Preoperative Growth Hormone Response to Thyrotropin-Releasing Hormone and Oral Glucose Tolerance Test in Acromegaly: A Retrospective Evaluation of 50 Patients

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The objective of this study was to investigate the relationship between growth hormone (GH) dynamic tests (thyrotropin-releasing hormone [TRH] test and oral glucose tolerance test [OGTT]), insulin-like growth factor-I (IGF-I) plasma values, tumor size, and clinical outcome in patients with GH-secreting pituitary adenomas. Furthermore, we investigated the potential prognostic utility of the above biochemical parameters in the follow-up of patients with acromegaly. We studied 50 acromegalic patients (18 males and 32 females; mean age, 40 years; range, 16 to 69) who underwent trans-sphenoidal removal of a GH-secreting pituitary adenoma from 1990 to 1994. Preoperatively, we evaluated (1) GH plasmatic levels after an oral glucose load (OGTT) (blood samples were drawn at –15, 0, 30, 60, 90, 120, 150, and 180 minutes after oral administration of 0.75 g/kg body weight [BW] of glucose), (2) GH plasma levels after a TRH test (200 μg as an intravenous [IV] bolus), and (3) basal IGF-I plasma levels after an overnight fast. From 3 to 12 months after surgery we evaluated (1) GH plasma values after an OGTT, and (2) basal plasma IGF-I, free triiodothyronine (FT_3), free thyroxine (FT_4), thyroid-stimulating hormone (TSH), and urinary free cortisol. The same tests were performed every year for 5 years. All of the patients were classified into 4 subgroups according to the system of Hardy and Vezina. Preoperatively, "controlled" patients (n = 29) had a GH paradoxical response to TRH (n = 28) and an unresponsiveness to OGTT (n = 29); 23 of them belonged to the I and II classes. Only 5 poorly controlled patients (n = 21) showed a preoperative paradoxical response to TRH and 9 had a preoperative GH partial inhibition after OGTT; 19 of them belonged to the III and IV classes. Our data suggest that in the preoperative period in acromegalic patients the simultaneous presence of a GH paradoxical response to TRH and lack of GH inhibition after OGTT is inversely related to the tumor size and therefore more likely to be restored to normal by surgical treatment.

ACROMEGALY is a complex disease characterized by high growth hormone (GH) plasma levels and related metabolic and clinical aspects usually caused by a GH-secreting pituitary adenoma. The natural history of affected patients presents both a variable clinical course and various biological features so that several markers, in the past, have been investigated in order to show which "prognostic markers" were the most important.

A paradoxical GH response to thyrotropin-releasing hormone (TRH) in acromegalic patients was first described in 1972. Some investigators ascribed this paradoxical response to the presence of adenomatous tissue, with de-differentation and the appearance of specific receptors for TRH.[1] On the other hand, a GH response to TRH has been illustrated in other pathological conditions,[2] including renal failure,[3] depression,[4] anorexia nervosa,[5] primary hypothyroidism,[6] insulin-dependent diabetes mellitus,[7] schizophrenia,[8] and aging.[9] This GH response to TRH, absent in normal subjects,[10] is of diagnostic importance in acromegaly: as suggested in our previous study,[11] an increased "somatostatinergic" tone is conceivable in diseases with increased GH levels. TRH may cause acute GH dismission due to inhibition of somatostatin release.[12]

The lack of inhibition of GH levels after an oral glucose tolerance test (OGTT) is considered a marker of inappropriate GH secretion in acromegaly, even though GH levels in acromegalic patients can decrease, remain unchanged, or increase paradoxically in response to oral glucose.[13] The suppressive effect of oral glucose administration in normal subjects is caused by the increase of hypothalamic somatostatin. It has been suggested that somatostatin release in response to acute hyperglicemia is impaired in most acromegalic patients and that this abnormality may be one of the causes for the absence of normal GH suppression in this disorder.[14] At present, OGTT is considered to be the most useful test for the diagnosis of active acromegaly in untreated patients and for the follow-up of patients after treatment for the disease.[15] As for the paradoxical response to TRH, an absent inhibitory effect of OGTT may be hypothesized to be caused by an already maximally activated endogenous somatostatin tone.

The following retrospective study presents data on 50 acromegalic patients, each evaluated over a 5-year follow-up period in order to investigate the relationship between the response to GH dynamic tests (TRH test and OGTT), insulin-like growth factor-I (IGF-I) plasma values, and the clinical outcome of GH-secreting pituitary adenomas, as well as to clarify whether any of these parameters, or tumor size, may have prognostic value in the follow-up of patients affected by acromegaly.

