%) were treated with SSA, either as first line therapy (31.4%), post-surgery (25.7%) or in combination with dopamine-agonists (DA) (20%) or pegvisomant (15.7%). The use of SSA in diabetic patients is common clinical practice for Italian endocrinologists. Only 5 (7.1%) patients had been treated by surgery alone, without other treatments in the follow-up period. In the study group no patients were treated with pegvisomant alone (Table 1). Of the 11 cases treated with pegvisomant, 7 had been previously treated with surgery.

Several different treatments were used for DM. Most patients were treated with metformin (65.7%), either alone (41.4%), in combination with other oral hypoglycemic drugs (OHD) (15.7%) or insulin (2.9%) or in association with both hypoglycemic drugs and insulin (5.7%). After metformin, the most frequently used therapy was insulin (21.5%), alone (10% of cases) or associated with metformin and/or other hypoglycemic drugs (11.5% of subjects). Eleven patients (15.7%) were treated only with diet (Table 1). Other than metformin, oral hypoglycemic drugs used in this cohort included sulfonylureas and glinides, whereas no other class of drugs for diabetes such as insulin sensitizers (thiazolidinediones), α-glucosidase inhibitors, glucagon-like peptide-1 (GLP-1) analogs or dipeptidyl peptidase (DPP-IV) inhibitors were used.

Metabolic control of acromegalic patients with diabetes

The whole group showed a very good control of acromegaly and diabetes. Median IGF-I was 202 ng/ml (interquartile range 144.5-335.5), with 64% of the patients showing IGF-I levels within the normal range for their age group. Fasting median glycemia was 120.5 mg/dl (interquartile range 102-140.75) and median HbA_{1c} was 6.4% (interquartile range 5.9-7). No relation was observed between the duration of acromegaly and diabetes and metabolic control (all *p*=ns, data not shown).

This good control was confirmed also when patients were stratified on the basis of their treatments for acromegaly and for diabetes (Table 2). None of the treatment for acromegaly showed a significant difference from the others. On average, 70% of acromegalic patients achieved a good control (HbA_{1c}<7%) of their diabetes in any treatment group. Moreover, when we looked at possible differences in glucose control between different dosages we did not observe significant changes (data not shown). When we looked at the percentage of patients that achieved a good metabolic control (HbA_{1c}<7%) according to type of SSA, we did not observe any difference between subjects treated with octreotide (HbA_{1c}=6.17%; 5.87-6.92) *vs* lanreotide (HbA_{1c} =7.0%: 6.0-7.1). In both these groups in subjects with HbA_{1c}<7% metformin was

Table 1 - *Treatments for acromegaly and diabetes mellitus in the study group.*

Therapy of acromegaly			Therapy of diabetes mellitus		
Treatment	No.	%	Treatment	No.	%
Surgery only	5	7.1	Diet only	11	15.7
SSA only	22	31.4	Met only	29	41.4
Surgery+SSA	18	25.7	Insulin only	7	10
SSA+DA	14	20	OHD	4	5.7
SSA+peg	11	15.7	OHD+met	11	15.7
			Met+insulin	2	2.9
			OHD+met+insulin	4	5.7
			OHD+insulin	2	2.9
Total	70	100	Total	70	100

SSA: somatostatin analogs; DA: dopamine agonists; peg: pegvisomant; met: metformin; OHD: oral hypoglycemic drugs.

