Decrease of Serum IGF-I following Transsphenoidal Pituitary Surgery for Acromegaly

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BACKGROUND: In the immediate postoperative period following resection of growth hormone (GH)-secreting pituitary tumors, serum concentrations of GH have limited ability to predict remission of acromegaly. Since many actions of GH actions are mediated by insulin-like growth factor-1 (IGF-I), we aimed to determine the rates of fall of IGF-I during 72 h after surgical resection of pituitary tumors.

METHODS: We studied patients who were undergoing pituitary surgery for acromegaly. IGF-I was measured by LC-MS and GH by immunoassay. Remission was defined by the combination of serum GH ≤ 0.4 ng/mL during oral glucose tolerance testing performed 8 weeks after the surgical procedure and normal IGF-I at ≥8 weeks.

RESULTS: During the first 72 h after surgery, the mean (SD) rate of decline of IGF-I was 185 (61) ng/mL per 24 h in those who achieved remission (n = 23), with a mean (SD) apparent half-life of 55 (19) h. IGF-I had decreased to <65% of the preoperative IGF-I on postoperative day 2 in 20 of 23 remission patients (87%) vs none of 5 patients who did not achieve remission. GH was <2.7 ng/mL on day 2 in 21 of 23 remission patients (91%), but in none of the nonremission patients. The combination of IGF-I and GH on day 2 separated the remission and nonremission groups of patients.

CONCLUSIONS: Rapid decline of serum IGF-I during the immediate postoperative period warrants further study as an analytically independent adjunct to GH measurement for early prediction of biochemical remission of acromegaly.

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4 Nonstandard abbreviations: GH, growth hormone; IGF-I, insulin-like growth factor 1; OGTT, oral glucose tolerance testing; eGFR, estimated glomerular filtration rate.
IGF-I (12, 13). IGF-binding proteins, which prolong the clearance of IGF-I, are increased in acromegaly and may prolong the clearance of IGF-I, such that IGF-I does not reach normal concentrations during the early postoperative period (13).

The free fraction (approximately 1% of total IGF-I) in serum may represent the biologically active form (13–15). Feelders et al. (16) described a decrease of free IGF-I within the first week after surgery in patients who were later shown to be in remission. The fall in free IGF-I preceded normalization of total IGF-I as measured by immunossays, but assays for free IGF-I are not widely available.

We aimed to determine the rates of decline of IGF-I during the first 72 h after removal of functioning GH-secreting pituitary tumors. IGF-I was measured by an LC-MS method (17, 18) that is free of interference from IGF-binding protein-3. To the best of our knowledge, the rates of decline have not been assessed previously.

**METHODS**

**STUDY PARTICIPANTS**

Inclusion criteria were: age ≥18 years; preoperative diagnosis of acromegaly, based on increased IGF-I and GH >0.4 ng/mL during oral glucose tolerance test (OGTT); treatment by transsphenoidal surgery between September 2012 and January 9, 2015; diagnosis of remission or nonremission at 8 weeks after the surgical procedure; and IGF-I measurements by mass spectrometry before surgery and, at a minimum, on postoperative days 2 or 3 or both. IGF-I results from other days were to be collected when available.

Exclusion criterion was treatment with a somatostatin analog or a dopamine agonist before surgery since these drugs affect both GH and IGF-I.

The study and data retrieval were planned before the first patient underwent surgical intervention and before IGF-I and GH tests were performed. The study was approved by the Institutional Review Board of the University of Virginia. Data were retrieved from the electronic medical record with waiver of consent.

Remission was defined by the combination of serum GH <0.4 ng/mL during OGTT performed 8 weeks after the surgical procedure and normal IGF-I at ≥8 weeks.

**SURGICAL PROCEDURES**

All surgical procedures were performed by one of two neurosurgeons (J.A. Jane, Jr., E.H. Oldfield) using either endoscopic or microscopic methods, respectively.

