Defining Growth Hormone Deficiency in Adults

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The absence of a distinct clinical syndrome calls for a strategy to reliably identify patients with hyposomatotropism. However, there is no consensus as to the most appropriate method of defining growth hormone (GH) deficiency in adults. Since GH secretion falls with senescence and is also reduced by obesity, both of these factors must be controlled for in such an evaluation. We have investigated the relative diagnostic merits of measuring (1) peak GH response to insulin-induced hypoglycemia (ITT), (2) mean 24-hour GH concentration derived from 20-minute sampling (IGHC), (3) serum IGF-I levels, and (4) serum insulin-like growth factor (IGF)-binding protein-3 (IGFBP-3) levels. These tests were undertaken in 23 patients considered GH-deficient from extensive organic pituitary disease and in 35-sex-matched normal subjects of similar age and body mass index. The ITT was the only test capable of distinguishing patients with organic GH deficiency from matched normal subjects. The sensitivity of the GH radioimmunoassay (0.2 ng/mL) limited the utility of IGHC measurements, since many subjects from both groups had undetectable values. Using a GH assay with a 100-fold greater sensitivity, we found a better but still incomplete separation of values between the two groups. There was a significant overlap of IGF-I and IGFBP-3 values, with only a third of GH-deficient subjects having low IGF-I values. The limitation of IGF-I has been confirmed by others, although its sensitivity as a diagnostic test is greater in young adults. We conclude that organic GH deficiency in adults can be reliably diagnosed by the ITT. IGF-I and IGFBP-3 measurements are unreliable, because these levels may be normal in GH deficiency.

RECENT CLINICAL STUDIES of growth hormone (GH) treatment in adults suspected of having GH deficiency have demonstrated beneficial effects on body composition, physical fitness, and psychological well-being.[1,2] The evidence has been sufficiently persuasive that it is likely that adult GH deficiency will be a well-accepted indication for recombinant human GH. It is therefore timely to reevaluate the most appropriate method of defining GH deficiency to focus this expensive and at times inconvenient treatment on those most in need.

To define GH deficiency requires a review of current methods used to assess GH secretory status. There are three widely accepted modalities for assessing GH secretory status: (1) peak GH response to provocative stimuli, (2) spontaneous GH secretion, and (3) biological markers of integrated GH action, including serum insulin-like growth factor-I (IGF-I) and IGF-binding protein-3 (IGFBP-3). An evaluation of the extensive pediatric experience demonstrates significant discordance between the various tests, resulting in a long-standing controversy as to which is the most useful test in the diagnosis of GH deficiency.[3-5] This issue has now surfaced in the adult world as new studies have emerged reevaluating traditional tests of GH deficiency in adults.[6,7] Defining GH deficiency in adults is difficult because (1) the clinical syndrome lacks specificity and is characterized by changes in body composition and function that mimic those of the aging process, (2) GH secretion is significantly reduced by aging,[8-12] and (3) aging is associated with a progressive increase in adiposity, which itself reduces GH secretion.[8-10] Thus, it is not clear whether the healthy old and/or obese can be distinguished clinically or biochemically from patients with acquired GH deficiency due to organic pituitary disease. We will review each of the major testing modalities, identify the influence of age and adiposity, and attempt to address how GH deficiency might best be defined.

PROVOCATIVE TESTS OF GH SECRETION

A number of provocative tests have been developed over the past decades primarily for evaluation of GH secretion in short-statured children. Such tests include the insulin tolerance test (ITT), or administration of clonidine, arginine, and GH-releasing hormone (GHRH). The recognition of occasional failure to induce an adequate GH response has led pediatricians to recommend that GH deficiency be confirmed by failure to respond to at least two provocative tests.[13] The ITT, first described as a test for GH deficiency in 1963,[14] is generally accepted as the standard against which other tests are compared.[13] The diagnostic criteria for GH deficiency in children for these tests appear to have been arbitrarily adopted by general consensus and have not been adequately defined from studies in normal children.

