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Clinical Implications of Residual Growth Hormone (GH) Response to Provocative Testing in Adults with Severe GH Deficiency

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Context: The diagnosis of GH deficiency (GHD) in adults is based on provocative tests of GH release, all influenced by clinical factors. It is unknown whether the amount of residual GH reserve under the cutoff value has any physiological implication.

Objectives: We used a large pharmacoepidemiological database of adult GHD (KIMS) and tested the impact of confounding factors on GH release of no greater than 3 μg/liter after an insulin tolerance test (ITT) and evaluated its potential physiological role.

Design, Settings, and Patients: A total of 1098 patients fulfilled the criteria of having a GH peak of no greater than 3 μg/liter during ITT as well as documented IGF-I levels.

Outcomes: The impact of underlying hypothalamic-pituitary disease, age, gender, body weight, as well as treatment modalities such as irradiation on peak GH level to ITT was evaluated, and the correlations between GH peak and targets of GH action were analyzed.

Results: The GH response to ITT was regulated by gender, age, and the number of additional pituitary deficiencies. In a multivariate evaluation, the extent of hypothalamic-pituitary dysfunction was the most important single predictor of GH peak in ITT. GH peaks in ITT were positively related to IGF-I levels and high-density lipoprotein-cholesterol, as well as inversely to triglycerides.

Conclusions: Even in adult severe GHD, GH release appears to be regulated by factors defined to play an important role in normal GH secretion. The impact of very low GH release on IGF-I and lipid parameters indicates a persistent physiological role of low GH concentrations in severely affected patients with GHD. (***J Clin Endocrinol Metab* 92: 2604–2609, 2007**)

GH DEFICIENCY (GHD) in adults is now widely recognized as an important consequence of pituitary disease that may contribute to the increased mortality observed in patients with hypopituitarism (1). Identified features are higher body fat mass with insulin resistance, an unfavorable lipid profile, and endothelial dysfunction, all associated with an increased cardiovascular risk. Cardiac performance is also reduced, and GHD patients experience decreased aerobic performance, contributing, along with reduced energy levels, to a diminished quality of life (2). GH replacement therapy may reverse these clinical problems, although unequivocal positive effects on mortality are still lacking (3).

It is important to identify patients who warrant GH replacement therapy. Due to the pulsatile nature of GH secretion, the diagnosis of GHD is typically based on GH stimulation tests. There are numerous provocative tests in use, with wide differences in procedures, side effects, and their accuracy to define severe GHD (4–6). Historically, the insulin tolerance test (ITT) is regarded as the "gold standard" (7), but practicability and safety may lead to a change in its widespread use, as indicated in the recently published Consensus guidelines of the Endocrine Society for the diagnosis and treatment of adult GHD (3). A GH stimulation to levels less than the commonly accepted threshold concentration of 3 μg/liter in the ITT is considered diagnostic for severe GHD in adults.

All provocative tests are influenced by confounding factors, including localization and extent of the hypothalamic-pituitary disease, age of the patient, gender, body weight (8–11), as well as treatment modalities such as irradiation or application of exogenous sex steroids (4, 12). The relative importance of these modulating factors in severe GHD is unclear based on the small studies currently available. In the present study, we chose a large study population to provide sufficient statistical power as well as a cohort with consistent

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Abbreviations: BMI, Body mass index; GHD, GH deficiency; HDL, high-density lipoprotein; ITT, insulin tolerance test; LDL, low-density lipoprotein; SDS, SD score.

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TABLE 1. Baseline characteristics of the study population (n = 1098)

Age at enrollment (mean ± SD)	44.3 ± 13.8 yr
No. of males/females	531/567
Cause of GHD	
Pituitary adenoma	618 (56.3)
Craniopharyngioma	105 (9.6)
Other pituitary/hypothalamic tumors	61 (5.6)
Nonpituitary, nonhypothalamic cranial tumors	42 (3.8)
Treatment for malignancy outside the cranium	10 (0.9)
Idiopathic GHD	109 (9.9)
Other causes	153 (13.9)
Adult-onset GHD	1000 (91.1)
Isolated GHD	132 (12.0)
Pituitary surgery performed	704 (64.1)
Radiotherapy performed	363 (33.1)

Unless stated otherwise, values represent number (percentage).

stimulation testing approaches, GH determinations, and clinical data. In addition, the relationships between GH release after stimulation and biochemical GH targets such as IGF-I serum levels and lipid parameters were investigated in this group of most severely affected patients.

