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Growth hormone measurements in the diagnosis and monitoring of acromegaly

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Abstract Before the availability of immunoassays for IGF-I, growth hormone (GH) measurement was the sole method used in the biochemical assessment of acromegaly. IGF-I has since been established as the most reliable biochemical indicator of acromegaly. The last 25 years has seen important advances in the understanding of the neuroregulation and in the characterization of GH secretion in acromegaly. The availability of supersensitive GH has changed many aspects of the interpretation of GH-value in the management of acromegaly. Hypersecretion and abnormal neuroregulation characterize GH secretion in acromegaly. GH can be measured in many ways: as a single random sample, as multiple samples, either spontaneously or as an integral part of a dynamic test. These approaches give useful information on diagnosis, therapy, and prognosis. There is a place for measuring GH in the management of acromegaly although it complements that of IGF-I.

Keywords Growth hormone · Insulin-like growth factor I · Acromegaly

Introduction

Hypersecretion of growth hormone (GH) is the hallmark of acromegaly. Yet, the value of measuring GH in clinical practice is not clear. Before the availability of immunoassays for IGF-I, endocrinologists relied solely on GH measurements in the biochemical assessment of acromegaly. IGF-I has since been established as the most reliable biochemical indicator of acromegaly.

The last 25 years has seen important advances in the understanding of the neuroregulation and in the characterization of GH secretion in normal and acromegalic subjects. These have been brought about by intensive study and analysis of dynamic tests, spontaneous secretion and by improvements in assay sensitivity. These data have allowed the physiology and pathology of GH secretion to be defined. Resurgent interest in epidemiology of acromegaly has provided valuable data linking biochemical evaluation to health outcomes.

Growth hormone can be measured in many ways: as a single random sample, as multiple samples, either spontaneously or as an integral part of a suppression or stimulatory test. This review will give a perspective on the place of GH measurement in acromegaly. We will review the neuroregulation of GH in normal and acromegalic subjects and the value of single measurements and dynamic testing in the diagnosis and evaluation of treatment of the disease.

GH secretion

Normal

Growth hormone secretion is normally episodic and exhibits a diurnal rhythm with approximately two-thirds of the total daily GH secretion produced at night triggered by the onset of slow wave sleep. Normal GH secretion is characterized by minimal basal secretion and highly regulated secretary episodes (Fig. 1) [1]. For 70–80% of a 24-h period GH levels remain below the level of detection of conventional immunoassays.

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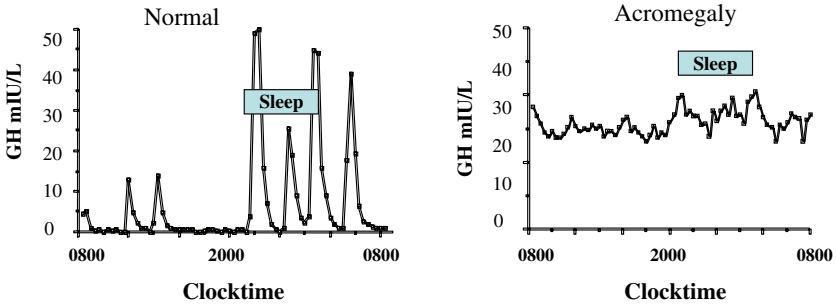

Fig. 1 *Left* panel shows 24-h GH profiles in normal subjects. *Right* panel shows 24-h GH profiles in untreated acromegaly

The ultradian rhythm of GH secretion is generated by coordinated interaction between GHRH and somatostatin. GHRH increases the transcription of the GH gene, promoting synthesis, and secretion of GH. Somatostatin appears to determine the timing and amplitude of GH pulses but has no major effect on GH synthesis. Somatostatin inhibits GH release directly through somatostatin reception expressed on somatrotrophs.

Ghrelin is a newly discovered natural ligand of the GH secretagogues receptor [2] and a potent stimulator of GH release [3]. Ghrelin acts synergistically with GHRH to regulate GH release [4, 5]. The dual control of GH secretion postulated for GHRH and somatostatin should be expanded to incorporate ghrelin.

Although GH secretion is mainly regulated by GHRH and somatostatin, multiple neurotransmitter pathways as well as a variety of peripheral feedback signals modulate its secretion [6]. Factors, which influence GH release, include cholinergic and adrenergic stimuli, oestrogens, thyrotropin-releasing hormone (TRH), IGF-I, glucocorticoids, and opioid [7]. Their effects are exerted at the hypothalamic and pituitary level [8].

