Discontinuation of Growth Hormone (GH) Treatment during the Transition Phase Is an Important Factor Determining the Phenotype of Young Adults with Nonidiopathic Childhood-Onset GH Deficiency

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Context: Little is known about the impact of childhood-onset GH deficiency (GHD), in particular the duration of GH cessation during the transition phase, on adult phenotype.

Objective: We investigated the association between the manifestations and management of GHD during childhood/adolescence and the clinical features of GHD in adulthood.

Design/Setting/Patients/Intervention: Patients with reconfirmed childhood-onset GHD who resumed GH treatment as adults were identified from two sequential databases (n = 313). The cohort was followed up longitudinally from GH start in childhood to reinitiation of treatment in adulthood and 1 yr beyond. Analyses were performed in the total cohort and in subgroups of patients with idiopathic GHD (IGHD) and non-IGHD. The cohorts were stratified based on duration of GH cessation (short, $\leq$2 yr; long, $>$2 yr).

Main Outcome Measures: Regimen of pediatric GH administration, duration of GH interruption, IGF-I SD score, lipid concentrations, and quality of life were measured.

Results: Mean duration of GH interruption was 4.4 yr. IGF-I SD score in adulthood was related to severity of childhood GHD. In non-IGHD patients, a longer duration of GH interruption was associated with a worse lipid profile ($P < 0.0001$). Non-IGHD patients who gained more height during childhood GH treatment reported better quality of life than those who gained less height ($P < 0.05$).

Conclusions: Pediatricians should tailor GH treatment, not only for its beneficial effect on growth but also for future health in adulthood. In adults with reconfirmed GHD, particularly those with non-IGHD, early recommencement of GH should be considered. **(*J Clin Endocrinol Metab* 95: 2646–2654, 2010)**

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Abbreviations: BMI, Body mass index; CO-GHD, childhood-onset GHD; GHD, GH deficiency; HDL, high-density lipoprotein; IGHD, idiopathic GHD; LDL, low-density lipoprotein; QoL, quality of life; QoL-AGHDA, QoL-Assessment of GHD in Adults; SDS, SD score.

Many adolescents who are diagnosed with GH deficiency (GHD) during childhood and discontinue GH therapy at completion of linear growth remain GH deficient in adulthood. It is therefore recommended that they should be retested when growth and pubertal development are complete, and those with confirmed GHD should be considered for recommencement of GH replacement (1). The optimization of management during this transition period, when patients attain full somatic development, has been a subject of great interest (1–4).

Typical manifestations of GHD in adulthood include low serum IGF-I concentrations, an adverse cardiovascular profile, an impaired quality of life (QoL), and alterations in bone metabolism (5). Approximately 22% of adult hypopituitary patients receiving GH replacement have childhood-onset GHD (CO-GHD) (6). The clinical characteristics of these adults may differ from those of patients with adult-onset GHD, particularly with regard to QoL (7). In addition, the severity of adverse consequences of CO-GHD varies among patients with organic pituitary disease, nonorganic pituitary disease, and brain tumor (6).

Little information is available on the extent to which the degree of CO-GHD and the GH treatment regimen during childhood and transition impact on the phenotype of GHD in young adults and, in particular, whether the duration of discontinuation of GH therapy during transition is associated with an adverse lipid profile and impaired QoL in adult patients with CO-GHD. Our study aimed to address these questions by considering data on patients with GHD who were treated with Genotropin (Pfizer, Strängnäs, Sweden), available in two pharmacoepidemiological surveys: KIGS-Pfizer International Growth Database, and KIMS-Pfizer International Metabolic Database.

Patients and Methods

Databases

KIGS collects information on GH-treated children with various growth disorders and currently contains data from more than 63,000 patients in 58 countries. KIMS contains data on almost 14,000 GH-deficient adults from 31 countries. Both surveys aim to monitor the safety and outcomes of long-term GH replacement and have been conducted in accordance with the Helsinki Declaration (8). Each patient and/or their legal representative received adequate information, consented to participation according to local regulations, and had the right to withdraw from the survey at any time (9, 10).

