



Biochemical markers of acromegaly: GH vs. IGF-I

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Abstract

The development of sensitive and specific growth hormone (GH) and insulin-like growth factor I (IGF-I) assays opened a new page in the diagnosis and surveillance of acromegaly. Currently, it is possible to make an accurate pre-operative diagnosis even in patients with virtually no typical clinical signs of the disease and to monitor the efficacy of therapeutic intervention with a high degree of precision. This review briefly discusses the performance parameters of GH and IGF-I as diagnostic and surveillance tools in patients with acromegaly. In brief, whereas GH-based parameters may offer the advantage of disclosing dysregulation of GH secretion, a single plasma IGF-I measurement provides the most comprehensive assessment of both the overall GH output as well as the pattern of GH presentation to the peripheral tissues. Judicious use of both biochemical markers allows accurate and early diagnosis, precise assessment of the efficacy of therapeutic interventions, permits adjustment in the dose of medication and allows for unequivocal demonstration of a final cure.

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Keywords: Acromegaly; Insulin-like growth factor; Growth hormone; Biochemical markers; Diagnosis

1. Introduction

Acromegaly is a chronic disease that, in the majority of cases, is due to the presence of a benign growth hormone (GH)-producing tumor of the pituitary gland. Chronic hypersecretion of GH leads to an increased production of insulin-like growth factor-I (IGF-I) by virtually all organs and tissues. High levels of IGF-I cause increased somatic and visceral growth and, therefore, mediate virtually all symptoms and signs of acromegaly. In the absence of IGF-I generation, high plasma GH levels cannot promote growth as witnessed by the dwarfism in individuals with genetic mutations of GH receptors (Laron's Syndrome). High levels of GH, however, are diabetogenic—independent of IGF-I—and impaired glucose tolerance or frank diabetes is frequently seen in patients with acromegaly.

In the distant past, the diagnosis of acromegaly was established based solely on physical grounds, and only the patients with the most severe clinical picture were brought to medical attention. In the 1960s, the devel-

opment of a radioimmunoassay (RIA) for detecting GH levels radically changed the diagnostic approach; for the first time it became possible to confirm the diagnosis biochemically and to judge the success of therapeutic interventions. Methods for measuring IGF-I (formerly known as somatomedin C [SmC]) levels became widely available about 20 years later and added yet another biochemical marker to the diagnostic and follow-up armamentarium. Progressive improvements in assay development have allowed for progressively better definitions of “normality” and, as a result, have permitted the diagnosis to be biochemically established in patients with only mild forms of disease.

We are now at the stage where it is possible to diagnose even pre-clinical acromegaly and to gauge precisely the completeness of therapeutic interventions. The recent refinement in surgical techniques and radiation therapy, coupled with the widespread availability of effective pharmacologic suppressors of GH secretion or action, makes it possible to prevent the appearance of clinical acromegaly early on and to arrest its development in virtually every patient with this disease. Thus, further refinement of the definition of “normality” of GH and IGF-I milieus has become imperative, and the

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criteria by which active disease is defined appears to change almost constantly. The existence of two potential analytical markers—GH and IGF-I—as well as a plethora of dynamic tests allegedly identifying abnormalities in GH regulation prompted a major question: which biochemical parameter is best for use in clinical practice?

Like virtually all other endocrine systems, the somatotrophic axis consists of the trophic hormone (GH) and the target hormone (IGF-I) that exerts negative feedback at the pituitary and hypothalamic level. As a rule, the diagnosis of endocrine dysfunction is established by abnormal concentrations of the target hormone. For example, the diagnosis of Cushing's syndrome is made not on the basis of adrenocorticotrophic hormone (ACTH) measurements (which are often in the normal range in Cushing's disease), but by demonstrating high output of cortisol. The same is true in cases of thyroid-stimulating hormone (TSH)-producing tumors in which the TSH level is often "normal" in the presence of high T₄/T₃ levels. Measurements of the trophic hormones are mainly used to demonstrate the level of endocrine pathology (primary vs. secondary) and to establish the diagnosis of subclinical target gland hypofunction. Thus, on purely theoretical grounds, acromegaly should not be an exception; the target hormone (IGF-I) should be a better biochemical indicator of the disease than the trophic hormone, GH. On the other hand, the majority of studies assessing biochemical parameters of disease control as determinants of the mortality rate relied on assessments of plasma GH rather than IGF-I levels. Additionally, dynamic studies of GH secretion are purported to uncover subtle abnormalities in the integrity of the somatotrophic axis and even to predict the recurrence of disease in the apparently "cured" patients. Also, the increased sensitivity of GH assays (immunochemiluminometric assay [ICMA] or immunofunctional assay [IFMA] vs. formerly used RIA) offer a promise to uncover even minimally elevated GH levels.