Nutrients also modulate GH release. Glucose and fatty acids suppress GH release while certain amino acids stimulate GH secretion (including arginine and leucine). Exercise and physical stress stimulate GH secretion. Poorly controlled diabetes is associated with increased basal and exercise-induced GH levels while obesity reduces basal and stimulated GH secretion [9]. Emotional depression is associated with suppressed GH secretion [10, 11]. Chronic malnutrition and prolonged fasting are associated with elevated GH pulse frequency and amplitude [12].

Acromegaly

In acromegaly, there is derangement in the neuroregulation of GH secretion causing increased output and a highly abnormal pattern of release. GH secretion in acromegaly is characterized by marked blunting of pulsatile secretion and the failure of GH to fall to undetectable levels at any time during the 24-h day [1, 13]. Serum GH levels are elevated continuously throughout the 24-h period [1, 14]. Although GH secretion in acromegaly appears episodic, the pattern is disorderly [15, 16]. Whether this defect arises from abnormal hypothalamic regulation or from random events intrinsic to adenomatous tissue is unresolved. There is loss of negative feedback by IGF-1 on GH secretion [17–19].

The dysregulation of GH secretion in acromegaly is exemplified by the lack of inhibition of GH release after an oral glucose tolerance test. Patients with acromegaly frequently harbor abnormal GH responsiveness to various pharmacological stimuli such as to bromocriptine, TRH and GnRH. Of these, a paradoxical GH response to TRH occurs in 50–75% of untreated acromegaly. The mechanism underlying this phenomenon is not understood but could stem from inappropriate expression of TRH receptors [20]. It has been postulated that TRH produced and released locally by pituitary adenomas act as an autocrine and/or paracrine regulator and affect hormone release or tumor growth [21, 22]. Ray et al. [23] has proposed that adenoma formation and altered physiological/pathological conditions may result in the induction of a range of locally produced chemical mediators. 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 [24].

The OGTT is considered a useful test for the diagnosis of active acromegaly and for the follow-up of patients after treatment for the disease [25]. Stimulatory tests (TRH, GnRH) offer no advantage over OGTT and their use is not recommended in the management of acromegaly.

GH assays

Significant technological advances in the biochemical assessment of acromegaly have been made in recent years. The measurement of GH has evolved from polyclonal radioimmunoassay (RIA) to modern two-site monoclonal antibody, non-isotopic assays with enhanced sensitivity. The old assays were limited by sensitivity and unable to distinguish zero from a measurable low concentration. The development of sensitive GH assays has allowed accurate quantification of previously undetectable values. GH-values that were once considered ‘‘normal’’ can no longer be

applied to the interpretation of GH-values measured with new highly sensitive GH assays [26]. Availability of supersensitive assays has changed many aspects of the interpretation of GH value in the management of acromegaly.

Diagnosis

The interpretation of a GH-value should always be made in conjunction with an IGF-I measurement. A Consensus Statement published in 2000 states that if a random GH level is <0.4 μg/l and IGF-I is in the age- and gender-matched normal range, the diagnosis of acromegaly is excluded in a patient who has no other intercurrent illness [25]. The biochemical diagnosis of acromegaly is usually based on and confirmed by the demonstration of a high level of IGF-I.

Random measurements

Measurement of a random GH level alone lacks the specificity to make or exclude the diagnosis of acromegaly. Although random GH levels may be high in many patients, the GH levels frequently overlap with the range of pulsatile GH secretion in healthy subject (Fig. 1). Serum GH levels can also be elevated in poorly controlled diabetes mellitus, renal failure, malnutrition as well as in the setting of stress. Therefore, measurement of random GH level alone is not reliable for diagnosis of acromegaly. However, highly elevated levels, e.g., >100 μg/l are not usually encountered under normal physiological circumstance and if present should raise a high suspicion of acromegaly.

As GH secretion is quiescent for most of the time during day time, the finding of an ''undetectable'' GH level in a conventional assay renders a diagnosis of acromegaly very unlikely. What constitutes a normal baseline or nadir concentration of GH is difficult to define, as this is dependent on assay sensitivity. This issue has been highlighted by Freda et al. who reported basal GH level may be <1.0 μg/l in five of 25 newly diagnosed patients [27], which is below the limit of detectability of many commercial assays.

Multiple GH measurements over a sustained period give much more information about the pattern and amount of GH secretion but are impractical for routine diagnostic use. The approach has limited diagnostic merit but may be useful in evaluating the outcome of treatment. GH levels obtained from limited blood measurements, random or nadir GH after OGTT, correlate with serum IGF-I levels [28]. Some centers have advocated five measurements from a single day as a means of obtaining a more accurate estimate of GH status [29].