Patient selection

Patient data have been anonymized in KIGS and KIMS, and therefore a two-step matching procedure was performed to select a study cohort restricted to patients with data entered in both databases. First, data on country of origin, gender, and date of birth of all patients with CO-GHD followed in KIMS (n = 2712) were cross-checked with corresponding information in KIGS, providing a total number of 648 matches. In the next step, individual records from KIGS and KIMS were compared to exclude any inconsistent pairs based on initials, primary diagnosis, and date of commencement of GH therapy. This process resulted in a study cohort of 313 patients (194 males, 62%) with confirmed identity in both KIGS and KIMS.

Other selection criteria for inclusion were: age at entry into KIGS younger than 18 yr and age at exit from KIGS older than 13 yr; height recorded at KIGS entry and at last KIGS visit; and being off GH therapy for 6 months or longer before KIMS entry. All patients in the study cohort had GHD during adulthood confirmed by a GH-stimulation test after completion of linear growth.

Patient cohort

The total cohort was divided into two groups based on the etiology of GHD: patients with idiopathic GHD (IGHD; n = 127; 80 males, 62%) and non-IGHD (n = 186; 114 males, 61%). Additionally, the cohort was stratified based on duration of interruption in GH treatment during transition (GH gap): patients in whom GH was stopped for 2 yr or less (short GH gap; n = 82) and patients in whom GH was stopped for longer than 2 yr (long GH gap, n = 231).

The mean age at entry into KIGS (KIGS start; a marker of initiation of pediatric GH treatment) was 8.3 ± 3.88 yr in the IGHD group and 10.8 ± 3.61 in the non-IGHD group. The mean age at the end of follow-up in KIGS (KIGS stop; a marker of completion of pediatric GH treatment) was 17.5 ± 1.84 in the IGHD group and 17.1 ± 1.91 yr in the non-IGHD group. Mean age at entry into KIMS (KIMS start; a marker for recommencing GH treatment as adults) was 21.9 ± 3.60 yr in the IGHD group and 21.5 ± 3.47 in the non-IGHD group (Table 1).

The mean GH peak at diagnosis during childhood was 3.15 ± 3.25 μg/liter (median 2.10 μg/liter; 10th to 90th percentile: 0.50–7.55 μg/liter), and at retesting during adulthood, it was 1.31 ± 1.57 μg/liter (median 0.67 μg/liter; 10th to 90th percentile: 0.10–3.00 μg/liter). During adulthood approximately half of the patients were diagnosed using the insulin tolerance test (n = 175), followed in frequency by arginine (n = 52) and glucagon (n = 14) stimulation tests. Mean GH peaks for the two etiology groups were similar, as were mean GH peaks for patients with long and short GH gaps (data not shown).

In the IGHD and non-IGHD groups, isolated GHD was reported in 46 (36%) and 34 (19%) of the patients, respectively; either one or two additional pituitary hormone deficits were reported in 38 (30%) and 55 (29%) patients, respectively; and panhypopituitarism was reported in 42 (34%) and 97 (52%) patients, respectively. Pituitary hormone deficit profiles for patients with a long GH gap and a short GH gap were similar to each other (data not shown).

Craniopharyngioma (n = 43; 23%) was the most frequent single cause of GHD in the non-IGHD group; however, when all types of cranial tumors distant from the pituitary were combined, they accounted for a similar proportion of patients (Table 2). The distributions of underlying etiologies in both GH-gap groups were similar (data not shown). Etiology was classified based on reported diagnoses reported and in accordance with the KIMS classification list (11).