The recent introduction of Somavert[®] (pegvisomant for injection), a competitive GH antagonist, into clinical practice changed the equation even further by lowering plasma IGF-I levels while increasing plasma GH levels. Thus, it becomes imperative to re-assess the diagnostic utility of both analytes to determine which is a better parameter for evaluation of disease control. The purpose of this review is to provide an evidence-based approach to this dilemma.

2. Plasma GH measurements

Originally, plasma GH was measured with the use of polyclonal RIAs. Inherent limitations of these assays included relatively low sensitivity of about 1 µg/L. Additionally, high variability in the low assay range precluded accurate distinction of the values below

approximately 2 µg/L. These assays did not allow for a clear definition of basal GH levels in normal individuals. Development of sensitive ICMA or IFMA improved sensitivity to about 0.002–0.01 µg/L and disclosed active GH pulsatility in the previously undefined low GH range in healthy controls. However, some of these monoclonal assays are specific for the 22 kd isoform of GH; this lowers the absolute values of measured GH concentrations by about 30%. Additionally, the use of different GH standards (World Health Organization's [WHO] standard code 80/505, WHO 88/624, HS 2243E [National Institutes of Health standard] or AFP-44793 B) makes comparisons of the results obtained with a particular GH assay inappropriate for other assay systems. Plasma GH levels are influenced by a variety of physiological and pathological conditions (age, gender, nutritional status, stress, liver and renal diseases, diabetes, etc.) and drugs (estrogen, dopamine, etc.). Careful consideration of these pitfalls is essential for the proper interpretation of GH values.

2.1. Random GH levels

Both in healthy individuals and in patients with acromegaly, plasma GH exhibits a prominent pulsatile secretion pattern. In healthy people, most GH values throughout the day are <0.1–0.2 µg/L, and periods of secretory quiescence are interspersed by GH pulses that may reach values as high as 20–30 µg/L. Since, with the possible exception of a nocturnal GH pulse (around midnight), the location of GH pulses is not predictable, a randomly drawn blood sample is unlikely to permit differentiation between health and disease. It is possible that only exceedingly high GH values (in excess of 50 µg/L) can indicate GH hypersecretion with a high degree of confidence. Thus, strict adherence to the recent recommendation that random plasma GH <0.4 µg/L excludes active disease may be misleading.

2.2. Multiple GH sampling

The previously mentioned limitations can be partially overcome with the use of several GH samples drawn throughout the day (for example, by drawing samples every 2 h over a 10-h daytime period) or even with frequent (every 10–20 min) sampling throughout the entire 24-h period. The latter approach is obviously reserved for purely research protocols; whereas, the former one is feasible even in a clinical setting. However, even the most stringent sampling procedure does not always differentiate between health and disease [1]. We have shown recently that a proportion of newly diagnosed and untreated patients sampled every 10 min for 24 h may have mean daily GH levels within normal range [2]. The real frequency with which such patients come to medical attention is unknown, but their number

has grown rapidly over the past several years. Perhaps as many as 10–20% of all new patients with acromegaly seen in large referral pituitary centers fall into this category. The problem becomes even more acute when disease status is assessed in previously treated patients [3]. In this population, mean GH levels within the “normal” range are very common.

The interpulse plasma GH level is a much better indicator of GH normalcy, since it rarely overlaps with the very low (<0.1–0.2 µg/L) interpulse GH levels in normal controls [2]. However, the correct definition of this parameter requires very frequent blood sampling, which is impractical in a clinical setting. Additionally, even this parameter may be misleading in a subpopulation of patients with active disease [2,3].

2.3. GH response to TRH

About 50% of patients with acromegaly experience a rapid increase in plasma GH concentrations after an IV bolus of 200–500 µg of thyrotropin-releasing hormone (TRH). The mechanism of TRH action in acromegaly is unknown and does not appear to depend on the presence of TRH-receptor messenger ribonucleic acid (mRNA) in the tumor [4]. The exact criteria by which this “paradoxical” response is interpreted are arbitrary: GH elevations by 50% or 100% above baseline or absolute GH increases by 1.4 or 5 µg/L have been used by different investigators. Obviously, this introduces major discrepancies in the frequency with which “abnormal” responses are seen in different study groups. Also, this GH response to TRH is seen in a variety of conditions not associated with acromegaly, such as depression, psychosis, liver cirrhosis, chronic renal failure, uncontrolled diabetes mellitus type 1 (DM-1) and even in healthy women or in adolescents. Biermasz et al. [5] have suggested that a rise of plasma GH >1.4 µg/L in a surgically cured patient predicts the probability of relapse with 100% certainty. However, Mukada [6] has shown that the GH response to TRH may fluctuate spontaneously in the same patient, and may even appear after surgery in the patients who were “TRH negative” before surgery. This makes the TRH test less than reliable in assessing the residual activity of the disease or in predicting a permanent cure.

