Slow Postoperative Decline in Blood Concentration of Insulin-like Growth Factor-1 (IGF-1) in Acromegalic Patients

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Abstract. Recent criteria for cure of acromegaly require normalization of the insulin-like growth factor (IGF-1) level. A retrospective study was conducted to assess postoperative sequential changes in the blood IGF-1 level and to determine the appropriate timing for endocrinologic assessment of the effect of surgery. Blood IGF-1 levels were measured at least 3 times (4.9 ± 2.0, mean $\pm$ SD) during the first postoperative year in 36 acromegalic patients whose glucose tolerance test results, obtained 3 months after surgery, showed the growth hormone level to be suppressed to under 1 ng/mL. Postoperative IGF-1 parameters, *i.e.* the actual IGF level and %IGF-1 compared to the nadir during the first postoperative year, rapidly decreased during the first 2 postoperative weeks and then slowly declined over the next 2 weeks. They reached a plateau (stable nadir) during the 2nd postoperative month. Assessment of the postoperative endocrinologic status should be delayed at least one month after surgery in acromegalic patients.

Key words: Acromegaly, Growth hormone, Insulin-like growth factor, Transsphenoidal surgery

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MOST of the major activities of growth hormone (GH) are mediated by insulin-like growth factor-1 (IGF-1) [1, 2], which is primarily produced in the liver under the control of GH [1–4]. As the blood IGF-1 concentration reflects overall GH secretion during the previous 24 hrs and minimally fluctuates over this period [5–7], the blood IGF-1 concentration provides a reliable indicator of GH secretion [1, 3, 8].

Although recent criteria for surgical cure of acromegaly mandate normalization of IGF-1 [9–11], the time required for its postoperative decrease can vary from case to case (Figs. 1, 2) and the appropriate timing for postoperative IGF-1 evaluation remains to be determined. Therefore, we conducted a retrospective survey of postoperative changes in the blood IGF-1 level of acromegalics to identify the optimal timing for IGF-1 evaluations.

Subjects and Methods

The subjects were 36 acromegalic patients who had undergone transsphenoidal surgery (TSS) between March 1994 and December 2000 and whose nadir GH during postoperative administration of 75 g oral glucose tolerance test (OGTt) was under 1 ng/mL. There were 14 males and 22 females ranging in age from 23 to 76 years (50.2 ± 11.3, mean + SD). The sizes of their tumors ranged from 4 to 32 mm (15.9 ± 7.0 mm, mean + SD); the tumor types were classified as microadenomas (7 patients), macroadenomas without invasiveness (expansive adenomas, 23 patients), and macroadenomas with invasion into adjacent structures including the cavernous sinus (invasive adenomas, 6 patients). All patients underwent TSS performed by 2 authors (K.A. & A.T.) and none received adjuvant therapy.

Postoperative OGTt was performed 3 months after surgery. The GH concentration was measured by immunoradiometric assay (IRMA) using a GH Daiichi Kit (Daiichi Radioisotope Lab., Ltd., Tokyo, Japan). The sensitivity of this assay was 0.1 ng/mL. Intra- and inter-assay coefficients of variation were under 2.0%.

The IGF-1 concentration was measured by IRMA using the Somatomedin C II Bayer Kit (Yuka Medias Co., Ltd., Ibaragi, Japan). The sensitivity of this assay was 0.3 ng/mL. Intra- and inter-assay coefficients of variation were under 5.5%.

Blood IGF-1 was measured at least 3 times (4.9 ± 2.0, mean $\pm$ SD) during the first postoperative year. The general trend in postoperative changes of blood IGF-1 was evaluated by taking the average of the patients' actual IGF-1 value and the %IGF-1 compared to the respective patients' nadir IGF-1 value during the 1st postoperative year. These values were recorded during the 1st, 2nd, 3rd, and 4th postoperative week and during the 2nd, 3rd, 4th–6th, and 7th–12th postoperative month.

Representative Cases

Case 1 (Fig. 1)

The preoperative GH- and IGF-1 levels of this 49-year-old man with a 25-mm GH-producing expansive adenoma were 24.7 ng/mL and 669.4 ng/mL, respectively. The GH nadir (OGTt at 3 mos after surgery) was 0.85 ng/mL. His blood IGF-1 concentration was as high as 330 ng/mL on the morning following surgery. It was within the normal range (204 ng/mL) on the 4th morning and at 5 other time points during the first 100 postoperative days and remained within normal limits thereafter.