Patients and Methods

Patients

The KIMS database represents a large pharmacoepidemiological survey that was started in 1994 to evaluate the long-term safety and outcome of GH replacement therapy in adults. In this database, initial GH stimulation tests are reported in a standardized fashion along with basal IGF-I levels that are determined in a central laboratory and the factors known to influence GH secretion (13). We have restricted this evaluation to the most widely used test in KIMS, the ITT (7), and included only patients with severe GHD defined as a GH peak of no greater than 3 μg/liter after ITT. A total of 1899 patients had a peak GH level during ITT available in the database and met the criteria of a peak no greater than 3 μg/liter.

The following additional inclusion criteria were defined: the ITT had to be performed within 1 yr of inclusion into KIMS, and before the start of GH replacement therapy, or 6 months after GH replacement therapy was discontinued. Documentation of the cause of pituitary dysfunction and baseline IGF-I levels measured in the central laboratory were required for inclusion in the analysis. Patients with the following characteristics were excluded from further analysis: body mass index (BMI) more than 50 kg/m^2 (n = 3), and baseline IGF-I more than +2 SD score (SDS) (n = 6). Thus, a total of 1098 patients were included in the present analysis. The baseline characteristics of this patient population at inclusion into KIMS are given in Table 1. The majority of patients had hypothalamic or pituitary tumors and multiple pituitary hormone deficiencies, and were receiving standard hormone replacement therapy. The database also included 10 patients with GHD related to treatment of extracranial malignancies (leukemia and Hodgkin). All patients gave their informed consent for inclusion in the database.

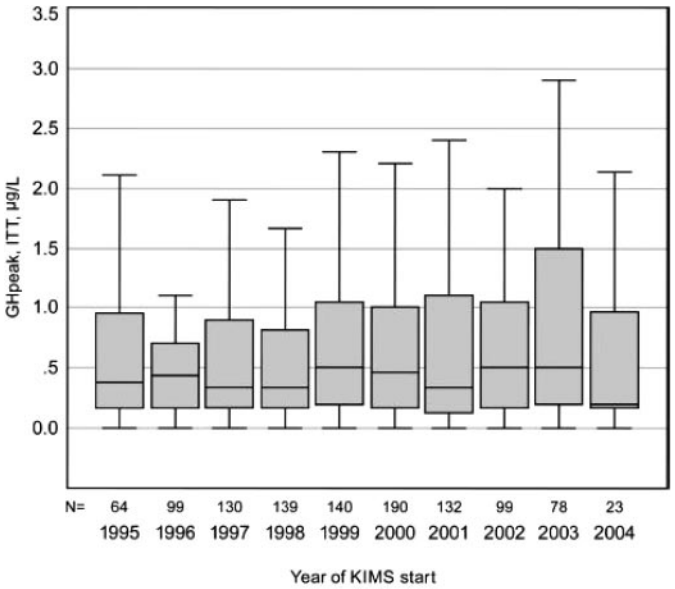

FIG. 1. Box-and-whisker plot showing median, interquartile range, and values within ±1.5 interquartile range of GH peaks in ITT stratified by years of entry into the database.

