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TESI DI DOTTORATO DI RICERCA

PASIREOTIDE-INDUCED HYPERGLYCEMIA IN ACROMEGALY PATIENTS: EVALUATION OF PATHOPHISIOLOGICAL MECHANISMS AND EFFICACY OF ANTIDIABETIC TREATMENT

Relatore
Ch.ma Prof.
Annamaria Colao

Candidato
Ludovica F. S. Grasso

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1. INTRODUCTION

Acromegaly is a slowly progressive disease resulting from the increased release of growth hormone (GH) and, consequently, insulin- like growth factor I (IGF-I), which in most cases is induced by a GH- secreting pituitary tumor (1). Prolonged exposure to hormone excess induces progressive somatic disfigurement and a wide range of systemic manifestations, resulting in an increased mortality (2-5). To reduce morbidity and normalize life expectancy to that of the general population, the key treatment goals are to achieve and maintain control of GH and IGF-I levels, reduce or stabilize tumor volume, preserve pituitary function, and prevent recurrence (2). Acromegaly treatment approaches, which include surgery, radiotherapy and medical therapy, have changed considerably over time owing to improved surgical procedures, development of new radiotherapy techniques and availability of new medical therapies (1,6).

Medical therapy is currently an important treatment option and can even be the first-line treatment in patients with acromegaly who will not benefit from or are not suitable for first-line neurosurgical treatment (2). First-generation somatostatin analogs (SSA, octreotide long-acting release and lanreotide Autogel) are the first- line medical therapy in most patients with acromegaly (2). The biochemical control rate is ~55% for

patients treated with first-generation SSA, although large differences in the hormonal efficacy of SSA between different case series have been reported (7,8). Moreover, first-generation SSA induce tumor shrinkage in up to 80% of patients, and the reduction in tumor volume is greater when SSA are used as first- line therapy (9,10). However, despite the clinical success of first-generation SSA in the treatment of acromegaly, approximately half of patients remain inadequately controlled, resulting exposed to the deleterious effects of hormone hypersecretion, increasing mortality risk (11-19). Alternative medical therapies are available, including dopamine agonists (DAs) and the GH receptor antagonist pegvisomant (PEG, 2). DAs have a limited role in acromegaly and are mostly used as a first-line medical therapy in patients with mildly elevated GH and IGF-I levels or are used in combination with first-generation SSA in patients who are partially resistant to SSA, being effective in ~35% of patients (2,20,21). PEG is indicated after surgery failure and/or resistance to first-generation SSA treatment, either as a monotherapy or in combination with SSA, with IGF-I levels being normalized by PEG therapy in roughly 60-97% of patients (22-25). However, PEG does not reduce GH levels and tumor volume. Thus, alternative therapeutic options are needed. The second-generation SSA pasireotide-LAR (PAS) represents the last approved medical therapy in

acromegaly. PAS, a multireceptor-targeted somatostatin analog, has a high binding affinity for SSTR1, 2, 3, and 5 (exhibiting a 39-fold higher binding affinity for SSTR5 compared with octreotide, 26), with more profound suppression of GH and IGF-I than octreotide (27,28). PAS have been approved by both the Food and Drug Administration and the European Medicines Agency in 2014 for the treatment of acromegaly when surgery is unsuccessful or is not an option and when treatment with first- generation SSA is not effective in controlling acromegaly, especially in patients with clinically relevant residual tumor and/or clinical concern of tumor growth (6,29). In a randomized, Phase III study in medically naive patients with acromegaly (30), PAS demonstrated superior efficacy in achieving biochemical control over octreotide LAR. More recently, in the PAOLA study (31), PAS provided superior efficacy versus continued treatment with first-generation SSA octreotide LAR or lanreotide Autogel (control group) in patients with inadequately controlled acromegaly. Furthermore, a >25% reduction in tumor volume occurred in more patients receiving PAS than in patients receiving first-generation SSA (31). Thus, PAS is a valid new treatment option for patients with acromegaly, especially those who are resistant to first- generation SSA(1,29). In both studies (30,31), the safety profile of PAS was generally similar to that of first-generation SSA, except for a

higher frequency and degree of hyperglycemia. In the PAOLA study (31), all grade hyperglycemia-related adverse events were reported in 67% of patients on PAS 40 mg, 61% of patients on PAS 60 mg, and in 30% of patients on first-generation SSA, whereas diabetes mellitus (DM) was reported in 21%, 26% and 8% of patients, respectively. However, knowledge about pathophysiology of PAS-induced hyperglycemia is still matter of debate. The mechanism of PAS-induced hyperglycaemia has been explored in two studies (32,33) conducted in healthy human volunteers. These investigations have demonstrated that PAS acts on the incretin system, known to modulate insulin secretion, as it inhibits insulin secretion simultaneously with the decrease in glucagon, glucagon-like peptide 1 (GLP-1), and glucose-dependent insulinotropic polypeptide (GIP) secretion. However, pathophysiological effects of pasireotide on glucose metabolism are yet to be completely elucidated, and consensus on the best management of PAS-induced hyperglycemia in acromegalic patients has still to be defined.