**MEASUREMENTS**

For measurements of serum concentrations of IGF-I, blood was collected in plain containers (BD Vacutainers, without cell separator). Blood was allowed to clot, and the containers were centrifuged to separate serum from cells. Serum was shipped, refrigerated, by courier to Nichols Institute/Quest Diagnostics for IGF-I testing. IGF-I was measured by high-performance liquid chromatography with high-mass-accuracy mass spectrometry (LC-MS) (17, 18). IGF-I was released from binding proteins by acid-ethanol extraction, followed by neutralization and cryoprecipitation (19). Mass spectrometry of the LC effluent used a high-mass-accuracy, quadrupole TOF mass spectrometer (Agilent 6530 qTOF) operating in full-scan mode. This instrument allowed measurement of the intact IGF-I molecule and thus avoided problems associated with proteolytic digestion. The recombinant IGF-1 used for calibration was obtained from Ajinomoto Science. It was aliquoted in solution, lyophilized, and sealed under argon in amber glass ampoules, and stored at −60 to −80 °C. Amino acid analysis (AA Service Laboratory) was carried out to determine the amino acid content and protein concentration. The final assigned concentration was confirmed by comparison to the WHO 02/254 reference material. The working calibrator was prepared daily, and external controls from Bio-Rad Laboratories were run in each assay to monitor the interassay variation. All measurements of IGF-I were performed at Nichols Institute/Quest Diagnostics, where the assay was developed (17, 18). z Scores were calculated at the Nichols Institute by use of a polynomial fit of the reference population. The IGF-1 mean and SD were calculated based on age of the subject. The z scores were then calculated by subtracting the measured IGF-I from the mean and dividing this by the SD. The polynomial equations used to calculate the z scores were different from those presented in the PLoS One article by Bystrom et al. (18). The published recovery of IGF-I by this LC-MS assay was 103%–104%. The interassay imprecision (as CV) was 2.8%–5.2% at concentrations of 55–700 ng/mL.

Measurements of serum GH were performed at the University of Virginia by a chemiluminescent immunoassay (Immulite; Siemens), which used WHO International Standard for Somatropin (recombinant DNA–derived human growth hormone) 98/574 for calibration; the interassay imprecision (CV) was 2.9%–3.7% at mean concentrations of 5.0–19.5 ng/mL. The laboratory participates in the external quality assurance program of the UK NEQAS for Peptide Hormones (Edinburgh); laboratory biases were ≤2.5% (mean 0.4%) for 6 consecutive samples that had GH concentrations of 0.22–0.52 ng/mL, near the cutpoint of 0.4 ng/mL used for the GH suppression test. Creatinine was measured in lithium-heparin plasma by a kinetic alkaline picrate method (Abbott Architect). The estimated glomerular filtration rate (eGFR) was calculated by the CKD-EPI equation (20).
DETERMINATION OF APPARENT HALF-LIVES AND RATES OF FALL OF IGF-I

The kinetics of the fall of total IGF-I after surgery are complex, reflecting, among other things, contributions of continuing (and potentially changing) production of IGF-I and separate kinetics for clearance of free IGF-I and clearances of the binary complex (IGF-I and IGF-binding proteins), and the ternary complex, which also includes an acid-labile subunit. We therefore analyzed the fall of IGF-I after surgery with descriptive measures only: (a) the rate of decline of IGF-I concentration per 24 h in each patient and (b) the apparent half-life of IGF-I in each patient.

For these analyses, time 0 was the recorded time of the end of the surgical procedure (typically within minutes of removal of the pituitary tumor). The preoperative IGF-I was plotted at time 0 and used as an estimate of the concentration at the time of removal of the pituitary tumor. The recorded times of collection of samples were used to calculate time (in hours) after the end of the surgical procedure.

The decline of IGF-I per 24 h was determined from the slopes of the regression equations of IGF-I vs time (in hours) (Fig. 1A). The decline of IGF-I (ng/mL) per h was multiplied by 24 to obtain the decline per 24 h, as reported in the Results. The apparent half-lives of decline of IGF-I were determined from slopes of the plots of the log of IGF-I vs time (in hours) (Fig. 1B).

STATISTICAL ANALYSES

Data were analyzed and plotted by the use of R software (R-3.2.2 for Microsoft Windows). Results are presented as means and SDs, as indicated. The significance of difference of means was assessed by the use of Student t-test in Microsoft Excel. A P value of <0.05 was used as the threshold for statistical significance.