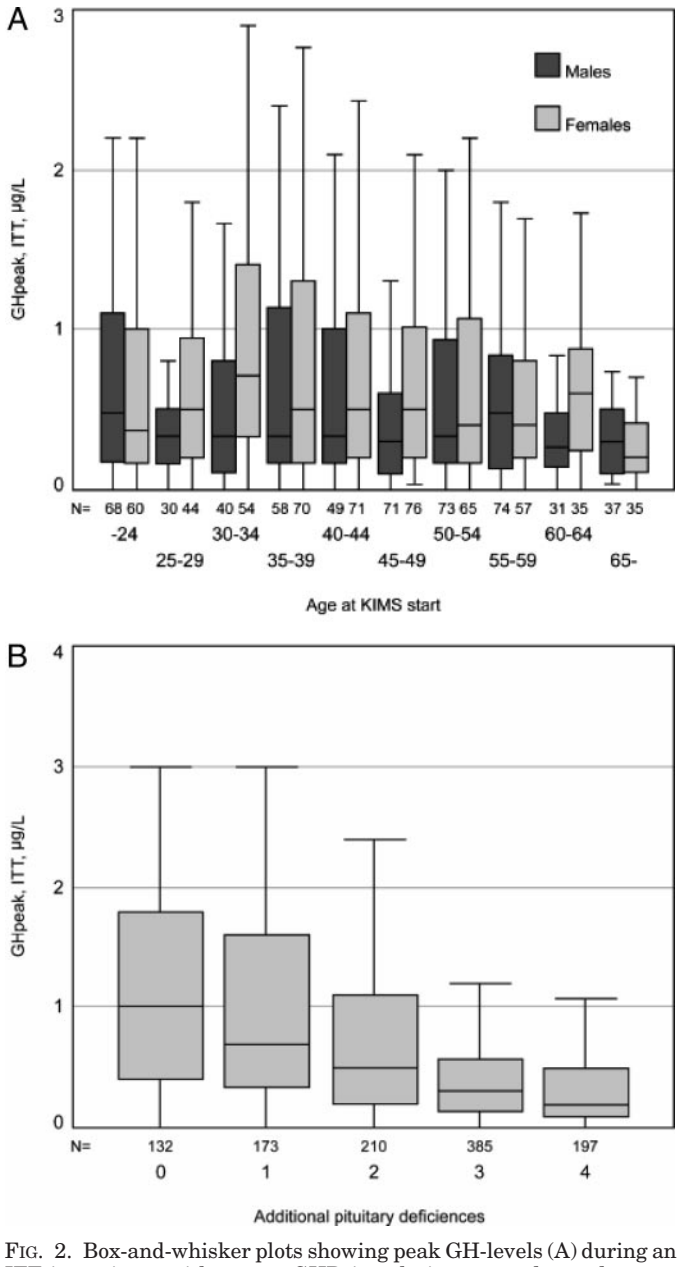

FIG. 2. Box-and-whisker plots showing peak GH-levels (A) during an ITT in patients with severe GHD in relation to gender and age at enrollment into the KIMS database, and in relation to the number of additional pituitary deficiencies (B).

TABLE 2. Correlation of peak GH levels during the ITT and IGF-I SDS with various factors with potential influence on GH secretion and IGF-I levels in patients with severe GHD (Spearman's ρ)

	Median	Peak GH ITT			IGF-I SDS		
		ρ	*P* value	n	ρ	*P* value	n
Gender (0/1)		0.10	<0.001	1098	−0.14	<0.001	1098
Age at KIMS start (yr)	45.2	−0.07	<0.029	1098	0.39	<0.001	1098
BMI (kg)	27.3	−0.09	<0.002	1084	0.23	<0.001	1084
Waist (cm)	95.0	−0.11	<0.001	1018	0.29	<0.001	1018
Waist to hip ratio (cm)	0.92	−0.11	<0.001	1013	0.22	<0.001	1013
Additional pituitary deficiencies	3	−0.39	<0.001	1097	−0.17	<0.001	1097
GHD before 18 yr (0/1)		−0.02	NS	1098	−0.32	<0.001	1098
Irradiation performed (0/1)		−0.03	NS	1098	0.06	<0.067	1098

NS, Not significant.

Methods

All ITTs were performed by the responsible physicians according to local protocols, with peak GH levels during the ITT available in all subjects.

The GH levels entered into KIMS were measured using the available GH assay at the investigator's institution. To exclude any long-term trend in GH measurements, we analyzed GH serum concentrations in relation to entry into the database without showing a time-dependent trend (Fig. 1). Serum concentrations of IGF-I were measured centrally by RIA after acid/ethanol precipitation of binding proteins (Nichols Institute Diagnostics, San Juan Capistrano, CA) (14). Intraassay, interassay, and total coefficients of variation were less than 9% in the concentration range 125–1046 μg/liter. The assay detection limit was 13.5 μg/liter. Age and gender-specific reference ranges were used to determine an IGF-I SDS for each patient. Serum total cholesterol, high-density lipoprotein (HDL)-cholesterol, and triglycerides were measured centrally by standardized methods (15). Serum low-density lipoprotein (LDL)-cholesterol was calculated according to the Friedewald formula (16).

In this cohort of adult severe GHD patients, age, gender, BMI, waist-to-hip ratio, severity of hypopituitarism, and previous radiotherapy to the hypothalamic-pituitary region were tested for their relative importance as predictors of peak serum GH level obtained during ITT as well as IGF-I level. In addition, the relationship between peak GH and serum IGF-I levels and lipid parameters (total cholesterol, LDL- and HDL-cholesterol, and triglycerides) were analyzed to determine the potential physiological significance of residual GH secretion.

