

Human Growth Hormone Replacement in Adult Hypopituitary Patients: Long-Term Effects on Body Composition and Lipid Status—3-Year Results from the HypoCCS Database

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The Hypopituitary Control and Complications Study is an international surveillance study evaluating efficacy and safety of GH therapy of adult GH-deficient patients in clinical practice. The present report examined baseline data from 1,123 adult onset (AO) and 362 childhood onset (CO) patients, as well as efficacy in 242 patients who had completed 3 yr of GH treatment. At study entry, mean height, body mass index, waist to hip ratio, and lean body mass were significantly ($P < 0.001$ for each) lower in CO compared with AO patients. After 3 yr on GH, lean body mass was significantly increased in AO males and females and CO males but not CO females, whereas fat mass was significantly decreased in AO males only. Serum total cholesterol was decreased in females (-0.32 ± 1.00 mmol/liter; $P = 0.045$) and males (-0.36 ± 0.96 mmol/liter; $P = 0.004$). High-density lipoprotein (HDL) cholesterol was increased for females (0.10 ± 0.26 mmol/liter; $P = 0.026$) and males (0.10 ± 0.34 mmol/liter; $P = 0.022$). The low-density lipoprotein/HDL ra-

tio was decreased in AO males (-0.93 ± 2.00 ; $P = 0.003$), AO females (-0.65 ± 0.74 ; $P < 0.001$), and CO females (-0.69 ± 0.76 ; $P = 0.038$), but the decrease in CO males was not significant (-0.84 ± 2.85 ; $P = 0.273$). In AO patients, lean body mass increase from baseline was greatest in the those younger than 40 yr old, less but still significant in the middle group (40–60 yr) and unchanged in older (>60 yr) patients; conversely, decreases in the low-density lipoprotein/HDL ratio were small and not significant in the younger patients but greater and significant in the middle and older age groups. During the 3-yr treatment, 114 (7.7%) patients discontinued, including 9 (0.6%) for tumor recurrences, 9 (0.6%) for neoplasia, and 9 (0.6%) for side effects. Therefore, these observational data showed significant long-term efficacy of adult GH replacement therapy on body composition and lipid profiles and indicate that age is an important predictor of response. (*J Clin Endocrinol Metab* 87: 1600–1606, 2002)

GH REPLACEMENT THERAPY of adult hypopituitary patients with GH deficiency (GHD) is now a registered indication. Approval was based on controlled studies of 1–1.5 yr duration (1, 2). Therefore, efficacy and safety information was based on a limited treatment period so surveillance studies were started shortly after registration to collect long-term data. Although surveillance studies lack a formal hypothesis and are designed to collect observational data, they are a useful tool to assess treatment trends and evaluate long-term outcomes. The Hypopituitary Control and Complication Study (HypoCCS) is an ongoing surveillance of adult hypopituitary patients started in 1995 at the time of the approval of the adult GHD indication by the European Regulatory

Agency. The European database collects information on adult patients with GHD and hypopituitarism with the objective of monitoring long-term safety of GH replacement therapy in endocrine clinical practice.

In the current report, we present 3-yr efficacy and safety data of the patients in HypoCCS. Effects of GH replacement on body composition and lipid profile have been demonstrated previously (3–5). Increased morbidity and mortality associated with increased body fat and dyslipidemia has been reported in adult GHD patients compared with non-GHD controls (6). Some studies (7, 8), although not all (9, 10), have shown that the reduced life expectancy is mainly related to vascular disease. Overall, the relative risk of cardiovascular disease appears to be increased with GHD (11). Although it has been suggested that the increased mortality may be due to effects of hypopituitarism other than GHD (12), any treatment-induced changes in body composition and lipid status that reduce long-term risk of complication can only be beneficial.

Abbreviations: AO, Adult onset; BIA, bioelectrical impedance; BMI, body mass index; CO, childhood onset; DEXA, dual-energy x-ray absorptiometry; GHD, GH deficiency or GH-deficient; HDL, high-density lipoprotein; HypoCCS, Hypopituitary Control and Complications Study; LDL, low-density lipoprotein.

Patients and Methods

Patients

Patient selection into HypoCCS is based on establishment of the diagnosis of GHD, either as a single deficiency or with multiple pituitary hormone deficiencies, by clinical history and by biochemical testing using standard GH stimulation tests and a peak GH cut-off of 3 $\mu\text{g}/\text{liter}$. Patients were excluded if there was suspected malignancy or presence of an active tumor; all intracranial lesions were inactive, and antitumor therapy was completed before entry. The study currently involves 56 centers located in 11 countries: Austria, Belgium, Canada, Denmark, Germany, Italy, The Netherlands, Spain, Sweden, and the United Kingdom. The database is locked annually, and the total number of patients enrolled at the datalock of October 2000 was 1,487. At entry, patients were categorized according to time of onset of GHD as either during adulthood [adult onset (AO); $n = 1124$] or childhood [childhood onset (CO); $n = 362$]. In the CO group, 256 patients had previously been treated with GH at some time during their childhood. Baseline demographic characteristics are shown by gender and GHD onset in Table 1. At the datalock for the current analysis, 242 patients had completed 3 yr of GH replacement therapy.