MATERIALS AND METHODS

From 1990 to 1994, 50 patients (18 males and 32 females) underwent trans-sphenoidal removal of GH-secreting pituitary adenomas. The mean age at the time of surgery was 40 years (range, 16 to 69). Forty-six patients presented the clinical characteristics of acromegaly, while the remaining four those of gigantism. At the time of diagnosis,

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Table 1. Individual Data From Controlled Patients

Controlled Patients	Age (yr)	Sex	Class	Preoperative TRH Test: GH (μg/L)		Preoperative OGTT Test: GH (μg/L)		Preoperative IGF-I (μg/L)	Postoperative OGTT Test: GH (μg/L)		Postoperative IGF-I (μg/L)	Urinary Cortisol (μg/24 h)	FT_3 (ng/mL)	FT_4 (ng/mL)	TSH (mU/L)
				Basal	Peak	Basal	Nadir		Basal	Nadir					
1*	24	F	I	7	14	7	7	340	0.7	0.1	150	42	3.5	14.7	1,3
2*	28	F	I	4	9	6	7	360	0.8	0.7	160	66	3.3	15.9	2
3*	35	F	I	15	25	19	17	390	0.9	0.6	130	45	2.8	10.8	1,9
4*	52	F	I	5	10	5	6	363	0.8	0.3	150	58	3.0	11.6	1,8
5*	53	F	I	12	21	14	13	402	0.8	0.6	120	28	3.4	15.4	0,8
6*	33	M	I	15	25	12	10	500	0.9	0.4	155	42	3.0	12.2	1,7
7*	38	M	I	8	13	8	7	600	0.9	0.3	210	47	3.5	14.7	1,2
8*	52	M	I	22	35	18	18	380	0.7	0.2	180	49	2.1	12.9	2,5
9*	52	M	I	19	40	17	16	340	0.8	0.2	150	91	2.5	12.2	1,9
10*	54	M	I	29	35	23	21	330	0.9	0.4	170	50	3.2	13.7	1,8
11*	58	M	I	7	18	9	9	449	0.9	0.9	172	55	3.3	10.7	1,9
12*	20	F	II	12	20	13	12	461	0.8	0.3	143	49	2.8	13.0	1,9
13*	32	F	II	16	28	18	18	454	0.8	0.2	130	61	3.3	13.4	0,9
14	37	F	II	18	27	16	15	327	0.8	0.5	134	49	3.3	13.6	1,3
15*	38	F	II	15	24	15	14	348	0.9	0.3	132	69	3.2	13.7	1,3
16*	39	F	II	12	25	12	10	353	0.6	0.5	121	65	2.8	11.9	2,6
17*	50	F	II	7	18	6	5	333	0.7	0.2	210	32	3.7	15.1	1
18*	51	F	II	19	41	16	15	350	0.7	0.3	140	42	2.7	11.8	2,8
19*	22	M	II	21	40	24	25	400	0.7	0.3	135	47	2.6	11.5	2
20*	41	M	II	19	38	18	16	512	0.8	0.3	145	45	2.9	12.3	1,4
21*	44	M	II	19	38	16	16	437	0.9	0.3	128	39	3.2	13.7	1,4
22*	46	M	II	37	51	33	25	423	0.9	0.7	149	74	2.8	11.1	1,9
23*	47	M	II	37	60	35	36	374	0.8	0.4	170	45	2.8	12.9	2,3
24*	61	F	III	15	35	18	16	398	0.5	0.2	140	74	2.9	12.5	2,3
25*	63	F	III	17	28	15	15	411	0.8	0.2	160	76	2.8	10.7	1,1
26*	42	F	IV	19	31	21	21	396	0.8	0.4	158	87	2.6	10.5	2
27*	57	F	IV	21	60	22	20	533	0.9	0.4	166	58	3.3	13.4	1,3
28*	23	M	IV	17	28	15	14	478	0.8	0.3	151	58	2.8	9.3	2,3
29*	44	M	IV	19	31	18	19	502	0.9	0.4	165	40	2.7	11.6	3

NOTE. FT_3, FT_4, TSH, and urinary free cortisol values were determined postoperatively.
*TRH responders.