Dynamic testing

Oral glucose tolerance test (OGTT)

The failure of GH suppression after OGTT suggests the diagnosis of acromegaly. The results should always be considered in conjunction with an IGF-I measurement, because the lack of GH suppression in response to OGTT is not specific for acromegaly. Several conditions listed in Table 1 display inadequate GH suppression after oral glucose. Many patients with acromegaly display a paradoxical rise in serum GH a feature, which provides no additional value beyond that attained by failure to suppress GH. The OGTT has no additional diagnostic value when an age-stratified IGF-I level is clearly elevated. However in a patient suspected of acromegaly with borderline IGF-I levels, an OGTT may be helpful as an adjunctive diagnostic test.

With the development of highly sensitive and specific GH assays, there has been great interest in determining what constitutes normal suppression, as a greater level of precision is likely to aid interpretation. With the threshold gradually falling over the years in paralleled with sensitivity of assay constitute normal GH and GH suppression to OGTT has been carefully defined (Table 2).

Table 1 Conditions associated with a lack of growth hormone suppression to a glucose load

Acromegaly
Laron dwarfism
Puberty
Pregnancy
Diabetes mellitus
Hepatic disease
Renal disease
Malnutrition

Table 2 What is normal GH suppression during OGTT

	GH (ng/ml)
Stonesifer et al. [30]	<5.0
Jadresic [31]	<2.5
Quabbe [32]	<2.0
Nabarro [33]	<2.0
Stewart et al. [34]	<1.0
Chapman et al. [35]	<0.5
Guistina et al. [25]	<0.4
Trainer [36]	<0.3
Freda [26]	<0.2

Chapman et al. [35] found the mean nadir GH level after an OGTT to be 0.25 μg/l in six young women and 0.029 μg/l in nine young men. From a study of 46 healthy subjects, Freda et al. [37] reported the mean nadir GH level to be 0.09 μg/l in women and 0.08 μg/l in men with a upper limit of 0.14 μg/l. In another study, Costa et al. [38] reported in 56 normal subjects that the mean nadir GH levels after OGTT was 0.07 μg/l, with a range from 0.06 to 0.7 μg/l. On the basis of these data, Freda [26] concluded that nadir GH level after OGTT using precise sensitive assays is <0.2 μg/l in healthy subjects except in some young women.

It has been well known that there are gender related differences in the GH-IGF-I axis in healthy subjects [39, 40]. Basal and mean 24-h GH levels are higher in women than in men [40]. Chapman et al. [35] reported higher nadir GH levels after OGTT in young healthy females. Freda et al. [37] did not find significant gender and age-related differences in nadir GH levels after OGTT in patients with acromegaly though basal GH levels were higher in normal women than men. It remains to be established whether separate OGTT criteria for men and women are required.

The value and significance of a nadir GH following an OGTT in the diagnosis of acromegaly have also been carefully studied. Freda et al. reported that nadir GH levels were <1 μg/l, and as low as 0.42 μg/l, in 5 of 15 patients with newly diagnosed acromegaly using a GH assay with a sensitivity of 0.05 μg/l [27]. Dimaraki et al. [28] reported that 8 of 16 patients with newly diagnosed acromegaly had nadir GH levels <1 μg/l and in one patient the nadir GH after OGTT was as low as 0.13 μg/l. In all the cases, the IGF-I levels were elevated. The authors cautioned that the diagnosis of acromegaly could be missed if only the GH-based criteria based on GH suppression were used. Thus, an OGTT is not always a reliable diagnostic test for acromegaly even when the normal limits of suppression have been carefully defined by a very sensitive assay.

Stimulatory tests

Thyrotropin-releasing hormone, GnRH, and GHRH have been investigated as potentially useful tests in the diagnosis of acromegaly. A paradoxical response to TRH in patients with acromegaly was first described in 1972 [41]. This occurs not only in patients with acromegaly but also in other pathological conditions such as renal failure, depression, anorexia nervosa, primary hypothyroidism, insulin-dependent diabetes mellitus, schizophrenia, and normal aging.

The presence of abnormal GH response to TRH have been proposed to be of diagnostic importance [42] but this has not been substantiated. However TRH test offers no advantage over the OGTT and has little place in the diagnosis of acromegaly.

The GHRH was initially isolated from pancreatic tumors causing acromegaly [43]. The GH response to GHRH has also been studied in patients with acromegaly. Although nearly all patients respond to GHRH stimulation [44, 45], the test is not useful in differentiating patients with acromegaly from normal subjects. GnRH has been shown to stimulate GH secretion in some patients with acromegaly. However like TRH and GHRH, GnRH has little diagnostic utility in acromegaly.