Results

PATIENTS

Demographic and clinical data on the 28 study patients are shown in Table 1; also see Table 1 in the Data Supplement that accompanies the online version of this article at http://www.clinchem.org/content/vol63/issue2. All patients in remission had GH concentrations <0.4 ng/mL during the OGGT at 8 weeks after the surgical procedure (Table 1) and IGF-I was within the reference interval at follow-up in all of them, though not yet at 8 weeks for one patient, whose preoperative IGF-I was extremely high (z score 5.6; see Table 1, patient 11); the patient’s IGF-I was normal at one-year follow-up (z score 1.4). In all patients, the eGFR was ≥60 mL · min⁻¹ · (1.73 m²)⁻¹. All 5 patients in the non-
remission group underwent ancillary treatment, and in each of the 5, residual tumor was demonstrated by MRI. Two patients with endocrine testing consistent with biochemical remission had residual tumor on their postoperative MRI; both had sparsely granulated tumors and low GH concentrations. Related comorbidities are indicated for individual patients in Table 1. No patients were taking oral contraceptives, and no hypogonadism was observed.

### RATE OF FALL OF IGF-I AFTER SURGERY IN PATIENTS WHO WERE IN REMISSION

To examine the rates of decline of IGF-I, its concentrations were examined in relation to time (in hours) after surgery. IGF-I was plotted as concentration (ng/mL) (Fig. 1A) or as log concentration (Fig. 2B) to visualize the patterns of decline as either linear with time or exponential.

#### Table 1. Perioperative IGF-I concentrations expressed as z scores.

| Patient no. | Sex | Remission | Perioperative IGF-I, z score | 8-week OGTT GH nadir, ng/mL |
|-------------|-----|-----------|----------------------------|----------------------------|
| Day 0 (Preoperative) Day 1 Day 2 Day 3 | |
| 1           | F   | Yes       | 4.7 4.2 3.7 NA            | 1.0 0.23                   |
| 2           | F   | Yes       | 2.2 1.7 0.9 NA            | 0.9 0.25                   |
| 3           | F   | Yes       | 5.1 3.9 3.4 NA            | −0.6 0.05                  |
| 4           | F   | Yes       | 2.9 0.4 0.7 NA            | −0.8 0.06                  |
| 5           | F   | Yes       | 3.8 3.0 2.0 NA            | 1.8 0.16                   |
| 6           | F   | Yes       | 6.7 4.7 3.9 3.3 1.4      | 0.1                        |
| 7           | F   | Yes       | 4.0 2.2 1.3 NA            | −0.6 0.05                  |
| 8           | F   | Yes       | NA 3.3 1.7 NA            | 0.9 0.14                   |
| 9           | F   | Yes       | 3.4 2.6 2.0 NA            | 1.4 0.05                   |
| 10          | M   | Yes       | 5.0 3.6 3.2 3.4 1.8      | 0.2                        |
| 11          | M   | Yes       | 5.6 5.4 4.2 NA            | −0.6 0.05                  |
| 12          | M   | Yes       | 5.0 3.6 3.2 2.6 1.3      | 0.26                       |
| 13          | M   | Yes       | 4.9 2.7 3.4 NA            | 1.7 0.34                   |
| 14          | M   | Yes       | 3.4 2.7 2.2 1.5 1.3      | 0.1                        |
| 15          | M   | Yes       | 4.0 3.6 1.8 NA            | 1.4 0.09                   |
| 16          | M   | Yes       | 3.7 NA 1.1 NA            | 0.5 0.15                   |
| 17          | M   | Yes       | 3.8 1.8 1.5 1.5 0.5      | 0.09                       |
| 18          | M   | Yes       | 5.2 4.2 3.2 2.1 1.5      | 0.05                       |
| 19          | M   | Yes       | 5.2 4.4 3.6 2.9 1.6      | 0.11                       |
| 20          | M   | Yes       | 4.7 3.6 3.2 NA            | −0.2 0.09                  |
| 21          | M   | Yes       | 5.1 NA 4.2 NA            | 1.8 0.3                    |
| 22          | F   | Yes       | 3.6 2.3 2.1 NA            | 1.9 0.38                   |
| 23          | M   | Yes       | 5.5 4.7 3.9 NA            | 0.8 0.06                   |
| 24          | F   | No        | 4.6 4.6 4.7 NA            | 4.3 13.9                   |
| 25          | F   | No        | 4.3 NA 3.4 NA            | 2.4 11.3                   |
| 26          | M   | No        | 5.0 4.5 3.9 NA            | 3.9 NA                     |
| 27          | M   | No        | 4.9 4.6 4.5 NA            | 5.0 NA                     |
| 28          | M   | No        | 5.7 4.3 4.5 NA            | 4.5 3.81                   |