2.4. GH suppression by oral glucose

GH suppression using the oral glucose tolerance test is, by far, the most popular means of assessing the integrity of the somatotrophic axis in acromegaly. After oral ingestion of 75 or 100 g glucose, plasma GH levels invariably decline to low levels in healthy people, but the degree of inhibition is impaired in patients with active acromegaly. The cut-off limit for defining normal response has been steadily declining over the past several

years. Using the old RIAs, it was 2 µg/L, and the recent consensus statement [1] lowered it to 1 µg/L, based on the data by Stewart et al. [7].

However, only two studies addressed this issue in a systematic fashion. Freda et al. [8] used a 22-kd specific immunoradiometric assay (IRMA) and found that the upper limit of a normal response (mean + 2 SD) was 0.14 µg/L. This would translate into approximately 0.21 µg/L using the WHO standard code 80/505 and assays measuring other GH isoforms. Costa et al. [9] have defined an upper normal GH level post-glucose administration as 0.25 µg/L, which is in agreement with the aforementioned data by Freda et al. However, there are rare patients with active disease who would still exhibit normal GH levels after receiving oral glucose. This is to be expected, as no statistical definition of normality based on the 95% confidence limits and obtained in a limited sample can cover the entire population range. Importantly, many patients fulfilling these most stringent criteria still exhibit frankly elevated plasma IGF-I levels, and many patients with normal IGF-I levels may have abnormal GH suppression [8,9]. Perhaps, plasma IGF-I and GH suppressibility by glucose reflect different facets of the disease: overall GH hypersecretion and secretory dysregulation.

3. Plasma IGF-I

Plasma levels of IGF-I are maintained primarily by the ambient levels of GH. However, malnutrition of any etiology and use of oral estrogens profoundly lower plasma IGF-I levels. Similarly, as the majority of circulating IGF-I comes from the liver, hepatic pathologies may be accompanied by very low IGF-I levels. With these limitations in mind, it can be certain that plasma IGF-I reflects the prevailing GH milieu. Normality of IGF-I levels was difficult to define with the older assays, and this limited the applicability of IGF-I measurements to diagnosis and follow-up of acromegaly.

Currently, it is well known that IGF-I concentrations depend on sex and age; only when the normative data for a particular assay are grouped according to these variables can the assertion be made that a particular IGF-I concentration is normal for a given patient. Recently, it has become apparent that IGF-I may have both endocrine and autocrine/paracrine components of action. The studies by LeRoith's group [10] have shown that a 60–80% reduction in circulating IGF-I levels does not affect growth rate; only when both the liver *IGF-I* gene and the acid-labile subunit (*ALS*) gene were disrupted and IGF-I concentrations declined even further was growth affected. Whether these data addressing the issue of low IGF-I levels are applicable to the conditions of IGF-I excess is unknown. Isgaard et al. [11] have shown that both pulsatile and continuous GH infusions increase

hepatic IGF-I mRNA (which is responsible for the majority of circulating IGF-I); whereas, only pulsatile GH rapidly increases IGF-I mRNA in the tissues responsible for the somatic growth (cartilage and muscle) and actually amplifies skeletal growth. Thus, the pattern of GH delivery to peripheral tissues may be yet another determinant of growth regulation. However, the equipotency of both modes of GH presentation in terms of hepatic IGF-I mRNA induction suggests that plasma IGF-I is a valid parameter of GH hypersecretion. Recently, Jaffe et al. [12] have reproduced these data in humans.

The relationship between GH and IGF-I in acromegaly is log-linear; at plasma GH concentrations above 20 µg/L, there is very little additional increase in IGF-I levels [13]. Clemmons et al. [14] have shown that a single IGF-I measurement reflects the degree of clinical severity of acromegaly much better than either basal or glucose-suppressed GH. Plasma IGF-I is elevated even in patients with very mild disease and virtually normal GH secretory parameters [2].

In the past, variability between IGF-I assays cast doubt on its usefulness as a valid biochemical parameter for assessing the activity of acromegaly. Currently, there are many commercial assays available that provide good reliability and age- and sex-adjusted norms. This will unquestionably make IGF-I a more widely used analyte in the work-up of acromegaly.

4. Conclusions

The question whether GH or IGF-I is the preferred marker for the diagnosis and surveillance of acromegaly is still open.

There are certain disadvantages in using GH as a yardstick: its levels are constantly changing so that a single value is not reliable, it is a poor reflector of clinical status, and results of dynamic tests are often discrepant with IGF-I results. On the other hand, IGF-I has a long half-life, allowing a single value to be used; it mediates virtually the entire spectrum of clinical manifestations of the disease, and IGF-I levels are elevated even in patients with the mildest activity whose plasma GH levels are within the “allegedly” normal range.

Plasma GH levels are useful in assessing partial biochemical responses to therapy when IGF-I levels may still be maximally increased, and its dynamic responses may provide information about persistent dysregulation of the somatotrophic axis. However, a persistently high plasma IGF-I level is a clear indication to consider therapy; whereas, abnormal GH responses per se are not. Patients with normal IGF-I and abnormal GH responses to glucose need not be treated, but they do require closer follow-up to document potential disease recurrence [15].

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