A review of recent clinical studies of GH deficiency in adults shows that the diagnosis of GH deficiency has mainly been based on a single provocative test, most commonly the ITT (Table 1). The diagnostic criteria appear to be either arbitrary or else based on values adopted from the pediatric literature. In addition to concerns arising from the use of empirically derived threshold values from data in children, extrapolation of such criteria for application in adults is inappropriate for the following reasons. The GH response to provocative tests changes with puberty and is markedly dependent on sexual maturation.[19] The blanket application of a single threshold value defining GH deficiency across the various stimulation tests must also be questioned. Since each stimulation test modulates different components of the complex neuroendocrine control mechanism, GH-releasing potency varies among the different stimuli.[20-23] Koppeschaar et al[22] examined GH responses to an ITT,

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Table 1. Diagnostic Criteria of GH Deficiency From Some Recent Clinical Studies

Study	Test	Criteria
Salomon et al, 1989[1]	ITT	GH < 1.5 ng/mL*
Jørgensen et al, 1989[2]	2 "classic" GH stimulation tests	GH < 5 ng/mL
Binnerts et al, 1992[15]	GHRH	GH < 5 ng/mL*
	IGF-I	IGF-I < 0.3 U/mL
Whitehead et al, 1992[16]	ITT	GH < 3.5 ng/mL*
Orme et al, 1992[17]	"Standard" provocative tests	GH < 2.5 ng/mL*
Bengtsson et al, 1993[18]	ITT	GH < 0.5 ng/mL*

*Converted from original units of mU/L assuming 2 U/mg.

arginine, and GHRH in six healthy adults. The integrated GH response was significantly higher for the ITT than for either arginine or GHRH (Fig 1). These observations suggest that the threshold criteria for defining GH deficiency from provocative tests must be established for each test, and that definitions based on extrapolations from other tests are unlikely to be valid.

The effect of age on peak GH response to provocative testing is unclear. In a study reported by Dudl et al,[24] aging was not correlated with a diminished GH response to arginine. The response to GHRH has been found to be unchanged[25] or reduced,[26] and the response to the ITT has been variably reported as unchanged[27] or reduced.[28] The conflicting observations between different secretagogues probably reflect the fact that each modulates different components of the complex neuroendocrine control mechanism of GH secretion. The discordant findings observed for the same secretagogue are difficult to reconcile, but underscore the critical importance of defining and controlling modulating factors such as obesity.

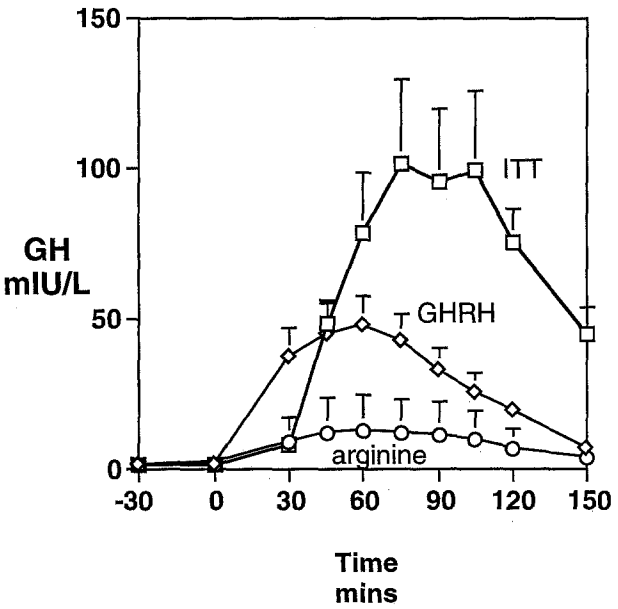

Fig 1. GH responses (mean ± SEM) to ITT, GHRH, and arginine in 6 normal subjects. (Data from Koppeschaar et al.[22])

