

COMMENT

Seeking the Optimal Target Range for Insulin-Like Growth Factor I during the Treatment of Adult Growth Hormone Disorders

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Impaired GH activity at target tissues, occurring when GH action is blocked or during suboptimal GH replacement therapy, may result in a pathological state associated with lowering of IGF-I, but not GH levels. Such a state represents functional but not necessarily actual GH deficiency (GHD). The aim of this study was to identify a range of IGF-I values commensurate with GHD, which could be used to determine the risk of functional GHD during the treatment of adult GH disorders. Centrally measured baseline IGF-I data from the Kabi International Metabolic Study European GHD database were analyzed. Inclusion criteria were adult-onset GHD and two or more additional anterior pituitary hormone deficits. Adults with childhood-onset GHD and cured acromegaly were excluded. The cohort was stratified into six gender-based age

ranges. Baseline IGF-I measurements from 376 females (median age, 48 yr; range, 21–77 yr) and 434 males (median age 52 yr; range 21–80 yr) were analyzed. Data were not normally distributed and are presented as medians (quartiles). The median serum IGF-I and IGF-I SDS in males were 94.0 $\mu\text{g/liter}$ (64 and 141) and -1.52 (-2.53 and -0.456 ; $n = 434$). Both were significantly greater than the equivalent values of females, which were 73 $\mu\text{g/liter}$ (46 and 103.5) and -2.30 (-3.28 and -1.328 ; $n = 376$; $P < 0.0001$ for both). Age and gender-related 90th and 95th percentiles for IGF-I SDS were determined to generate risk estimates for functional GHD, which, in conjunction with the clinical status of the patient, may be used to aid dose titration during treatment of GH disorders in adulthood. (*J Clin Endocrinol Metab* 88: 5865–5870, 2003)

A STATE OF GH deficiency (GHD) may occur because of a lack of endogenous GH, when the latter state is insufficiently replaced with exogenous GH, or when endogenous GH levels are normal or high but GH action is pharmacologically blocked. In the latter two situations, GH levels are not useful in guiding therapy. Most clinicians managing such patients rely on the measurement of IGF-I as the primary biochemical marker of GH status, but to date there has been little agreement as to the levels of IGF-I that constitute appropriately safe targets of therapy.

The diagnosis of GHD in adults with hypothalamic-pituitary disease is usually based on provocative tests of GH secretion. However, patients with two or more additional anterior pituitary hormone deficits may be predicted to have a peak GH response to an insulin tolerance test of less than 1.9 ng/ml with approximately 90% certainty and a peak GH response to the insulin tolerance test of less than 4.4 ng/ml with close to 100% certainty (1–3). IGF-I has not traditionally been viewed, as a reliable marker for the diagnosis of GHD. This is in part because a large overlap exists between values for IGF-I in adult-onset (AO)-GHD patients and normal subjects matched for age, even in those with the most severe GHD identified by provocative tests of GH secretion (4) or

number of additional pituitary hormone deficits (3). However, its usefulness has been shown to vary with the age of the patient and the timing of onset of GHD (5–10). Targeting IGF-I levels broadly to within the normal age-related reference range during treatment of GH disorders in adults does not therefore preclude the presence of functional GHD. The identification of target levels for IGF-I that determine the risk of functional GHD in at risk populations is therefore warranted to ensure that inappropriately low IGF-I values are avoided if possible.

The GH-receptor antagonist pegvisomant is a highly effective therapy for acromegaly (11, 12). Pegvisomant blocks GH action (13) and does not lower endogenous GH levels, which are rendered uninterpretable because of cross-reactivity of pegvisomant in standard GH assays. The goal of treatment for acromegaly is to lower IGF-I levels to within the age- and gender-related reference range (14, 15). In a proportion of patients reported by van der Lely *et al.* (12), pegvisomant treatment resulted in IGF-I levels below the normal age-related range; such low levels of IGF-I may represent overtreatment. Because of the high efficacy of pegvisomant (11, 12), the risk of inadvertent overtreatment requires further evaluation.