* Scores of 2.0 or less are in bold font.
* NA, not available.
* Patients 2 and 22 were in endocrine remission despite residual tumor on MRI.
* Patients on thyroid hormone replacement before and after surgery.
* Patients who had diabetes mellitus.
* 2 Scores of 2.0: patient 5, day 2: the IGF-I concentration was 0.99 times the upper limit of the reference interval; patient 9, day 2: the IGF-I concentration was 1.07 times the upper limit of the reference interval.
* Patients on hydrocortisone treatment after surgery.
* Patient 11: 1 year after his surgical procedure IGF-I z score was 1.4.
The concentration of IGF-I appeared to decrease steadily with time in most patients who were later found to have achieved remission (Fig. 1A). During the first 48–72 h after surgery, the mean (SD) decrease of IGF-I was 185 (61) ng/mL per 24 h, with comparable results in men and women (Table 2). By contrast, the rate of decline was inconsistent in patients who did not achieve remission (Table 2).

To estimate the “apparent” half-lives of decline of IGF-I, we examined the relationship of log(IGF-I) and time (h) after surgery (Fig. 1B). The mean apparent half-life of the fall of IGF-I (and the 95% CI) was 55 (18–93) h (Table 2). Given this long half-life, IGF-I was unlikely to reach normal values during a 2- or 3-day hospitalization, except in patients whose preoperative IGF-I was only mildly increased.

IGF-I concentrations on the mornings of postoperative days 1–3

The concentrations of IGF-I before pituitary surgery and on the mornings of postoperative days 1–3 are shown in Fig. 2A. The decline of IGF-I appeared to be faster in patients who later were judged to have achieved remission (Fig. 2A, right panels) than in those who did not achieve remission (left panels), consistent with the expected lower production of IGF-I after complete removal of GH-secreting tumors. The rates of decline of IGF-I appeared to be similar in women and men (upper and lower panels, respectively).

Because the reference intervals for IGF-I vary widely with age and sex, Fig. 2A does not show which values were within the reference interval. In Fig. 2B, the data of Fig. 2A are replotted with IGF-I expressed as multiples of the reference interval.

**Table 2. Rate of decrease and half-life of IGF-I decrease in patients during 48–72 h after pituitary surgical procedures.**

|                  | Rate of decrease (ng/mL per 24 h) | Half-life (h) |
|------------------|----------------------------------|--------------|
|                  | Nonremission | Remission     | Remission    |
| Total            | 111 (–65 to 286) | 185 (62–308) | 55 (18–93)  |
| Female           | 62 (–176 to 282) | 183 (27–339) | 48 (16–79)  |
| Male             | 143 (3–283)    | 187 (91–283) | 61 (23–99)  |

* Data are expressed as means and 95% CI.
the upper limit of the reference interval for the patient’s age and sex. The corresponding z scores for the IGF-I concentrations of each patient are reported in Table 1. As shown in Fig. 2B, only 9 of 23 patients who achieved remission had an IGF-I concentration during hospitalization that was below the upper limit of the appropriate reference interval (value $<1.0$ in the figure), and these patients all had z scores of 2.0 or less (Table 1). A 10th patient (patient 9 in Table 1) had a z score of 2.0, although the patient’s IGF-I concentration was slightly above the upper limit of the reference interval. Thus, consistent with expectations based on the apparent half-lives of IGF-I shown in Table 2, only 10 of 23 patients who achieved remission had a z score of 2.0 or less during hospitalization. Not surprisingly, none of the nonremission patients had normal values (Fig. 2A), and the lowest z score in the nonremission group was 3.4 (Table 1).

