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Adult Growth Hormone (GH)-Deficient Patients Demonstrate Heterogeneity Between Childhood Onset and Adult Onset Before and During Human GH Treatment*

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ABSTRACT

The onset of adult GH deficiency may be during either adulthood (AO) or childhood (CO), but potential differences have not previously been examined. In this study the baseline and GH therapy (12.5 μg/kg per day) data from CO (n = 74; mean age 29 yr) and AO (n = 99; mean age 44 yr) GH- deficient adult patients have been compared. The first 6 months comprised randomized, double-blind treatment with GH or placebo, then all patients were GH-treated for a further 12 months.

At baseline the height, body weight, body mass index, lean body mass, and waist/hip ratio of AO patients were significantly ($P < 0.001$) greater than in CO patients. Serum insulin-like growth factor-I (IGF-I) levels were below normal but were lower in CO than AO patients ($P < 0.001$), and the correlation with IGF binding protein-3 was stronger in CO than in AO patients. Osteocalcin concentration in CO patients was above the normal range and significantly greater than in AO patients. Both groups had significant psychosocial distress, but the deviation from normality was greater in AO patients. Throughout GH therapy there was a significant increase in lean body mass and significant decrease in percent body fat and sum of skinfolds in each group. Waist/hip ratio was decreased by long-term therapy in AO but not CO patients. Total and low density lipoprotein cholesterol levels were decreased from baseline at 6 months in AO but not CO patients and high density lipoprotein cholesterol was increased in both groups throughout therapy. IGF-I and IGF binding protein-3 were increased into the normal range by GH therapy in both groups. Mean osteocalcin level in AO patients was increased at 6 months with no further change with GH therapy, whereas in CO patients there was a steep increase up to 12 months but then a sharp decrease. Nottingham Health Profile scores showed significant improvements in physical mobility and energy at 18 months of therapy in AO patients but no consistent effects in CO patients. GH-induced side effects were mainly reported by AO patients; very few CO patients reported treatment-emergent adverse events.

These results demonstrate significant differences in clinical and biochemical presentation and responses to therapy of the adult GH deficiency syndrome. This is consistent with the existence of two entities, developmental (CO) and metabolic (AO), and the different functions of GH at different periods of life. (*J Clin Endocrinol Metab* **82:** 82–88, 1997)

GH DEFICIENCY in adults is recognized as a clinical syndrome with symptoms that respond to administration of human GH. Adults with GH deficiency have abnormal body composition (1–3), reduced physical performance (4), altered lipid metabolism (5), increased cardiovascular disease (6), and reduced quality of life (7, 8). Administration of GH to these patients reduced adipose tissue and increased lean body mass (LBM) (9, 10), increased physical and cardiac performance (11–14), normalized lipid metabolism (15), and improved quality of life (16, 17).

However, adult GH deficiency is not a single clinical entity because the onset may occur during either childhood (CO) or adult life (AO). GH deficiency occurring in children is mainly idiopathic and is recognized as growth failure. Appropriate therapy with GH, standardized over the past decade, is discontinued when final height is reached. Somatic development is unlikely to be complete at this stage, and when GH therapy is withdrawn the untreated deficiency results in increased prevalence of obesity (18, 19). However, these CO patients adapt to the GH-deficient situation during development, whereas patients who have not been deficient during childhood undergo normal somatic development. Acquiring GH deficiency as an adult because of pituitary damage or removal leads to reversal of previously normal GH effects.

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Although previous studies with only small numbers of patients may have focused on one group more than the other, differential effects of therapy for AO and CO adult GH-deficient patients have not been reported. The present report involved a large number of adult patients enrolled in a placebo-controlled clinical trial of efficacy and safety of long-term GH therapy. This is the first report that differentiates therapeutic effects in patients on the basis of the time of onset of the deficiency.