2. **AIM**

The current study aimed at:

1. Investigating the effects of long-term PAS treatment on glucose metabolism, besides GH and IGF-I control, by evaluating the clinical management of hyperglycemia adverse events in acromegalic patients participating to the PAOLA study, followed in two Italian referral Centers (University Federico II of Naples, Università Cattolica del Sacro Cuore, Rome).
2. Investigating the role of metabolic parameters (weight, BMI, fasting glucose and HbA1c levels) and markers of disease activity (GH, IGF-I, duration of PAS treatment) as potential predictors of hyperglycemia development.

3. PATIENTS AND METHODS

3.1. Patients

The current study considered male and female patients aged 18 years or older with inadequately controlled acromegaly, defined as five-point, 2 h mean GH concentration >2.5 μg/L and IGF-1 concentration >1. 3 times the sex-adjusted and age adjusted upper normal limit, as per protocol (31). Eligible patients had received either 30 mg octreotide LAR or 120 mg lanreotide Autogel as monotherapy continuously for 6 months or longer before screening (31). Patients who had received combination therapy with a PEG or DAs were eligible, but these drugs had to be discontinued at least 8 weeks before screening (31). Patients could have received previous pituitary surgery (31).

The exclusion criteria (31) were the following:

– Patients with compression of the optic chiasm causing acute clinically significant visual field defects.

– No pituitary irradiation within the last 10 years.

– Patients with poorly controlled diabetes mellitus (HbA1C > 8%).

– Patients treated for < 6 months with PAS.

The study was done in accordance with the Declaration of Helsinki, and an independent ethics committee or institutional review board for each

study site approved the study protocol. All patients provided written informed consent prior to study participation.

3.2. Study design

The current is a prospective, multicenter, randomized, parallel-group, phase 3 study (31). After a 4-week screening period, patients were randomized to receive double blind PAS 40 mg every 28 days for 24 weeks, or double-blind PAS 60 mg every 28 days for 24 weeks (group 1), or to continue on the same treatment with open label octreotide LAR 30 mg or lanreotide Autogel 120 mg every 28 days for 24 weeks (group 2). Transient dose decreases were permitted for tolerability issues in all treatment arms (31).

All patients who completed the 6-month treatment (core study) were eligible to participate in the extension phase, except for patients who achieved biochemical control in the open-label active control arm (31). All patients in the active control group who remained uncontrolled at week 24 had the opportunity to switch to PAS in the extension phase (31).

For the current study primary objectives were to assess changes in glucose homeostasis biomarkers (fasting plasma glucose [FPG] and HbA1c) during long-term (mean time 34 months) treatment with PAS,

regardless from PAS dose, and the management of hyperglycemia-related adverse events. As for the Paola study (31), the secondary endpoint was the proportion of patients achieving biochemical control, defined as GH< 2.5 μg/L and normalization of sex- and age-adjusted IGF-I during long-term treatment, regardless from PAS dose.

3.3 Biochemical assessments

Blood samples for assessment of total IGF-I were taken at the same visits as for the assessment of mean GH level, before the administration of study drug. Samples were analyzed as follows: GH was assessed as the mean of an average of five individual measurements taken pre-dose at 0, 30, 60, 90, and 120 min within a 2-h time period after 1 h at rest at the hospital and was measured using the Siemens Immulite 2000 S/N 1832 assay by a central contract research organization (Quest Diagnostics Clinical Trials, Valencia, CA, USA). IGF-1 were analysed from individual serum samples using the Siemens Immulite 2000 S/N 1832 IGF-1 assay (Quest Diagnostics Clinical Trials, Valencia, CA, USA); FPG and HbA1c were centrally analyzed (Quest Diagnostics Clinical Trials, Valencia, CA, USA) by spectrophotometry using an Olympus AU 640/2700/5400 analyser and by high-performance liquid chromatography (HPLC) using a TOSOH G7/G8 automated HPLC analyser, respectively. Analyses

were conducted on patients who had available samples. Hyperglycaemia was defined as one post-baseline FPG measurement of >100 mg/dL or necessity of antidiabetic medication at any time during this study. Impaired fasting glucose (IFG) was defined as fasting glucose levels > 100 mg/dl, impaired glucose tolerance (IGT) was defined as glucose levels of 140 to 199 mg/dL after an oral glucose tolerance test (OGTT).

3.4. Statistical analyses

Data were analyzed using SPSS Software for Windows, version 20.0 (SPSS, Inc., Cary, NC package). Data are reported as Mean±SD, unless otherwise specified. The comparison between the numerical data before and after treatment with first-generation SSA and PAS was made by non-parametric Wilcoxon test. In each treatment arm, the comparison between the numerical data during treatment with first-generation SSA and PAS was made by non-parametric Friedman test corrected by Dunn test when necessary. The comparison between prevalence was performed by $\chi 2$ test corrected by Fisher exact test when necessary. The correlation study was done by calculating the Pearson's correlation coefficients. Regression analysis was done to evaluate the association of PAS-induced hyperglycemia adverse events with metabolic profile and/or with hormonal levels. Significance was set at 5%.