Table 2 - *Metabolic control of acromegaly and diabetes on the basis of treatments.*

	Therapy of acromegaly				Therapy of diabetes mellitus		
Treatment	IGF-I	FPG	HbA_{1c}	Treatment	IGF-I	FPG*	HbA_{1c}*
Surgery only (no.=5)	193 (106-197)	113 (99-166)	6.7 (6-9.4)	Diet only (no.=11)	196 (123-370)	98 (91-127)	6.1 (5.9-6.7)
SSA only (no.=22)	181 (137-300)	117 (98-156)	6.3 (5.9-7)	Met only (no.=29)	226 (146-341)	117 (105-132)	6.2 (5.8-6.5)
Surgery+SSA (no.=18)	198 (159-283)	124 (101-136)	6.3 (5.9-7)	Insulin only (no.=7)	257 (177-319)	140 (102-213)	7 (6-8.7)
SSA+DA (no.=14)	318 (198-439)	124 (97-139)	6.4 (5.9-7)	OHD (no.=4)	155 (141-193)	127 (101-159)	7 (6.1-8.3)
SSA+peg (no.=11)	243 (177-476)	126 (110-152)	6.5 (5.8-7.4)	OHD+met (no.=11)	228 (141-347)	130 (108-167)	6.6 (5.9-7.2)
				Met+insulin (no.=2)	263 (84-442)	126 (121-132)	7.4 (7.4-7.4)
				OHD+met+insulin (no.=4)	214 (114-810)	221 (103-368)	7.2 (6.7-7.5)
				OHD+insulin (no.=2)	337 (198-476)	135 (135-135)	7.4 (7-7.9)
p	ns	ns	ns	*p*	ns	ns	<0.046

Results are expressed as medians (interquartile range). Multiple comparisons were performed by Kruskal-Wallis Test. SSA: somatostatin analogs; DA: dopamine agonists; peg: pegvisomant; met: metformin; OHD: oral hypoglycemic drugs; FPG: fasting plasma glycemia; HbA_{1c}: glycosylated hemoglobin. *HbA_{1c} $p<0.004$ and FPG $p<0.038$ for treatment with insulin (alone or in combination) *vs* no insulin (diet and/or OHD and/or metformin).

the most used therapy, alone (54.3%) or in combination with OHD (22%), followed by insulin (12%). When patients in combined therapy (SSA + pegvisomant) were compared to patients in SSA only there were no significant differences in mean HbA_{1c} (6.3%, range 5.9-7 in SSA + pegvisomant *vs* 6.5%, range 5.85-7.42 SSA only). Again metrformin, alone or in combination, was used in 70% of the subjects achieving HbA_{1c}<7%.The use of insulin was higher in patients in combined SSA + pegvisomant therapy (54%) compared to SSA only (18.2%), although this difference was not significant.

In those patient achieving a safe GH concentration (<2.5 µg/l according to (16), we did not observe any difference in median HbA_{1c} compared to subject with a GH>2.5 µg/l. Also in these two groups the percentage of patients with a good metabolic control was similar (77 and 80%, respectively), and metformin alone or in combination was the most used treatment (72%) in patients with either GH <2.5 or >2.5 µg/l.

When patients were stratified according to normal or abnormal IGF-I concentrations, the percent of subject with a HbA_{1c}<7% was similar between the two groups (75% and 78.9%, respectively, *p*=ns). Also mean HbA_{1c} was not different between the two groups (6.1% range 5.8-7 and 6.5%, range 6.2-7, respectively). Finally, comparing patients who normalized both GH and IGF-I to those with one or both parameters in the abnormal range did not show any significant difference in either median HbA_{1c} (6.2% *vs* 6.4%) and percentage of well-controlled diabetes (73% and 80%, respectively).

A significant difference ($p<0.046$) in HbA_{1c} was only observed for diabetes treatments in a multiple comparison analysis. This difference was attributable to the patients treated with insulin, alone or in association with other hypoglycemic drugs. Indeed these patients showed a significantly higher HbA_{1c} (7%, range 6.4-7.7), when compared to patients treated without insulin (6.25, range 5.9-6.92; $p<0.004$). Also fasting glycemia was significantly different between the two treatment groups (135 mg/dl, range 109-213 with insulin; 117 mg/dl, range 98.5-137 without insulin; $p<0.038$). Patients treated with insulin had a significantly longer duration of diabetes, having 14 (9-19) years of disease compared to patients without insulin, who had 10 (7-15; $p<0.046$) years of diabetes. On the other hand, these groups were not different in their control of acromegaly (IGF-I 239, range 177-434, *vs* 200.5, range 140.75-334.75, *p*=ns) and in their duration of acromegaly (data not shown).

