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Low insulin resistance after surgery predicts poor GH suppression one year after complete resection for acromegaly: a retrospective study

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Abstract. Remission of acromegaly is defined as a nadir in GH <1.0 ng/mL during a 75-g oral glucose tolerance test (75gOGTT) and insulin-like growth factor-1 (IGF-1) normalization. Recently, a lower cut-off value for GH nadir (<0.4 ng/mL) has been proposed. We retrospectively evaluated the prevalence and clinical characteristics of postoperative cases with normalized IGF-1 levels and a GH nadir of 0.4–1.0 ng/mL one year after complete resection of GH-secreting pituitary adenoma (GHoma). We included 110 cases of acromegaly with complete adenoma resection, no preoperative treatment, preoperative glycosylated hemoglobin <6.5%, preoperative basal plasma glucose <126 mg/dL, GH nadir <1.0 ng/mL during a 75gOGTT, and normalized IGF-1 at the first postoperative year evaluation, whereupon patients were divided into two groups: control (GH nadir <0.4 ng/mL) and high GH (GH nadir >0.4 ng/mL). Clinical parameters, including measures of insulin secretion and resistance, were compared between groups. The high GH group included 10 patients (9.1%) and had a lesser level of insulin resistance immediately following surgery and at the first postoperative year evaluation. On single regression analysis, insulin resistance immediately following surgery was predictive of and correlated with the GH nadir at the first postoperative year evaluation. The GH nadir at the first postoperative year evaluation may be insufficient in patients with normalized IGF-1 with low insulin resistance immediately following complete resection of GHoma. Careful evaluation is needed to assess remission in such patients.

Key words: Acromegaly, Insulin sensitivity, Growth hormone, Pituitary gland

ACROMEGALY is typically caused by a benign growth hormone (GH)-secreting pituitary adenoma. GH stimulates target tissues to synthesize and secrete insulin-like growth factor-1 (IGF-1). Oversecretion of GH and IGF-1 increases the risk of various comorbidities (cardiovascular disease, diabetes, hypertension, malignancy) and reduces life expectancy [1-4]. Both random GH and IGF-1 levels correlate with mortality, but when the oversecretion of GH and IGF-1 is controlled, mortality is similar to that in the general population [5, 6]. Therefore, a major goal of acromegaly treatment is to control oversecretion of GH

and IGF-1. Transsphenoidal surgery is the treatment of choice for most microadenomas and some macroadenomas, as well as cases where the tumor is causing compression symptoms [7]. Especially in patients with microadenomas, complete surgical removal of GH-secreting pituitary adenoma results in reductions in GH and IGF-1, recovery of autonomous GH secretion, and preservation of normal pituitary function of other hormones.

In many cases of surgical treatment for acromegaly, optimal disease control is evaluated by means of 1) the nadir in GH levels during a 75-g oral glucose tolerance test (75gOGTT) and 2) IGF-1 levels adjusted for age and sex. In the Cortina criteria, control is defined as an age- and sex-adjusted normal range of IGF-1 levels and a GH nadir <1.0 ng/mL [8]. However, accumulating studies have reported that

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postoperative patients with active disease show elevated IGF-1 levels and a GH nadir <1.0 ng/mL [9–11]. In addition, some patients with active acromegaly were reported to have elevated IGF-1 levels and 24-h mean plasma GH levels within the normal range of healthy individuals [12]. Moreover, the availability of more sensitive GH assays has suggested the possible introduction of a cut-off value for disease remission approaching the GH nadir obtained in healthy subjects [13–16]. Therefore, in some guidelines, the cut-off value for the GH nadir was revised to 0.4 ng/mL [17]. Nevertheless, GH nadirs >0.4 ng/mL are found in some cases, despite successful complete resection of adenomas and normalization of age- and sex-adjusted IGF-1 levels. Furthermore, the adequacy of the conventional cut-off value (age- and sex-adjusted normal range of IGF-1 levels and GH nadir <1.0 ng/mL) has still been indicated in several subsequent studies [18–20].