Pharmacologically stimulated GH release is clearly impaired in the presence of marked obesity. This has been demonstrated for a variety of stimuli, including clonidine,[29] arginine,[24] insulin-induced hypoglycemia,[30,31] and GHRH.[25,30,31] Furthermore, the response improves with weight reduction.[31,32]

We have recently undertaken a systematic assessment of the merit of the ITT as a tool for diagnosing GH deficiency in adults. The peak GH response to the ITT in 21 patients with hypopituitarism was compared with that in 25 normal subjects matched for sex, age, and body mass index. Patients with hypopituitarism were considered likely to be GH-deficient on the basis of severe organic hypothalamic pituitary disease requiring substitutive treatment for at least two pituitary hormone deficits. There was a clear separation of peak GH responses to the ITT between normal and GH-deficient subjects; all GH-deficient subjects had peak GH responses no greater than 3.1 ng/mL. All normal subjects had peak GH responses no greater than 5.3 ng/mL (Fig 2). This clear separation indicates that the ITT may be a simple and reliable tool for defining GH deficiency in adults.

24-HOUR GH CONCENTRATION

Because of the episodic nature of GH release, assessment of spontaneous GH secretion necessitates frequent sampling over a 24-hour period. Sampling at 15- to 20-minute intervals is required to detect all major GH pulses.[33] Development of computer algorithms for pulse analysis and deconvolution analysis for determination of production and clearance rates has provided interesting insights into the regulation of GH secretion. A reliable estimate of the amount of GH secreted spontaneously can be obtained by measuring the mean GH concentration from samples pooled over a 24-hour period to give an integrated GH concentration (IGHC). However, assessment of GH secretion by this technique is greatly limited by the resources required to undertake these labor-intensive studies.

There are distinct age-related alterations in IGHC, with levels increasing during puberty, peaking at middle and late puberty, and subsequently declining into old age.[8,9,12,34,37] Mean 24-hour GH concentrations relative to the prepubertal years are 130% to 210% in late puberty, 60% in the third decade, 35% to 50% in the fourth to sixth decades, and 25% to 40% in the seventh decade and beyond.[38] That is, spontaneous GH secretion beyond the sixth decade is less than one fifth of that during peak output in puberty. It can be argued that a state of relative GH deficiency develops with aging, which raises for clarification the issue of whether the normal elderly can be distinguished from those with pathological pituitary abnormalities.

In some adult studies, obesity has been shown to be associated with a reduction in serum GH levels.[8,10,37] Recent studies reported by Weltman et al[39] suggest that a negative correlation between adiposity and IGHC is gender-dependent. Using intensive 10-minute sampling over 24 hours, they were unable to demonstrate a significant relationship between body mass index and IGHC in a group of 46 normal young men and women, although they did observe a significant relationship between percent body fat