4. RESULTS

4.1. Baseline

A total of 31 patients entered the present study, including 18 randomized to PAS (group 1), and 13 to continued treatment with octreotide LAR 30 mg or lanreotide Autogel 120 mg (group 2). *Table 1* shows patient demographics characteristics, and disease history at baseline. Twelve patients (61%) in group 1 and nine (69%) in group 2 had previously received surgery (p=0.93). Pre-existing diabetes mellitus was found in five patients (27.7%) in group 1 and one (7.7%) in group 2 (p=0.34), whereas pre-existing prediabetes, defined as IGT or IFG, was seen in one patients (5.5%, IGT) in group 1 and in three patients (23.1%, 2 IGT, 1 IFG) in group 2 (p=0.34).

4.2. Primary objective

Changes in glycemic metabolism

Patients were treated with PAS for a mean time of 34 months (6-67 months). In group 1, mean FPG and HbA_{1c} concentrations significantly increased (p=0.005) after 6 months of treatment, at the end of the core phase, further increasing until the last follow-up (p=0.0005). In group 2, mean FPG and HbA1c concentrations remained similar to that of the baseline levels in the core phase, but they significantly increased in the

extension phase at 6 months of PAS treatment (p=0.005), further augmenting until the last follow-up (p=0.005, *figure 1*).

Hyperglycemia-related adverse events were reported in 15 patients (83.3%) in group 1, occurring after a mean time of 5 months (1-16 months); all cases were of mild-to-moderate severity, defined as grade 2-3. In all patients hyperglycemia-related adverse events were judged to be related to study drug. One patient required treatment discontinuation because of diabetes adverse event. Four out five patients with diabetes mellitus at baseline (80%) reported worsening of hyperglycemia during PAS treatment. One patient with IGT at baseline (100%) developed overt diabetes mellitus. Six (50%) and four (33.3%) patients with normal glucose tolerance at baseline developed IFG and diabetes mellitus, respectively, during PAS treatment. In group 2, three (23%) patients reported hyperglycemia-related adverse events during the core phase (during first-generation SSA therapy), after a mean time of two months. Particularly, overt diabetes mellitus occurred in two patients (15.3%) with baseline normal glucose tolerance and in one patient (7.7%) with IGT at baseline. All cases were of mild severity, defined as grade 1. During the extension phase, nine patients (69.2%) reported hyperglycemia-related adverse events after a mean time of seven months (2-17 months) from the beginning of PAS treatment. One diabetic

patient (33.3%) reported worsening hyperglycemia. Among patients with normal glucose tolerance at baseline, three (16.6%) developed pre-diabetes (2 IFG, 1 IGT), and two patients (15.3%) developed overt diabetes mellitus during PAS treatment. All cases were of mild-to-moderate severity, defined as grade 2-3, and were judged to be related to study drug. No patient required treatment discontinuation because of hyperglycemia adverse event. *Table 2* shows hyperglycemia related adverse events according to baseline diabetic status.

The risk to develop hyperglycemia correlated neither with baseline BMI, weight, GH, IGF-I, glucose and HbA1c levels, or duration of PAS treatment ($p=0.41$). Similarly, glucose status did not significantly correlate with biochemical control at the last follow-up ($p=0.66$).

Effect of antidiabetic drugs on glucose control

At study entry, three patients (16.6%) in group 1 and one patient (7.7%) in group 2 were already treated with antidiabetic drugs. In group 1, starting of new antidiabetic treatment was required in eight patients (44.4 %, *figure 2*) throughout the study, and metformin was the drug of choice in all these patients. Four (50%) out eight patients did not control glucose and HbA1c levels despite metformin monotherapy, needing further therapies. In fact, metformin was associated with DPP-4 inhibitor in one patient (25%), GLP-1 agonist in two patients (50%), and

GLP-1 agonist and glargine insulin in one patient (25%) to control hyperglycemia. Two patients previously treated with antidiabetic drugs (1 patient with metfomin plus glargine insulin, and 1 patient with glargine insulin monotherapy) needed a dose adjustment to control hyperglycemia. In group 2, one patient (7.7%) started metformin during the core phase. During the extension phase, starting of new antidiabetic treatment was required in seven patients (53.8%), and metformin was the drug of choice in all these patients. Three (42.8%) out seven patients did not control glucose and HbA1c levels despite metformin monotherapy, requiring further therapies. In fact, metformin was associated with DPP-4 inhibitor in one patient (33.3%), GLP-1 agonist in two patients (33.3%), and GLP-1 agonist and detemir insulin in one patient (33.3%) to control hyperglycemia. *Figure 3* shows the antidiabetic drugs used during the long-term treatment in group 1 and group 2, respectively.