Study design

Because this is a surveillance study, individual patient entry is at the discretion of the investigating physician. At study entry, all patients commenced therapy with GH (Humatrope, Eli Lilly & Co., Indianapolis, IN) at the dosage approved by regulatory agencies (0.04–0.08 mg/kg-wk). At baseline, disease history, clinical presentation, and diagnostic features of hypopituitarism were recorded. Anthropometric measurements of height, weight, waist and hip circumferences, and sum of skinfold thicknesses at biceps, triceps, suprascapular, and suprailiac sites were determined. Body composition, in terms of percentage body fat and lean body mass, was determined by bioelectrical impedance (BIA), or in some cases by dual-energy x-ray absorptiometry (DEXA), dependent on the methodology available to the investigator, but for individual patients the same method was used throughout the study. Patients were requested to fast overnight before serum samples were taken for laboratory measurements of lipid profiles and IGF-I. All determinations were made initially at baseline and subsequently at intervals according to the routine management of hypopituitary patients at each investigator site.

Laboratory measurements

Serum samples were frozen and shipped to a central laboratory for assay of IGF-I concentration by RIA (13). Serum lipid profiles were determined by the local laboratories associated with investigator sites. The serum lipid measurements included determination of total cholesterol, low density lipoprotein (LDL) cholesterol and high density lipoprotein (HDL) cholesterol concentrations.

Statistical analyses

After entry into the database, data completeness and accuracy were assessed using a series of checks to identify missing essential data and internal consistency of data. Height measurements and IGF-I concentrations were converted to SD scores by reference to a normal population to allow for differences due to age and gender. Changes from baseline within onset/gender groups were analyzed by *t* tests or by a signed-rank test. Differences between onsets and genders were analyzed using an ANOVA model incorporating onset, gender, and the interaction between them. All analyses used two-sided tests, and a *P* value of less than 0.05 was considered statistically significant.

Adverse events reported during the study were analyzed for overall incidence. In addition, for all patients having more than one follow-up visit ($n = 1265$), events were classified into clinical categories and analyzed by age, onset, and gender. Logistic regression was used to fit models for probability of an event class to occur as a function of age, gender, and onset by age and gender.

Results

Baseline data

Most patients in each gender and with AO or CO GHD had multiple pituitary trophic hormone deficiencies (Table 1). The responses to GH stimulation tests and the profound decreases in IGF-I SD score values indicate that the patients were severely GHD. IGF-I concentration was higher in AO than CO patients ($P < 0.001$) and in males compared with females (AO, $P < 0.001$; CO, $P = 0.029$). IGF-I SD score was greater in AO than CO in males ($P = 0.001$) but not females ($P = 0.221$) and higher in males compared with females for AO ($P < 0.001$) but not CO ($P = 0.166$).

Baseline anthropometry and body composition derived from BIA are summarized in Table 2. Height SD score was well within the normal range in AO patients but was reduced below the normal average in CO patients. The CO patients also had lower BMI values ($P < 0.001$) and waist to hip ratios ($P < 0.001$), but sum of skinfolds was similar ($P = 0.213$). Lean body mass was higher in AO than in CO ($P < 0.001$) patients and was also higher in males than females ($P < 0.001$) in each onset. Percentage body fat was greater in females than males ($P < 0.001$) in both AO and CO but did not differ between onsets. Both systolic and diastolic blood pressure were higher in AO than CO ($P < 0.001$ for each), consistent with the greater age of the AO patients.

Baseline serum lipid values are shown in Table 3 for pa-

TABLE 1. Patients' characteristics, responses to GH stimulation tests, IGF-I values, and pituitary hormone deficiencies at baseline