A possible influence on glucose control could be determined by glucocorticoid therapy. Only 7% (5/70) subjects were receiving glucocorticoids, but no difference could be found relative to glycemia, HbA_{1c}, GH, IGF-I, and all other metabolic parameters.

A further demonstration of the good metabolic control of these patients is in the prevalence of the diabetes complications nephropathy and retinopathy. Nephropathy was detected in less than 6% of the whole group. Of the 4 patients with nephropathy, 2 had macroalbuminuria. None of these patients had renal insufficiency, despite a high prevalence of hypertension (70%). Retinopathy was detected by fundus examination in 20% of the patients, but proliferative retinopathy was seen in only 2.9%.

With regards to the different treatments of acromegaly, as mentioned above only 5 (7.1%) patients in our cohort were not treated with SSA. It is therefore very difficult to evaluate the possible effects of SSA on metabolic control. As an indication, no differences were seen between SSA-treated *vs* non-treated in median glycemia, HbA_{1c} and IGF-I (all *p*=ns, data not shown).

Insulin-sensitivity and insulin secretion parameters in acromegalic patients with diabetes

To further evaluate insulin-sensitivity parameters (fasting insulin, HOMA-IR and HOMA-B%) in acromegalic patients affected by diabetes, we excluded the insulin treated pa-

Table 3 - *Insulin sensitivity and secretion parameters in acromegalic patients with diabetes on the basis of treatments for acromegaly.*

Treatment	Therapy of acromegaly		
	Insulin (μU/ml)	HOMA-IR	HOMA-B%
Surgery only (no.=4)	24.7 (16-29.5)	8.2 (6.8-8.6)	124 (36-181)
SSA only (no.=18)	12.3 (5.3-16.3)	2.9 (1.2-4.3)	85 (34-152)
Surgery+SSA (no.=15)	9.4 (6.6-15.1)	2.6 (1.7-4.8)	54 (50-85)
SSA+DA (no.=13)	16.9 (5.6-22)	5.5 (1.8-6.6)	99 (44-170)
SSA+peg (no.=5)	19.5 (14.4-21.5)	5.4 (3.6-6.9)	152 (68-214)
p	<0.019	<0.013	ns

Results are expressed as medians (interquartile range). Multiple comparisons were performed by Kruskal-Wallis Test. HOMA-IR: homeostasis model assessment for insulin resistance; HOMA-B%: homeostasis model assessment for beta cells secretion; SSA: somatostatin analogs; DA: dopamine agonists; peg: pegvisomant; met: metformin.

tients (no.=15). The whole group showed median insulin levels of 13.95 μU/ml (8-19), median HOMA-IR of 3.7 (2.15-6.33), median HOMA-B% of 83.6 (50-152.1).
When the group was stratified on the basis of treatments for acromegaly, there were significant differences in fasting insulin (p<0.019) and HOMA-IR (p<0.013). Notably, patients treated only with surgery (no.=4) showed higher insulin levels (24.7 μU/ml, range 16-29.5), when compared to all other patients treated with SSA (12.9 μU/ml, range 7.1-18.5; p<0.047). Beta-cell function (HOMA-B%), although not significant, showed the same trend (data not shown). Conversely, patients treated only with surgery had significantly higher HOMA-IR than all the other patients (8.2, range 6.8-8.6 *vs* 3.5, range 1.9-5.7). The addition of pegvisomant to SSA significantly increased insulinemia compared to all other therapies (SSA + dopamine-agonist and or surgery). Insulin levels were 19.5 μU/ml with SSA + pegvisomant (range 14.4-21.5) and 12.5 without (range 6.2-16.8; p<0.037). HOMA-B% followed the same trend, although it was not significant, and HOMA-IR was similar after the addition of pegvisomant (data not shown). Finally, both HOMA-IR and HOMA-B% did not show significant correlations with GH and IGF-I levels (data not shown)
Finally, when patients were analyzed according to their diabetes treatment, we observed no differences in parameters of insulin sensitivity (Fig. 1). Also, no differences were found when comparing patients in dietetic therapy to patients with any type of diabetes treatment. The patients in diet only had insulin levels of 17 μU/ml (3.8-26), HOMA-IR of 3.8 (0.9-6.6) and HOMA-B% of 154.2 (36.9-260), whereas in the drug-treated patients insulin was 12.9 μU/ml (8.2-18.5), HOMA-IR was 3.6 (2.2-6.3) and HOMA-B% was 83.5 (50.3-131.3) (p=ns for all comparisons) (Fig. 1).