Waist and hip measurements were conducted according to KIMS Guidelines circulated to all participating physicians, and BMI was calculated as body weight (kg)/height (m^2) (17).

Statistics

Nonparametric statistical tests were used throughout. Differences between groups were calculated using the Mann-Whitney *U* test. χ^2 tests were used when analyzing cross tabulations. In bivariate correlation analyses, Spearman's ρ was applied.

The influence of the various clinical factors were also tested by multiple regression analyses with the inclusion of the following predictors: gender, age at diagnosis of GHD, age at onset of pituitary deficiency, BMI, number of additional pituitary deficiencies, childhood onset of GHD, history of pituitary surgery, history of irradiation, and diagnosis of craniopharyngioma. Analyses were performed using data from all patients and also subgrouping for adult and childhood onset patients' data separately. The predictors entered the analyses in the same order in the overall analysis of all patient data and in the analysis of the adult onset patient data. Step-wise multiple forward regression analyses were performed. The standard Statistical Package for the Social Sciences for Windows, V11.0 (SPSS, Inc., Chicago, IL), was used in the statistical calculations.

A P value < 0.05 was considered statistically significant.

Results

Influence of clinical factors on peak GH levels

In this population of patients with severe GHD, defined by a GH peak less than 3 μg/liter during an ITT, the peak GH was significantly related to gender, with a higher level observed in females than in males (Fig. 2A and Table 2). In addition, mean GH peaks decreased significantly with increasing age and higher BMI (Table 2). Waist circumference and waist to hip ratio were significantly negatively correlated to the GH peak. GH peaks became progressively lower with increasing numbers of additional pituitary deficiencies, an indicator of the severity of the underlying pituitary disease (Fig. 2B and Table 2). No significant differences in GH peaks during the ITT were seen between patients with severe GHD of childhood compared with adult onset, or between patients subjected to pituitary irradiation or not (Table 2).

In multiple regression analysis, the number of additional pituitary deficiencies was the strongest predictor of peak GH response between undetectable and 3 μg/liter in ITT as it entered all regressions first (Table 3). Patients with isolated

TABLE 3. Predictors of peak GH levels during an ITT in patients with severe GHD (multiple regression analysis)

		Unstandardized coefficients			R^2
		B	SE	*P* value	
All patients	(Constant)	1.14	0.049	<0.000	
	Additional pituitary deficiencies	−0.21	0.015	<0.000	
	Irradiation performed	−0.08	0.042	<0.043	
	Gender	0.08	0.039	<0.046	0.15
Adult onset	(Constant)	1.34	0.090	<0.000	
	Additional pituitary deficiencies	−0.21	0.016	<0.000	
	Irradiation performed	−0.08	0.043	<0.055	
	Age at pituitary disease onset	0.01	0.002	<0.000	
	Gender	0.09	0.041	<0.027	0.18
Childhood onset	(Constant)	0.71	0.170	<0.000	
	Additional pituitary deficiencies	−0.19	0.048	<0.000	
	Age at pituitary disease onset	0.03	0.015	<0.028	0.14

GHD (n = 132) had a mean GH peak of 1.1 ± 0.8 μg/liter, whereas those with a loss of three or four additional pituitary functions (n = 582) had a mean GH peak of 0.4 ± 0.5 μg/liter ($P < 0.001$). In addition, gender was a borderline significant independent predictor of GH peak response in the whole cohort of patients with severe GHD, with higher peak GH levels during the ITT observed in women (0.7 ± 0.7 μg/liter) than in men (0.6 ± 0.7 μg/liter; $P < 0.001$). Hypothalamic-pituitary irradiation also influenced GH status; patients who had received radiotherapy had lower GH peaks than patients who had not received it (Table 3).

In patients with childhood onset GHD, the number of additional pituitary deficiencies together with the age at diagnosis was the only variable to influence GH status in this cohort (Table 3). In patients with adult onset of GHD, the number of additional pituitary deficiencies, gender, and age at diagnosis of pituitary disease were significant predictors of GH peak in ITT, while previous irradiation did not reach statistical significance. Older patients at database entry had lower peaks than younger patients. In this cohort of patients with severe GHD, BMI was not a predictor of GH-peak response during the ITT, neither was a history of pituitary surgery or a diagnosis of craniopharyngioma.