TABLE 1. Patient characteristics

	IGHD			Non-IGHD		
	KIGS start	KIGS stop	KIMS start	KIGS start	KIGS stop	KIMS start
Age (yr)	8.3 ± 3.88	17.5 ± 1.84	21.9 ± 3.61	10.8 ± 3.61	17.1 ± 1.91	21.5 ± 3.47
Height SDS	−3.3 ± 1.35	−0.8 ± 1.15	−0.6 ± 1.28	−1.8 ± 1.50	−0.6 ± 1.40	−0.5 ± 1.55
Distance to target height SDS[a]	−3.2 ± 1.38	−0.7 ± 1.17	−0.5 ± 1.17	−2.0 ± 1.35	−0.7 ± 1.30	−0.6 ± 1.45
Height SDS gain during KIGS[b]	N/A	2.5 ± 1.36	N/A	N/A	1.3 ± 1.40	N/A
BMI (kg/m^2)	16.4 ± 2.94	21.7 ± 4.32	23.4 ± 4.76	19.0 ± 3.97	23.0 ± 5.17	25.3 ± 5.64
GH dose (mg/kg · wk), as reported in KIGS		0.19 ± 0.05	N/A		0.18 ± 0.06	N/A
Time on GH in childhood (yr)	8.9 ± 3.53			6.1 ± 3.37		
Time off GH between KIGS and KIMS (yr)	4.4 ± 3.09			4.4 ± 3.18		

Data are shown as mean ± SD. N/A, Not applicable.

[a] Defined as the difference between height SDS and target height SDS.

[b] Defined as the difference between height SDS at KIGS stop and at KIGS start.

Target height was defined as midparental height plus 6.5 cm for boys and midparental height minus 6.5 cm for girls (12). Puberty was induced in approximately half of the patients (n = 163).

Mean pediatric GH dose during follow-up in KIGS was 0.19 ± 0.05 mg/kg · wk in the IGHD group and 0.18 ± 0.06 mg/kg · wk in the non-IGHD group. Mean duration of GH treatment during childhood was 8.9 ± 3.53 yr in the IGHD group and 6.1 ± 3.37 yr in the non-IGHD group. The mean time interval between cessation of pediatric treatment and start of adult treatment was similar in both IGHD and non-IGHD groups (4.4 ± 3.09 and 4.4 ± 3.18 yr, respectively). Patient characteristics for IGHD and non-IGHD groups are shown in Table 1.

Adult outcomes and potential predictors

To assess the outcome of childhood GH treatment in adults with CO-GHD, IGF-I SD score (SDS), lipid profile [serum total cholesterol, low density lipoprotein (LDL) cholesterol, high density lipoprotein (HDL) cholesterol, and triglyceride levels] and QoL were measured at KIMS entry and 1 yr after the restart of GH therapy.

Until November 2002, serum IGF-I concentrations were determined by RIA after acid-ethanol precipitation of IGF-binding proteins (Nichols Institute Diagnostics, San Juan Capistrano, CA). Thereafter a chemiluminescence immunoassay (Nichols Advantage System) was introduced (13). Long-term reproducibility, measured during a period of more than 1 yr, showed a coefficient of variation of less than 9% in the concentration range of 130.0–850.0 μg/ml (17.0–111.0 nmol/liter). The assay detection limit was 30.0 μg/ml (3.9 nmol/liter). Absolute IGF-I values were converted into gender- and age-specific SDSs using assay-specific reference values. All measurements of IGF-I were performed in a central laboratory, as were all assays of lipid variables. Serum concentrations of total cholesterol (14), HDL-cholesterol (15), and triglycerides (16) were measured directly and expressed in millimoles per liter. Serum concentrations of LDL-cholesterol were estimated using Friedewald's formula (17).

QoL was evaluated using the score of QoL assessment of GHD in adults (QoL-AGHDA) (18). The QoL-AGHDA, for which a high score denotes poor QoL, was developed specifically to assess the impact of GHD in adults (18).

TABLE 2. Distribution of primary etiologies in patients with non-GHD (non-IGHD group)

Etiology	Male (n)	Female (n)
Pituitary adenomas[a]	3	4
Craniopharyngioma	29	14
Other pituitary/hypothalamic tumors	13	9
Cranial tumors distant from pituitary/hypothalamus area	32	14
Treatment for malignancy outside the cranium	13	5
Other causes of acquired GHD	24	26
Total	114	72

[a] Includes one patient with nonfunctioning pituitary adenoma, two patients with Cushing's disease, three patients with prolactinoma, and one with other pituitary adenoma.