9 of the acromegalic patients had fasting plasma glucose levels between 110 and 140 mg/dL; 7 were affected by blood hypertension and 21 by headache; 3 presented with partial anterior hypopituitarysm and needed replacement therapy and the remaining 6 presented with alterations in their visual field. In all patients, the histological findings confirmed the presence of GH-secreting tissue.

On the basis of radiologic findings, using computerized tomography (CT) and magnetic resonance imaging (MRI), the patients were classified into 4 subgroups according to the system of Hardy and Vezina[16] (Tables 1 and 2).

Before surgery in all patients we evaluated GH plasma levels after an OGTT and after a TRH test, as well as IGF-I plasma values after an overnight fast. GH plasma levels after an oral glucose load (OGTT) were determined at 9 AM, after an overnight fast, with the patients in a recumbent position; an indwelling cannula was inserted into an arm vein and kept open by a 0.9% saline infusion, and blood samples were drawn at –15, 0, 30, 60, 90, 120, 150, and 180 minutes after the oral administration of 0.75 g/kg body weight (BW) of glucose. Evaluation of GH plasma levels after a TRH test was performed at 9 AM, after an overnight fast, with the patients in a recumbent position; an indwelling cannula was inserted into an arm vein and kept open by a 0.9% saline infusion, blood samples were drawn at –15, 0, 20, 40, and 60 minutes after TRH administration (200 μg as an intravenous [IV] bolus; Relefact, Hoechst). The preoperative evaluations of IGF-I plasma levels were also performed after an overnight fast. All patients underwent trans-sphenoidal surgery.

Three to 12 months after surgery and every year for a period of 5 years, we evaluated (1) basal IGF-I plasma values, after an overnight fast; (2) basal plasma free triiodothyronine (FT_3), free thyroxine (FT_4), thyroid-stimulating hormone (TSH), and urinary free cortisol; and (3) GH plasmatic values basal and after an oral glucose load (OGTT).

Blood samples were centrifuged within 2 hours after collection and plasma aliquots were frozen at −20°C until assayed. GH assays were performed by the immunoradiometric assays (IRMA) method, using commercial kits by Nichols Institute (San Juan Capistrano, CA). Interassay and intra-assay variations were 5.4% and 2.3%; the sensitivity limit of the assay was 0.06 μg/L. Plasma IGF-I was measured with the IRMA method using kits from Medgenix Diagnostix SA (Fleurus, Belgium). Interassay and intra-assay variations were 9.6% and 4.1%. Soluble IGF-I was separated from interfering binding proteins using the acid-ethanol procedure of Daughaday et al.[17]

In our laboratory, normal plasma values of IGF-I in adults range from 80 to 330 μg/L. Normal FT_3 ranges from 2.3 to 4.2 pg/mL, FT_4 from 9 to 16.5 pg/mL, and TSH from 0.35 to 3.8 mU/L. Normal urinary free cortisol ranges from 20 to 90 μg/24 h. As previously suggested, a positive GH response to TRH was defined as a serum GH increase greater than 50% of basal values.[18] Partial GH inhibition after OGTT was defined, according to data in the literature,[14,19] as a GH nadir at least 30% below basal levels. These definitions allow us to distinguish a GH response from spontaneous changes in the GH secretion.[14,18,19]

Concerning the postoperative results, we considered "controlled" the patients who presented undetectable GH (<1 μg/L) in the course of a