	AO male	AO female	CO male	CO female
No.	585	538	211	151
Age (yr)	51.7 \pm 13.2	47.7 \pm 12.5	27.9 \pm 8.5 ^a	29.0 \pm 10.1 ^a
Duration of GHD (yr)	6.4 \pm 7.2	7.8 \pm 8.8	17.2 \pm 10.3 ^a	17.1 \pm 10.7 ^a
GH response to ITT ($\mu\text{g}/\text{liter}$)	0.65 \pm 0.79	0.93 \pm 2.11	0.80 \pm 1.23	0.84 \pm 1.10
GH response to arginine ($\mu\text{g}/\text{liter}$)	0.65 \pm 1.04	0.95 \pm 1.44	1.13 \pm 2.06	1.10 \pm 1.46
IGF-I ($\mu\text{g}/\text{liter}$)	103.5 \pm 66.0	79.8 \pm 65.4 ^b	82.7 \pm 82.4 ^a	70.8 \pm 65.0
IGF-I SD score	-2.05 \pm 1.89	-3.14 \pm 2.28 ^b	-4.80 \pm 2.77 ^a	-5.43 \pm 3.00 ^{a,b}
Isolated GHD [n (%)]	26 (4)	42 (8)	30 (14)	26 (17)
Multiple deficiencies [n (%)]	559 (96)	496 (92)	180 (85)	125 (83)
Hypothyroidism [n (%)]	475 (81)	421 (78)	164 (78)	101 (67)
Hypogonadism [n (%)]	529 (90)	414 (77)	162 (77)	112 (74)
Hypoadrenalism [n (%)]	450 (77)	395 (73)	129 (61)	80 (53)
Diabetes insipidus [n (%)]	141 (24)	138 (26)	38 (18)	38 (25)

Values are mean \pm SD or number of patients with percentage of total. ITT, Insulin-induced hypoglycemia.

^a $P < 0.05$ AO vs. CO within gender.

^b $P < 0.05$ male vs. female within onset.

TABLE 2. Mean (\pm SD) anthropometry, body composition, and blood pressure determinations at baseline

	AO male	AO female	CO male	CO female
Height SD score	0.19 \pm 1.31	-0.12 \pm 1.31 ^b	-1.24 \pm 1.60 ^a	-1.17 \pm 1.61 ^a
BMI (kg/m ²)	28.7 \pm 5.1	29.4 \pm 6.3 ^b	25.6 \pm 5.9 ^a	28.0 \pm 7.3 ^{a,b}
Waist/hip ratio	0.97 \pm 0.08	0.89 \pm 0.08 ^b	0.93 \pm 0.08 ^a	0.87 \pm 0.08 ^{a,b}
Sum of skinfolds (mm)	78.6 \pm 30.2	97.2 \pm 28.8 ^b	80.9 \pm 37.1	101.2 \pm 35.2 ^b
Lean body mass (kg)	59.1 \pm 11.4	43.6 \pm 8.6 ^b	48.9 \pm 11.7 ^a	39.1 \pm 10.2 ^{a,b}
Body fat mass (kg)	30.2 \pm 11.1	33.3 \pm 12.3 ^b	27.1 \pm 14.3	33.2 \pm 16.1 ^b
Percentage body fat (%)	33.5 \pm 9.1	42.5 \pm 9.1 ^b	34.3 \pm 9.7	44.4 \pm 11.6 ^b
Systolic BP (mm Hg)	132.0 \pm 18.9	129.0 \pm 19.6 ^b	119.3 \pm 14.1 ^a	115.6 \pm 14.4 ^a
Diastolic BP (mm Hg)	81.2 \pm 10.6	79.9 \pm 10.5 ^b	75.5 \pm 10.5 ^a	73.7 \pm 10.6 ^a

BP, Blood pressure.

^a $P < 0.05$ AO vs. CO within gender.^b $P < 0.05$ male vs. female within onset.**TABLE 3.** Mean (\pm SD) baseline serum lipid concentrations by gender and onset for patients not on lipid-lowering drugs or who received lipid-lowering drugs at some time during the study

	AO male	AO female	CO male	CO female
Not on lipid lowering drugs	n = 400	n = 302	n = 132	n = 112
Total cholesterol (mmol/liter)	5.61 \pm 1.48	5.69 \pm 1.47	4.63 \pm 1.81 ^a	5.32 \pm 1.45 ^{a,b}
LDL cholesterol (mmol/liter)	4.33 \pm 1.13	4.12 \pm 1.10	3.67 \pm 1.08 ^a	3.90 \pm 1.13 ^a
HDL cholesterol (mmol/liter)	1.11 \pm 0.40	1.36 \pm 0.53 ^b	1.05 \pm 0.44	1.31 \pm 0.41 ^b
LDL/HDL ratio	4.21 \pm 1.97	3.30 \pm 1.52 ^b	3.30 \pm 1.29 ^a	3.16 \pm 1.87 ^a
On lipid lowering drugs	n = 51	n = 32	n = 9	n = 3
Total cholesterol (mmol/liter)	6.04 \pm 1.50	6.37 \pm 1.72	6.32 \pm 1.22	7.66 \pm 2.29
LDL cholesterol (mmol/liter)	4.49 \pm 1.28	4.87 \pm 1.41	4.60 \pm 1.30	5.80 \pm 3.17
HDL cholesterol (mmol/liter)	1.13 \pm 0.29	1.36 \pm 0.39 ^b	1.17 \pm 0.61	1.58 \pm 1.09
LDL/HDL ratio	4.20 \pm 1.94	3.87 \pm 1.90	4.68 \pm 2.67	10.45 \pm 14.85 ^{a,b}