Case 2 (Fig. 2)

The preoperative GH- and IGF-1 levels of this 55-year-old woman with a 22-mm GH-producing expansive adenoma were 17.5 ng/mL and 532 ng/mL, respectively. Her blood GH was sufficiently suppressed; the GH nadir (OGTt at 3 mos after surgery) was 0.7 ng/mL. Her blood IGF-1 level at 7 and 11 days after surgery was still fairly high at 476 ng/mL and 485 ng/mL, respectively; however, at one month it reached a level slightly above the upper normal limit (271 ng/mL) and stabilized at 188 and 210 ng/mL at 2 and 3 months. No subsequent increase was noted during follow-up.
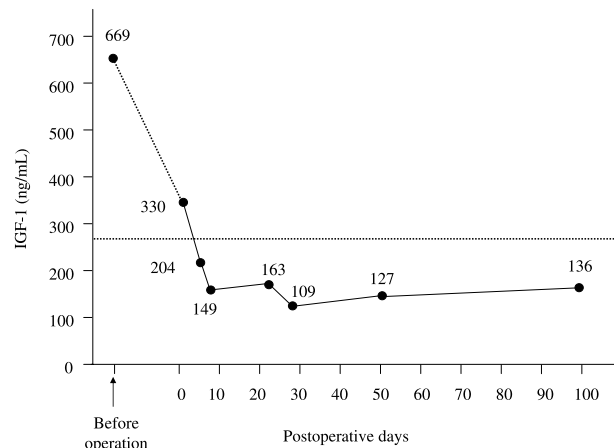

Fig. 1. Postoperative changes in IGF-1 in a 49-year-old male with acromegaly. Dotted line: upper normal limit (mean + 2 SD) in a sex- and age-matched control population.
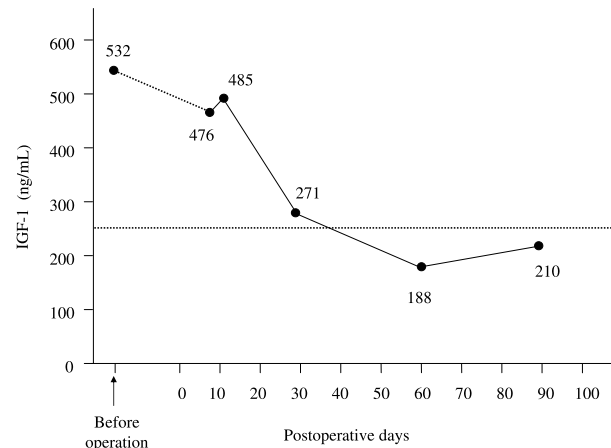

Fig. 2. Postoperative changes in IGF-1 in a 55-year-old female with acromegaly. Dotted line: upper normal limit (mean + 2 SD) in a sex- and age-matched control population.
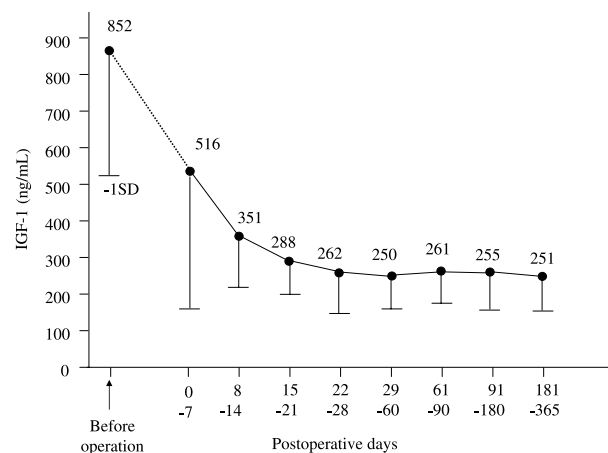

Fig. 3. Sequential changes in the actual blood IGF-1 level during the first postoperative year in 36 acromegalic patients.

Results

1. Changes in postoperative IGF-1 (Table 1, Fig. 3)

In our 36 acromegalic patients, the mean IGF-1 level decreased rapidly from a preoperative level of 852 ng/mL to 351 ng/mL during the first 2 postoperative weeks and continued its gradual decrease over the next 2 weeks. Mean IGF-1 stabilized at 250 ng/mL during the 2nd postoperative month and fluctuated minimally thereafter.