Comparisons between long- and short-GH-gap groups

Mean IGF-I SDS, lipid concentrations (total cholesterol, LDL cholesterol, HDL cholesterol and triglycerides) and QoL-AGHDA score at KIMS start were compared in patients who had either a long or short interruption in GH treatment (long *vs.* short GH gap groups). The impact of the GH-gap variable was also assessed within the two etiology groups (IGHD and non-IGHD). Mean changes after 1 yr of GH therapy in the variables studied were calculated in the total cohort and etiology groups.

Statistical analysis

To assess the relationship between childhood clinical variables and signs and symptoms of GHD in adulthood, stepwise regression was performed in the total cohort and separately in the IGHD and non-IGHD groups. In the first step, all parameters related to GHD in childhood were tested as three groups against adult outcomes (Table 3): 1) background variables, 2) clinical characteristics at baseline, and 3) variables related to GH treatment in KIGS. Thereafter significant variables identified in the first step were regressed, together with gender, age at KIMS en-

TABLE 3. Variables in childhood entered into the stepwise regression prediction model as potential predictors of adult outcome of GH therapy (derived from data in KIGS)

Background variables
Etiology (entered as a binary variable: IGHD/non-IGHD)
Maximum GH peak from stimulation test during childhood
Number of pituitary hormone deficits in addition to GHD
Birth weight SDS
Clinical variables measured/calculated at baseline (KIGS start)
Height SDS
Difference between height SDS and target height SDS
BMI SDS
Age
GH dose
Variables related to treatment during KIGS
Mean GH dose in KIGS
Age at KIGS stop
Duration of time on GH therapy in KIGS
Height velocity below 2 cm at KIGS stop (entered as a binary variable yes/no)
Height velocity at KIGS stop
Height SDS at KIGS stop
Difference between height SDS at KIGS stop and height SDS at baseline
Difference between height SDS at KIGS stop and target height SDS

try, and the interval without GH treatment between KIGS stop and KIMS start (GH gap), with adult outcomes.

Stepwise regression was used to identify the variables that explain variation in adult outcome data; $P < 0.05$ was used to define statistical significance. However, for ease of interpretation, significant relationships are shown as univariate Spearman's rank correlations with associated P values.

Values at KIMS start and changes 1 yr after restart of GH treatment were compared using Student's t test for normally distributed variables and the Wilcoxon rank-sum test for non-normally distributed variables.

Data analyses were performed using SAS version 8.2 (Statistical Analysis System, SAS Institute, Cary, NC). Data are presented as mean ± SD, unless otherwise stated.

Results

Mean values for the clinical parameters at restart of GH replacement in adulthood are shown in Table 4. Significant regression analyses are summarized in Table 5.

IGF-I SDS in adults at baseline

Regression analysis performed in the total cohort confirmed that IGF-I SDS at KIMS start was higher in men than women ($P < 0.05$) and was positively associated with GH peak ($P < 0.05$). These associations were significant in both IGHD and non-IGHD groups (Table 5).

IGHD group

IGF-I SDS correlated positively with GH peak at KIMS start ($P < 0.05$). No other associations were identified.

TABLE 4. Values of clinical outcomes at the restart of GH replacement as adults (entry into KIMS/KIMS start) included in stepwise regression analyses with variables from childhood (Table 3)