Monitoring

What is the value of measuring GH after therapeutic intervention? Measuring GH levels can give useful information the effectiveness of therapy and prognosis.

Random measurements

Measurement of random GH levels has value in providing a reasonable indication of the efficacy of treatment, regardless of the mode. Because GH secretion is relatively constant in acromegaly, a random GH gives a reasonable approximation of 24 h secretion. The correlation coefficient between a random GH and mean 24 h GH concentration obtained from 20 min sampling was 0.82, and with IGF-1 was 0.48 [1]. The relation between mean GH concentration and IGF-1 concentration in the same group of acromegalic patients was slightly higher at 0.57 [1]. A random GH measurement reflected 67% of 24 h output and accounted for 23% of variance in IGF-1 concentration in acromegaly. Kaltsas et al. [29] have reported that a mean GH concentration of 2.5 μg/l based on five measurements approximates a threshold that corresponds to a normal IGF-I level in blood. The IGF-I level was elevated in 83% of 44 patients with a mean GH >2.5 μg/l and only in 13% of 23 patients below this level. The relationship between mean GH concentration and IGF-I is log linear; this means that a doubling of IGF-I concentration occurs with a tenfold higher output of GH. For this reason, quite significant reduction in GH concentrations may be accompanied by only modest lowering in IGF-I.

Dynamic testing

The value of accurately quantifying the GH nadir response to an OGTT in patients after surgery has been the subject of intensive study. Several investigations have addressed this by defining the upper limit of suppression in normal subjects and then studying the characteristics of acromegalic

patients who attain or fail to suppress into the normal range. In an excellent study of 60 acromegalic subjects after surgery, Freda et al. studied the relationship between IGF-1 status and GH suppression after an OGTT [46]. Among patients in remission, as defined by a normal IGF-1 level, not all displayed GH suppression into the normal range (Fig. 2). However all acromegalic subjects who suppressed into the normal range had a normal IGF-1 level. In a follow up study they demonstrated that the subgroup with abnormal suppression displayed a higher level of spontaneous GH secretion and in the response to arginine [47]. The failure of adequate GH suppression suggest that normal mechanism underlying GH regulation had not been restored and that these patients may be at risk of disease recurrence.

Further insight into the significance of a post OGTT GH nadir in acromegaly has come from a study by Dimarki et al. [28]. These investigations observed a very tight relationship between GH nadirs achieved after OGTT and trough levels occurring spontaneously over a 24-h period (Fig. 3). The finding indicates that a postglucose GH nadir is an estimate of the basal tonic level of GH secretion in acromegaly. The finding is in keeping with that of Freda et al. in that an OGTT detects persistence of abnormal GH neuroregulation. Thus, a postglucose nadir conveys information on neuroendocrine control of GH secretion after surgery with a non-suppressed level indicative of persistent abnormality. There is no value in undertaking dynamic testing in the evaluation of medical treatment.

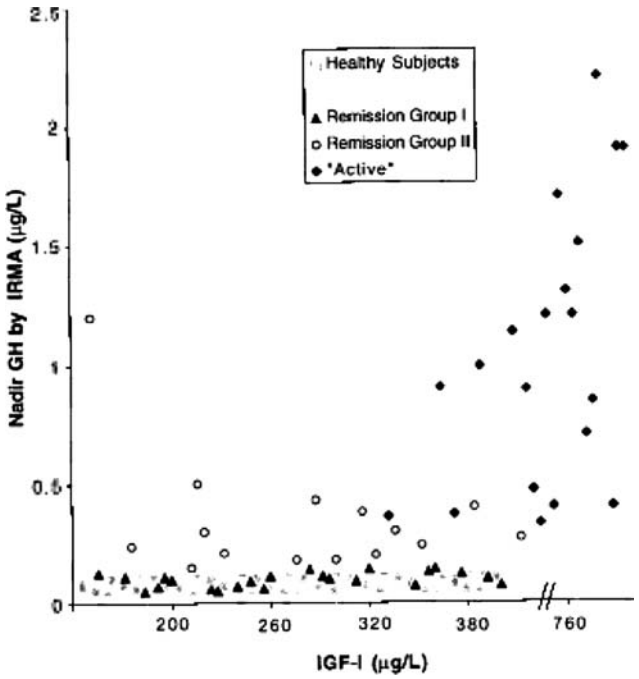

Fig. 2 Nadir GH in subjects with active acromegaly (◆), subjects in remission with normal GH suppression (group I; ▲), and subjects in remission with abnormal GH suppression (group II; ○) in relation to the normal range of GH suppression (mean ± 2SD of the health subjects responses, ◆) versus IGF-I levels. In healthy subjects and subjects in remission group I, nadir GH did not correlate ($r = 0.076$). In subjects with active disease combined with those in remission with failure of adequate GH suppression (group II), the nadir GH level correlates with the IGF-I level ($r = 0.705$; $P < 0.0001$) [46] (Reproduced with Permission).