2. Change in %IGF-1 compared to the IGF-1 nadir recorded during the 1st postoperative year (Table 1)

To obtain this value, we used the formula: %IGF-1 of nadir IGF-1=actual IGF-1×100/respective patients' nadir IGF-1 recorded during the first postoperative year. %IGF-1 decreased rapidly during the first 2 postoperative weeks and continued to fall gradually over the next 2 weeks. The % IGF-1 value was still 130.9% during the 4th week after the surgery. The plateau (approximately 120%) was reached during the 2nd postoperative month; subsequently there were only minimal fluctuations.

3. Comparison between patients whose postoperative IGF-1 decreased rapidly (group 1) or slowly (group 2)

As shown in Table 2, 15 patients (group 1) experienced a rapid decrease in postoperative IGF-1 (%IGF-1 <130.9% within one month after surgery). The other

Table 1. Postoperative modification of IGF-1

Timing of measurement	No. of patients who underwentmeasurement	Actual IGF-1 value		% IGF-1	
		mean	SD	mean	SD
before surgery	36	852.4	328.4	421.0	147.4
0–7 days	28	519.5	390.1	299.9	234.1
8–14 days	11	351.0	135.5	165.4	56.3
15–21 days	12	287.9	88.8	137.6	32.2
22–28 days	11	261.7	113.8	130.9	26.8
29–60 days	18	249.8	98.0	121.0	19.7
61–90 days	16	261.4	100.3	117.8	27.4
91–180 days	28	255.1	122.7	115.2	21.5
180–365 days	36	250.8	101.1	117.2	19.5

% IGF-1: % IGF-1 of respective patients' nadir IGF-1 during the first postoperative year
SD: standard deviation

Table 2. Comparison between patients with rapid (group 1) and slow (group 2) decrease in blood IGF-1

	Group 1 (n = 15)	Group 2 (n = 21)
Age (years)	49.5 ± 12.5	51.0 ± 10.1
Male/Female	5/10	9/12
Tumor size (mm)	14.8 ± 5.5	15.4 ± 6.4
Preoperative GH (ng/mL)	50.6 ± 76.8	39.2 ± 41.4
Preoperative IGF-1 (ng/mL)	766.4 ± 380.6	965.7 ± 318.5
Concomitant Disease		
Preoperative DM	60.0% (9/15)	42.9% (9/21)
Postoperative DM	13.3% (2/15)	14.3% (3/21)
Hypothyroidism	13.3% (2/15)	9.5% (2/21)
Liver dysfunction	0% (0/15)	9.5% (2/21)
Renal failure	0% (0/15)	0% (0/21)
Malnutrition	0% (0/15)	0% (0/21)

In group 1 (rapid decrease), %IGF-1 decreased to under 130.9% within one month after surgery
In group 2 (slow decrease), %IGF-1 remained at over 130.9% at one month after surgery
DM: diabetes mellitus

21 patients (group 2) manifested a slow decrease (%IGF-1 >130.9% at one month after surgery). Between the 2 groups there were no significant differences (p>0.19, Mann-Whitney test) with respect to age, gender, tumor size, preoperative GH level, preoperative IGF-1 level, and prevalence of concomitant illness, such as preoperative diabetes mellitus (DM), postoperative DM, hypothyroidism, liver dysfunction, renal failure, and malnutrition.

Discussion

Previous studies reported the half-life of free IGF-1 as around 20–30 min and the half-life of carrier protein-bound IGF-1 as 4 to 15 hr [12, 13]. The biological half-life of GH is only about 20 min [14] and the GH level decreases rapidly after successful transsphenoidal adenomectomy [15]. Under GH control, IGF-1 is mainly produced in the liver [1, 2, 16], and a few days may be required after successful surgery for the IGF-1 level to fall to within the normal range [4] (see representative case 1). However, our study showed that the decline in blood IGF-1 was generally much slower.

Blood IGF-1 fell relatively rapidly during the first 2 postoperative weeks and continued to decline more gradually over the subsequent 2 weeks, reaching a plateau during the 2nd postoperative month. We observed some slight fluctuations thereafter; however, there was no general tendency toward any further subsequent decrease.