Table 2. Individual Data From Poorly Controlled Patients

Poorly Controlled Patients	Age (yr)	Sex	Class	Preoperative TRH Test: GH (μg/L)		Preoperative OGTT Test: GH (μg/L)		Preoperative IGF-I (μg/L)	Postoperative OGTT Test: GH (μg/L)		Postoperative IGF-I (μg/L)	Urinary Cortisol (μg/24 h)	FT_3 (ng/mL)	FT_4 (ng/mL)	TSH (mU/L)
				Basal	Peak	Basal	Nadir		Basal	Nadir					
1	16	F	II	31	40	30	30	364	7.8	7	400	52	2.8	12.2	3
2*†	33	F	II	16	25	16	10	463	15	14.5	320	47	2.6	13.3	2,2
3*†	38	M	III	37	60	33	19	423	19	18	340	75	2.7	11.8	1,9
4*	48	M	III	24	32	23	15	512	30	27	430	51	2.7	12.3	2,4
5*	40	F	III	30	37	31	21	601	15	13	360	52	2.8	11.1	1,5
6†	22	M	IV	21	40	19	14	341	15	14	640	60	3.2	14.7	1
7	26	M	IV	45	60	43	31	399	24	21.8	610	55	3.5	15.1	1,7
8	30	M	IV	60	61	63	45	500	29	27.9	350	29	3.5	15.4	1,7
9*	40	M	IV	71	75	75	43	342	35	34	520	40	3.0	10.1	2
10	49	M	IV	31	45	35	26	448	15	7	512	44	2.3	11.4	2,1
11	21	F	IV	41	61	46	35	412	40	38.8	500	36	3.3	12.3	1,9
12*	31	F	IV	87	90	89	60	550	5	4.3	350	57	3.0	14.5	2
13	34	F	IV	45	66	47	35	496	18	18	580	41	3.5	13.7	1
14*	37	F	IV	27	38	35	21	432	12	11	375	78	1.8	11.1	2,2
15	38	F	IV	35	45	33	24	465	19	18	380	85	3.3	14.0	1,8
16*	40	F	IV	48	60	45	28	403	4	3.7	461	28	2.7	11.8	1,8
17†	49	F	IV	30	48	33	24	385	3	2.8	350	55	2.0	9.4	1,5
18†	60	F	IV	33	50	34	24	480	4.5	4.3	510	48	2.6	10.0	2
19	69	F	IV	51	60	53	44	471	15	11.8	460	39	3.5	15.5	0,9
20*	20	F	IV	60	68	58	39	574	12	11.1	380	47	3.3	13.3	1,1
21	56	F	IV	14	19	15	14	602	4	3.7	360	65	2.9	9.7	2,3

NOTE. FT_3, FT_4, TSH, and urinary free cortisol values were determined postoperatively.
*Partial GH inhibition after OGTT.
†TRH responders.

glucose tolerance test, IGF-I plasma values in the normal range, matched for age and sex, no clinical activity,[15] and no neuroradiologic recurrence (CT scan and MRI, respectively, in 28 and in 22 patients) after a 5-year follow-up. We considered "poorly controlled" those patients who still showed elevated GH and IGF-I plasma levels, uninhibited GH (>1 μg/L) after a glucose tolerance test, and clinical activity[15] and/or radiologic signs of adenoma recurrence, even if a reduction of tumour size had been demonstrated.

Statistical Analysis

Statistical evaluation was performed by 1-way analysis of variance (ANOVA) and by χ^2 test. Computerized analysis was performed using the Statistica (Statsoft, Tulsa, OK; release 5.0) for Windows software package.

RESULTS

Individual data of our patients are reported in Tables 1 and 2. Considering the 5-year follow-up, we classified 29 patients as controlled and the remaining 21 patients as poorly controlled.

In the preoperative period, a paradoxical GH response to TRH was present in the 66% (33/50) of tested patients (responders). Average GH values in TRH responders were significantly lower than those in nonresponders (18.24 $\pm$ 1.56 *v* 43.75 $\pm$ 4.69 μg/L; $P < .05$). In the postoperative period, mean GH values in preoperative TRH responders were significantly lower than in nonresponders (2.39 $\pm$ 0.79 *v* 17.8 $\pm$ 2.78 μg/L; $P < .05$); postoperative GH was less than 1 μg/L in 84.8% (28/33) of responders versus 5.3% (1/17) of nonresponders. Also, postoperative plasmatic IGF-I levels in TRH responders were significantly lower than in nonresponders (195.45 $\pm$ 19.95 *v* 439.25 $\pm$ 26.72 ng/mL; $P < .05$).

On the other hand, during the preoperative period a partial GH inhibition after OGTT was observed in 18% (9/50) of patients: 7 of these patients were preoperative TRH responders and all had mean GH values significantly higher than other patients (45 $\pm$ 8.13 *v* 22.43 $\pm$ 2.11 μg/L; $P < .05$). Basal GH levels were less than 1 μg/L in 70.7% (29/41) of patients, who were preoperatively nonresponders to OGTT. These patients showed GH inhibition after a postoperative OGTT (nadir GH < 1 μg/L). Table 3 depicts the distribution of patients with respect to the qualitative response to TRH and OGTT.