4.3. Secondary objective

Biochemical control

Biochemical control, defined as 5-point, 2 h mean growth hormone concentration less than 2.5 μg/L and normalized IGF-I concentrations, was achieved by nine patients (50%) in group 1 at 6 months, compared with no patients in group 2 (p=0.009). Eight patients (44.4%) in group 1

and five (38.4%) in group 2 achieved biochemical control, respectively, after 12 months of treatment (p=0.97), whereas nine (50%) and seven (53.8%) patients in group 1 and group 2, respectively, achieved biochemical control at the last follow-up (mean time 34 months, p=0.84, *figure 4*). In group 1, mean GH concentrations significantly decreased from baseline to month 6 ($p<0.0005$) and month 12 ($p<0.005$) and remained stable until the last follow-up. Mean IGF-I concentration significantly decreased from baseline to month 6 ($p<0.005$) and remained stable at 12 months until the last follow-up. In group 2, mean GH and IGF-I concentrations slightly but not significantly decreased during the core phase. During the extension phase, mean GH and IGF-I concentration significantly decrease from baseline to month 12 ($p<0.005$), further decreasing until the last follow-up ($p<0.0005$, *figure 5*).

5. DISCUSSION

The present study first reports the long-term effect of PAS on glucose metabolism and biochemical control. Differently from the PAOLA study (31), where glucose homeostasis was relatively undisturbed throughout the treatment period in those patients receiving continued therapy with either octreotide LAR or lanreotide Autogel, in the present study a rapid initial increase in FPG and HbA1c levels was observed in all patients for

both treatment arms following the first 6 months of treatment with PAS, inducing a further increase over time, until the last follow-up. Hyperglycemia-related adverse effects were reported in 83.3% and 69.2% of patients during PAS therapy in group 1 and group 2, respectively. Conversely, in the PAOLA study (31) mean glucose and HbA1c levels were reported to initially increase rapidly after PAS treatment starting; subsequently glucose and HbA1c levels plateaued, remaining stable to 6 months. Consequently, the rate of hyperglycemia found in the current investigation was higher than that reported in the PAOLA study (31), where 67% of patients reported hyperglycemia-related adverse events. These findings may be explained considering the different treatment duration in the current study as compared to the Paola one (only 6 months of therapy with PAS), and hypothesizing long-term effects of PAS on glucose metabolism, since in the present study hyperglycemia-related adverse events occurred up to 17 months after PAS treatment starting.

Given the physiological role of natural somatostatin, as well as the SSTR binding profile of PAS (34), disturbances in glucose metabolism are not unexpected during treatment with PAS. Endocrine cells of the pancreas consist of α-, β-, and δ-cells, which secrete glucagon, insulin, and somatostatin, respectively, in response to changes in blood glucose (34).

Insulin and glucagon are antagonistic hormones that regulate glucose uptake and metabolism, while localized release of somatostatin suppresses secretion of insulin and glucagon (34). In humans, glucagon-producing α-cells predominantly express SSTR2 (35), whereas SSTR5 and SSTR2 are found mainly on insulin-producing β-cells (36). As PAS binds with higher affinity to SSTR5 than to SSTR2 (34), insulin secretion is substantially reduced while glucagon secretion is less markedly suppressed, resulting in an overall increase in glucose levels. Preclinical studies (37) showed that pasireotide and octreotide suppressed insulin secretion to a similar degree, whereas pasireotide was a weaker inhibitor of glucagon secretion than octreotide. Indeed, the SSTR5/SSTR2 activation ratio has been hypothesized to be the main driver of pasireotide-induced hyperglycemia (37). Interestingly, Schmid et al. (37) showed that co-administration of octreotide and pasireotide in rats negated the hyperglycemia seen with pasireotide alone, implying that strong activation of SSTR2 by octreotide was sufficient to restore normoglycemia. The mechanism of pasireotide-induced hyperglycemia has been further explored in two studies (32,33) conducted in healthy human volunteers. Henry *et al.* (32) reported that twice-daily subcutaneous pasireotide administration of 600 or 900 μg significantly decreased plasma levels of insulin, glucagon-like peptide 1 (GLP-1), and

glucose-dependent insulinotropic-polypeptide. Glucagon secretion was only minimally affected, and insulin sensitivity was unaffected. In the second study (33), the incretin-based antihyperglycemic agents liraglutide (GLP-1 agonist) and vildagliptin (DPP-4 inhibitor) were shown to effectively ameliorate hyperglycaemia when co-administered with pasireotide. Taken together with the aforementioned studies, the role of the incretin system affecting insulin secretion is strongly implicated in the mechanism of action of pasireotide.