Most of the discordance between the GH nadir and IGF-1 levels involves the measurement of a normalized GH nadir and elevated IGF-1 levels, with some cases exhibiting an elevated GH nadir and normalized IGF-1 levels. The factors responsible for this discordance have not been clearly identified. However, it is assumed that they might include factors such as sex, age, body mass index (BMI), or insulin resistance, in addition to the variability of GH and IGF-1 assays [19, 21, 22].

To better understand these factors, the first aim of this study was to evaluate clinical characteristics of patients with acromegaly who had a normal range of age- and sex-adjusted IGF-1 levels and a GH nadir of 0.4–1.0 ng/mL during a 75gOGTT one year after complete resection of pituitary adenomas. The second aim was to evaluate predictive factors of insufficient GH suppression one year after surgery.

Subjects and Methods

Japanese patients with acromegaly who received pituitary operations at Toranomon Hospital (Tokyo, Japan) between 2007 and 2013 were examined retrospectively. This study was approved by the institutional review board of Toranomon Hospital.

Clinical diagnosis was made based on physical symptoms, laboratory findings, 75gOGTT, and pituitary magnetic resonance imaging (MRI); definitive diagnosis was confirmed using a pathological evalua-

tion, including immunofluorescence staining for GH. After excluding patients with nutritional or gastrointestinal disorders such as chronic inflammatory bowel disorder and anorexia nervosa, hepatic or renal failure, or hypothyroidism as well as those using oral estrogens, we enrolled 110 patients (56 men and 54 women, aged 46.4 ± 12.9 years) who met the following criteria: preoperative glycosylated hemoglobin $<6.5\%$, fasting plasma glucose <126 mg/dL, normal range of age- and sex-adjusted IGF-1 levels one year after surgery, no preoperative treatment such as somatostatin analogs or dopamine antagonists, and complete tumor resection confirmed using MRI and operative and postoperative clinical findings.

Subjects were divided into two groups according to the GH nadir determined one year after surgery: the control group had a GH nadir <0.4 ng/mL ($n = 100$), and the high GH group had a GH nadir of 0.4–1.0 ng/mL ($n = 10$).

Data collection and measurement

Patients underwent a 75gOGTT and had serum IGF-1 measured three times: before, immediately after, and one year after surgery. Immediate postoperative evaluation was performed around 10 days after surgery (9.8 ± 2.6 days) and was not significantly different between groups (control: 9.8 ± 2.5 days, high: 8.9 ± 3.3 days, $p = 0.273$). After an overnight fast, a 75gOGTT was performed. Plasma glucose, serum GH, and insulin were evaluated at baseline and then at 30, 60, 90, and 120 min after oral glucose administration. The GH nadir was defined as the lowest GH value measured. Serum IGF-1 values were determined from baseline samples. We used the homeostatic model assessment (HOMA) model to estimate pancreatic β -cell function (HOMA-beta; $360 \times \text{fasting insulin } [\mu\text{U/mL}] / [\text{fasting plasma glucose (mg/dL)} - 63]$) and insulin resistance (HOMA-IR; $\text{fasting plasma glucose [mg/dL]} \times \text{fasting insulin } [\mu\text{U/mL}] / 405$, and Matsuda index; $10,000 / \text{square root of fasting glucose [mg/dL]} \times \text{fasting insulin } [\mu\text{U/mL]} \times \text{mean glucose [mg/dL]} \times \text{mean insulin } [\mu\text{U/mL}]$) [23, 24]. The insulinogenic index (IGI) is an OGTT-based estimate of early-phase insulin secretion, calculated as $(\text{insulin at 30 min} - \text{insulin at 0 min } [\mu\text{U/mL}]) / (\text{glucose at 30 min} - \text{glucose at 0 min [mg/dL]})$ [25] and as the incremental area under the insulin curve (AUC_{insulin}: the sum of insulin at 0, 30, 60, 90, and 120 min). Preoperative BMI and preoperative and immediate postoperative HOMA-IR, HOMA-

beta, IGI, AUCinsulin, and plasma glucose levels (0 min, peak level, and 120 min) were compared between groups. When comparing IGF-1 levels between groups, each serum IGF-1 value was transformed into an age- and sex-adjusted standardized curve (IGF-1 [SD]) score, based on a report regarding reference intervals of serum IGF-1 values in a healthy Japanese population [26].