^a $P < 0.05$ AO vs. CO within gender.^b $P < 0.05$ male vs. female within onset.

tients not on lipid-lowering drugs as well as for those receiving lipid-lowering drugs. In the AO group, 83 subjects were taking lipid-lowering drugs, compared with only 12 in the CO group. Both total and LDL cholesterol were higher in AO than CO patients ($P < 0.001$ for each) not on lipid-lowering drugs. HDL cholesterol levels were lower in males than females ($P < 0.001$) but similar for AO and CO patients ($P = 0.168$). As a result, the LDL/HDL ratio was greater in AO than CO patients and also higher in males than females. The patients on lipid-lowering drugs had higher total and LDL cholesterol levels, but similar HDL cholesterol levels, compared with those not on lipid-lowering drugs.

Changes from baseline to 3 yr

Baseline data for the 242 patients who completed 3 yr of therapy were very similar to baseline data of the entire group shown in Tables 1–3, with differences generally less than 10%. However, efficacy was examined as changes from baseline, which involves only patients with both baseline and 3-yr data, and hence takes account of any small differences at baseline. Overall, statistically significant changes in efficacy measures were observed at the end of the first treatment year and persisted over the second and third years. This trend was consistent in all efficacy measures analyzed, and therefore only data for the 3-yr endpoint are presented.

Total daily dose of GH administered at the start of therapy was similar between onsets and genders (AO males, 322 \pm 197; AO females, 319 \pm 395; CO males, 376 \pm 464; and CO females, 321 \pm 220 μ g/d). This increased within the first year, then remained fairly constant; at the end of 3 yr, gender differences in total dose were not significant (males, AO,

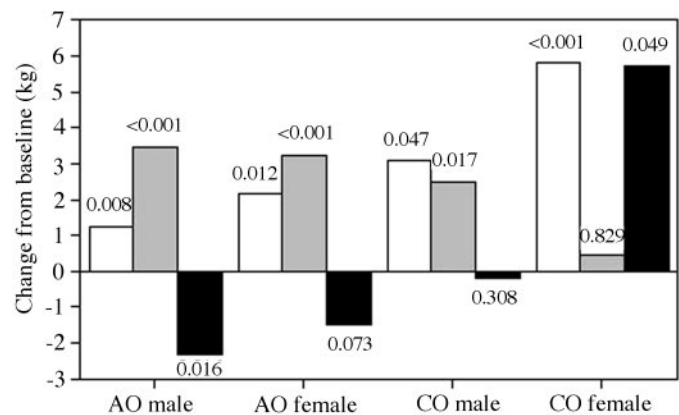


FIG. 1. Mean changes from baseline in body weight (white bars), lean body mass (gray bars), and body fat mass (black bars) after 3 yr of GH replacement therapy, with P values shown for within group changes.

514 \pm 375, and CO, 566 \pm 331; females, AO, 629 \pm 399, and CO, 668 \pm 321 μ g/d; $P = 0.063$), but the dose of GH per body weight was lower ($P = 0.004$) in males (AO, 5.97 \pm 4.32; CO, 4.70 \pm 7.36 μ g/kg·d) than females (AO, 8.06 \pm 4.62; CO, 9.35 \pm 3.95 μ g/kg·d). The differences between AO and CO were not significant for either total dose ($P = 0.432$) or dose per body weight ($P = 0.055$).

Body composition changes

Body weight (Fig. 1) and body mass index (BMI) (Table 4) increased in each gender and GH onset group, and the changes were significant except for BMI in CO males. The decrease in waist to hip ratio only achieved significance

TABLE 4. Changes from baseline in anthropometry, body composition determined from BIA, serum IGF-I concentration and blood pressure in adult GHD patients treated for 3 yr with GH