Arosio *et al*. [17], who also observed a slow decrease in IGF-1 after adenomectomy for acromegaly, reported that a stable nadir of IGF-1 was reached at 7–15 days after the operation. Our study, on the other hand, showed a much slower decrease in the postoperative IGF-1 concentration. However, in 10 of their successfully operated patients, blood IGF-1 levels continued their downward trend over the course of the 2nd postoperative week [17]. Others [18] who compared the postoperative biochemical status, cured or continued active, of 50 acromegalic patients at 1–3 and more than 12 months after surgery, found a change from continued active to cured in 12 patients and attributed it to delayed normalization of their IGF-1 level. They suggested that this delay could be due to the persistence of an altered metabolic environment characteristic of acromegaly, *e.g.* insulin resistance, hyperinsulinemia, and an impaired carbohydrate and lipid metabolism.

They also posited that the persistence of an acquired autonomy of the GH receptor in the target organ may lead to GH-independent IGF-1 synthesis.

Although the major regulator of IGF-1 is GH, blood IGF-1 level is influenced by concomitant illnesses such as liver dysfunction and renal failure [19, 20]. We compared our 2 groups with respect to possible factors that may have influenced the speed of their postoperative IGF-1 decrease but found no significant differences in any of the parameters assessed.

Kristof *et al*. [21] reported delayed normalization of GH suppression upon oral glucose loading. The rate of false OGTt results when the test was performed within 2 weeks of surgery was 16.4%; 14.9% of cases were falsely judged as still active and 1.5% were falsely judged as cured. When OGTt was performed not earlier than 3 months after surgery, the rate of false results dropped to 1.5%. They speculated that a transient disturbance in the hypothalamic- pituitary axis during the early postoperative weeks led to the erroneous results. Alternatively, they posited that the gradual postoperative decline in GH hypersecretion due to an ongoing reduction in the blood supply to the residual adenoma cell nests may have brought about the eradication of the tumor. Reports of spontaneous normalization of GH levels [22] and disappearance of the abnormal GH response to the thyrotropin-releasing hormone (TRH) test [23, 24] after unsuccessful TSS also suggest that a slow postoperative necrotic process may occur in tiny residual tumors.

To monitor the effect of TSS in patients with acromegaly, some [8, 10] suggested a 2–4 month delay before OGTt and IGF-1-based outcome assessment without providing the rationale for this delay. Kao *et al*. [4], whose study population included a relatively small number of patients whose postoperative IGF-1 levels were measured infrequently, also suggested a 2-month waiting period for proper assessment of postoperative IGF-1. Our study is the first to document the sequential changes in the postoperative IGF levels of acromegalic patients and provides evidence to justify a delay by at least one month in the endocrinologic assessment of operated acromegalic patients. Based on the results obtained at that time, it may be possible to avoid subjecting these patients to unnecessary postoperative adjuvant therapy.

Conclusion

In operated acromegalic patients, the decrease in IGF-1 was much slower than would be expected from the half-life of the carrier protein-bound peptide. We suggest that the slow speed of this decrease supports postponing decisions regarding the patients' postoperative status and the administration of additional therapy for at least one month after surgery.

References

1. Le Roith D (1997) Seminars in medicine of the Beth Israel Deaconess Medical Center. Insulin-like growth factors. *N Engl J Med* 336: 633–640.

2. Brabant G (2003) Insulin-like growth factor-I: marker for diagnosis of acromegaly and monitoring the efficacy of treatment. *Eur J Endocrinol* 148: (Suppl) 15–20.

3. Frohman LA (1991) Clinical review 22: Therapeutic options in acromegaly. *J Clin Endocrinol Metab* 72: 1175–1181.

4. Kao PC, Laws ER Jr, Zimmerman D (1992) Somatomedin C/Insulin-like growth factor I levels after treatment of acromegaly. *Ann Clin Lab Sci* 22: 95–99.

5. Barkan AL, Beltins IZ, Kelch RP (1988) Plasma insulin-like growth factor-I/somatomedin-C in acromegaly: correlation with the degree of growth hormone hypersecretion. *J Clin Endocrinol Metab* 67: 69–73.

6. Bercu BB, Shulman D, Root AW, Spiliotis BE (1986) Growth hormone (GH) provocative testing frequently does not reflect endogenous GH secretion. *J Clin Endocrinol Metab* 63: 709–716.

7. Giovanelli M, Losa M, Mortini P (1996) Acromegaly: surgical results and prognosis. In: Landolt AM, Vance ML, Reilly PL (eds) Pituitary Adenoma. Churchill Livingstone, New York, 333–351.

8. Thorner MO, Vance ML, Laws ER Jr, Horvath E, Kovacs K (1998) The anterior pituitary. In: Wilson JD, Foster DW, Kronenberg HM, Larson PR (eds) Williams Textbook of Endocrinology, 9th edition. WB Saunders, Philadelphia, 249–340.