The group of controlled patients exhibited preoperative and postoperative GH levels significantly lower than those of poorly controlled patients. In controlled patients, the preoperative mean GH plasma level was 16.17 $\pm$ 1.32 versus 40.76 $\pm$ 4.11 μg/L in poorly controlled patients ($P < .0001$). The postoperative mean GH plasma level was, respectively, 0.8 $\pm$ 0.01 versus 16.25 $\pm$ 2.28 μg/L ($P < .0001$). Controlled patients also presented IGF-I plasma levels lower than poorly controlled patients both in the preoperative period (411.86 $\pm$ 12.99 *v* 460.14 $\pm$ 17.02 ng/mL; $P < .05$) and in the postoperative period (152.55 $\pm$ 4.16 *v* 437.52 $\pm$ 20.92 ng/mL; $P < .05$).

According to the criteria of Hardy and Vezina, patients were classified as follows: grade I (n = 11), grade II (n = 14), grade III (n = 5), and grade IV (n = 20) (Tables 1 through 3). The percentage of controlled patients for each class is also reported

Table 3. Outcome of Patients Classified According to Preoperative GH Dynamic Tests and Classes of Hardy and Vezina

Preoperative Test	Total No. of Patients	Class I (11/50)	Class II (14/50)	Class III (5/50)	Class IV (20/50)	Postoperative Outcome	
						Controlled (29/50)	Poorly Controlled (21/50)
TRH^+, $OGTT^-$	31	11	11	2	7	28/31	3/31
TRH^+, $OGTT^+$	2	0	1	1	0	0	2/2
TRH^-, $OGTT^+$	7	0	0	2	5	0	7/7
TRH^-, $OGTT^-$	10	0	2	0	8	1/10	9/10
Controlled patients *v* class (%)	29	11/11 (100%)	12/14 (85.7%)	2/5 (40%)	4/20 (20%)		
Poorly controlled patients *v* class (%)	21	0	2/14 (14.3%)	3/5 (60%)	16/20 (80%)		

Abbreviations: TRH^+, TRH responders; TRH^-, TRH nonresponders; $OGTT^+$, patients with partial GH inhibition after OGTT; $OGTT^-$, OGTT nonresponders.

in Table 3. Most of controlled patients belonged to the I (n = 11) and II (n = 12) classes, while poorly controlled patients were more frequently in the IV class (n = 16).

Our data showed that controlled patients, after surgery (n = 29), had preoperative GH paradoxical responses to a TRH test (28/29 or 96.5%; Fig 1) and preoperative unresponsiveness to an OGTT (29/29 or 100%; Fig 2); most belonged to the I and II classes (23/29 or 79.3%). Only 5 of 21 (23.8%) poorly controlled patients showed a preoperative paradoxical response to the TRH test (Fig 1) and 9 (42.8%; Fig 2) had preoperative GH partial inhibition after an OGTT; the majority belonged to the III and IV classes (n = 19).

DISCUSSION

Our objective was to investigate the relationship between GH dynamic tests (TRH test and OGTT), IGF-I plasma values, tumor size, and clinical outcome in patients affected by GH-secreting pituitary adenomas. We investigated the potential prognostic usefulness of these biochemical parameters in the follow-up of the same patients.

The clinical importance of a GH paradoxical response to a TRH test is related to its diagnostic usefulness and prognostic indication in the postoperative period. Some investigators have ascribed this paradoxical response to the presence of residual adenomatous tissue, with a de-differentiation and the appearance of specific receptors for TRH,[1] but this hypothesis has not been verified by others.[20,21] However, the GH response to TRH can be also observed in normal subjects after pharmacological manipulation of the complex interactions between the hypothalamus and pituitary or in various pathological situations, other than acromegaly, in which an alteration of these relationships could be present.[2-9] The mechanism of this response in acromegaly remains unknown. A direct pituitary-stimulating action[22] and an indirect effect mediated via a decrease in the hypothalamic release of somatostatin or an increase in GH-releasing hormone (GHRH) secretion[12,23] have been proposed as possibilities. Recent in vitro studies[24] in adenomas from acromegalic patients indicate that adenoma formation and alterated physiological/pathophysiological conditions may result in a formation of a vast array of chemicals mediators products locally (paracrine factors) by the intrapituitary signaling network.[25] Thus, rather than TRH or the components of the TRH signaling system, paracrine factors produced locally may be the important elements mediating the effect of TRH on GH secretion.[25]

An increased somatostatinergic tone could also be hypothesized to be present in acromegaly.[26] Our data suggest that the paradoxical GH response to TRH is often present in small adenomas and that, in patients with a GH response to TRH, basal GH levels appear to be significantly lower in both the preoperative and postoperative periods. It can be suggested that the paradoxical response can be expressed only when the hypothalamus-pituitary interactions are intact and feedback mechanisms, linking GH, somatostatin, and TRH, can occur.[11]