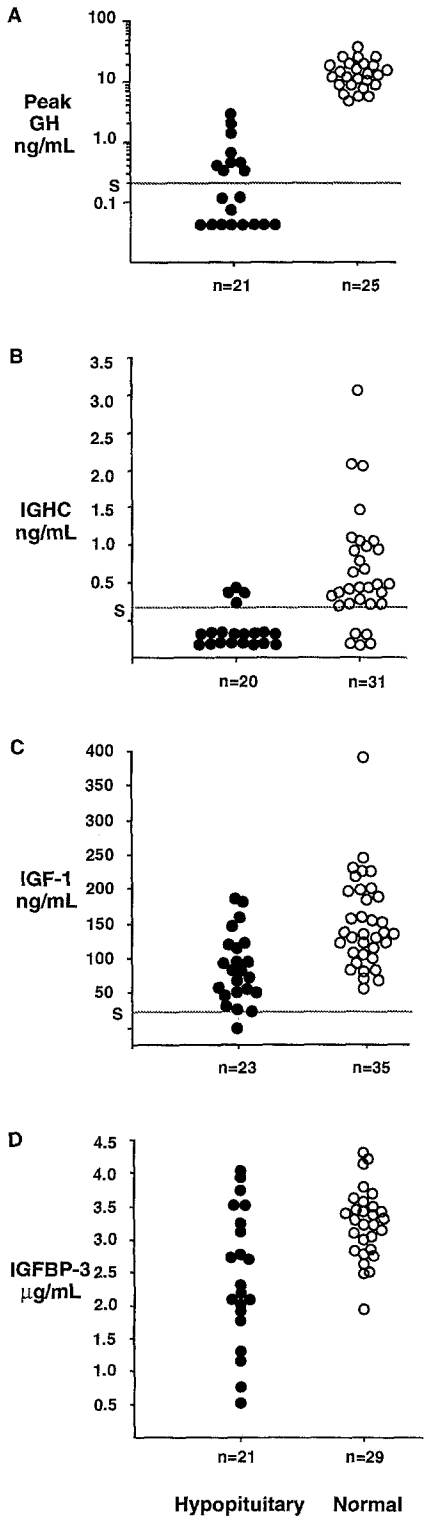

Fig 2. Comparison of peak GH response to ITT (A), 24-hour IGHC (B), IGF-I (C), and IGFBP-3 (D) in patients with organic hypopituitarism and age-, sex-, and body mass index–matched normal subjects. (Reprinted with permission.[6] © by The Lancet, Ltd, 1994.)

(measured by hydrodensitometry) and IGHC in a subgroup of young men.

Thus, age, sex, and to a lesser extent adiposity are important considerations when IGHC is to be used to define GH deficiency. Despite controlling for these factors, we have shown a significant overlap of IGHC values between normal and GH-deficient subjects.[6] One third of young normal subjects (aged <50 years) had values within the range of their GH-deficient counterparts. Since it is known that interindividual variation in 24-hour GH secretion may be as high as 58%,[40] it is possible that repeat testing would have improved discrimination. Discrimination by IGHC was also limited by sensitivity of the GH radioimmunoassay of 0.2 ng/mL (0.6 mIU/L). IGHC values in 16% of normal subjects and 80% of GH-deficient subjects were less than the limit of assay sensitivity (Fig 2). Thus, it was not possible to ascertain whether patients with organic GH deficiency produced virtually no GH or continued to do so at a much lower level than their matched normal subjects.

We have recently modified a GH enzyme-linked immunosorbent assay to achieve a greater than 100-fold improvement in sensitivity of 1 ng/L, and have used this assay to reappraise the diagnostic utility of IGHC in the same study groups of GH-deficient and matched normal subjects.[41] All IGHCs from both groups were within the dynamic range of the assay. GH-deficient subjects clearly continue to secrete low but measurable amounts of GH. While the mean IGHC from the GH-deficient group was significantly lower, there remained an overlap in values with those of normal subjects, although discrimination between the two groups was improved. Although the supersensitive assay improved the diagnostic performance of an IGHC measurement, it did not match the simplicity and reliability of an ITT in separating patients with severe organic GH deficiency from normal subjects.

IGF-I AND IGFBP-3

The changes in IGF-I levels throughout life mimic those of GH. With the onset of puberty, there is a twofold to threefold increase in serum IGF-I concentrations (with levels being slightly higher in girls), followed by a decline such that average adult levels are reached by the early twenties.[42] There follows a gradual decline with advancing age.[36,37,43,44] The similarity in ontogeny of these GH and IGF-I hormones in blood is regarded as good evidence that circulating IGF-I is a biological marker of GH status. However, there is only a modest correlation between mean 24-hour GH and IGF-I levels in normal subjects,[36,44] indicating that factors other than GH play a role in modulating IGF-I levels. Nutritional factors are known to be important.[45] Fasting, for example, causes a progressive decrease in IGF-I (and an increase in GH secretion).[46,47] Animal experiments have shown that IGF-I gene transcription in the liver is regulated by insulin,[48,49] as well as by the availability of amino acids.[50]