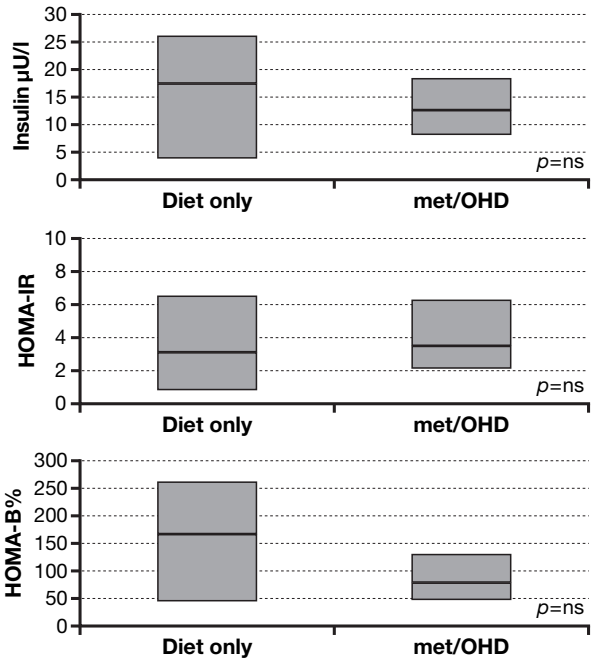

Fig. 1 - *Insulin sensitivity parameters in acromegalic patients with diabetes on the basis of different treatments for diabetes. Subjects with acromegaly were grouped into patients receiving diet only and patients treated with metformin (met) and/or oral hypoglycemic drugs (OHD) sulfonliureas and/or glinides or combinations of all). All comparisons were non-significant. HOMA-IR: homeostasis model assessment for insulin resistance; HOMA-B: homeostasis model assessment for β-cells secretion.*

DISCUSSION

Here we show that, in a large cohort of acromegalic patients with diabetes, metabolic control measured as fasting plasma glycemia and HbA_{1c} is near-normal (HbA_{1c} 6.4% in the whole group). This result is independent from the type of treatment for acromegaly, and from the duration of both acromegaly and diabetes. The only difference we observed was in the group of insulin-treated patients. This group of patients, which included those treated with insulin alone and/or in combination with OHD and/or metformin, showed a significantly higher mean HbA_{1c} (7% *vs* 6.2%, p<0.004) than patients without insulin therapy. These insulin-treated acromegalic patients were also those with a longer duration of diabetes. It is thus possible that they represent those long-standing diabetic patients who need insulin because of a worst metabolic control. On the other hand, the control of acromegaly in these patients was identical to that in patients without insulin, thus suggesting that acromegaly and its treatment were not a major factor in determining their worst glucose control.
The observation of a good metabolic control in acromegalic patients, regardless of their treatment for GH/IGF-I excess, has been previously reported for patients treated with pegvisomant (9), and, more recently, in a meta-analysis of patients treated with SSA (17). In our large cohort we confirm that, on average, acromegalic patients treated with surgery and/or SSA variably associated with DA and pegvisomant have near-normal HbA_{1c} and fasting plasma glucose. With regards to SSA, pre-