Fig. 3 shows the rate of decrease of IGF-I by hospital day for all patients, with IGF-I expressed as a percentage of the value before surgical intervention. By day 2 after the surgical procedure, IGF-I had fallen to $<65\%$ of its preoperative concentration in 20 of the 23 patients (87\%) who were later found to be in biochemical remission, but in none of the patients who did not achieve remission. By the day of hospital discharge (day 2 or day 3 after the surgical procedure), the mean (SD) IGF-I concentrations decreased to 52\% (13\%) of the preoperative values in the patients who achieved remission. In the patients who did not achieve remission, the corresponding mean (SD) decrease of IGF-I was 19\% (15\%) from the preoperative IGF-I.

In patients who achieved remission, IGF-I continued to fall after hospital discharge (Table 1). The mean (SD) concentrations at 8 weeks were 62\% (24\%) of the IGF-I concentrations at the time of discharge. In the group of patients who did not achieve remission, IGF-I did not continue to fall and remained above the upper limit of the appropriate reference interval (Table 1; $P = 0.0007$, remission vs nonremission groups).

IGF-I measurements were available at follow-up beyond 8 weeks for all but 6 patients in the remission group (see online Supplemental Table 2) and confirmed remission. Only one patient in that group had an abnormal IGF-I z score during that time; the IGF-I z score remained $\leq 2$ for the rest of the 22 patients in the remission
The IGF-I z score remained above 2 in all patients who had not achieved remission.

COMPARISON OF EARLY POSTOPERATIVE CONCENTRATIONS OF GH AND IGF-I

Fig. 4A shows the changes of GH during the perioperative period. On the first postoperative day, mean GH decreased from preoperative values in all patient groups, whether in remission or not ($P < 0.001$). GH then increased on the second postoperative day in 13 of the 28 (total) patients, but showed no significant change between days 2 and 3 (Fig. 4A), suggesting that the concentrations on day 2 represented stable GH concentrations after any temporary effects of the surgical procedures.

Fig. 4B shows the relationship of GH and IGF-I on postoperative day 2. For all nonremission patients, IGF-I was >65% of preoperative values and GH was >2.7 ng/mL. By contrast, all patients in whom IGF-I was <65% of preoperative values and GH was <2.7 ng/mL on day 2 were subsequently found to be in remission (Fig. 4B). A diagonal line on the bivariate plot separated the 2 patient groups.

Discussion

Following pituitary surgery, many patients in whom GH-secreting tumors have been successfully removed notice clinical improvement, starting when they wake up from the anesthetic and note that the hyperhidrosis of their hands, feet, and face has resolved. In the next day or two, diuresis often ensues and the tightness and joint stiffness in their hands resolves and their hands feel more supple. The patients remain anxious, however, regarding whether they are in remission. Assessment of remission requires later follow-up, with measurement of IGF-I and performance of OGTT, which in our center is performed at the patients’ 8-week follow-up. Our preliminary results here suggest that rapid decline of IGF-I measured by LC-MS, along with GH >2.7 ng/mL, identifies some patients as being in remission within 3 days of the operation. This would make further management simpler and, particularly for patients who need to travel long distances, facilitate communicating with them about their prognosis.

The roles of GH and serum IGF-I in the evaluation of patients with acromegaly have been extensively reviewed by Clemmons (13). His early study on the measurement of IGF-I (then called somatomedin C) showed that successful therapy of acromegaly was associated with normalization of values, but measurements were made weeks to months after treatment (21). As pointed out by Clemmons (13), IGF-I results can be difficult to interpret. Analytical variables that affect interpretation include the changing methods of assay, the lack of universally adopted calibrators, the variable effects of IGF-binding proteins (which are increased in acromegaly), and the lack of linearity between the earlier RIA and later immunoassays. The assay used in the
current study employed LC-MS and was not subject to interference by IGFBP-3. In addition, the assay’s imprecision allowed the analytically sensitive detection of changes in IGF-I concentrations over time. Moreover, the reference intervals for this assay have been determined in >2000 individuals in the United States (16) and thus could be used in the population of patients in the study.