Laboratory tests

Insulin levels were determined using a chemiluminescent enzyme immunoassay (LUMIPULSE Presto insulin, Fujirebio, Inc., Tokyo, Japan). Plasma glucose levels were determined using the hexokinase method (Liquitech Glucose HK Test, Roche Diagnostics K. K., Tokyo, Japan). GH levels were measured using a fluorescent enzyme immunoassay (ST AIA-PACK HGH, Tosoh Co., Tokyo, Japan), whose sensitivity was 0.07 ng/mL. Serum IGF-1 levels were measured using an immunoradiometric method (IGF1 IRMA Daiichi, TFB Co., Tokyo, Japan).

Statistical analysis

All variables were compared for significant differences between groups using the nonparametric Mann-Whitney U test. Differences in the prevalence between men and women were evaluated using the χ^2 test. Relationships were assessed using Pearson's correlation coefficient analysis. All statistical analyses were performed using R 3.1.0 statistical software (The R Foundation for Statistical Computing). A two-tailed p value <0.05 was considered significant.

Results

Characteristics of the high GH group

Table 1 shows the details of the GH nadir and IGF-1 (SD) of the high GH group. One patient (No. 7) had an IGF-1 (SD) of −2.2 one year after surgery that was included in the analysis because GH response after a 100-μg dose of GH-releasing peptide-2 (GHRP-2) was sufficiently reserved. The GHRP-2 loading test has already been validated and has been widely used in Japan as a simple diagnostic test to evaluate severe adult GH deficiency [27]. The peak GH level (22.4 ng/mL) was sufficiently higher than the cut-off value (9.0 ng/mL) to diagnose severe adult GH deficiency.

The comparison of parameters at the first postoperative year evaluation between groups is shown in Table 2. HOMA-IR and basal plasma glucose were significantly lower and Matsuda index tended to be higher in the high GH group. However, there was no significant difference between peak plasma glucose and plasma glucose at 120 min.

Changes in GH nadir and IGF-1 (SD)

Fig. 1 shows changes in the GH nadir and IGF-1 (SD) between the immediate postoperative evaluation and the evaluation at one year post-surgery. The high GH group comprised 4.2% of the “normalized GH nadir and IGF-1” pattern, 35.3% of the “high GH nadir and normalized IGF-1” pattern, and 14.3% of the “high GH nadir and high IGF-1” pattern. No patients showed change from a “normalized GH nadir and high IGF-1” pattern to the high GH group.

Table 1 Laboratory data for the patients with acromegaly who underwent pituitary operations in the high GH group (GH nadir, 0.4–1.0 ng/mL; n = 10)

No.	Age	Sex	Pre-operation		Immediate post-operation		One year post-surgery	
			GH nadir	IGF-1 (SD)	GH nadir	IGF-1 (SD)	GH nadir	IGF-1 (SD)
1	37	F	9.1	7.8	1.4	−0.2	0.6	0.3
2	28	M	22.7	4.8	1.6	0	0.8	−1
3	32	F	7.9	3.4	0.5	2.6	0.9	1.4
4	55	F	27.9	8.7	0.5	0.3	0.6	0.5
5	37	F	2.4	5.4	0.2	1.5	0.4	1.7
6	53	F	12.7	7.5	0.5	3.5	0.4	1.2
7	62	M	4.1	2.9	0.6	−0.1	0.4	−2.2
8	58	M	7.7	4.3	0.5	−0.7	0.7	−0.7
9	46	F	12.3	5.9	0.3	1.6	0.4	−1
10	65	M	3.2	2.6	0.8	0.2	0.5	−1

IGF-1 (SD), age- and sex-adjusted insulin-like growth factor-1 standardized curve score.