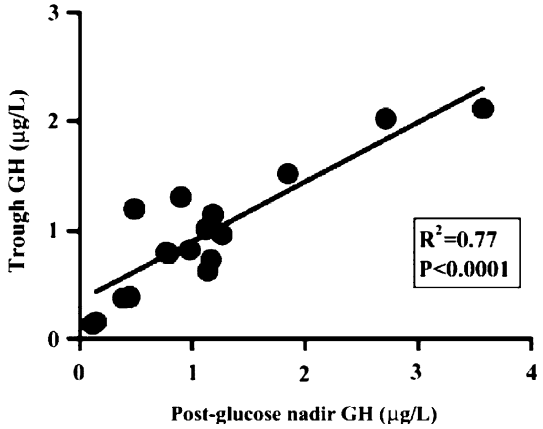

Fig. 3 Correlation between the postglucose plasma GH nadir and the 24-h through GH ($R^2 = 0.77$, $P < 0.0001$) and nadir ($R^2 = 0.84$, $P < 0.0001$) in newly diagnosed acromegalic patients [28] (Reproduced with Permission)

Mortality

The therapeutic goals in acromegaly are to eliminate morbidity and to reduce mortality to the expected age- and sex-adjusted rates by using safe treatments that remove the tumor mass or control its growth and restore GH secretion and action to normal [25]. Analysis of the determinants of mortality outcome in acromegaly indicates that ~60% of patients succumb to cardiovascular disease; 25% from respiratory disease; and in 15% of the patients, the cause of death attribute to malignancy [48]. However, a decrease in or even normalization of GH/IGF-I status may not always result in reversal of the indices of cardiovascular morbidity, hypertension, and sleep apnea. Therefore, cotreatment of hypertension, diabetes, heart disease, and hyperlipidemia should be instituted in keeping with conventional clinical practice. Whether acromegaly increases the risk of cancer remains controversial [49]. Uncontrolled acromegaly may provide a growth advantage to concurrently occurring neoplasms in these patients. However, there is no clear evidence for enhanced cancer initiation in acromegaly and no direct evidence of a casual relationship between acromegaly and malignant disease [48].

Failure to control GH hypersecretion is associated with a 3.5-fold enhanced mortality, as compared to patients in whom GH is controlled [50, 51]. Therefore, it is recommended that patients with acromegaly should be

Table 3 Level of posttreatment GH-levels associated with normalizing mortality

Series	GH levels (μg/l)	*N*
Abosch et al. [46]	<5.0	214
Bates et al. [46]	<2.5	79
Orme et al. [50]	<2.5	1,362
Swearingen et al. [47]	<2.5	149
Holdaway et al. [51]	<2	208

treated effectively to lower the GH/IGF-I indices as close to normal.

Several studies have reported that GH status as determined by a GH measurement is the most significant single determinant of mortality in acromegaly regardless of the cause of death [52, 53]. Bates et al. [53] reported that mortality was restored to that of the age-matched normal population in treated patients with acromegaly who achieved GH levels <2.5 μg/l. A number of studies have reported that the controlling GH secretion restores mortality rates in acromegaly to those of the background population [50, 54–56] (Table 3). Holdaway et al. [56] identified the last serum GH level as a significant predictive factor of survival. Current evidence suggests that a posttreatment random serum GH <1–2 μg/l and a normal serum IGF-I value define a safe treatment target [56].

Conclusion

There is a place for measuring GH in the management of acromegaly although it complements that of measuring IGF-I. The relative constancy of secretion underlies its utility in acromegaly. The value differs between the clinical context of diagnosis and treatment.

In a patient suspected of acromegaly, an extremely high or an ''undetectable'' level has good predictive value, however confirmation should be obtained from an IGF-I measurement. In the presence of an elevated IGF-I level, a random GH measurement gives some indication of disease severity while dynamic testing provides no additional useful diagnostic information.

In the evaluation of treatment outcome, a random GH gives an indication of the status of residual disease after surgery and a nadir GH obtained after an OGTT gives additional information as to whether neuroregulation has been restored as an indication of cure. In patients whose IGF-I is reduced into the normal range after surgery, the failure to attain normal suppression after an OGTT indicates that cure has not been achieved despite normalization of GH output. Dynamic testing has no role in the evaluation of response to drug therapy. Finally a random GH level is a strong prognostic indicator of mortality.

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