Variable	Total cohort			IGHD			Non-IGHD			IGHD *vs.* non-IGHD *P* value
	n	Median (10–90th percentile)	Mean ± SD	n	Median (10–90th percentile)	Mean ± SD	n	Median (10–90th percentile)	Mean ± SD	
Total cholesterol (mmol/liter)	168	5.0 (3.9 to 6.8)	5.2 ± 1.1	66	4.8 (3.9 to 6.6)	5.0 ± 1.1	102	5.2 (4.0 to 6.9)	5.3 ± 1.2	<0.05
LDL-cholesterol (mmol/liter)	164	3.2 (2.0 to 4.5)	3.2 ± 1.0	66	2.9 (2.0 to 4.3)	3.1 ± 0.9	98	3.2 (2.1 to 4.5)	3.2 ± 1.0	NS
HDL-cholesterol (mmol/liter)	168	1.2 (0.8 to 1.8)	1.3 ± 0.4	66	1.3 (0.9 to 2.1)	1.3 ± 0.4	102	1.2 (0.8 to 1.8)	1.2 ± 0.4	NS
Triglyceride (mmol/liter)	168	1.2 (0.7 to 2.9)	1.6 ± 1.0	66	1.0 (0.6 to 2.5)	1.2 ± 0.7	102	1.5 (0.7 to 3.1)	1.8 ± 1.1	<0.001
QoL-AGHDA score[a]	219	9.0 (1.0 to 18.0)	9.3 ± 6.6	84	7.0 (0.0 to 17.0)	8.0 ± 6.2	133	10.0 (2.0 to 19.0)	10.2 ± 6.7	<0.05
IGF-I SDS	174	−3.4 (−6.0 to −1.2)	−3.6 ± 2.1	69	−4.1 (−6.0 to −1.4)	−3.9 ± 1.9	105	−3.1 (−6.2 to − 1.2)	−3.4 ± 2.1	<0.05

NS, Not significant.

[a] A high QoL-AGHDA score indicates a poor QoL.

TABLE 5. Significant relationships between clinical outcomes at restart of GH replacement in adulthood and variables in childhood

Variable	Total cholesterol	LDL-cholesterol	HDL-cholesterol	Triglycerides	QoL-AGHDA score	IGF-I SDS
Sex	Total and non-IGHD ($P < 0.05$)		Total and non-IGHD ($P < 0.005$)			Total, IGHD, and non-IGHD ($P < 0.05$)
Etiology				Total ($P < 0.005$)		
BMI SDS at KIGS start					Total and non-IGHD ($P < 0.001$)	
GH duration[a]			Total ($P < 0.05$)			
Height SDS gain[a]					Total and non-IGHD ($P < 0.05$)	
GH gap[b]	Total and non-IGHD ($P < 0.0001$)	Total and non-IGHD ($P < 0.0001$)		Total and non-IGHD ($P < 0.01$)	Total ($P < 0.01$)	
Maximum GH peak						Total, IGHD and non-IGHD ($P < 0.05$)
Difference between height SDS and target height SDS at baseline						Total and non-IGHD ($P < 0.05$)
Age at KIGS start						Total and non-IGHD ($P < 0.01$)
Age at KIMS start	IGHD ($P < 0.05$)	IGHD ($P < 0.05$)		IGHD ($P < 0.05$)		
GH mean dose						Total ($P < 0.05$)

All regressions had a positive relationship except for the regression between QoL-AGHDA score and height SDS gain (note that a negative relationship with QoL-AGHDA score indicates a positive impact on QoL). If no *P* value is given, the regression was not significant; however, not all nonsignificant regressions are included. Total, total cohort.

[a] During GH treatment in childhood (in KIGS).

[b] During transition (between KIGS stop and KIMS start).

Non-IGHD group

IGF-I SDS at KIMS start correlated positively with the severity of short stature during childhood before GH replacement ($P < 0.05$), expressed as the difference between height SDS at KIGS start and target height SDS. Age at KIGS start was positively correlated with IGF-I SDS ($P < 0.01$). In summary, at restart of GH replacement in adulthood, IGF-I SDS was closer to age- and gender-specific reference ranges in those patients who had a greater degree of preserved somatotroph cell function (indicated by higher GH peak and less profound growth retardation) and were older at the start of childhood GH treatment.