The results of the present study confirm the direct effect of PAS in inducing hyperglycemia, independently from patients baseline characteristics and disease control. In particular, the risk to develop hyperglycemia resulted not significantly related either to baseline BMI, weight, GH, IGF-I, glucose and HbA1c levels, or duration of PAS treatment. Similarly, glucose status did not significantly correlate with biochemical control at the last follow-up. In contrast, a recent study by Schmid *et al.* (38) investigating the mechanism of action of PAS in 198 patients who completed the PAOLA study, has reported that patients with baseline FPG >100 mg/dL experienced higher levels of FPG and HbA1c after treatment with PAS, compared with those with normoglycemia at baseline, supporting the hypothesis of baseline glucose status as a potential predictive factor for the development of

hyperglycemia during PAS treatment. The inconsistency between findings from results of the current study and those of the study by Schmid (38) can be attributable to the smaller number of patients analyzed in the present study.

In the present study, 44.4% in group 1 and 53.8% of patients in group 2, respectively, required to start antidiabetic drugs during PAS treatment, and metformin was the treatment of choice in all these patients. In patients not adequately controlled by metformin monotherapy, DPP-4 inhibitors and GLP-1 agonists were administered to control hyperglycemia, followed by insulin. Similar findings have been recently reported (39) in a sub-analysis of the phase III, randomized study in medically naive patients with acromegaly (30), evaluating patients treated with PAS who started antidiabetic medication during the study. Metformin was the most commonly initiated antidiabetic medication during the study, in line with its role as first-line medical therapy for glycemic management. Metformin monotherapy (n= 24) or in combination with other oral antidiabetic medication (n= 19) was found to be effective in controlling hyperglycemia-related adverse events (39). Although metformin exerts its therapeutic effect mainly by reducing hepatic glucose production, it also reduces DPP-4 activity and increases GLP-1 secretion (40), resulting the best choice in patients with PAS-

induced hyperglycemia. Moreover, a previous study (33) conducted in healthy male volunteers evaluated various strategies for managing PAS-induced hyperglycemia. Ninety volunteers were randomized to receive either pasireotide s.c. alone or in combination with metformin, nateglinide (meglitinide), vildagliptin (DPP-4 inhibitor), or liraglutide (GLP-1 agonist) for 7 days. On Day 7, the glucose area under the curve increased by 69% from baseline in the pasireotide -only group. The increase from baseline was substantially lower in the groups that were concomitantly treated with metformin (60%), nateglinide (49%), vildagliptin (38%), and liraglutide (19%), indicating that GLP-1 agonists and DPP-4 inhibitors might be the most viable antidiabetic agents to co-administer with pasireotide in order to manage PAS-induced hyperglycemia in patients not controlled by metformin monotherapy (33). A recent study (41) on patients receiving PAS for medical treatment of Cushing's disease has investigated the best management of PAS-induced hyperglycemia, and has suggested to administer treatment with metformin as early as possible after occurrence of hyperglycemia and, if not controlled on metformin, with DPP-4 inhibitor or GLP-1 agonist, keeping therapy with insulin in patients experiencing the failure of oral antidiabetic drugs. On the basis of the association between PAS and hyperglycemia, these recommendations could also be applicable to

patients with acromegaly, even though further studies are needed to determine the best management for hyperglycemia in acromegalic patients.

The therapeutic approach for diabetes mellitus used in the present study confirm that PAS-induced hyperglycemia is correctly managed in clinical practice in the two Italian referral centers participating to the current study. Moreover, approximately half of patients treated with PAS did not receive antidiabetic medication at any time during this study, therefore leading to the conclusion that a substantial proportion of patients with acromegaly do not experience disturbances in glucose homeostasis during PAS treatment so that to require the initiation of antidiabetic medication. Whether glucose response to PAS treatment can be predicted is still matter of debate. Besides FPG at baseline, other clinical and metabolic parameters, such as patient age and sex, disease duration, previous medical or surgical treatment, gonadal status, and other concomitant metabolic or cardiovascular complications, might play a role as modulator of glucose profile during PAS treatment, and further studies are required to better elucidate the burden of such factors as predictors of glycaemic homeostasis while on PAS therapy.

Altogether, the results of these studies suggest that blood glucose concentrations should be closely monitored in patients treated with PAS and that antidiabetic treatment should be promptly initiated.

The secondary endpoint of the present study was the proportion of patients achieving biochemical control, defined as GH< 2.5 μg/L and normalization of sex- and age-adjusted IGF-I during long-term treatment, as for the PAOLA study. In line with the results of the PAOLA study (31), the present study confirms the superior efficacy of PAS over continued treatment with first-generation SSA in controlling acromegaly up 67 months of treatment. In particular biochemical control at 6 months (core phase) was achieved in 50% of patients in group 1, compared with no patients in group 2. At 12 months (extension phase) 44.4 % of patients in group 1 and 38.4% of those in group 2 achieved biochemical control; the proportion raised up to 50% and 53.8% of patients in group 1 and group 2, respectively, at the last follow-up. The percentage of biochemical control reported in the present study resulted even higher than the PAOLA study (31), where 18% of patients were controlled after 6 months of treatment with PAS. This differences can be explained considering the longer treatment duration in the current study (mean 34 months) as compared to the PAOLA study (6 months),

therefore hypothesizing a progressive additive effect of PAS on GH and IGF-I normalization.