	AO male	AO female	CO male	CO female
BMI (kg/m ²)	0.45 ± 1.43 (90)	0.64 ± 2.62 (81)	0.85 ± 2.81 (36)	2.19 ± 2.42 (19)
<i>P</i> value	0.003	0.030	0.080	0.001
Waist/hip ratio	-0.01 ± 0.05 (82)	-0.01 ± 0.06 (72)	-0.01 ± 0.07 (34)	-0.03 ± 0.07 (18)
<i>P</i> value	0.017	0.461	0.241	0.061
Body fat (%)	-2.84 ± 6.76 (54)	-3.07 ± 7.77 (58)	-1.36 ± 8.02 (21)	3.49 ± 12.79 (14)
<i>P</i> value	0.003	0.004	0.446	0.325
IGF-I (nmol/liter)	113 ± 95 (73)	114 ± 102 (72)	109 ± 129 (27)	65 ± 69 (17)
<i>P</i> value	<0.001	<0.001	<0.001	<0.001
IGF-I SD score	2.56 ± 1.67 (73)	3.01 ± 2.11 (72)	3.80 ± 3.59 (27)	3.15 ± 2.89 (17)
<i>P</i> value	<0.001	<0.001	<0.001	<0.001
SBP (mm Hg)	3.0 ± 15.7 (91)	0.4 ± 17.9 (81)	1.8 ± 15.1 (36)	1.8 ± 11.5 (19)
<i>P</i> value	0.068	0.828	0.488	0.493
DBP (mm Hg)	0.6 ± 9.5 (91)	-0.4 ± 11.3 (81)	0.1 ± 10.4 (36)	-1.1 ± 10.3 (19)
<i>P</i> value	0.575	0.735	0.937	0.638

Values are mean ± SD (n) with *P* values for within-group changes. SBP, Systolic blood pressure; DBP, diastolic blood pressure.

TABLE 5. Changes from baseline in serum cholesterol concentrations by gender and onset in patients not receiving lipid-lowering drugs

	AO male	AO female	CO male	CO female
Total (mmol/liter)	-0.40 ± 1.04 (46)	-0.31 ± 1.04 (33)	-0.25 ± 0.67 (16)	-0.39 ± 0.88 (8)
<i>P</i> value	0.012	0.099	0.159	0.250
LDL (mmol/liter)	-0.43 ± 1.00 (44)	-0.43 ± 0.85 (31)	-0.52 ± 0.91 (15)	-0.53 ± 0.73 (8)
<i>P</i> value	0.006	0.008	0.043	0.079
HDL (mmol/liter)	0.06 ± 0.20 (45)	0.08 ± 0.27 (32)	0.21 ± 0.56 (16)	0.15 ± 0.26 (8)
<i>P</i> value	0.044	0.088	0.159	0.150
LDL/HDL ratio	-0.93 ± 2.00 (44)	-0.65 ± 0.74 (31)	-0.84 ± 2.85 (15)	-0.69 ± 0.76 (8)
<i>P</i> value	0.003	<0.001	0.273	0.038

Values are mean ± SD (n) with *P* values for within-group changes.

in the AO male patients. Lean body mass (Fig. 1) was significantly increased in AO males and females and CO males, but not in CO females. Body fat mass was significantly decreased only in AO males, although percentage body fat was significantly reduced in AO males and females. By contrast, in CO patients the decrease in fat mass was minimal in males, whereas a significant increase was observed in females, but percentage body fat did not change significantly in either sex. Similar results were observed with DEXA to the second year of treatment (data not shown), but at 3 yr there were insufficient patients assessed by this method to warrant analysis.

Lipid profile changes

The change from baseline in serum lipid concentration at the 3-yr endpoint is shown in Table 5 for patients not receiving lipid-lowering drugs during the study. The change in total cholesterol was only significant for the AO male patients, although the decreases were significant for all females (-0.32 ± 1.00; *P* = 0.045), all males (-0.36 ± 0.96; *P* = 0.004), and all patients combined (-0.35 ± 0.97; *P* < 0.001). The LDL cholesterol concentration was decreased in each gender/onset group, and the change from baseline was significant for all except the CO females. HDL cholesterol concentration was increased in each group, but the increase was only significant for the AO males. However, the increase was significant for all females (0.10 ± 0.26; *P* = 0.026), all males (0.10 ± 0.34; *P* = 0.022), and all patients combined (0.10 ± 0.31; *P* = 0.002). The LDL/HDL ratio was significantly decreased in AO males and females as well as in CO females.

In CO males, the change at 3 yr was not statistically significant, but this may be due to the large SD and small patient number because the 2 yr change was significant (-0.75 ± 1.14; *P* = 0.001).

