Correlation between GH and IGF-1 during treatment for acromegaly

Edward H. Oldfield, MD,1 John A. Jane Jr., MD,1 Michael O. Thorner, MBBS, DSc,2 Carrie L. Pledger, MA,1 Jason P. Sheehan, MD, PhD,1 and Mary Lee Vance, MD2

Departments of 1Neurological Surgery and 2Medicine, University of Virginia Health System, Charlottesville, Virginia

OBJECTIVE The relationship between growth hormone (GH) and insulin-like growth factor–1 (IGF-1) in patients with acromegaly as serial levels drop over time after treatment has not been examined previously. Knowledge of this relationship is important to correlate pretreatment levels that best predict response to treatment. To examine the correlation between GH and IGF-1 and IGF-1 z-scores over a wide range of GH levels, the authors examined serial GH and IGF-1 levels at intervals before and after surgery and radiosurgery for acromegaly.

METHODS This retrospective analysis correlates 414 pairs of GH and IGF-1 values in 93 patients with acromegaly.

RESULTS Absolute IGF-1 levels increase linearly with GH levels only up to a GH of 4 ng/ml, and with IGF-1 z-scores only to a GH level of 1 ng/ml. Between GH levels of 1 and 10 ng/ml, increases in IGF-1 z-scores relative to changes in GH diminish and then plateau at GH concentrations of about 10 ng/ml. From patient to patient there is a wide range of threshold GH levels beyond which IGF-1 increases are no longer linear, GH levels at which the IGF-1 response plateaus, IGF-1 levels at similar GH values after the IGF-1 response plateaus, and of IGF-1 levels at similar GH levels.

CONCLUSIONS In acromegaly, although IGF-1 levels represent a combination of the integrated effects of GH secretion and GH action, the tumor produces GH, not IGF-1. Nonlinearity between GH and IGF-1 occurs at GH levels far below those previously recognized. To monitor tumor activity and tumor viability requires measurement of GH levels. 

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of the normal population for the patient’s age and sex, in addition to the measured values.

The results refine the knowledge of the relationship between GH and IGF-1 in general, define the GH/IGF-1 relationship at GH levels less than 20 ng/ml, establish the range of GH levels in which the relationship to IGF-1 levels is linear (≤ 4 ng/ml for absolute IGF-1 levels and ≤ 1 ng/ml for IGF-1 z-scores, rather than the current generally accepted value of 20–60 ng/ml), establish GH levels at which IGF-1 levels plateau (10 ng/ml, rather than the current generally accepted level of 20–60 ng/ml), reveal the wide array of GH levels at which IGF-1 levels plateau in individual patients, and validate that a very wide range of IGF-1 levels occurs in different individuals with similar levels of GH.

Methods

In this retrospective analysis, after receiving institutional review board approval, we examined the relationship between GH and IGF-1 in 118 patients with acromegaly who were treated with surgery and Gamma Knife radiosurgery (Elekta AB) at the University of Virginia Health System between December 2002 and April 2014. Patients were excluded from analysis if no GH and IGF-1 samples were obtained within 1 month of each other or if all measured values were obtained under the influence of pegvisomant therapy; 25 patients were excluded, leaving 93 patients for analysis, which included 52 women (age 18–72 years) and 41 men (age 28–76 years). Values of IGF-1 obtained within 8 weeks of surgery or within 4 weeks of the introduction of, or a change in the dose of, medical therapy, or within 4 weeks of pegvisomant therapy, were excluded, as the IGF-1 level might not have had enough time to adjust to the new level of GH produced by the therapy. All patients underwent surgery and all received Gamma Knife radiosurgery. There were 414 pairs of GH and corresponding IGF-1 values for analysis. GH and IGF-1 assays performed were as previously described.26 65 of the 414 sets of samples were taken while the patient was on stable medical therapy (a dopamine agonist, 9 patients; a somatostatin analog, 56 patients).

GH was measured by using 2-site enzyme-labeled chemiluminescent immunoassays on the Nichols Advantage system until February 28, 2006, and on the Siemens Immulite 2000 system thereafter. The coefficient of variation (CV) of the Nichols assays was less than 10%. The CV of the Siemens GH assay was 3%–6% at concentrations of 6–25 ng/ml. The Immulite assay was restandardized in 2012. Thus, for normalization of the GH over the course of the study to the current assay, the values before February 28, 2006 (Advantage to Immulite transition), were multiplied by 1.63, and for restandardization of the Immulite assay in 2012 all GH values before February 25, 2012, were calculated by (value before 2–25–2012) × (0.77) − 0.02 to yield a result comparable to the results using the current assay.