6. CONCLUSION

The results of the present study confirm the known negative effect of PAS on glucose metabolism, however treatment intensification with DPP4 inhibitor and GLP-1 agonist resulted in good glycemic control in most patients. Moreover, a considerable number of acromegaly patients resistant to first-generation SSA may benefit from treatment with monthly injections of PAS, since in this cohort over 50% of patients achieved long-term normalization of GH and IGF-I levels. Further studies are needed to deeply evaluate the mechanism of PAS-induced hyperglycemia in acromegalyc patients, investigating the effect of PAS on insulin secretion and hepatic/peripheral insulin sensitivity.

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9. TABLES AND FIGURES

	Group 1	Group 2	p
Patient n.	18	13	0.61
Age (years)	44.8 ±9.6	47.7 ± 11.1	0.44
Previous surgery	12 (61%)	9 (69%)	0.55
Baseline GH (ug/L)	22.4 ± 47.7	12.04 ± 23.5	0.55
Baseline IGF-I (ng/ml)	540.2±218.5	696.9±320.5	0.61
Baseline fasting glucose (mg/dl)	104±32	102±10	0.66
Baseline HbA1c	5.82±0.45	5.86±0.27	0.62

Table 1: Patients' profile at study entry. GH: growth hormone.

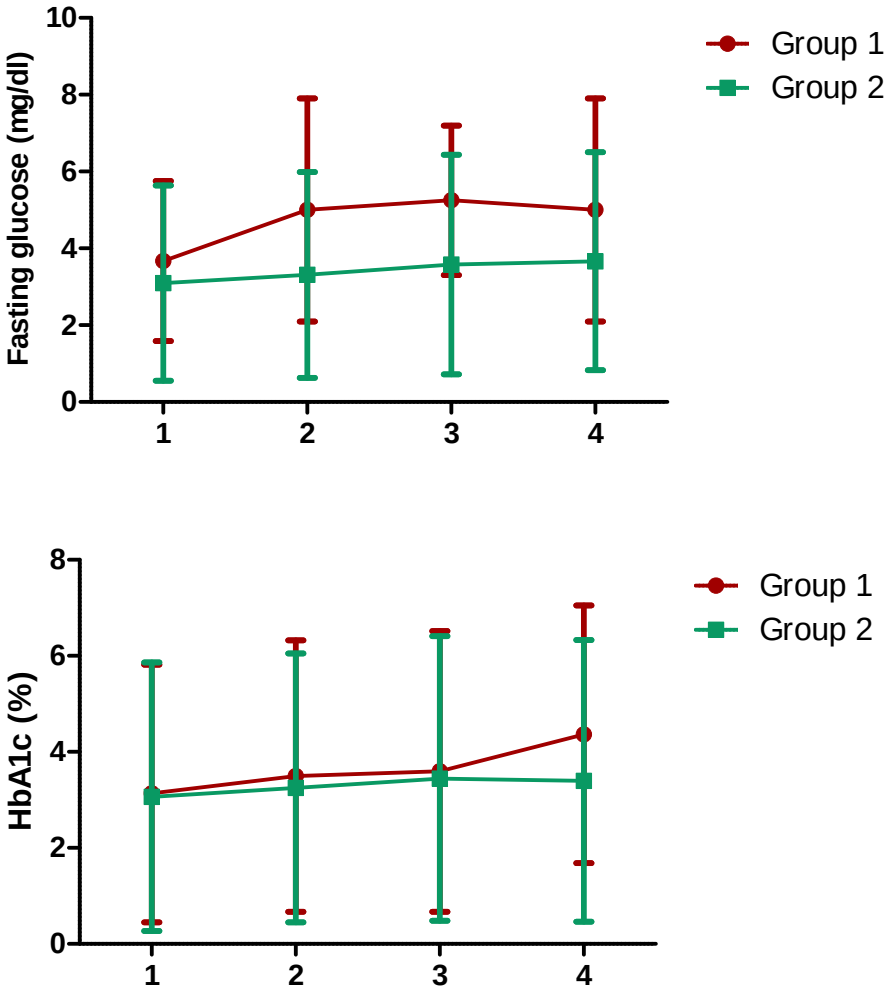


Figure 1: Fasting glucose and HbA1c levels modifications during long-term treatment in group 1 and group 2.

GROUP 1	BASELINE	LAST FU
NGT	12 (66.6%)	2 (11.1%)
Pre-DM	1 (5.5%)	6 (33.3%)
DM	5 (27.7%)	10 (55.5%)
GROUP 2	BASELINE	LAST FU
NGT	9 (69.2%)	2 (15.3%)
Pre-DM	3 (23.1%)	3 (23.1%)
DM	1 (7.7%)	8 (61.5%)

Table 2: Hyperglycemia-related adverse events according to baseline glycemic status.

NGT= normal glucose tolerance; DM= diabetes mellitus.