Changes by age groups in AO patients

The AO patients were grouped according to age at entry to the study as those younger than 40 yr, those 40–60 yr old, and those older than 60 yr; changes from baseline were evaluated after 1, 2, and 3 yr of GH treatment. Baseline values (Table 6) were similar between age groups, although IGF-I level was significantly (ANOVA, *P* = 0.025) lower in the older patients. The IGF-I increase from baseline in the first year was greater (*P* = 0.006) in the younger patients (<40 yr, 102.0 ± 86.1 μg/ml) than the older patients (>60 yr, 72.0 ± 82.8 μg/ml), but there were no significant differences between groups for the change from baseline to 2 yr or 3 yr. The waist to hip ratio decreased significantly in each age group after 1 yr of treatment (<40 yr, -0.01 ± 0.05, *P* = 0.006; 40–60 yr, -0.01 ± 0.06, *P* < 0.001; >60 yr, -0.01 ± 0.05, *P* = 0.001). However, after 2 yr the decrease was only significant in the middle age group (-0.01 ± 0.05; *P* = 0.018) and the older age group (-0.02 ± 0.06; *P* = 0.014); after 3 yr of GH treatment, the change was only significant in the older age group (-0.03 ± 0.04; *P* = 0.002). BMI increased progressively over the 3 yr, but the greatest changes were in the younger patients (Fig. 2A). Lean body mass by BIA increased most in the younger age group (Fig. 2B) and the increases were also significant in the middle age group, but changes in the older

TABLE 6. Number of AO patients and baseline values by age groups for BMI, lean body mass (LBM), LDL/HDL cholesterol ratio, and IGF-I concentration

	<40 yr	40–60 yr	>60 yr
BMI (kg/m ²)			
n	259	591	258
Mean ± SD	28.6 ± 6.2	29.5 ± 5.7	28.4 ± 4.8
LBM (kg)			
n	129	292	147
Mean ± SD	47.9 ± 11.7	52.7 ± 12.9	52.7 ± 12.8
LDL/HDL			
n	141	363	160
Mean ± SD	3.59 ± 1.63	3.91 ± 1.97	3.68 ± 1.63
IGF-I (μg/liter)			
n	186	448	217
Mean ± SD	98.9 ± 68.8	92.5 ± 66.7	85.7 ± 64.6

age group were small and not significant. The increases in lean body mass were reflected by the decreases in percentage body fat by BIA, with large decreases in younger patients and no change in older patients. Body composition trends measured by DEXA were consistent with BIA trends, although the number of observations in the group older than 60 were very limited (data not shown). The decrease in the LDL/HDL ratio was not significant at any time in the younger patients (Fig. 2C), whereas most changes occurred in the middle age group and the decreases were also significant in the older age group of patients.

Safety

During the first 3 yr of treatment in HypoCCS, 1,988 adverse events were reported, 248 of which were classified as serious. Of the 1,487 patients with baseline data, 114 [7.7%; AO, 84 (5.6%), and CO, 30 (2.1%)] discontinued within 3 yr of treatment for the following reasons: serious adverse events (2.2%), lack of efficacy (2.0%), lost to follow-up (1.3%), personal conflict (0.9%), physician decision (0.6%), sponsor decision (0.3%), and death (0.4%). Of the 33 patients reported to discontinue for adverse events, specified reasons were: 9 (0.6%) tumor re-growth, 9 (0.6%) neoplasia, 9 (0.6%) side effects such as arthralgia/myalgia/headache/paresthesia, 2 (0.1%) diabetes development and single cases of wheezing in head, visual field disturbance, transient ischemic attack, and nosebleed. All 6 patients who died were AO and in the age range 50.8–80.7 yr; causes of death were myocardial infarction, respiratory failure, cerebral hemorrhage, suicide, duodenal cancer, and unspecified. *De novo* malignant neoplasia was reported for 11 (0.9%) patients as follows: 3 cases of breast cancer (1 male), 3 cases of prostate cancer, 2 skin carcinoma, 1 pharynx carcinoma, 1 kidney carcinoma, and 1 lymphoma.

Adverse events reported with a frequency greater than 5% were edema, arthralgia, pain, myalgia, and headache. Events grouped by clinical categories and analyzed by age, gender, and onset are summarized in Table 7 with *P* values for logistic regression for each factor after adjustment for the other two factors. In most categories, event frequency increased with age, except for craniopharyngioma where the age trend was inverse. Gender effects were observed for pituitary adenomas and cardiological complications, and onset effects were observed for diabetes.