IGF-1 was measured by chemiluminescent immunoassays on the Advantage analyzer and, beginning on January 26, 2006, on the Immulite analyzer. The immunoassay approaches were replaced in 2010–2011 with a mass spectrometric method at Nichols Institute/Quest Diagnostics (San Juan Capistrano), which agreed closely with the Immulite assay (regression slope and intercept not significantly different from 1 and 0, respectively).10 For consistency with the current assay, values before January 26, 2006, were multiplied by 0.92. The CV of the IGF-1 immunoassay was 3%–7% at concentrations of 70–500 ng/ml. The day-to-day CV of the IGF-1 mass spectrometric assay was 3.1%–5.2% at concentrations of 57–740 ng/ml.10 IGF-1 z-scores specific for age and sex were derived from the study by Elmlinger et al.16 External quality assurance was provided through programs of the United Kingdom National External Quality Assessment Service (UK NEQAS) and the College of American Pathologists.

Statistical Analysis

For comparisons of sets of IGF-1 values among categories of GH levels, the Mann-Whitney U-test was used. Nonlinear regression lines used the least-squares method (see Fig. 3). GraphPad Prism (GraphPad Software) was used for the statistics and graphs.

Results

In many patients, examination of the GH and IGF-1 values over time following surgery, radiosurgery, and medical therapies demonstrates a close correlation between GH and IGF-1 as the levels drop in individual patients in response to the therapies (Figs. 1 and 2), but this close correlation only occurs at very low levels of GH. Note the close correspondence of the relative changes in IGF-1 and GH levels as the GH levels drop below 5 ng/ml following surgery and during the response to Gamma Knife radiosurgery in the patients shown in Figs. 1 and 2. When values within various categorical ranges of GH are examined, there is a clear correlation between GH and IGF-1 as GH increases, but only until a plateau of IGF-1 levels begins to be reached at levels of GH in the range of 10 ng/ml (Fig. 3). However, this plateau occurs at lower levels of GH in many individuals (Fig. 2).

When all data are plotted (Fig. 4), the relationship at the lower levels of GH demonstrates a linear correspondence of absolute levels of IGF-1 to increasing levels of GH only until GH reaches 4 ng/ml, and only to 1 ng/ml using IGF-1 concentrations adjusted for age and sex, and then there are diminishing increases in IGF-1 with increasing levels of GH until GH reaches a level of 10 ng/ml, when IGF-1 levels plateau (Fig. 4). As expected, the results demonstrate a wide array of IGF-1 levels at similar GH levels among patients (Fig. 4). The previously described log-linear relationship between GH and IGF-1 exists only to GH levels of about 7 ng/ml (Fig. 4C).

A recent report examined the range of normative values obtained by 6 different commercial assays for IGF-1. Although the authors concluded that there was moderate to good agreement between the methods, and that the lower limits of the reference intervals of the 6 assays were similar, the upper limits varied substantially.12 To validate the curves produced in the analyses above, and to compare the results using each of the different assays over time, we also analyzed curves separately for each of the 3 large sets of samples in which all GH and IGF-1 measurements
FIG. 1. Relationship between GH and IGF-1 in a representative patient. Left: Levels of GH and IGF-1 obtained simultaneously over time before surgery, after surgery, after radiosurgery, and with Sandostatin LAR (at 20 months only, squares) and in a single patient. The black arrow indicates surgery, and the gray arrow indicates radiosurgery. Right: Graph showing the relationship between GH and IGF-1 over the range of GH values in the same patient.

FIG. 2. Graphs showing the relationship between GH and IGF-1 z-scores in 8 patients, each in a separate frame, demonstrating a typical “saturation” curve in individuals as GH levels increase. Data points in gray were obtained during treatment with a somatostatin analog. Data points in triangles are values acquired before surgery. Data points in open circles or gray-filled circles represent values when sampling probably occurred during a pulse of GH; note that there are only 3 such points among all 63 samples. Note the relatively linear correlation of GH and IGF-1 only at GH values of 2 ng/ml or less in most patients, but variation in the level of GH at which the IGF-1 levels plateau from patient to patient, and a wide range in IGF-1 z-scores after IGF-1 plateaus among patients.
were performed with the same assay (Supplementary Fig. 1). Note that the comparison of each of those curves to one another demonstrates that they correspond closely to each other and to the curves produced using the normalized values shown in Fig. 4.