Influence of clinical factors on IGF-I SDS values

In this cohort of adults with severe GHD, IGF-I SDS values were significantly lower in younger patients (Table 2) and women. The number of pituitary hormone deficiencies also influenced IGF-I levels, with the lowest values in patients with three or more pituitary hormone deficits. Subjects diagnosed with GHD before the age of 18 had lower IGF-I levels than those who developed it in adult life (Table 2). The significant correlation of IGF-I SDS to gender was not influenced by estrogen replacement ($P = 0.497$).

There was an inverse U-shaped association between IGF-I and BMI (Table 2 and Fig. 3), and a positive correlation between IGF-I, and both waist circumference and waist to hip ratio.

Relation of GH increments in ITT to IGF-I levels and variables of lipid metabolism

Peak GH levels were significantly correlated with IGF-I SDS (Spearman's $\rho = 0.261$; $P < 0.001$) (Fig. 4). In addition, GH peaks were significantly associated with HDL-cholesterol as well as triglyceride levels, but not with levels of total cholesterol and LDL-cholesterol (Table 4).

Discussion

The KIMS database (a large international pharmacoepidemiological database for adult GHD containing data on more than 10,000 patients) registers the results of locally performed GH provocative tests with standardized auxology and centrally measured outcome variables, such as serum IGF-I and lipid levels. The present analysis based on data pool previously evaluated for GH testing procedures confirms that the ITT, usually regarded as the "gold standard," was indeed the most commonly used stimulation test in this predominantly European data set (7). This study focused on

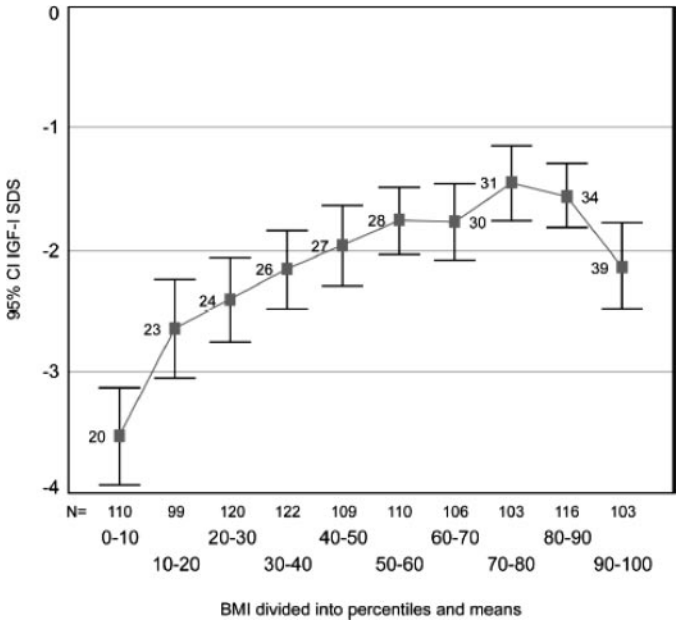

FIG. 3. Error bars (means and 95% confidence intervals) showing the relationship between IGF-I SDS values and BMI in severe GHD (BMI divided into percentiles on x-axis; BMI means shown within figure).

the most severe form of GHD, namely patients with a peak GH level in ITT less than 3 μg/liter. The 1098 patients meeting these and the other inclusion criteria represent the largest group for a specific provocative GH test in severe GHD studied to date. Previous studies were restricted to much smaller numbers of patients and were performed under highly standardized conditions in selected groups diagnosed with partial or complete GHD. At least partially they were compared with carefully matched controls, which allowed the detection of small differences between groups but rendered them prone to type 2 errors, especially when test results were modulated by multiple factors (18–24). The

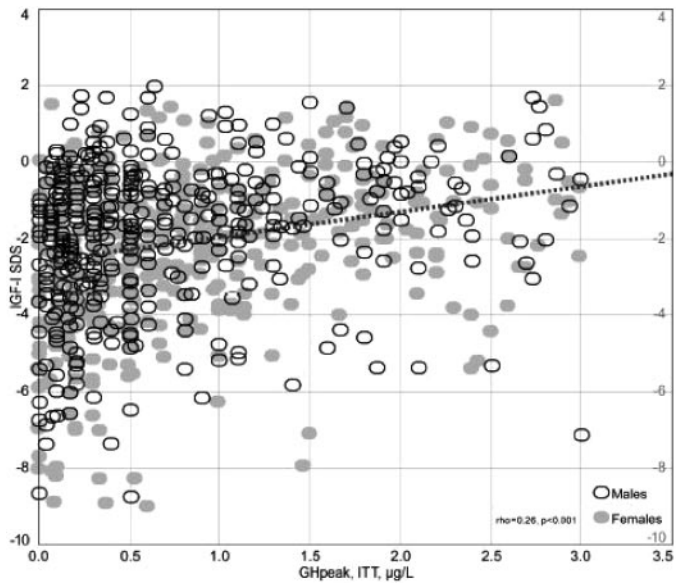

FIG. 4. Scattergram showing the correlation between peak GH levels in ITT and IGF-I SDS values in patients with severe GHD.