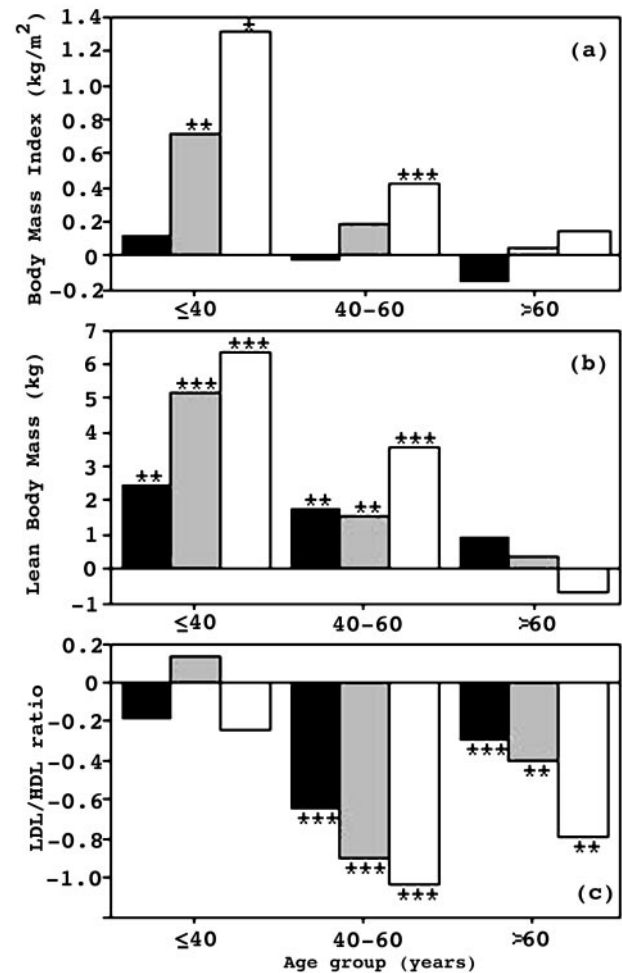


FIG. 2. Mean changes from baseline in body mass index (A), lean body mass (B), and LDL/HDL ratio (C) after 1 yr (black bars), 2 yr (gray bars), and 3 yr (white bars) of GH treatment of AO GHD patients, by age groups. < 0.05; **, *P* < 0.01; ***, *P* < 0.001 for change from baseline.

Discussion

HypoCCS is a surveillance study and as such is noninterventional and provides only observational and descriptive data on patients' exposure. The cornerstone objective of surveillance studies is to evaluate safety, clinical outcomes, and patient functioning outside of the clinical trial setting. Conclusions from clinical trials of GH in adult GHD patients have essentially been based on short-term surrogate markers. Thus, monitoring treatment outcomes in actual practice and confirming clinical trial findings is critical to both attending physicians and regulatory organizations.

The results of the 3-yr analysis from the HypoCCS database show significant and sustained improvements in body composition and lipid profiles and confirm and extend previous reports from other surveillance studies (14, 15). They also confirm the differences in clinical presentation between AO and CO GHD, previously described (1). The changes in body composition in the present analysis were consistent with reports of adult GHD patients who were given GH replacement therapy over shorter time periods (16), as well as for longer periods in small numbers of patients (17, 18).

TABLE 7. Frequency of occurrence of categories of adverse events during 3 yr of GH treatment of GHD adult patients, and analysis of influencing factors

	Total		Frequency by age [n (%)]			P value for logistic regression		
	n	%	<40	40–60	>60	Age	Gender	Onset
Growing pituitary adenoma	17	1.3	0	6 (1.09)	9 (1.19)	0.248	0.013 ^a	0.091
Growing craniopharygeoma	6	0.5	6 (1.23)	0	0	0.012	0.780	0.234
Benign tumor/neoplasia	10 ^b	0.8	2 (0.41)	5 (0.91)	3 (1.32)	0.099	0.113	0.886
Breast tumors	5 ^c	0.4	4 (0.82)	1 (0.18)	0	0.130	0.736	0.157
Prostate tumors	5 ^d	0.4	0	0	5 (2.19)	0.005		0.674
Hypertension	38	3.0	6 (1.23)	20 (3.64)	12 (5.26)	0.003	0.982	0.255
Cardiological complications	5 ^e	0.4	0	1 (0.18)	4 (1.75)	0.006	0.033 ^a	0.676
Myocardial infarction	1	0.08		1 (0.18)				
Stroke	9	0.7	1 (0.21)	5 (0.91)	3 (1.32)	0.024	0.232	0.739
Other cerebral complications	21 ^f	1.7	4 (0.82)	9 (1.64)	8 (3.51)	0.003	0.687	0.107
Diabetes	11	0.9	3 (0.6)	6 (1.1)	2 (0.9)	0.180	0.616	0.029
Fractures	16	1.3	5 (1.03)	5 (0.91)	6 (2.63)	0.049	0.057	0.925

^a Male > female.

^b Included four dermal tumors, three lipomas, two naevi, one endometrial polyps.

^c Female, two (carcinoma); male, three (one carcinoma, two fibroadenoma).

^d Cancer, three; hyperplasia, two.

^e Included cardiac arrhythmia, valvular heart disease, congestive heart failure, cardiac enlargement/hypertrophy, and related surgical procedures.