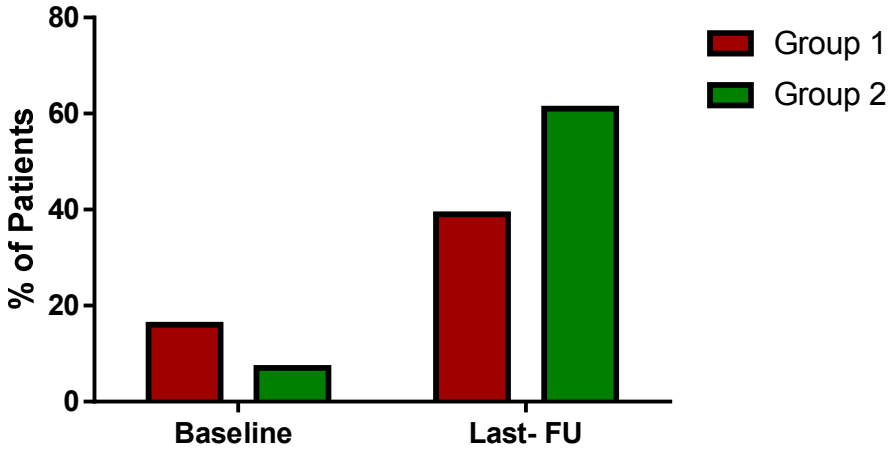
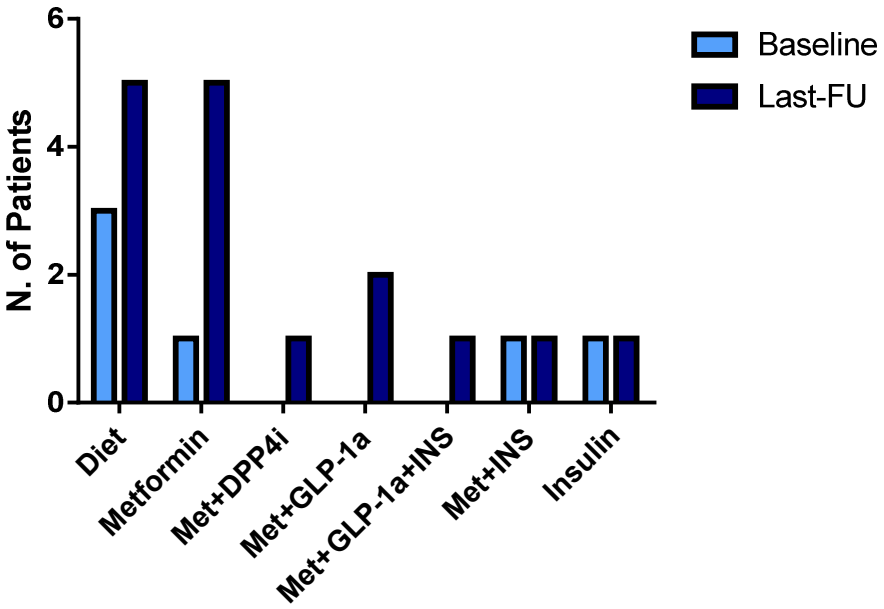
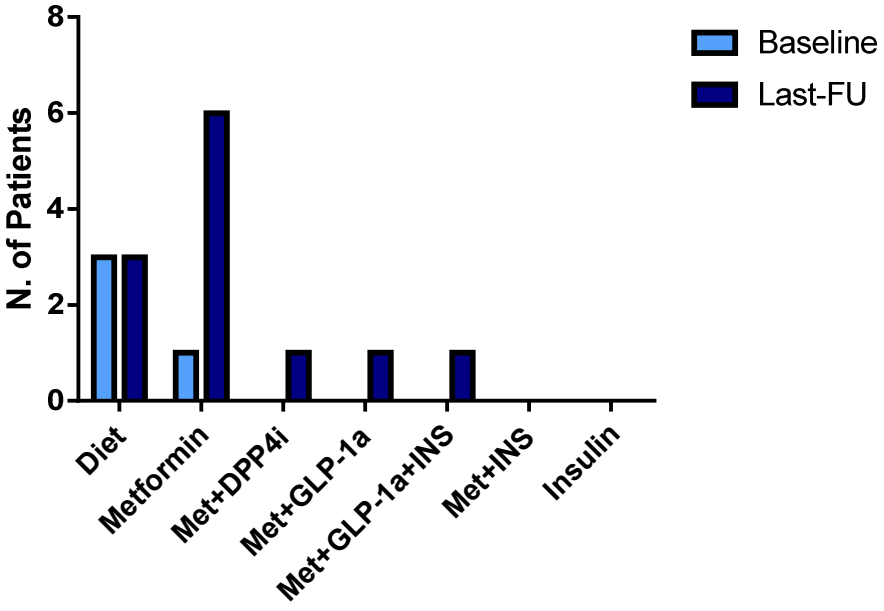


Figure 2: Percentage of patients treated with antidiabetic drugs in group 1 and group 2.



Group 1



Group 2

Figure 3: Antidiabetic drugs used during long-term treatment in group 1 and group 2.