GH replacement therapy in adults with GHD has benefits in terms of body composition, metabolic sequelae, bone mineral density, and quality of life (16). Once such patients are

Abbreviations: AO, Adult onset; GHD, GH deficiency; KIMS, Kabi International Metabolic Study; SDS, SD score.

commenced on GH replacement therapy, IGF-I monitoring is used to aid dose titration to minimize the risk of overtreatment. Indeed, some patients with GHD receiving GH replacement therapy may have been overtreated as evidenced by supraphysiological IGF-I levels (17). Furthermore, to date, no data are available that quantify risk of undertreatment of such patients. Thus, suboptimal replacement therapy may be associated with unresolved morbidity and increased mortality risk from a continuing state of relative GHD.

The risk of functional GHD in these situations of overtreatment of acromegaly and insufficient replacement of GHD has not previously been evaluated. A logical first step in identifying safe target IGF-I values during treatment of growth disorders in adulthood would be to identify a range of IGF-I values that are higher than those found in patients with untreated GHD.

The aim of this study was to determine IGF-I-based guidelines for risk of functional GHD, which may be used, in conjunction with clinical parameters, to aid dose titration of medical therapies for GH disorders in adulthood. It was hypothesized that the most appropriate cohort from whom a risk estimate for functional GHD could be generated would be patients known to have untreated severe GHD.

Patients and Methods

Patients

Centrally measured baseline IGF-I data from the Kabi International Metabolic Study (KIMS) European metabolic database were included in the analysis. The KIMS metabolic database is part of an ongoing clinical surveillance program for adult GH replacement, and in all cases informed consent was obtained from patients before enrollment in the program. Inclusion criteria were AO-GHD (defined by peak GH < 5 ng/ml to one or more provocative tests of GH secretion) and two or more additional anterior pituitary hormone deficits, the latter criteria being used as additional confirmation of severity of GHD (3). All patients were receiving conventional replacement therapy for pituitary deficits other than GH, and no patients had received GH replacement in the preceding 6 months. Adults with childhood-onset GHD and cured acromegaly were excluded. The most common underlying diagnoses resulting in GHD in the cohort were pituitary adenomas (526 patients), craniopharyngioma (101 patients), idiopathic GHD (35 patients), and Sheehan's syndrome (33 patients).

Baseline IGF-I measurements from 376 females (median age 48 yr; range 21–77 yr) and 434 males (median age 52 yr; range 21–80 yr) were included in the analysis. A total of 211 patients had two additional anterior pituitary hormone deficits (TSH + ACTH, TSH + LH/FSH, or ACTH + LH/FSH), and 31 also had vasopressin (antidiuretic hormone) deficiency. A total of 599 patients had three additional anterior pituitary hormone deficits (TSH, ACTH, and LH/FSH), and 212 patients also had vasopressin deficiency.

The cohort was stratified into six gender-based age ranges, and IGF-I and IGF-I age-adjusted SD scores (SDSs) were calculated for each group.

Assays

IGF-I assays were performed by a hydrochloric acid-ethanol extraction radioimmunoassay method using synthetic IGF-I for labeling. The assay was performed by Pharmacia and Upjohn until October 1997 (in-house assay) and thereafter by Sahlgrenska Hospital, Gothenburg (Nichols Institute Diagnostics, San Juan Capistrano, CA). The reference range of the pre-October 1997 assay was calculated using normative data from 156 healthy Swedish individuals, and that of the post-October 1997 assay was calculated using normative data from 400 healthy Swedish individuals.

Statistics

Data are presented as medians (quartiles) as the data were not normally distributed. Differences between groups were calculated using the Mann-Whitney rank sum test for two group comparisons and the ANOVA on ranks for multiple group comparisons. A *P* value of <0.05 was accepted as significant.