Table 2 Parameters at the first postoperative year evaluation

	Control group (GH nadir <0.4 ng/mL)	high GH group (GH nadir 0.4–1.0 ng/mL)	<i>p</i> score
n (women)	100 (48)	10 (6)	0.523
Baseline PG	94.1 ± 6.9 (81–113)	89.5 ± 7.0 (82–106)	<0.05
PG at 120 min	129.7 ± 27.1 (63–192)	129.3 ± 28.1 (94–177)	0.830
Peak PG	165.3 ± 27.4 (106–246)	166.1 ± 22.9 (140–212)	0.904
GH nadir	0.14 ± 0.07 (0.03–0.35)	0.57 ± 0.18 (0.40–0.90)	<0.05
IGF-1 (SD)	0.2 ± 1.0 (–1.9–2.0)	–0.1 ± 1.3 (–2.2–1.7)	0.519
HOMA-IR	1.10 ± 0.60 (0.21–4.32)	0.75 ± 0.44 (0.42–1.83)	<0.05
Matsuda index	8.72 ± 3.95 (2.30–27.18)	11.26 ± 4.25 (5.39–19.54)	0.060
HOMA-beta	54.7 ± 25.8 (7.5–153.0)	46.4 ± 15.8 (24.8–72.0)	0.414
IGI	0.58 ± 0.50 (–1.83–2.69)	0.58 ± 0.45 (0.14–1.56)	0.700
AUCinsulin	147.4 ± 70.2 (27.0–471.0)	126.3 ± 82.0 (53.0–334.0)	0.105

PG, plasma glucose (mg/dL); GH, growth hormone (ng/mL); IGF-1 (SD), age- and sex-adjusted insulin-like growth factor-1 standardized curve score; HOMA-IR, homeostatic model assessment of insulin resistance; HOMA-beta, homeostatic model assessment of β -cell function; IGI, insulinogenic index; AUCinsulin, area under the insulin curve (μ U/mL).

Fig. 1 Changes in the GH nadir and in the age- and sex-adjusted standard deviation score for serum insulin-like growth factor-1 between immediate post-surgery and one year post-surgery. M, men; W, women

Comparison of hormonal and metabolic parameters

Tables 3 and 4 show comparisons of preoperative and immediate postoperative parameters, respectively. Among preoperative parameters, there were no significant differences between groups, although HOMA-IR and IGF-1 (SD) tended to be lower in the high GH group (Table 3). On the other hand, among immediate postoperative parameters, parameters of insulin resistance were significantly different (HOMA-IR: 0.76 ± 0.19 [high GH group] and 1.05 ± 0.48 [control group], $p < 0.05$; Matsuda index: 9.68 ± 3.25 [high GH group] and 7.87 ± 3.75 [control group], $p < 0.05$), and all HOMA-IR values of patients in the high GH group were <1.01 (Table 4). In addition, in the high GH group, the GH nadir at the immediate postopera-

tive evaluation was significantly higher, while IGF-1 (SD) tended to be lower. However, no significant differences were found in parameters of glucose metabolism, including baseline plasma glucose, peak plasma glucose, and plasma glucose at 120 min. Although subjects were compared according to sex, there was no significant difference for any parameters.

Association between GH nadir and parameters of insulin resistance

The association between immediate postoperative HOMA-IR and GH nadir at one year post-surgery was evaluated in all subjects. The single regression analysis is shown in Table 5. The GH nadir correlated negatively with immediate postoperative HOMA-IR ($r =$

Table 3 Preoperative parameters

	Control group (GH nadir <0.4 ng/mL)	High GH group (GH nadir 0.4–1.0 ng/mL)	<i>p</i> score
n (women)	100 (48)	10 (6)	0.523
Age at operation (y)	46.1 ± 12.8 (18–76)	47.3 ± 13.1 (28–65)	0.751
BMI (kg/m ²)	23.4 ± 2.9 (18.5–36.2)	21.7 ± 3.0 (15.4–26.1)	0.160
HbA1c (%)	5.6 ± 0.3 (4.8–6.4)	5.7 ± 0.3 (5.1–6.2)	0.406
Baseline PG	99.2 ± 9.3 (68–123)	94.3 ± 7.8 (82–106)	0.421
PG at 120 min	145.9 ± 36.3 (84–250)	149.1 ± 41.9 (56–226)	0.765
Peak PG	188.4 ± 35.4 (100–285)	187.8 ± 31.8 (146–264)	0.505
GH nadir	9.10 ± 10.13 (0.23–80.39)	11.00 ± 8.40 (2.40–27.90)	0.341
IGF-1 (SD)	6.9 ± 2.2 (2.4–13.1)	5.3 ± 2.1 (2.6–8.7)	0.055
HOMA-IR	2.40 ± 1.74 (0.14–9.94)	1.51 ± 0.64 (0.74–2.72)	0.067
Matsuda index	4.64 ± 3.15 (1.03–18.81)	5.75 ± 2.86 (1.03–10.01)	0.175
HOMA-beta	94.0 ± 50.3 (3.5–298.5)	80.9 ± 49.6 (32.8–208.4)	0.310
IGI	0.89 ± 0.72 (–0.09–4.15)	0.80 ± 0.58 (0.16–1.64)	0.622
AUCinsulin	276.2 ± 133.1 (79.0–658.0)	271.0 ± 257.1 (79–867)	0.171