Discussion

Correlation Between GH and IGF-1

The early report by Clemmons et al. demonstrated that circulating GH and IGF-1 levels correlate in a nonlinear fashion,13 likely because of saturation of GH receptors when GH exceeds certain threshold levels.13 Lamberts et al. examined the relationship between GH and IGF-1 in 22 patients with acromegaly and concluded that there was “a statistically significant linear correlation, if only GH values of less than 100 mcg/L were considered.” He and his colleagues later summarized their findings by stating, “Only in GH concentrations up to 40–60 µg/L do GH and IGF-1 demonstrate a close correlation.”14 In 1988 Barkan et al. reported a study of the relationship of IGF-1 levels and 24-hour mean GH levels in 21 patients with acromegaly, 11 of whom were studied before and during medical treatment with a short-acting somatostatin analog.3 They concluded that a linear relationship exists between GH and IGF-1 until GH exceeds 20 ng/ml, when the response of IGF-1 peaks and the IGF-1 curve plateaus. Bercu et al. examined the correlation between GH and IGF-1 in normal children and children with GH deficiency and found a linear relationship with GH less than 10 ng/ml.7 However, in these studies the limited number of data points with GH below 20 ng/ml reduced the capacity to define precisely the relationship between GH and IGF-1 in the range between 0.5 and 20 ng/ml. Additionally, the early assays for GH were not standardized, and the accuracy and sensitivity of the assays have greatly improved since the 1970s, when the cutoff for glucose suppression of GH in normal subjects was 5 ng/ml, later fell to 1 ng/ml, and then fell further to 0.4 ng/ml. Moreover, it is now known that the normal range of values of IGF-1 concentrations varies with age and sex; no prior analyses of the correlation between GH and IGF-1 has been performed using z-scores for IGF-1 to account for these differences.

In normal subjects the majority of the 24-hour production of GH occurs during pulses, and the pulses occur against a low background of basal GH.5,18,19,34,39 In contrast, in patients with acromegaly most of the secreted GH derives from basal, not pulsatile, secretion, and the incremental changes of the GH levels during pulses in acromegaly are less prominent in relation to the elevated basal GH concentrations.18,19,34,39 Furthermore, in acromegaly a single random sample of serum GH corresponds to mean 24-hour levels obtained with sampling every 10–20 minutes ($r = 0.89$, $p < 0.0001$), to the mean of 5 samples taken every 1–2 hours, and to the mean of hourly samples for 3 or 8 hours ($r = 0.93–0.98$, $p < 0.0001$),2,4,23 which led Barkan et al. to conclude that, “Despite differences in some indi-

FIG. 3. **Left:** When categorical ranges of GH and absolute values of IGF-1 are examined, there is a linear correlation of GH and IGF-1 as GH increases to 3–6 ng/ml, and a plateau level of IGF-1 is reached at GH levels of 10 ng/ml or higher. Note that although there is a substantial range in the IGF-1 values for similar values of GH among individuals, as manifest by the large error bars, the points are significantly different from the adjacent group (GH 0–1 vs 1–2, $p = 0.0001$; GH 1–2 vs 2–3, $p = 0.001$; GH 2–3 vs 3–6, $p = 0.04$; GH 3–6 vs 6–10, $p = 0.001$; and GH 6–10 vs 10–15, $p = 0.01$ [Mann-Whitney U-test for unpaired samples]) until a GH level of 10 ng/ml is reached. **Right:** When categorical ranges of GH are compared with the mean z-scores, there is a linear correlation between GH and IGF-1 only until a level GH of 2–3 ng/ml is reached. Again, there is a substantial range in the IGF-1 z-scores for similar values of GH among individuals, as manifest by the large error bars; the points are significantly different from the adjacent group (GH 0–1 vs 1–2, $p = 0.0001$; GH 1–2 vs 2–3, $p = 0.003$; GH 2–3 vs 3–6, $p = 0.02$; GH 3–6 vs 6–10, $p = 0.002$; GH 6–10 vs 10–15, $p = 0.2$ [Mann-Whitney U-test for unpaired samples]) until a GH level of 6–10 ng/ml is reached. The ranges covered by the points in both graphs, from left to right, are the median GH values between 0–1 ng/ml ($n = 146$), 1–2 ng/ml ($n = 87$), 2–3 ng/ml ($n = 38$), 3–6 ng/ml ($n = 51$), 6–10 ng/ml ($n = 28$), 10–15 ng/ml ($n = 15$), and greater than 15 ng/ml ($n = 49$), respectively. Mean ± SDs of IGF-1 are shown in both graphs.
individual pairs of data, overall there was a good correlation between the mean 24-h GH concentration and a single GH value at 1600 h. Thus, a single GH value can serve as a valid estimate of the magnitude of GH hypersecretion in patients with active acromegaly. Finally, a recent study demonstrated that simplified blood sampling protocols accurately reflect the mean GH concentration of 144 samples taken at intervals of 10 minutes over 24 hours in patients with active acromegaly and patients being treated with somatostatin analogs; a single fasting GH level corresponded to the mean GH of 144 samples with a regression coefficient of 0.87 in patients with active acromegaly and of 0.81 in patients being treated with somatostatin agonists.