vious studies have reported a negative impact on insulin secretion (8, 18). We also observed this effect in our patients treated with SSA, who showed significantly lower fasting insulin levels and HOMA-B% compared to patients treated with surgery or receiving the addition of pegvisomant. Higher fasting insulin levels within the normal range (up to 19 μU/ml in the group treated with pegvisomant addition) could be advantageous for metabolic control. These SSA-only patients also had lower IR measured as HOMA-IR. Conversely, patients treated with surgery had higher insulin levels and worst insulin sensitivity, possibly because of the unopposed GH excess. These metabolic findings are expected, considering the known mechanism of action of SSA and pegvisomant (8, 9, 18-20). Some authors, in alternative, have hypothesized that the lower insulin levels and higher insulin sensitivity seen in SSA-treated patients reflect an improvement in IR as consequence of the control of acromegaly (10, 21). Our data are at variance with this hypothesis, since the control of IGF-I excess in our patients was acceptable independently of the type of treatment.

With regards to the type of treatment for diabetes, the vast majority of our patients were treated with metformin (alone in 41.4% of subjects, in association in 24.3%). The use of metformin as first-line therapy reflects a pathophysiological approach to diabetes in these patients, were GH excess determines increased IR. Second-line treatments were insulin or OHD, at similar percentages. Tiaziolidinediones were not used at all, and this probably reflects a particular attention in the choice of the treatment for diabetes, because of the high risk for heart failure and other cardiovascular diseases of these patients (1). Newer diabetes drugs, such as GLP-1 agonists and DPP4 inhibitors were not used in this patients. This because they have been available in Italy only recently, and have not been thoroughly studied in acromegalic patients.

Finally, we looked at diabetic complications in our study group, finding a low prevalence of nephropathy and retinopathy. Nephropathy was detected in less than 6% of the whole group, lower than that reported (19-26%) in the Italian diabetic population (22, 23). Retinopathy was detected in 20% of the patients, but proliferative retinopathy was seen in only 2.9%, again a prevalence lower than that reported in the Italian diabetic population (28.4 background and 6.2 proliferative) (24).

Our study has some limitations. All patients were recruited from those attending reference Centers for Acromegaly and Diabetes within University Hospitals, and this may constitute a selection bias. On the other hand, the great majority of these patients were very well controlled for both their acromegaly and diabetes, suggesting that referral to highly specialized Centers may be advantageous for these patients. Another limitation is that most of our patients were treated with SSA, thus limiting the possibility to perform some comparisons, but this is inevitable because of the central role of SSA in the treatment of acromegaly. Another question may arise from the fact that insulin sensitivity parameters were evaluated in patients treated with metformin and/or OHD, and OHD could indeed affect insulin secretion and/or insulin sensitivity. However, their actions appear negligible on these measures, since in our cohort patients treated only with diet showed the same insulin sensitivity parameters than patients treated with metformin and/or OHD. Finally, this is an observational non-controlled study with an inherent limitation due to the possibility that unknown confounding factors are not considered and examined. However, observational studies may complement, as it is in this case, previous randomized studies and meta-analyses, providing evidences from the clinical setting and daily medical practice.

In summary, our study shows that acromegalic patients with diabetes have a good metabolic control, independently from the type of treatment for GH excess. Our results confirm the known effects of SSA on insulin secretion, but these effects appear to be easily managed by a careful treatment of hyperglycemia. Also, the duration of both acromegaly and diabetes did not influence the achievement of a good metabolic control. In conclusion, although diabetes represents a major risk factor for complications in acromegalic patients, a good control of hyperglycemia can be obtained with good success in the majority of patients with a careful management of diabetes.

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