IGF-I SDS in adults after 1 yr of GH

IGF-I SDS increased (by 2.1 SDS in the total cohort, $P < 0.001$; 2.0 SDS in the IGHD group, $P < 0.001$; 2.2 SDS in the non-IGHD group, $P < 0.001$; 1.5 SDS in the short GH gap group, $P < 0.01$; and by 2.2 SDS in the long GH gap group, $P < 0.001$) after 1 yr of GH treatment.

Lipid levels in adults at baseline

Both total and HDL-cholesterol levels were higher in women than men ($P < 0.05$ and $P < 0.005$, respectively). IGHD in childhood was associated with low concentrations of triglycerides ($P < 0.01$; Table 5). An association between duration of GH replacement during childhood and HDL-cholesterol concentrations was observed: a longer duration of GH replacement was associated with higher levels of HDL-cholesterol ($P < 0.05$).

IGHD group

Age at KIMS start was positively associated with total cholesterol, LDL-cholesterol, and triglycerides (all $P < 0.05$). No associations were found between lipid levels and other variables.

Non-IGHD group

There were positive regressions between GH gap and levels of total cholesterol ($P < 0.0001$; Fig. 1A), LDL-cholesterol ($P < 0.0001$; Fig. 1B), and triglycerides ($P < 0.05$; Fig. 1C): a longer interruption in GH replacement was associated with higher serum lipid concentrations. In non-IGHD patients, the lipid profile was more adverse in the long-GH-gap than the short-GH-gap group: the former group had higher mean levels of total cholesterol (5.3 ± 1.1 *vs.* 4.7 ± 1.2 mmol/liter; $P < 0.01$), LDL-cholesterol (3.3 ± 0.9 *vs.* 2.8 ± 1.0 mmol/liter; $P < 0.01$), and triglycerides (1.7 ± 1.1 *vs.* 1.2 ± 0.7 mmol/liter; $P < 0.05$).

Lipid levels in adults after 1 yr of GH

After 1 yr of GH therapy, the only significant change in lipid concentrations was observed in the long-GH-gap group, in which an increase in HDL-cholesterol concentration was found by 0.06 mmol/liter ($P < 0.01$).

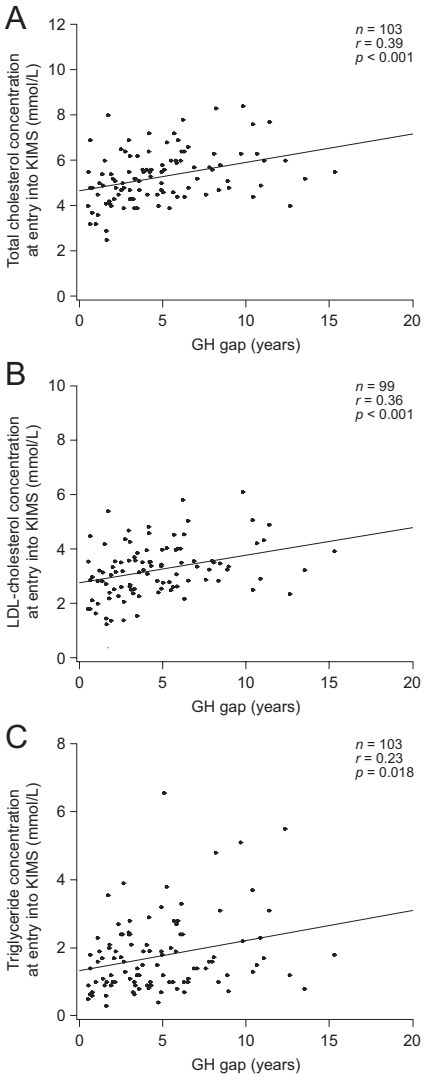

FIG. 1. A–C, Correlation of length of time between the end of pediatric GH therapy and the start of treatment in adulthood (GH gap) with total cholesterol concentration (millimoles per liter) (A), LDL-cholesterol concentration (millimoles per liter) (B), and triglyceride concentration (millimoles per liter) (C) in patients with non-IGHD. These univariate analyses were also significant in stepwise regression analyses; however, the *P* values are not always consistent between these two types of statistical analyses.