When the tumoral source of GH is removed, as occurs following successful surgery, concentrations of GH fall (Fig. 4A) and the release of IGF-I from the liver is reduced; however, the half-life of total IGF-I is prolonged vs that of free IGF-I, which mediates feedback on GH secretion (15). In the present study, the mean half-life of total IGF-I was 55 h. This is much longer than the half-life of free IGF-I, which is measured in minutes (14), but is similar to half-lives of approximately 42 h for total IGF-I that can be estimated from the data of Clemmons et al. (22) (Fig. 1B) following cessation of infusions of combined recombinant IGF-I and IGFBP-binding protein-3. If two half-lives of total IGF-I have elapsed since removal of the GH-secreting tumor, then IGF-I concentrations should fall by at least 75%, and this will often bring the concentration down into the normal range. For patients whose preoperative IGF-I is extremely high, longer times are required.

This study adds to the limited literature on the rate of decline of IGF-I in clinical settings. The kinetics are complex, reflecting changes in concentrations of at least 3 species: (a) free IGF-I, (b) IGF-I bound to IGFBP-3, and (c) the ternary complex of IGF-I, IGFBP-3, and acid labile subunit (11). Pharmacokinetic studies indicate that each is cleared with its own half-life (14, 23). In clinical settings, IGF-I is also being released into the circulation, as are IGFBPs and ALS. Despite this complexity, the rates of decline of total IGF-I in this study were similar among individuals who achieved remission.

The declines of IGF-I after pituitary surgery are similar in the present study and the study of Feelders et al. (16). The earliest time point studied by Feelders et al. was 7 days after pituitary surgery. In Fig. 1 of the Feelders article (16), the IGF-I concentrations had fallen by day 7 to approximately 35% and 62% of preoperative values, respectively, in patients who were and were not found to have suppressed GH concentrations during OGTT 1 year later. The corresponding values at postoperative day 2 in the present study were approximately 54% and 81% (Fig. 4B). These differences between the studies appear to be consistent with the differences between the 2 studies in the times of sample collection after the surgical procedures and with the rates of decline of IGF-I reported here during the early hours after pituitary surgery.

Our study has limitations. First, it was not a formal study of diagnostic accuracy, but rather was an exploratory study with a relatively small number of patients who did not achieve remission. Conclusions about diagnostic utility of IGF-I testing in the immediate postoperative period must await a diagnostic-accuracy study. Nonetheless, the data on the patients who achieved remission appear to be robust and have intrinsic value and help to define the expected rate of decline of IGF-I in patients who will be found to be in remission. Second, IGF-I and GH predict biochemical remission of acromegaly but cannot alone determine whether a tumor is completely removed. The evaluation of whether a tumor is completely removed depends not only on biochemical evidence, but also on imaging studies, as some tumors secrete little hormone (e.g., sparsely granulated GH-secreting tumors) (24), as seen in 2 patients in this study; thus, patients can be in biochemical remission while still having residual tumor. This limitation of hormonal studies is not specific to the immediate postoperative period but is present also in the later determination of remission of acromegaly, where measurements of GH and IGF-I are nonetheless important markers of remission.

In summary, our study defines the expected rates of decline of IGF-I following surgical treatment of GH-secreting pituitary tumors. The apparent half-lives of total IGF-I demonstrate that an increased IGF-I on day 2 or 3 after surgery cannot be used to predict persistent disease. Whether the rate of fall of IGF-I can be used to predict remission must await a study of its diagnostic accuracy. With the increasing availability of immunochromatographic (27) and mass spectrometric measurement procedures for human IGF-I in serum (25, 26), studies of the diagnostic accuracy of the rate of fall of IGF-I after pituitary surgery appear to be warranted to determine its diagnostic sensitivity and specificity, as an adjunct to GH testing, for early identification of patients who are in remission.

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