9. Giustina A, Barkan A, Casanueva FF, Cavagnini F, Frohman L, Ho K, Veldhuis J, Wass J, Von Werder K, Melmed S (2000) Criteria for cure of acromegaly: a consensus statement. *J Clin Endocrinol Metab* 85: 526–529.

10. Melmed S, Casanueva FF, Cavagnini F, Chanson P, Frohman L, Grossman A, Ho K, Kleinberg D, Lamberts S, Laws E, Lombardi G, Vance ML, Werder KV, Wass J, Giustina A (2002) Acromegaly treatment consensus workshop participants: Guidelines for acromegaly management. *J Clin Endocrinol Metab* 87: 4054–4058.

11. Arita K, Kurisu K, Tominaga A, Eguchi K, Iida K, Uozumi T, Kasagi F (2003) Analysis of mortality in 154 surgically treated patients with acromegaly — A 10-year follow-up survey. *Endocr J* 50: 163–172.

12. Guler HP, Zapf J, Schmid C, Froesch ER (1989) Insulin-like growth factors I and II in healthy man. Estimations of half-lives and production rates. *Acta Endocrinol (Copenh)* 121: 753–758.

13. Zapf J, Hauri C, Waldvogel M, Froesch ER (1986) Acute metabolic effects and half-lives of intravenously administered insulin like growth factors I and II in normal and hypophysectomized rats. *J Clin Invest* 77: 1768–1775.

14. Zapf J (1987) Growth hormone — Storage, half-life, turnover. In: Labhardt A (ed) Clinical Endocrinology, Theory and Practice. Springer-Verlag, New York, 92–93.

15. Luedecke DK (1988) Long term surgical results in acromegaly. Does the immediate postoperative growth hormone level predict the outcome? In: Landolt AM, Girard J, Heitz PhU, del Pozo E, Zapf J (eds) Progress in Pituitary Adenoma Research. Pergamon Press, Oxford, 243–252.

16. Isaksson OG, Jansson JO, Sjogren K, Ohlsson C (2001) Metabolic functions of liver-derived (endocrine) insulin like growth factor I. *Horm Res* 55 (Suppl 2): 18–21.

17. Arosio M, Bazzoni J, Bochicchio D, Aragona A, Faglia G (1988) Slow decrease of IGF-1 after adenomectomy in acromegaly. In: Landolt AM, Heitz PU, Zapf J, *et al.* (eds) Advances in pituitary adenoma research. Pergamon Press, Oxford, 257–260.

18. Espinosa-de-los-Monteros AL, Mercado M, Sosa E, Lizama O, Guinto G, Lopez-Felix B, Garcia O, Hernandez I, Ovalle A, Mendoza V (2002) Changing patterns of insulin like growth factor-I and glucose-suppressed growth hormone levels after pituitary surgery with acromegaly. *J Neurosurg* 97: 287–292.

19. Orskov H (1996) Somatostatin, growth hormone, insulin-like growth factor-1, and diabetes: friends or foes? *Metabolism*. 48 (Suppl 1): 91–95.

20. Underwood LE, Van Wyk JJ (1996) Normal and aber-

rant growth. In: Wilson JD, Foster DW (eds) Williams Textbook of Endocrinology 8th edition. WB Saunders, Philadelphia, 1079–1138.

21. Kristof RA, Neuloh G, Redel L, Klingmuller D, Schramm J (2002) Reliability of the oral glucose tolerance test in the early postoperative assessment of acromegaly remission. *J Neurosurg* 97: 1282–1286.

22. Landolt AM, Froesch ER, Koenig MP (1988) Spontaneous postoperative normalization of growth hormone levels in two patients with acromegaly not cured by transsphenoidal surgery. *Neurosurgery* 23: 634–637.

23. Watanabe M, Kuwayama A, Nakane T, Kanie N, Kato T, Takahashi T, Kageyama N (1985) Long-term growth hormone responses to non-specific hypothalamic hormones in acromegalic patients. *Surg Neurol* 24: 449–456.

24. Mukada K (1990) The natural course of growth hormone-secreting pituitary adenomas after surgery alone — Clinical significance of the growth hormone response to thyrotropin-releasing hormone and luteinizing hormone-releasing hormone. *Neurol Med Chir (Tokyo)* 30: 251–257.