TABLE 4. Correlation of peak GH levels during an ITT with IGF-I SDS and serum lipid concentrations (Spearman's ρ)

	GH peak ITT		
	ρ	*P* value	n
IGF-I SDS	0.26	<0.001	1098
Cholesterol	−0.02	NS	999
LDL-cholesterol	−0.04	NS	947
HDL-cholesterol	0.14	<0.001	1001
Triglycerides	−0.11	<0.001	999

NS, Not significant.

large number of patients in the present study reduces this problem. However, local variability of testing, especially the use of different GH assays, may influence the results. Standardized measurement of the same samples with different commercially available assay systems has shown significant variations (25). This has recently initiated efforts to better standardize GH determinations (26). Nevertheless, due to the large number of subjects in the present study, these factors were of less concern, and significant results may, therefore, be of general importance for the clinical situation of GHD patients.

The data showed in a large number of patients with severe GHD that peak GH during an ITT remained influenced by the number of pituitary hormone deficiencies, confirming previous pioneering data on patients with a wide range of GHD (11). We did not find a significant influence of hormone replacement therapy on GH peak, IGF-I, body composition, or lipids, apart from a borderline result for GH peak related to the substitution of the ACTH axis (data not shown), but the number of patients with no replacement therapy is far too small to exclude any methodological bias.

Our data on the influence of age and gender support the notion that severe GHD parallels the normal physiological situation on a low level. Thus, our results favor the concept that the somatotroph cells remain under the influence of some of the mechanisms observed in subjects with an intact hypothalamic pituitary axis, albeit at a much lower absolute level of operation. The close relationship of the GH peak response to the loss of other pituitary functions fits such a concept. The mass of normally functioning cells is presumed to be drastically reduced in panhypopituitarism. It can be speculated that in contrast to surgery, in which the remaining GH secreting cells respond normally, irradiated cells may be viable but have a secretory defect (12). Such secretory defects most likely occur in idiopathic forms of GHD and may provide a hypothetical explanation for the different responses observed in our study.

Our observation of a highly significant correlation between GH peak response and circulating serum IGF-I levels provides another line of support for this concept. These data in severe GHD contrast to previous studies, including partial GHD, but suggest that despite severe disease, the remaining GH producing cells are still active on target cells. Nutritional factors may explain the absent correlation between GH and IGF-I in the previous, much smaller trials, which is obviated by the large number studied here. Body fat appears to increase IGF-I directly, whereas GH release is suppressed in the very obese patient. This has been shown previously, and detailed studies by Weltman *et al.* (27) using 24-h sampling protocols estimated that every 1 U increase in BMI was associated with a 6% decrease in mean 24-h GH secretion, with abdominal visceral fat as a stronger predictor than total percentage body fat (28). In our study of severe GHD, there was no clear correlation between peak GH in the narrow range of 0–3 μg/liter and BMI, whereas the IGF-I measurements interestingly confirmed for this GHD population the relative decrease of IGF-I in normal subjects with very low and very high BMI levels (10). In contrast to BMI, waist circumference or the waist to hip ratio was related to GH peak. Thus, it may be speculated that visceral fat influenced the GH release more than BMI did.

In contrast to a recent study in patients with partial GHD developing into severe GHD, we could not confirm any impact of the severity of GHD among our highly affected patients on total or LDL-cholesterol (29, 30). However, in this very large group of patients with severe GHD, we showed a positive relation of HDL-cholesterol to the amplitude of releasable GH and an inverse relation to triglycerides. Due to the high number of patients included and the therapeutic aims to normalize other pituitary functions, it appears unlikely that thyroid hormones, gonadal steroids, and/or glucocorticoid alterations were responsible for the changes in lipid metabolism or body composition. Experimental evidence does suggest an impact of GH pulses on lipid composition. In comparison with a twice-daily application of a bolus of GH, continuous GH application in GH deficient patients differentially affects HDL-cholesterol levels (31). Thus, it may be speculated that a remaining small pulsatile GH release may positively impact lipid variables and the risk profile for arteriosclerosis (19).