As such, most random measurements of GH in patients with acromegaly reflect the relatively steady basal GH level, rather than a level associated with a secretory pulse. Moreover, irradiation attenuates the intensity of GH pulses in acromegaly, even after GH and IGF-1 levels reach normal levels after therapy. Accordingly, we examined the correlation of GH and IGF-1 in patients with acromegaly who had been treated with radiosurgery. Note the consistency of the relative changes in values of GH shown in Fig. 1 right, in which there were only 3 instances when the measured GH seemed to be associated with a secretory pulse among the 63 measurements.

Moreover, consider the influence on the curves, shown in Figs. 1, 2, and 4, of a sample taken during a pulse of GH secretion. A GH level sampled during a secretory pulse will be to the right of the true background level. Consequently, any samples taken during a secretory elevation of GH would pull the curve toward the right. Hence, in the absence of the effects of samples taken during GH pulses, the curves shown in all the graphs would be even farther to the left than shown here—and the curves presented here are already substantially to the left of the current understanding of the GH-versus-IGF-1 relationship.

When screening patients for a diagnosis of excess (acromegaly) or low (GH deficiency) GH production, it is important to assess levels of IGF-1 rather than GH, because of the risk of sampling during a pulse of GH secretion, and because most of the biological consequences of excess GH are effected via IGF-1. The adverse effects of incompletely treated acromegaly correlate with those effects. However, this does not diminish the importance of also assessing GH levels to monitor the effects of treatment on the tumor, since GH-producing tumors secrete GH, not IGF-1. Pretreatment GH levels, more accurately than IGF-1 levels, predict the outcome of therapies (see below). Despite this, today many centers routinely monitor only IGF-1 levels, and not GH levels, before and after treatment in patients with acromegaly.

Our results indicate that the transition to nonlinearity between GH and IGF-1 occurs at much lower GH levels than previously appreciated, as a linear correlation between GH and IGF-1 occurs only at very low levels of GH, up to about 4 ng/ml using raw IGF-1 values, and only up to 1 ng/ml when using IGF-1 z-scores appropriate for age and sex. Thus, IGF-1 levels do not accurately correspond to tumor GH production unless GH is in the range of 4 ng/ml or lower.

**Clinical Implications of Establishing the Correct Correlation of GH and IGF-1**

In acromegaly, each GH-producing tumor has its own intrinsic level of GH production per mass of tumor, which is homogeneous over the tumor mass, and the GH secretion per mass of tumor varies greatly among tumors. This relationship is not so for IGF-1, because in many patients presurgical GH levels far exceed those associated with plateau levels of IGF-1. Examine Fig. 4. Surgical removal of half of a tumor that is associated with a preoperative
GH level of 40 ng/ml will reduce the GH level by about 50% but will produce little change in the absolute level of IGF-1 or the z-score for IGF-1. For predicting remission of acromegaly after surgery, the chances for remission are greater if the preoperative GH level is less than 30–50 ng/ml, but IGF-1 levels cannot be used to predict remission.21,23