It is known that the suppressive effect of oral glucose administration on GH (caused by increases in hypothalamic somatostatin in normal subjects) is altered in acromegaly (the plasma GH levels can decrease, remain unchanged, or even increase paradoxically).[13] Elevated glucose levels may also stimulate somatostatin release in the gastrointestinal tract (pancreas and gut).[27] Experimental studies, performed on rats, suggest that hypothalamic rather than peripheral somatostatin secretion is responsible for GH suppression after metabolic fuels administration, with particular reference to free fatty acids.[28] Our data confirm that the GH response to OGTT is not homogeneous in acromegalic patients,[19] since a group of patients exhibited a suppression of GH to about 30% of baseline levels.

Yang et al demonstrated the presence of some acromegalic patients with higher hypothalamic somatostatinergic activity (HSA) and some others with normal or low HSA.[29] Higher HSA is most probably a result of a preserved negative feedback by GH; low HSA may reflect the low somatostatinergic neuronal reserve resulting from continuous neuron firing by increased GH levels.[29]

We observed that patients with a preoperative paradoxical GH response to TRH and GH unresponsiveness to OGTT had postoperative GH inhibition after OGTT and a long-term control of the disease. Conversely, patients without a preoperative paradoxical GH response to TRH and partial GH inhibition after OGTT more frequently had postoperative GH unresponsiveness to OGTT and were likely to be poorly controlled after surgery. It can be hypothesized that acromegalic patients with

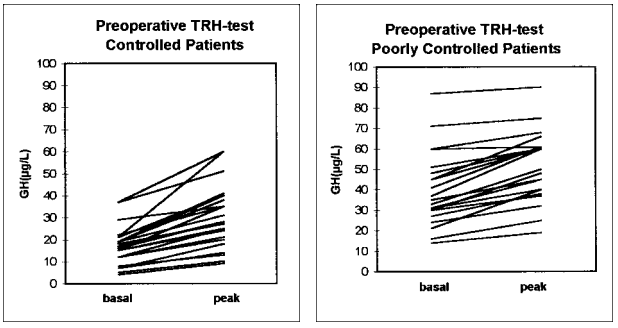

Fig 1. Plasma GH levels (basal and peak after TRH) in preoperative period in controlled patients (left) and poorly controlled patients (right).

high HSA are those in whom somatostatin secretion cannot yet be stimulated by glucose but can be inhibited by TRH. In the postoperative period, the reduction of GH hypersecretion and the presence of normal hypothalamic-pituitary connections may explain the reappearance of GH inhibition after OGTT. On the other hand, in acromegalic patients with low HSA, the hypothalamic somatostatin secretion cannot be inhibited by TRH administration because of the low baseline levels, while glucose can induce a partial inhibitory effect by increasing endogenous somatostatin. Moreover, even if somatostatin release from the gastrointestinal tract is of secondary importance in GH regulation in normal conditions, the phenomenon could be different in these acromegalic patients. A supersensitivity to peripheral somatostatin, in a situation of reduced hypothalamic somatostatin secretion and/or activity, could for example be hypothesized.[19] These patients, who are poorly controlled by surgery, have higher GH and IGF-I levels than the other acromegalic patients both in the preoperative and postoperative periods and did not show a postoperative GH inhibition after OGTT probably because the tumor size modifies the hypothalamic-pituitary connection.

In conclusion, our data demonstrate that in acromegaly the presence of preoperative GH paradoxical response to TRH and absence of GH inhibition after OGTT are inversely related to the tumor size and confirm the good outcome of class I and II tumors after surgery.

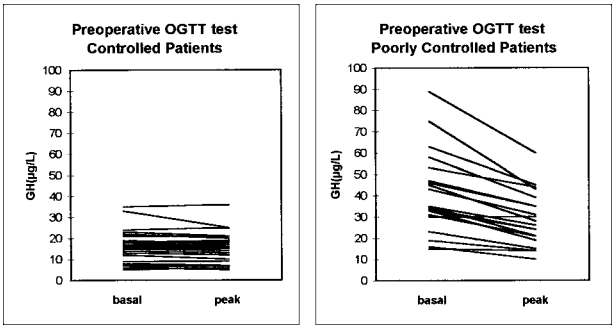

Fig 2. Plasma GH levels (basal and nadir after OGTT) in preoperative period in controlled patients (left) and poorly controlled patients (right).

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