QoL in adults at baseline

In the total cohort, there was a positive relationship between GH gap and QoL-AGHDA score ($P < 0.01$; Table 5): a longer GH gap indicated a poorer QoL. This association was, however, not evident in the IGHD and non-IGHD groups, separately.

IGHD group

No significant relationships were identified between variables in childhood and QoL at KIMS start.

Non-IGHD group

A higher body mass index (BMI) SDS at the start of GH replacement during childhood was associated with poorer QoL at entry into KIMS, as shown by the positive association between BMI SDS and QoL-AGHDA score ($P < 0.001$). There was a negative relationship between height SDS gain during GH replacement in childhood and QoL-AGHDA score ($P < 0.05$). This suggests that those patients who gained more height had a better QoL than those who gained less height. In non-IGHD patients, QoL-AGHDA score at KIMS start was higher in those who experienced a long GH gap than those who experienced a short GH gap (10.2 ± 6.7 *vs.* 6.9 ± 5.6; $P < 0.01$), suggesting that a longer interruption of GH treatment has an adverse effect on QoL.

QoL in adults after 1 yr of GH

QoL improved, as indicated by a decreasing QoL-AGHDA score, after 1 yr of GH treatment in the total cohort and the IGHD group (by 3.1 points in both cases, $P < 0.001$) as well as in the non-IGHD group (by 3.2 points, $P < 0.001$) and the long-GH-gap group (by 3.8 points; $P < 0.001$).

Discussion

In this study, we sought to identify factors related to GHD in childhood that may be associated with clinical characteristics at the restart of GH treatment in a large cohort of young adults with CO-GHD.

In our analysis, indicators of severe GHD, such as low GH peak, young age at diagnosis and severe short stature, were associated with a low IGF-I SDS. This finding is consistent with results published by Brabant *et al.* (19). IGF-I SDS was higher in men than women, in line with previous observations suggesting that the difference between the sexes is due to a lower androgen level in women (20).

Our study indicates that in non-IGHD patients the interval without GH during transition is an important determinant of lipid profile before recommencement of GH in adult life, irrespective of patients' age. The relationship between lipid profile and GH gap suggests that a longer interruption of GH replacement results in a more adverse lipid profile than a shorter interruption. Two previous studies of the interruption of GH therapy during transition reported that several cardiovascular risk factors became apparent when GH was stopped in young adulthood (21, 22). Conversely, the study of Carroll *et al.* (23) showed no change in lipid profiles during either GH treatment cessation or continuation, which could be related to the shorter interruption of GH treatment and the younger age of patients enrolled in this study, compared with our investigation.

It is worth acknowledging that after a mean interruption of GH replacement of 4.4 yr, almost half of our study cohort had total cholesterol, LDL-cholesterol, and triglyceride levels exceeding the target values of 5.2, 3.4, and 1.7 mmol/liter, respectively (24). Furthermore, in the non-IGHD group, mean total cholesterol and triglyceride levels after GH interruption were above these target values (25).

We observed that a longer duration of pediatric GH treatment was associated with higher HDL-cholesterol levels in adulthood. This association could indicate that the earlier GH treatment is started in childhood, the better the outcome in terms of HDL-cholesterol levels, although causality remains to be demonstrated. However, it has been shown in other studies that a longer period of GH treatment in GH-deficient adults resulted in higher HDL-cholesterol levels (26, 27). As previously reported in patients with GHD (28), women had higher concentrations of total cholesterol and HDL-cholesterol than men. This finding of Abs *et al.* (28) applied mainly to premenopausal women and women receiving estrogen replacement. Female patients in our study were also premenopausal, which may indicate that higher HDL-cholesterol levels are estrogen related.