Similarly, since the first studies of radiation therapy, it has been established that preirradiation GH levels decrease fractionally as a function of time, to 50% at 2 years, 20%–25% at 5 years, and 10% at 10 years.5,15 Hence, patients with pretreatment GH levels of 20 ng/ml or less are more likely to achieve normal levels of IGF-1 and to do so faster than patients with higher pretreatment GH levels. However, this fractional change does not occur with IGF-1, as pretreatment IGF-1 levels have plateaued in many patients. For example Barkan et al. observed that GH levels dropped to 41% of pretreatment values at 3.7 years, and to 19% at 7 years, but “plasma IGF-1 declined only modestly to 77% and 83% of the pre-radiation values at the same intervals.”94

The value of understanding the relationship between GH and IGF-1 levels is also evident in attempts to compare fractionated radiation therapy and radiosurgery. Three points are worthy of emphasis. In the era of fractionated radiation therapy most patients had not had prior surgery and had very high baseline levels of GH before the irradiation. For instance, in the studies of Eastman et al. and Barrande et al., the mean preirradiation GH levels were 60 ng/ml and 38 ng/ml, respectively.5,15 Compare these pretreatment levels to recent reports on the outcome of radiosurgery for acromegaly in which all patients had had surgery before radiosurgery and pretreatment median GH levels were 4.3 ng/ml20 and 7.0 ng/ml.27 Then, is it any surprise, if radiation has a fractional effect on GH levels over time, that the patients treated with radiosurgery, whose very low pretreatment IGF-1 levels were on the ascending portion of the IGF-1 versus GH relationship, had a faster therapeutic response than did the patients treated with conventional irradiation, whose pretreatment GH values were well beyond values at which IGF-1 plateaued? The second point is that, unlike with surgery, in which average presurgical GH levels are so high that there is a poor correlation between percentage of tumor removal and change in IGF-1 levels, in radiosurgical series pretreatment IGF-1 levels do correlate, at least statistically, with likelihood of response; however, this may simply reflect the fact that at these low pretreatment GH levels the pretreatment IGF-1 levels are on the ascending, and not the flat, portion of the relationship between GH and IGF-1. The third point is related to arguments that medical therapy during radiosurgery for GH-producing adenomas reduces the likelihood of remission.55

It is likely that the patients who received medical therapy during treatment did so because they had more severe elevation of GH and IGF-1 than patients who did not need, and thus did not receive, medical therapy. This is clear in the original report by Landolt et al., which concluded that medical therapy during radiosurgery had tumor-protecting effects; the patients on medical therapy during treatment had an average pretreatment GH level of 30 ng/ml, compared with 18 ng/ml for those without medical treatment.55

Finally, the likelihood of reaching normal concentrations of GH and IGF-1 with therapy with somatostatin analogs is higher in patients with lower GH levels.8,17,28 Moreover, partial surgical debulking to reduce GH levels increases the likelihood of normalizing GH and IGF-1 levels with somatostatin treatment, and most of the normal values are reached in patients whose pretreatment hormone levels are < 10 ng/ml, on the ascending portion of the GH-versus-IGF-1 curve.14,31

Conclusions

In summary, it is levels of pretreatment GH, rather than IGF-1, that are most informative when attempting to predict the outcome of surgery, the time to reach remission, and the final outcome of the response to fractionated radiation therapy or radiosurgery, and the results of medical therapies directed at the somatotroph, in large measure because of the nonlinear relationship between IGF-1 and GH. Thus, to monitor tumor activity and tumor viability it is GH concentrations that are the more reliable measure. The most accurate assessment of the patient, to examine tumor activity and the status of an abnormal hormonal milieu before and after therapy, requires measurement both of GH and IGF-1.

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The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

**Author Contributions**

Conception and design: Oldfield. Acquisition of data: all authors. Analysis and interpretation of data: Oldfield. Drafting the article: Oldfield. Critically revising the article: all authors. Reviewed submitted version of manuscript: all authors. Approved the final version of the manuscript on behalf of all authors: Oldfield. Statistical analysis: Oldfield. Administrative/technical/material support: Oldfield, Jane, Thorner, Sheehan. Study supervision: Oldfield.

**Supplemental Information**

Online-Only Content

Supplemental material is available with the online version of the article.

*Supplementary Fig. 1.* https://thejns.org/doi/suppl/10.3171/2016.8.JNS161123.

**Correspondence**

Edward H. Oldfield, Department of Neurological Surgery, University of Virginia, Box 800212, Charlottesville, VA 22908. email: eho4u@virginia.edu.