^f Included all vascular diseases and symptoms such as angina and transient ischemia.

AO patients showed a clear pattern of change, with an increase in lean body mass and a concomitant decrease in fat mass. This was not the case in CO, where males had only a limited decrease in fat mass and females even significantly gained fat mass. This difference may reflect the heterogeneity between the two conditions, but further studies are needed to establish this.

Mean baseline BMI values would suggest that a large proportion of the patients were overweight. BMI values increased slightly with GH therapy, particularly in the CO and in the younger AO patients. The reduction in waist to hip ratios indicated a decrease in abdominal fat, which has been associated with increased cardiovascular morbidity and mortality in epidemiological studies (19).

Both systolic and diastolic blood pressure were related to patient age, were higher in AO compared with CO patients, and increased with increasing age groups in the AO patients. However, there were no significant blood pressure changes from baseline at the end of 3 yr of GH treatment. The HypoCCS data in fact indicated a small decrease in systolic blood pressure at 1 yr, but the improvement was not maintained. Adult GHD patients are known to have changes in cardiac structure and increased intima/media arterial thickness (20, 21), and a study of vascular reactivity showed that blood flow was reduced (22). GH treatment improved the response to vasodilators and reduced intima/media thickness and plaque formation (21, 22). The lack of increase in blood pressure in the HypoCCS group would be consistent with this, but whether GH maintains blood pressure and reduces incidence of hypertension with long-term treatment remains to be established.

Previous studies determining lipid concentration changes with GH replacement therapy have fairly consistently shown decreased total and LDL cholesterol, but fewer studies have shown an increase in HDL cholesterol (1, 6). The Framingham data indicate that low levels of HDL cholesterol are a significant risk factor for coronary heart disease, as are high levels of total and LDL cholesterol. However, drug therapies target lowering of total and LDL cholesterol, but specific

therapies to increase HDL cholesterol are not highly effective or practical (23). Within individual gender/onset groups in the present study, the increase in HDL cholesterol reached significance only in the AO males. However, combining data from all of the groups showed increases that were significant. Risk can clearly be predicted from LDL cholesterol (24), and this was also significantly reduced with GH therapy. The LDL/HDL ratio is a strong discriminator of coronary heart disease risk (25), with the highest hazard ratio in the serum lipid profile (26). This ratio was significantly decreased at 3 yr of GH treatment in the HypoCCS patients. The lipid changes observed within this surveillance population are consistent with recently reported results of 3 and 5 yr of GH replacement in a single-center patient population (27).

Analysis by age indicated that the effect of GH replacement on body composition is most prominent in younger patients. The combined changes in BMI and lean body mass suggest that the effect of GH on body composition wanes with age. This is consistent with less reduction in lean body mass in elderly patients with GHD, compared with normal elderly controls (28), and smaller changes in body composition and bone mineral density with GH treatment in GHD patients older than 60 yr, compared with younger patients (29). On the other hand, the decrease in waist to hip ratio was more pronounced in older patients, and the changes in LDL/HDL ratio were greater in the older and middle age groups of patients and not significant in patients younger than age 40 yr. Previous reports have suggested no significant change in waist to hip ratio or waist circumference in elderly GHD patients treated with GH for 6–18 months (29, 30). Decreases in total and LDL cholesterol with 6 months of GH treatment were reported to be similar for GHD patients younger than 65 yr and older than 65 yr, with no changes in HDL cholesterol (30). Taken together, the present results would suggest that the magnitude of the major metabolic effects of long-term GH replacement are strongly related to the age of the GHD patient, with attenuated protein accretion but greater lipid lowering with increasing age.

The reported adverse event profile is consistent with accumulated experience with GH treatment in adults, specifically with respect to the most frequently occurring events. The overall occurrence of *de novo* malignancies, 0.9%, does not differ from the 1.1% reported from the U.S. HypoCCS database (31). Analysis of clinically relevant event categories by age, gender, and onset showed significant age trends but no onset differences, except for diabetes. This indicates that AO and CO tolerate GH replacement equally well but would also suggest that AO and CO do not differ with respect to disease-related morbidity.

In summary, observational data confirm some important aspects of diagnosis of the adult GHD syndrome and of efficacy and safety of GH replacement. Specifically, GH replacement therapy of GHD patients in HypoCCS induced significant long-term efficacy in terms of body composition and lipid profiles. Such changes are consistent with reductions in the relative risk of the patients for cardiovascular diseases. However, at present the number of patients and reported adverse events are insufficient to assess long-term morbidity and mortality outcomes of GH replacement. As patient numbers and exposure time increase, future analyses from the HypoCCS database will be able to provide an objective assessment of treatment and disease-associated risk over the long term.

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