IGFBP-3, being GH-dependent, also follows the changes in GH secretion through life. There is a gradual increase in early childhood, and a peak during the pubertal years, followed by a slow decline in adulthood.[51,52] IGFBP-3 is less GH-dependent than IGF-I, since levels reflect total IGF concentration, including non–GH-dependent IGF-II.[53] Hence, the correlation between age and IGFBP-3 is not as strong as for IGF-I.[54]

The literature concerning serum IGF-I levels in obesity is conflicting. There are data showing decreased,[9,32,37,55] normal,[10,56] and elevated IGF-I levels.[57] The elevated levels were described in obese children. On balance, it would seem that there may be a modest obesity-related decline in serum IGF-I in adults. There are few data available on the effect of adiposity on IGFBP-3 levels. We did not observe any relationship between adiposity and IGFBP-3 in 29 normal subjects.[6]

Thus, an evaluation of the diagnostic utility of IGF-I should take careful account of age, whereas adiposity is of less importance. After controlling for these factors, we found that neither IGF-I nor IGFBP-3 were useful diagnostic tests. Seventy percent and 72%, respectively, of IGF-I and IGFBP-3 values in hypopituitary subjects were within the range of normal subjects, even allowing for the effects of age (Fig 2). Moreover, there was only a modest relationship between IGF-I and IGHC, with GH accounting only for 30% to 40% of the variation in IGF-I.[41] The greater dependency of IGF-I on non–GH-related factors suggests that IGF-I is unlikely to be a reliable indicator of GH status and unlikely to be a useful marker to define GH deficiency.

DIAGNOSTIC TEST OF CHOICE

From the practical point of view, the most common condition confronting endocrinologists in which the question of GH secretory status may arise is in adults with pituitary and/or hypothalamic structural lesions such as tumors treated with or without surgery or radiotherapy. In these circumstances, the ITT is a simple, practical, and reliable test that provides a more accurate assessment of GH secretory status than IGHC, IGF-I, or IGFBP-3. Although there are risks associated with its implementation, it is safe when performed by an experienced endocrine unit.[58]

The diagnostic utility of the GH response to an ITT has recently been questioned with the report of an occasional subject who does not respond to an ITT even with repeat testing.[59] It is important to view the utility of this test in the context of its practical application, ie, in patients with suspected pituitary disease in whom the probability of GH deficiency is high. According to Bayes' theorem, the diagnostic merit of a test is dependent on the prevalence of the disease within the population under study.[60] Thus, the finding of an absent response to an ITT in the occasional normal subject (one in 51 from three studies[6,59,61]) has a negligible impact on the diagnostic reliability in patients with known or suspected pituitary disease in whom the probability of GH deficiency is high. For an estimated prior probability of GH deficiency in adults with pituitary disease of 0.64,[7] specificity of 98%,[6,59,61] and sensitivity of 100%,[6,61] the positive predictive value of a single ITT is 99%.

The substantial age-related decline in spontaneous GH secretion and serum IGF-I levels has led to the notion that a state of relative GH deficiency develops with aging. Our data show that the normal elderly can be distinguished from those with organic pituitary disease with an ITT. The question of accurate diagnosis is different from the question of who may benefit from GH treatment. The issue has been highlighted by the recent finding in an open-label study reported by Rudman et al[62] that GH treatment of normal elderly men was accompanied by positive changes in body composition, although no measure of body function was assessed. However, these observations have not been confirmed in a recent study using a placebo-controlled design[63] and must be considered inconclusive. Thus, accurate diagnosis of GH deficiency is imperative if we are to avoid treating adults who do not lack GH and for whom the overall benefit awaits detailed evaluation.

CONCLUSION

In conclusion, stimulatory testing of GH secretion is the most useful means of defining and diagnosing GH deficiency. Currently, only the ITT has been comprehensively evaluated, and it is not possible to draw conclusions about other provocative tests. The ITT allows a confident diagnosis of GH secretory status in those with suspected pituitary disease, and clearly differentiates the normal elderly from the GH-deficient.

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