In summary, we showed that in the most severely affected patients with GHD, peak GH response to ITT, even at the lowest levels, was regulated by the extent of pituitary deficiency, by gender, and age. These low GH levels in the 0–3 μg/liter range were related to endpoints such as serum levels of IGF-I and lipids, indicating that despite a greatly reduced concentration, residual GH release in severe GHD may still deserve a physiological function.

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References

1. **Rosen T, Bengtsson BA** 1990 Premature mortality due to cardiovascular disease in hypopituitarism. Lancet 336:285–288
2. **Woodhouse LJ, Mukherjee A, Shalet SM, Ezzat S** 2006 The influence of growth hormone status on physical impairments, functional limitations, and health-related quality of life in adults. Endocr Rev 27:287–317
3. **Molitch ME, Clemmons DR, Malozowski S, Merriam GR, Shalet SM, Vance ML, Stephens PA** 2006 Evaluation and treatment of adult growth hormone deficiency: an Endocrine Society Clinical Practice Guideline. J Clin Endocrinol Metab 91:1621–1634
4. **Biller BM, Samuels MH, Zagar A, Cook DM, Arafah BM, Bonert V, Stavrou S, Kleinberg DL, Chipman JJ, Hartman ML** 2002 Sensitivity and specificity

of six tests for the diagnosis of adult GH deficiency. J Clin Endocrinol Metab 87:2067–2079
5. **Cordido F, Alvarez-Castro P, Isidro ML, Casanueva FF, Dieguez C** 2003 Comparison between insulin tolerance test, growth hormone (GH)-releasing hormone (GHRH), GHRH plus acipimox and GHRH plus GH-releasing peptide-6 for the diagnosis of adult GH deficiency in normal subjects, obese and hypopituitary patients. Eur J Endocrinol 149:117–122
6. **Hartman ML, Crowe BJ, Biller BM, Ho KK, Clemmons DR, Chipman JJ** 2002 Which patients do not require a GH stimulation test for the diagnosis of adult GH deficiency? J Clin Endocrinol Metab 87:477–485
7. **Casanueva F** 2004 Biochemical diagnosis of growth hormone deficiency in adults. In: Abs R, Feldt-Rasmussen U, eds. Growth hormone deficiency in adults. Tubney, UK: OxfordPharmaGenesis Ltd.; 91–101
8. **Abs R, Feldt-Rasmussen U** 2004 10 years KIMS database. Tubney, UK: OxfordPharmaGenesis Ltd.
9. **Qu XD, Gaw Gonzalo IT, Al Sayed MY, Cohan P, Christenson PD, Swerdloff RS, Kelly DF, Wang C** 2005 Influence of body mass index and gender on growth hormone (GH) responses to GH-releasing hormone plus arginine and insulin tolerance tests. J Clin Endocrinol Metab 90:1563–1569
10. **Schneider HJ, Saller B, Klotsche J, Marz W, Erwa W, Wittchen HU, Stalla GK** 2006 Opposite associations of age-dependent insulin-like growth factor-I standard deviation scores with nutritional state in normal weight and obese subjects. Eur J Endocrinol 154:699–706
11. **Toogood AA, Beardwell CG, Shalet SM** 1994 The severity of growth hormone deficiency in adults with pituitary disease is related to the degree of hypopituitarism. Clin Endocrinol (Oxf) 41:511–516
12. **Darzy KH, Shalet SM** 2005 Hypopituitarism as a consequence of brain tumours and radiotherapy. Pituitary 8:203–211
13. **Abs R, Bengtsson BA, Hernberg-Stahl E, Monson JP, Tauber JP, Wilton P, Wuster C** 1999 GH replacement in 1034 growth hormone deficient hypopituitary adults: demographic and clinical characteristics, dosing and safety. Clin Endocrinol (Oxf) 50:703–713
14. **Brabant G, von zur Muhlen A, Wuster C, Ranke MB, Kratzsch J, Kiess W, Ketelslegers JM, Wilhelmsen L, Hulthen L, Saller B, Mattsson A, Wilde J, Schemer R, Kann P** 2003 Serum insulin-like growth factor I reference values for an automated chemiluminescence immunoassay system: results from a multicenter study. Horm Res 60:53–60