Results

The median (quartiles) serum IGF-I and IGF-I SDSs in AO-GHD males were 94.0 $\mu\text{g/liter}$ (64–141) and -1.52 (-2.53 and -0.456 ; $n = 434$). Both values were significantly greater than those observed in AO-GHD females: 73 $\mu\text{g/liter}$ (46–103.5) and -2.30 (-3.28 and -1.328 ; $n = 376$; $P < 0.0001$ for both). The median IGF-I SDSs for the male and female GHD groups were significantly lower than that of the normal population ($P = 0.001$) (Fig. 1). However, a large degree of overlap was evident for IGF-I values between normal subjects and those with severe GHD in five of the six age ranges studied (Tables 1 and 2). Although overlap of patients' IGF-I SDSs with those of normal subjects exists for both genders, the percentage of patients with IGF-I SDSs within the normal age-related range was significantly greater in male than female groups ($P = 0.0411$). Furthermore, overlap of IGF-I SDSs between GHD adults and normal subjects was predominantly limited to the lower half of the normal age-related range (Fig. 1). IGF-I levels in females ($r = -0.19$; $P < 0.01$) and males ($r = -0.32$; $P < 0.01$) declined with age. In contrast, IGF-I SDSs in females ($r = 0.21$; $P < 0.01$) and males ($r = 0.12611$; $P < 0.01$) increased with age. Age- and gender-related 90th and 95th percentiles for IGF-I SDSs are graphically illustrated in Fig. 2. IGF-I SDSs below these values are expected in 90 and 95% of severely GHD adults, respectively. In females, the 90th percentiles for IGF-I SDSs in the six age ranges studied ranged from -2.034 to -0.0384 , and the 95th percentiles ranged from -1.069 to 0.5016 . In males, the 90th percentiles for IGF-I SDSs in the six age ranges studied ranged from -0.408 to 0.8523 , and the 95th percentiles ranged from -0.341 to 1.2315 .

Discussion

This is the first study to address the risk of functional GHD during the treatment of GH disorders in adulthood. The inclusion criteria of two or more additional anterior pituitary hormone deficits for the analysis ensured a selection bias toward the most severely GHD patients (1–3). Even after stratifying the cohort by age and gender, a wide variation in IGF-I concentrations was evident for all ages. In keeping with previous observations (4, 18), a large overlap of IGF-I levels between patients with severe AO-GHD and normal subjects was demonstrated. However, age- and gender-related IGF-I SDS upper percentiles in GHD patients were almost exclusively limited to the lower half of the normal age-related range. The data presented in Fig. 2 demonstrate age- and gender-related IGF-I values, below which 95%, and above which 5%, of values from severely GHD adults are situated.

Specificity for functional GHD cannot be determined from these data in the absence of an alternative, additional marker of GH status. Nonetheless, it should be borne in mind that, by definition, some patients will have true normal GH status