Patients and Methods

Patients

A total of 173 patients were enrolled to participate in a multinational, randomly assigned, blinded, placebo-controlled study, sponsored and monitored by Lilly Research Centre, Windlesham, Surrey, U.K., and with ethical approval according to local and national requirements. Patients were included into two protocols, identical except that patients had GH deficiency arising either during adult life (AO) and that was present for at least 1 yr or during childhood (CO), with GH therapy to final height but no GH treatment in the previous 2 yr. Diagnosis of GH deficiency, from a peak serum GH level <5 μg/L in a standard stimulation test, was required for inclusion. The most frequently performed tests were arginine (AO: n = 31; CO: n = 24), insulin tolerance (AO: n = 42; CO: n = 3), and clonidine (AO: n = 1; CO: n = 31), but other test substances used were GHRH, L-dopa, and glucagon. Replacement therapy with cortisol, thyroxine, sex steroids, and vasopressin had to be stable for at least 6 months before the start of the study, and patients with hypertension were excluded.

Patients were randomly assigned to receive either human biosynthetic GH (Humatrope, Lilly Research Centre) or placebo, administered sc at 6.25 μg/kg per day for the first 4 weeks and then increased to a maximum of 12.5 μg/kg per day (double-blind) for a period of 6 months. Thereafter, all patients were treated with open-label GH for an additional 12 months. Thus patients were on GH for a total of either 18 months (GH/GH) or 12 months (placebo/GH). For the AO group, 52 patients were randomly assigned to GH/GH, and 46 patients were randomly assigned to placebo/GH; for the CO group, 32 patients were randomly assigned to GH/GH and 35 were randomly assigned to placebo/GH. One patient in AO and 7 in the CO group were enrolled but not randomly assigned to a treatment and were included in baseline but not therapy analyses.

Anthropometric measurements and body composition

Weight and height distributions were compared with reference standards for a normal adult population (20). Weight ranges were also evaluated using body mass index (BMI) calculated from weight/height^2. Waist and hip circumferences were measured and waist/hip ratio calculated. Skinfold thicknesses were measured at triceps, biceps, subscap-

TABLE 1. Etiology of GH deficiency in randomized childhood (CO) and adult (AO) onset patients

Clinical diagnosis	n	%
AO		
Functional adenoma	30	30.6
Nonfunctional adenoma	25	25.5
Craniopharyngioma	19	19.4
Dysgerminoma, pinealoma, epidermoid cyst	6	6.1
Posttubercular condition, histiocytosis	2	2.0
Trauma, Sheehan syndrome, empty sella	9	9.2
Idiopathic, hypothalamic origin	7	7.2
CO		
Idiopathic		
Isolated GH deficiency	19	28.4
GH plus TSH deficiency	7	10.4
GH plus LH/FSH deficiency	4	6.0
Multiple deficiency	30	44.8
Trauma, empty sella, posttubercular condition	4	6.0
Craniopharyngioma, dysgerminoma	3	4.4

TABLE 2. Demographic, anthropometric, and body composition data and serum IGF-I, IGFBP-3, osteocalcin, and lipid concentrations at baseline for all enrolled patients