BMI, body mass index; HbA1c, glycosylated hemoglobin (%); PG, plasma glucose (mg/dL); GH, growth hormone (ng/mL); IGF-1 (SD), age- and sex-adjusted insulin-like growth factor-1 standardized curve score; HOMA-IR, homeostatic model assessment for insulin resistance; HOMA-beta, homeostatic model assessment of β -cell function; IGI, insulinogenic index; AUCinsulin, area under the insulin curve (μ U/mL).

Table 4 Immediate postoperative parameters

	Control group (GH nadir <0.4 ng/mL)	High GH group (GH nadir 0.4–1.0 ng/mL)	<i>p</i> score
n (women)	100 (48)	10 (6)	0.523
Baseline PG	84.2 ± 6.5 (70–99)	83.1 ± 8.6 (72–105)	0.421
PG at 120 min	128.5 ± 32.2 (62–210)	131.3 ± 45.2 (51–197)	0.765
Peak PG	163.0 ± 28.6 (122–245)	170.6 ± 33.8 (131–230)	0.505
GH nadir	0.28 ± 0.28 (0.10–1.90)	0.69 ± 0.46 (0.20–1.60)	<0.05
IGF-1 (SD)	1.8 ± 1.5 (–1.6–7.5)	0.9 ± 1.4 (–0.7–3.5)	0.054
HOMA-IR	1.05 ± 0.48 (0.21–2.99)	0.76 ± 0.19 (0.40–1.01)	<0.05
Matsuda index	7.87 ± 3.75 (2.57–24.57)	9.68 ± 3.25 (5.35–14.86)	<0.05
HOMA-beta	93.9 ± 48.5 (10.9–308.6)	76.2 ± 34.3 (25.7–138.5)	0.248
IGI	0.88 ± 0.86 (–0.25–5.42)	0.65 ± 0.76 (0.03–2.63)	0.213
AUCinsulin	194.6 ± 86.9 (28–491)	158.9 ± 81.5 (67–342)	0.157

PG, plasma glucose (mg/dL); GH, growth hormone (ng/mL); IGF-1 (SD), age- and sex-adjusted insulin-like growth factor-1 standardized curve score; HOMA-IR, homeostatic model assessment for insulin resistance; HOMA-beta, homeostatic model assessment of β -cell function; IGI, insulinogenic index; AUCinsulin, area under the insulin curve (μ U/mL).

Table 5 Single regression analysis for parameters of insulin resistance

	β	95% confidence interval	<i>t</i>	<i>p</i> value
Immediate postoperative HOMA-IR	–0.25	–0.34 to –0.15	–2.59	<0.05

Values were transformed into Z-scores. Model R^2 , 0.060.

HOMA-IR, homeostatic model assessment of insulin resistance.

–0.321, $p < 0.01$); in addition, immediate postoperative HOMA-IR was a significant predictor for the GH nadir at one year post-surgery in the multivariate linear regression analysis. After transformation into Z-scores, immediate postoperative HOMA-IR had a β -coefficient of –0.25 ($p < 0.05$). However, immediate postoperative Matsuda index was not significant as a predictor for the GH nadir at one year post-sur-

gery, although the GH nadir correlated positively with immediate postoperative Matsuda index ($r = 0.247$, $p < 0.01$).

Furthermore, this association between immediate postoperative HOMA-IR and GH nadir at one year post-surgery was also found only in the control group (correlation score: $r = -0.254$, $p < 0.02$, single regression analysis: β -coefficient = –0.09, $p < 0.05$).