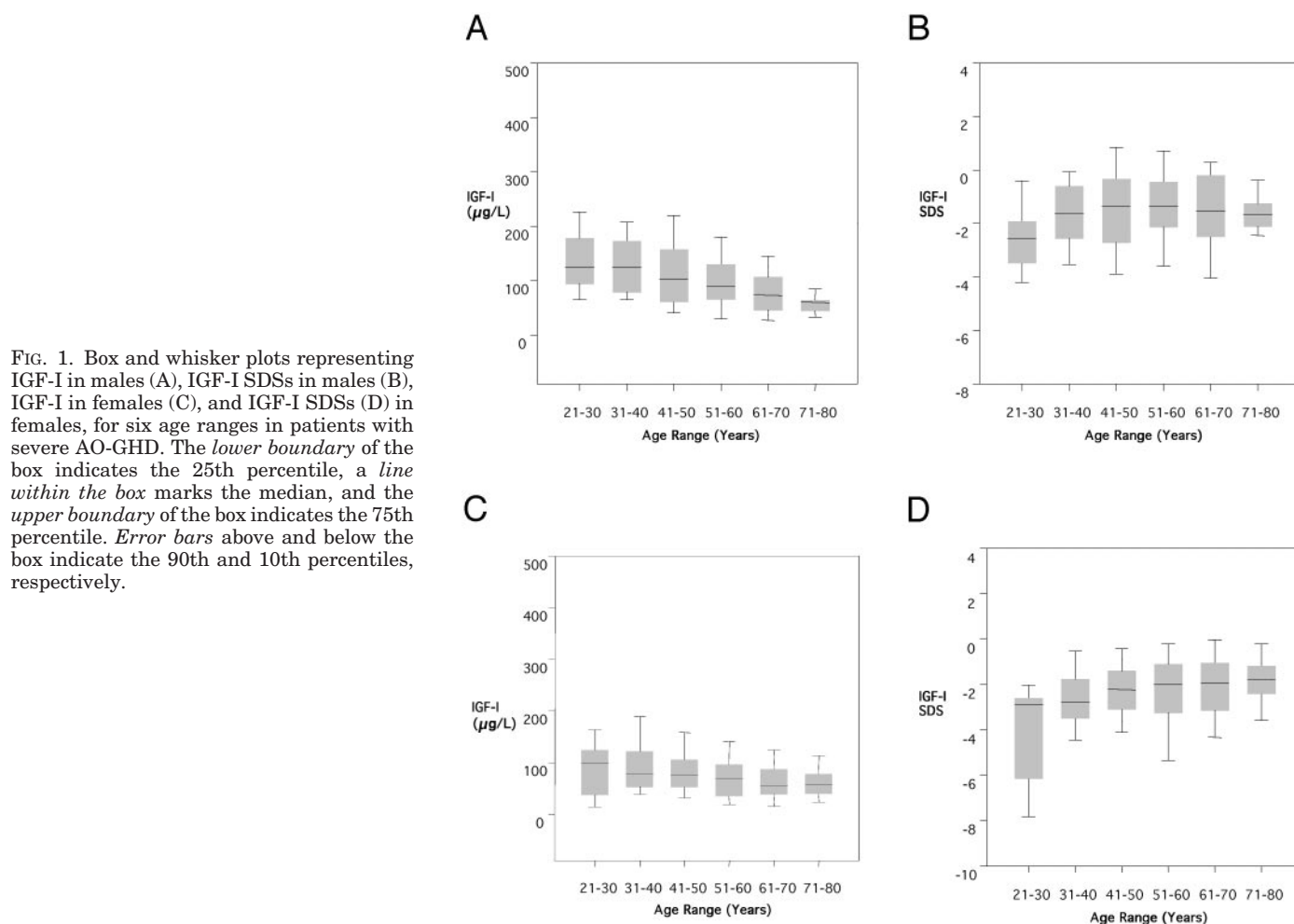


FIG. 1. Box and whisker plots representing IGF-I in males (A), IGF-I SDSs in males (B), IGF-I in females (C), and IGF-I SDSs (D) in females, for six age ranges in patients with severe AO-GHD. The lower boundary of the box indicates the 25th percentile, a line within the box marks the median, and the upper boundary of the box indicates the 75th percentile. Error bars above and below the box indicate the 90th and 10th percentiles, respectively.

TABLE 1. IGF-I and IGF-I SDS characteristics in the female AO-GHD cohort

Age range (yr)	No. per group	Median IGF-I (μg/liter) (n = 376)	Median IGF-I SDS (n = 376)	% Patients with IGF-I within age-related normal range
21–30	24	99.5 (37.5–124.0)	–2.91 (–6.16 to –2.59)	8.3
31–40	74	78.0 (53–122.0)	–2.76 (–3.50 to –1.76)	31.1
41–50	123	77.0 (52.5–105.5)	–2.22 (–3.10 to –1.39)	41.5
51–60	93	69.0 (34.8–96.3)	–1.97 (–3.25 to –1.10)	49.5
61–70	51	56.0 (38.0–87.0)	–1.92 (–3.14 to –1.03)	52.9
71–80	11	57.0 (39.3–77.8)	–1.78 (–2.42 to –1.17)	54.5

when their IGF-I is in the lower half of the normal range. These data are not, however, intended for use in isolation, but rather to provide the clinician with a marker of risk of GHD in the clinical setting. As such they should be interpreted, in conjunction with the clinical status of the patient, to aid dose titration of treatment, with a holistic approach governing the overall management strategy. Thus it is possible that during the treatment of GHD, some patients may exhibit symptoms of acromegaly when their IGF-I is in the upper half of the normal range, and similarly, some acromegalic patients may not achieve resolution of all the symptoms of acromegaly when their IGF-I level has been reduced into the upper half of the normal range. However, in these situations, informed by these data, the clinician would be directing the treatment strategy, in the full knowledge of the risk of functional GHD.

An expected but pertinent observation within these data were the discordance of IGF-I SDSs between GHD males and females of similar ages. These findings are in keeping with those of others (18–24) but notably discrepant from the situation in normal adults (25–28). The relationship between GH and IGF-I in normal adults is influenced by gender, which may be explained partly by a difference in GH secretory dynamics (27). It has been demonstrated that at similar IGF-I levels, females secrete three times more GH than males (27). As normal GH secretory physiology differs between genders, a paradox is apparent, because GHD diagnostic criteria are not gender specific. Similarly, the widely accepted diagnostic threshold for GHD after provocation testing does not take account of increasing age. Following on from these observations it may be inferred that diagnostic