We were unable to demonstrate a relationship between GH gap and QoL in patients with IGHD or non-IGHD, but a relationship was apparent in the pooled data. Additionally we observed a difference in QoL between patients with short and long GH gaps and an improvement in QoL 1 yr after reintroduction of GH treatment. A negative effect of GH cessation on QoL was previously reported (29). In another study, psychological complaints and depression became apparent after discontinuation of GH, but improvements in anxiety and QoL were observed after recommencement of GH therapy (30). The beneficial effects of GH therapy on QoL in adults were also highlighted in a study in which psychological difficulties before GH therapy were positively influenced by GH treatment but showed reversion after the end of treatment (31). Improvement in QoL after the reintroduction of treatment was also observed in our cohort.

The majority of these studies showed that GH therapy can improve cholesterol levels and QoL after a period of treatment interruption, which is in contrast to the study of Mauras *et al.* (4), who showed that stopping GH therapy at near completion of linear growth for a 2-yr period had no impact on cholesterol levels or QoL compared with reinstating therapy for this period. A possible explanation for the latter observation may be the use of high GH doses in childhood, particularly in the United States: this results

in lowering of cholesterol, followed by reversion to higher levels as the pharmacological effect of GH is released (32).

In patients with non-IGHD, greater height SDS gain was associated with improved QoL, suggesting that patients who responded better to GH replacement during childhood experienced better QoL at restart of GH treatment. It is worth highlighting that a similar association was not observed between QoL and height SDS at completion of growth, and therefore, an improvement in QoL is unlikely to be explained by absolute height, as could be suggested by the study of Christensen *et al.* (33), but rather by height gain during treatment. This hypothesis is supported by our results showing better mean QoL-AGHDA scores in patients in the 75th percentile and above of height SDS gain compared with those in the 25th percentile and below (data not shown).

Despite BMI being normal at KIGS entry, an increase was observed during KIGS follow-up. Higher BMI SDS at KIGS start was associated with worse QoL. It is possible that this finding is not linked to GHD but rather to being overweight; an overweight or obese child is at high risk of becoming an obese adult, and several studies demonstrated impaired QoL in obese patients (34). Nevertheless, an elevated BMI may be a consequence of severe GHD (35).

The cohort selected for this study is believed to be representative of patients with CO-GHD continuing GH therapy in adulthood. However, it is acknowledged that this study is informative only about patients who continued treatment as adults; nothing is known about how or whether the associations of childhood clinical variables with QoL or lipid profile in adulthood would change in GH-deficient patients not receiving GH as adults. The lack of this control group is a clear limitation of our study; however, we confirmed the positive effects of recommencing GH therapy for 1 yr. As already mentioned, patients in our study were on average older than those in previously published studies (4, 22, 23) but represented a similar distribution of etiologies (22, 23). One strength of our study is the central IGF-I and lipid measurements, greatly reducing the amount of variation. Additionally, this study is based on a large cohort of patients who were followed up longitudinally from childhood until adulthood in a similar setting of pharmacoepidemiological surveys.

Finally, it must be reiterated that in general any associations found held true for the total cohort and the non-IGHD group but not for patients with IGHD. Although it cannot be ruled out that by dividing our cohort into two groups the statistical power was decreased, this was necessary to take into account the heterogeneity of CO-GHD (6). Additionally, it is noteworthy that the proportion of patients with isolated GHD was higher in the IGHD group than in the non-IGHD group and the opposite was true for multiple pituitary hormone deficits. Therefore, both etiology and additional pituitary hormone deficits are likely to contribute to the differences between IGHD and non-IGHD groups.

In conclusion, the findings of our study imply that in non-IGHD patients the nature of CO-GHD may have an impact on the phenotype of young adults who remain GH deficient. The most important factor associated with IGF-I SDS in young adults is severity of GHD during childhood. A shorter duration of pediatric treatment and a longer interval before GH is reintroduced after cessation of childhood treatment are linked to an unfavorable lipid profile, particularly in patients with non-IGHD. Finally, a better outcome of GH replacement in childhood implies a better QoL in young adults with non-IGHD. Our data support the recommendation that the confirmation of GHD in young adults should be performed immediately after completion of linear growth and that GH replacement should be considered soon afterward (1). A close collaboration between pediatric and internist endocrinologists is therefore essential (2).

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