Discussion

In our hospital, 84.7% of postoperative patients with acromegaly are in remission [28]. However, in a biochemical evaluation of clinically controlled postoperative patients with acromegaly, some patients showed normalized IGF-1 (SD) and a GH nadir between 0.4–1.0 ng/mL during a 75gOGTT. In contrast, the biochemical status of some postoperative patients changed upon follow-up. Espinosa-de-los-Monteros *et al.* indicated that, in most cases, such changes of biochemical status occur within the first postoperative year after surgery [29]. Therefore, it is possible that there is some clinical significance in cases demonstrating divergence between the GH nadir and IGF-1 at the first postoperative year evaluation.

In the present data, among 110 patients with acromegaly with IGF-1 normalization and no recurrence after complete resection of GH-secreting pituitary adenomas, 10 patients (9.1%) with acromegaly exhibited a GH nadir >0.4 ng/mL during a 75gOGTT at one year post-surgery. This is similar to previous studies that also used an ultrasensitive GH assay. For instance, using 0.3 ng/mL as the cut-off value for the GH nadir as determined in healthy subjects, Freda *et al.* found that 39% of patients with normalized serum IGF-1 levels showed inadequate suppression of GH an average of 5.8 years after pituitary surgery [9]. In addition, Arafat *et al.* determined the cut-off value for the GH nadir was 0.5 ng/mL using healthy subjects, and they reported the prevalence rate of normalized IGF-1 levels and elevated nadir GH levels was 20–22%. However, the time between pituitary surgery and evaluation was unclear [21]. Regardless, a strict comparison cannot be made between these previous studies and the present study due to the different cut-off values for GH nadir and variability in GH assays.

On the other hand, there is disagreement regarding the cut-off value for a healthy GH nadir during a 75gOGTT. For instance, Freda *et al.* reported that the normal range for a GH nadir was 0.06–0.13 ng/mL, whereas Arafat *et al.* reported that it was 0.02–0.5 ng/mL [9, 21]. Therefore, although the exact prevalence rate is unclear, it seems that some normal subjects may show a GH nadir >0.4 ng/mL. In the present study, the comparison of biochemical data at one year post-surgery showed that HOMA-IR and baseline plasma glucose were significantly lower in the high GH group than in the control group. However, peak plasma glu-

cose and plasma glucose at 120 min were not different. In accordance with the present results, Ronchi *et al.* also reported that HOMA-IR was significantly lower in patients who showed insufficient suppression of GH during a 75gOGTT in a long-term follow-up [19].

As BMI is also related to insulin resistance, some reports have addressed its relationship to GH levels. For example, Ronchi *et al.* divided 40 patients into two groups based on the GH nadir; both groups had acromegaly that was cured by surgery followed by radiotherapy when appropriate. Hormonal and metabolic parameters were then compared between groups. The low GH nadir group had a significantly higher BMI at the time of remission and tended to have a higher BMI after long-term follow-up than that in the control group [20]. In addition, Arafat *et al.* divided 213 healthy subjects into lean, overweight, and obese groups and evaluated the association of BMI with GH levels. They showed that both basal and nadir GH levels were significantly higher in the lean group than those in the other groups [21]. Because both BMI and HOMA-IR are related to GH levels, the degree of insulin resistance should be considered in evaluating the results of the GH nadir during a 75gOGTT. On the other hand, GH nadir was also shown to be significantly higher in females than in males [21]. In the present study, the percentage of females was higher in the high GH group (Table 2 and Fig. 1); however, there were no significant differences between the sexes for any parameters.

The preoperative and immediate postoperative clinical characteristics and predictive factors for patients with a high GH nadir and normalized IGF-1 levels at the first postoperative year evaluation have not yet been identified. Here, we analyzed preoperative and immediate postoperative clinical characteristics of such patients with a GH nadir >0.4 ng/mL one year after pituitary surgery and compared them with patients with normalized IGF-1 levels and a GH nadir <0.4 ng/mL. As a result, immediate postoperative HOMA-IR was significantly lower in the high GH group, and immediate postoperative HOMA-IR was an explanatory variable for the GH nadir at the first postoperative year evaluation in the multivariate linear analysis. Furthermore, immediate postoperative Matsuda index was also significantly higher in the high GH group, but immediate postoperative Matsuda index was not an explanatory variable. Therefore, insulin resistance at the immediate postoperative evaluation may be related to the cause of a higher GH nadir at one year post-surgery; although the main