TABLE 2. IGF-I and IGF-I SDS characteristics in the male AO-GHD cohort

Age range (yr)	No. per group	Median IGF-I ($\mu\text{g/liter}$) (n = 434)	Median IGF-I SDS (n = 434)	% Patients with IGF-I within age-related normal range
21–30	30	125.5 (94.0–178.0)	–2.56 (–3.49 to –1.912)	26.7
31–40	62	125.0 (79.0–173.0)	–1.63 (–2.55 to –0.597)	62.9
41–50	102	103.5 (61.0–158.0)	–1.37 (–2.72 to –0.319)	61.8
51–60	149	90.0 (65.0–130.5)	–1.36 (–2.13 to –0.436)	73.1
61–70	75	73.0 (46.0–106.8)	–1.51 (–2.50 to –0.187)	60.0
71–80	16	60.0 (44.0–64.5)	–1.65 (–2.11 to –1.247)	75.0

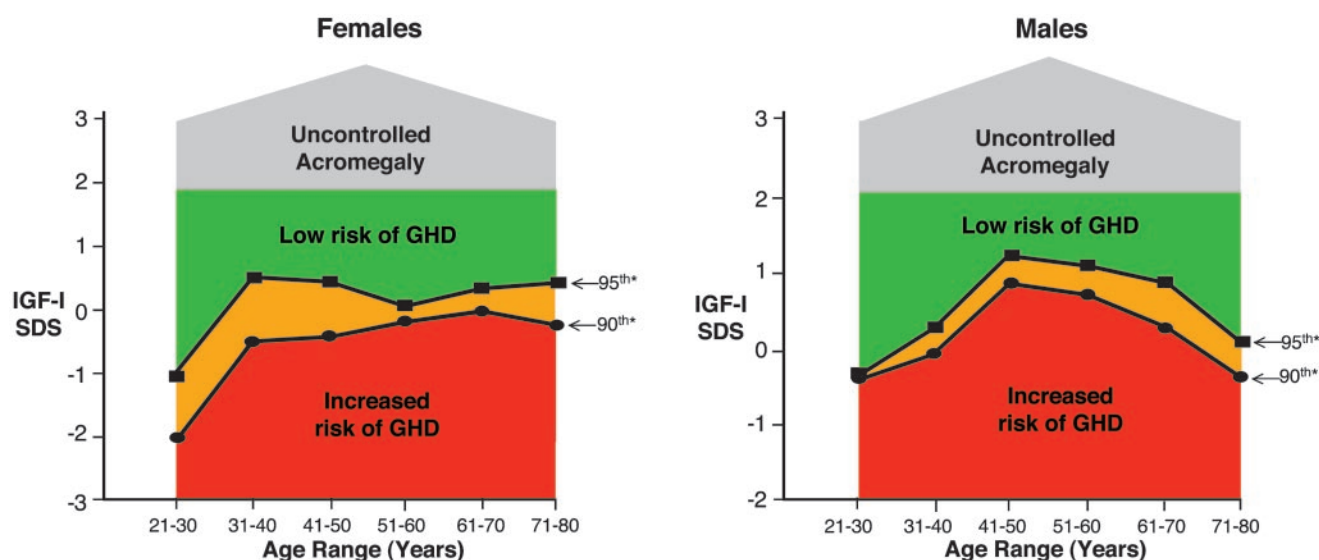


FIG. 2. Age-related IGF-I SDS 90th and 95th percentiles for GHD in females (A) and males (B), illustrated as a GHD risk estimate plot, which may aid dose titration of treatment during the management of GH disorders in adulthood. *, Percentiles.

criteria for GHD may be stricter in females and young adults and more lenient in males and the elderly, which may be a contributory factor to the difference in IGF-I levels between these groups. Currently, however, it is not possible to deduce for which of these groups the GHD diagnostic criteria are most biologically appropriate. These observations represent a possible limitation to the interpretation and utility of the data presented in Fig. 2, because it is possible that the IGF-I 95th percentiles for GHD may be either too strict in females and young adults or too lenient in males and the elderly, in terms of predicting risk of functional GHD. Nonetheless, in view of the gender difference in the relationship between GH and IGF-I in normal adults, it is not unexpected that adults with confirmed severe GHD and, by implication, comparable GH secretion, albeit markedly attenuated, display a gender difference in IGF-I values. In keeping with these observations, females with acromegaly have lower serum IGF-I values than males for equivalent mean serum GH levels. GH secretory dynamics appear abnormal in GHD adults (29), and different secretory patterns vary in their influence on IGF-I status (30). A greater change from normality of GH secretory pattern in severely GHD females compared with males may therefore in part underlie the gender difference in IGF-I status in this situation.