15. **Feldt-Rasmussen U, Abs R, Bengtsson BA, Bennmarker H, Bramnert M, Hernberg-Stahl E, Monson JP, Westberg B, Wilton P, Wuster C** 2002 Growth hormone deficiency and replacement in hypopituitary patients previously treated for acromegaly or Cushing's disease. Eur J Endocrinol 146:67–74
16. **Friedewald WT, Levy RI, Fredrickson DS** 1972 Estimation of the concentration of low-density lipoprotein cholesterol in plasma, without use of the preparative ultracentrifuge. Clin Chem 18:499–502
17. **Bengtsson BA, Abs R, Bennmarker H, Monson JP, Feldt-Rasmussen U, Hernberg-Stahl E, Westberg B, Wilton P, Wuster C** 1999 The effects of treatment and the individual responsiveness to growth hormone (GH) replacement therapy in 665 GH-deficient adults. KIMS Study Group and the KIMS International Board. J Clin Endocrinol Metab 84:3929–3935
18. **Shalet SM, Toogood A, Rahim A, Brennan BM** 1998 The diagnosis of growth hormone deficiency in children and adults. Endocr Rev 19:203–223
19. **Colao A, Cerbone G, Pivonello R, Aimaretti G, Loche S, Di Somma C, Faggiano A, Corneli G, Ghigo E, Lombardi G** 1999 The growth hormone (GH) response to the arginine plus GH-releasing hormone test is correlated to the severity of lipid profile abnormalities in adult patients with GH deficiency. J Clin Endocrinol Metab 84:1277–1282
20. **Colao A, Di Somma C, Pivonello R, Loche S, Aimaretti G, Cerbone G, Faggiano A, Corneli G, Ghigo E, Lombardi G** 1999 Bone loss is correlated to the severity of growth hormone deficiency in adult patients with hypopituitarism. J Clin Endocrinol Metab 84:1919–1924
21. **Colao A, Di Somma C, Cuocolo A, Filippella M, Rota F, Acampa W, Savastano S, Salvatore M, Lombardi G** 2004 The severity of growth hormone deficiency correlates with the severity of cardiac impairment in 100 adult patients with hypopituitarism: an observational, case-control study. J Clin Endocrinol Metab 89:5998–6004
22. **Murray RD, Adams JE, Shalet SM** 2004 Adults with partial growth hormone deficiency have an adverse body composition. J Clin Endocrinol Metab 89:1586–1591
23. **Murray RD** 2005 The phenotype of adults with partial growth hormone deficiency. Horm Res 64(Suppl 2):12–17
24. **Murray RD, Shalet SM** 2005 Insulin sensitivity is impaired in adults with varying degrees of GH deficiency. Clin Endocrinol (Oxf) 62:182–188
25. **Popii V, Baumann G** 2004 Laboratory measurement of growth hormone. Clin Chim Acta 350:1–16
26. **Trainer PJ, Barth J, Sturgeon C, Wieringaon G** 2006 Consensus statement on the standardisation of GH assays. Eur J Endocrinol 155:1–2
27. **Weltman A, Weltman JY, Hartman ML, Abbott RD, Rogol AD, Evans WS, Veldhuis JD** 1994 Relationship between age, percentage body fat, fitness, and 24-hour growth hormone release in healthy young adults: effects of gender. J Clin Endocrinol Metab 78:543–548
28. **Vahl N, Jorgensen JO, Jurik AG, Christiansen JS** 1996 Abdominal adiposity and physical fitness are major determinants of the age associated decline in stimulated GH secretion in healthy adults. J Clin Endocrinol Metab 81:2209–2215
29. **Colao A, Di Somma C, Spiezia S, Rota F, Pivonello R, Savastano S, Lombardi G** 2006 The natural history of partial growth hormone deficiency in adults: a prospective study on the cardiovascular risk and atherosclerosis. J Clin Endocrinol Metab 91:2191–2200
30. **Vahl N, Klausen I, Christiansen JS, Jorgensen JO** 1999 Growth hormone (GH) status is an independent determinant of serum levels of cholesterol and triglycerides in healthy adults. Clin Endocrinol (Oxf) 51:309–316
31. **Laursen T, Lemming L, Jorgensen JO, Klausen IC, Christiansen JS** 1998 Different effects of continuous and intermittent patterns of growth hormone administration on lipoprotein levels in growth hormone-deficient patients. Horm Res 50:284–291

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