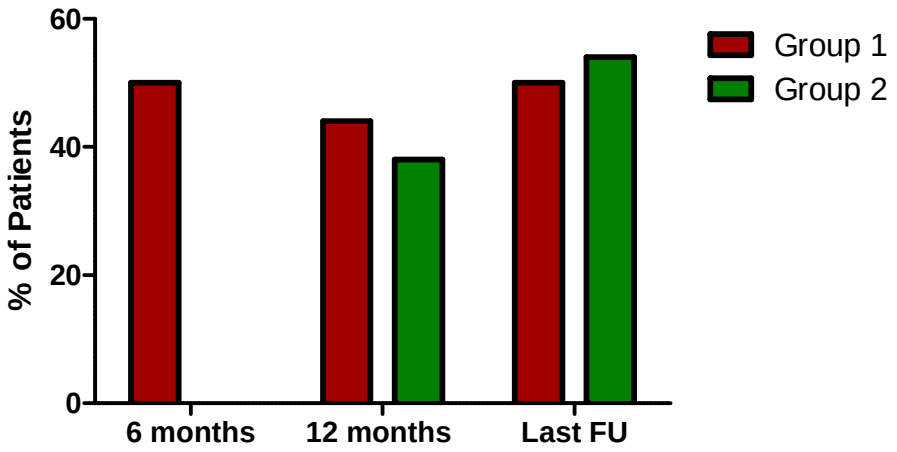


Figure 4: Percentage of patients achieving biochemical control (5-point, 2 h mean growth hormone concentration less than 2.5 μg/L and normalised IGF-I concentrations) during long-term treatment in group 1 and group 2.

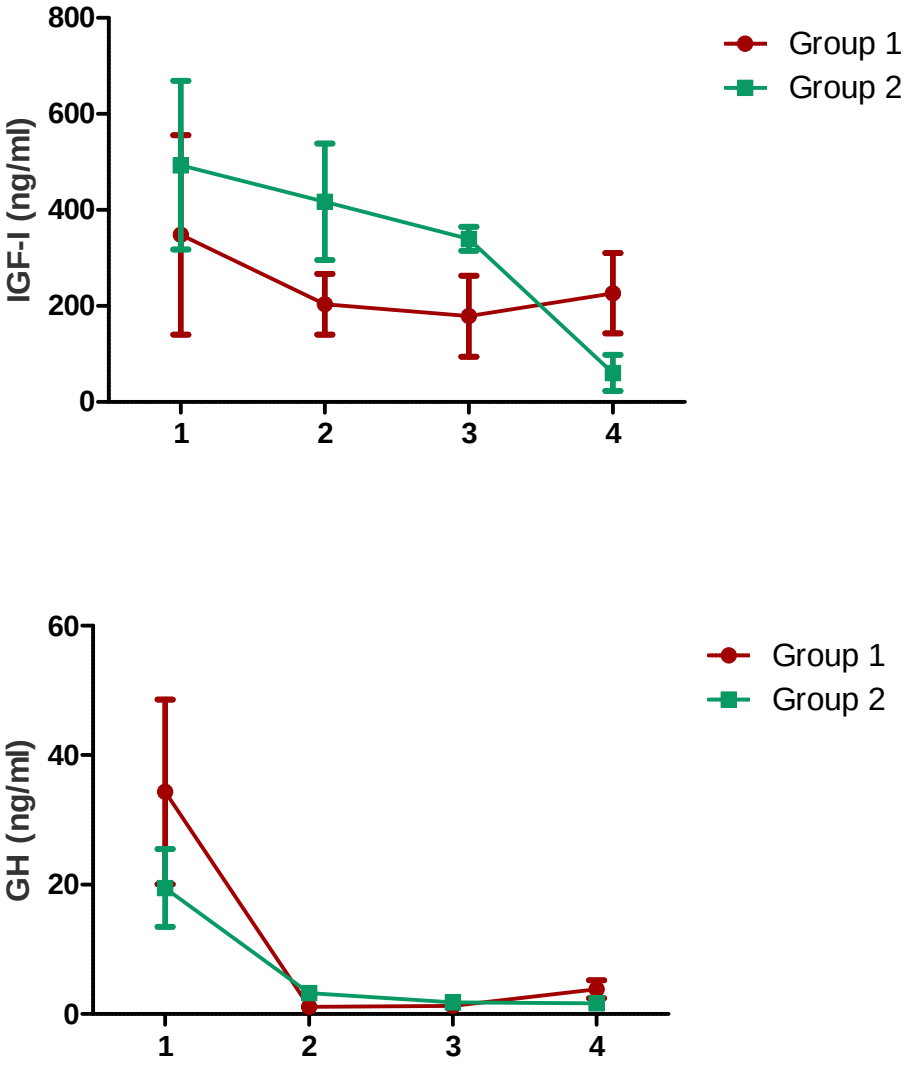


Figure 5: GH and IGF-I levels reduction during long-term treatment in group 1 and group 2.