The normative data used in this study were not gender based, although assuming broadly similar age-related IGF-I values between genders (25–28), it would be expected that

with such data, a decreased overlap of IGF-I SDSs with the normal range in females compared with males would still be evident.

The graphs in Fig. 2 suggest that adults at potential risk of functional GHD, IGF-I values maintained above the 95th percentile for GHD, would carry a low risk of functional GHD, of the order of 5%. It must, however, be emphasized that it is possible that some patients with IGF-I SDSs within the range deemed as safe may actually be under- or over-treated for their GH disorder.

The primary aim of this study was to address the potential risk of functional GHD during pegvisomant treatment of patients with acromegaly because during this novel treatment IGF-I is the sole biochemical marker of GH status currently in common use. The observations may also be applied to adults with GHD during GH replacement therapy or patients with acromegaly receiving other medical therapies, although in the latter situation GH data may also provide useful information about GH status.

The perceived success of any new treatment depends partly on the treatment goals aspired to. IGF-I is a major GH-dependent hormone and is responsible for many of the GH-related biological effects in active acromegaly. Indeed, plasma IGF-I concentrations correlate better than plasma GH levels with the clinical manifestations of acromegaly (31). However, only one study of patients treated for acromegaly

has claimed normalization of mortality outcome based on normalization of IGF-I (32).

Pegvisomant is highly effective at lowering IGF-I levels in acromegalic patients, and the dose-response curve appears to be linear without evidence of a threshold effect for the doses used to date. This ability suggests that manipulation of IGF-I levels within the normal range should be possible, analogous to other dose titration regimens. The findings of this study suggest that the current goal in the treatment of acromegaly, of reducing IGF-I levels to within the age-related normal range, may place a proportion of patients at risk of functional GHD. Pegvisomant has a different mechanism of action compared with conventional therapies for acromegaly, and although targets of therapy are broadly similar, pegvisomant is a more powerful treatment for acromegaly with an unprecedented ability to lower IGF-I (11, 12). The risk of functional GHD during pegvisomant therapy may therefore be greater than that occurring with conventional therapies for acromegaly. This possibility should be considered, bearing in mind the adverse morbidity and potential impact on mortality of an associated functional GHD state during long-term pegvisomant treatment.

IGF-I assessment may ultimately prove to be of superior predictive value in terms of assessing treatment response and cure of acromegaly compared with direct assessment of GH secretion. Age and gender significantly influence serum IGF-I concentrations in patients with acromegaly (33, 34), findings that further support the need for a large normative IGF-I reference range. However, although the precision of IGF-I assays has improved over the last decade, the lack of standardization of IGF-I assay methodology remains a major limitation (35). A further limitation of IGF-I measurement is that it does not reflect autocrine and paracrine IGF-I activity. If increased importance is to be applied to IGF-I measurement in the management of acromegaly, better assay standardization, validation of reference ranges, and IGF-I-related long-term outcome data are of paramount importance. Such requirements are achievable by the use of robust normative data for generation of age-related normal ranges and, by implication, centralization of IGF-I measurement.

GH replacement therapy in adults with GHD has become established in clinical practice over the last 10 yr. IGF-I is the primary biochemical marker of GH status during GH replacement in adults. To date, where in the normal range the IGF-I level should be placed to optimize GH replacement therapy remains unknown (36). Our data may help the clinician in GH dose titration for GHD patients who do not respond clinically to a conventional therapeutic trial of GH replacement, especially if the IGF-I level has remained below the 95th percentile for functional GHD.

In summary, the present study reinforces the current practice of many clinicians of aiming for the upper half or quartile of the IGF-I normal range as an initial target for patients treated for both acromegaly and AO-GHD. In particular, the data presented in Fig. 2 provide safety guidelines for risk of functional GHD during dose titration of medical therapies for adult GH disorders. They are intended to aid management by providing the clinician with a marker of risk of functional GHD. The guidelines may be of particular use in the management of patients treated with the new GH-

receptor antagonist pegvisomant. The data should be interpreted in conjunction with the clinical status of the patient and provide a basis for a logical and safe management strategy for disorders of GH secretion in adulthood.

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