organs contributing to insulin resistance and glucose-inducing GH suppression are unclear. Previous studies have also evaluated the relationship between the GH nadir and clinical parameters, but have only examined a single time point during the OGTT. The present results provide the first evidence that insufficient GH suppression at one year after pituitary surgery is related to a low HOMA-IR immediately after surgery. Additionally, this finding is compatible with the fact that those who showed insufficient GH suppression at the immediate postoperative evaluation moved to the high GH group with significantly higher frequency following the evaluation at one year post-surgery.

The clinical significance of postoperative patients with a normalized IGF-1 levels and an elevated GH nadir is uncertain. Although random serum GH and IGF-1 levels following treatment correlate with mortality [5, 6], the postoperative GH nadir during a 75gOGTT has not been indicated to predict mortality. Ronchi *et al.* demonstrated that, in postoperative patients with normalized IGF-1 levels and a GH nadir <1.0 ng/mL, there were no significant differences in the prevalence of abnormal glucose metabolism, hypertension, or dyslipidemia between a group with a GH nadir exceeding the upper limit (0.19 ng/mL) of a control group and a group with a GH level less than that limit [19]. Therefore, mortality risk is probably not elevated in patients with normalized IGF-1 levels and a GH nadir between 0.4–1.0 ng/mL. Furthermore, it may be that with normalized IGF-1 levels, lowering the GH nadir may be unsafe as it may indicate GH deficiency [30]. In support of this, Yamada *et al.* reported that severe GH deficiency was present in 9.1% of patients cured of acromegaly [31]. Therefore, titration of additional therapy must definitely be considered in patients with symptoms or morbidities of acromegaly. However, in patients with completely resected GH-secreting pituitary tumors, normalized IGF-1 levels, and no symptoms, it may be adequate to consider them in remission and to follow up carefully for recurrence.

The relationship between insulin resistance and GH suppression induced by glucose loading is unclear and might be explained by several mechanisms, including ghrelin. Ghrelin is a potent GH secretagogue and is suppressed during 75gOGTT and insulin infusion in both healthy and obese subjects [32–34]. In addition, there was a negative correlation between serum ghrelin concentration and insulin resistance [35, 36]. Therefore, low insulin resistance might contribute

to insufficient suppression of ghrelin during OGTT, potentially leading to insufficient suppression of GH. On the contrary, Verrua *et al.* showed that normal GH suppression was maintained in patients with hypothalamic-pituitary lesions other than acromegaly and that a higher GH nadir during a 75gOGTT in patients with controlled acromegaly (according to the 2010 criteria) does not reflect a lack of integrity of the hypothalamic-pituitary network. The authors suggested defective central somatostatin tone as a possible cause of impaired GH suppression [37].

There were some limitations to this study. Firstly, we were unable to obtain data for some parameters (BMI at immediate postoperative evaluation and first postoperative year evaluation). Secondly, the patients with normalized IGF-1 levels and a GH nadir >1.0 ng/mL were excluded so that only patients with acromegaly showing normalized IGF-1 levels and a GH nadir <1.0 ng/mL were included. Therefore, this study does not evaluate all patients with normalized IGF-1 levels and insufficient GH suppression. Further investigation is needed to evaluate the contribution of insulin resistance to GH suppression induced by glucose loading in a larger number of patients. Finally, the follow-up period is relatively short. Therefore, long-term follow-up should be undertaken to evaluate long-term remission, although complete tumor resection was confirmed using MRI and operative and postoperative clinical findings.

In conclusion, we found that HOMA-IR measured around 10 days after surgery was significantly lower in the high GH group, and that all HOMA-IR values of patients in the high GH group were <1.01. Furthermore, immediate postoperative HOMA-IR was identified as an explanatory variable for the GH nadir examined one year after pituitary surgery in a multivariate analysis. These findings indicate that immediate postoperative HOMA-IR may predict the degree of GH suppression during a 75gOGTT one year after pituitary surgery. Therefore, prudent evaluation and careful follow-up are needed to assess the remission of acromegaly in patients with HOMA-IR <1.01.

Disclosure

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