	Total		CO		AO	
	CO (n = 74)	AO (n = 99)	Male (n = 55)	Female (n = 19)	Male (n = 61)	Female (n = 38)
Demographic and anthropometric data (mean ± SD)						
Age (yr)	28.8 ± 8	43.5 ± 10[a]	28.6 ± 8	29.5 ± 8	43.6 ± 11	43.4 ± 7
Height (cm)	160.8 ± 11	171.0 ± 9[a]	163.9 ± 10	151.9 ± 8[b]	176.1 ± 7	162.6 ± 6[c]
Weight (kg)	63.8 ± 17	84.9 ± 17[a]	66.6 ± 17	55.4 ± 13[b]	88.7 ± 15	78.6 ± 19[c]
BMI (kg/m^2)	24.5 ± 6	28.9 ± 5.5[a]	24.7 ± 6	23.9 ± 5	28.5 ± 4	29.6 ± 6
Waist/hip ratio	0.90 ± 0.10	0.96 ± 0.06[a]	0.92 ± 0.06	0.86 ± 0.15[b]	0.98 ± 0.06	0.94 ± 0.05[c]
Body composition (mean ± SD)						
LBM (kg)	43.5 ± 12	57.3 ± 14[a]	46.8 ± 12	33.9 ± 6[b]	64.0 ± 13	46.3 ± 8[c]
Body fat mass (kg)	20.2 ± 11	27.7 ± 13[a]	19.8 ± 11	21.6 ± 10	24.8 ± 11	32.3 ± 14[c]
Percent body fat	31.1 ± 12	31.9 ± 13	28.9 ± 11	37.5 ± 10[b]	27.4 ± 12	39.3 ± 12[c]
Sum of skinfolds (mm)	83.3 ± 38	87.5 ± 31	83.2 ± 41	83.5 ± 28	80.3 ± 26	99.4 ± 34[c]
Serum IGFS and osteocalcin concentrations [median (interquartile range)]						
IGF-I (ng/mL) (normal 91–340)	34 (17–69)	66 (48–91)[a]	41 (19–69)	21 (12–80)	76 (61–101)	53 (37–70)[c]
IGFBP-3 (nmg/mL) (normal 1950–3800)	1145 (755–2166)	2397 (1641–3022)[a]	1309 (782–2100)	968 (583–2744)	2470 (1702–3038)	2306 (1516–2927)
Osteocalcin (ng/mL) (normal 1.8–6.6)	8.6 (6.3–10.3)	5.0 (3.5–7.2)[a]	8.7 (6.6–10.7)	7.8 (5.3–9.7)	5.7 (4.3–7.6)	4.4 (2.8–5.2)[c]
Serum lipid concentrations (mean ± SD)						
Total cholesterol (mg/dL) (normal 150–200)	215 ± 52	243 ± 54	210 ± 54	229 ± 48	240 ± 54	247 ± 55
HDL-cholesterol (mg/dL) (normal males: 35–55; females: 45–65)	36.5 ± 13	31.9 ± 11[a]	34.8 ± 12	40.7 ± 16	29.8 ± 10	35.3 ± 11[c]

[a] $P < 0.05$ *vs.* CO.
[b] $P < 0.05$ *vs.* CO males.
[c] $P < 0.05$ *vs.* AO males.

TABLE 3. Mean NHP scores, 95% confidence intervals (CI), and mean reference level of age- and sex-matched controls in CO and AO patients at baseline

	CO (n = 61)			AO (n = 87)		
	Mean	95% CI	Reference level	Mean	95% CI	Reference level
Social isolation	5.9	3.2–8.6	4.6	7.4	4.7–10.1	5.1
Physical mobility	8.8	4.7–12.9	1.4	17.2[a]	12.8–21.7	3.4
Emotional reaction	14.0	9.4–18.6	8.5	14.7	11.3–18.1	9.6
Energy level	14.8	8.6–20.9	6.4	28.4[a]	22.0–34.7	12.0
Sleep	14.8	9.4–20.1	8.5	20.7	15.8–25.6	12.1
Pain	8.2	4.5–11.9	2.8	9.5	6.3–12.7	5.0

[a] $P < 0.01$ *vs.* CO.

TABLE 4. Changes in efficacy parameters in GH-treated or placebo-treated patients during double-blind treatment period

Efficacy parameter	Treatment group	n	Baseline mean	Mean change from baseline	*P*-value[a]	*P*-value[b]
LBM (kg)	AO GH	52	57.9 ± 14.9	3.54 ± 8.5	<0.001	<0.001
	AO placebo	45	55.9 ± 14.2	−0.22 ± 5.5	0.718	
	CO GH	32	43.5 ± 9.5	3.68 ± 4.1	<0.001	<0.001
	CO placebo	35	43.4 ± 13.4	−1.91 ± 5.7	0.060	
Body fat (%)	AO GH	52	29.5 ± 13.8	−4.93 ± 12.3	<0.001	<0.001
	AO placebo	45	34.1 ± 12.0	0.19 ± 7.4	0.369	
	CO GH	32	32.2 ± 10.5	−5.50 ± 6.2	<0.001	<0.001
	CO placebo	35	30.8 ± 13.0	3.38 ± 8.2	0.011	
Sum of skinfolds (mm)	AO GH	52	82.0 ± 29.6	−9.6 ± 16.2	<0.001	0.002
	AO placebo	46	93.0 ± 34.7	−3.6 ± 13.6	0.104	
	CO GH	31	83.2 ± 39.3	−14.4 ± 17.9	<0.001	0.036
	CO placebo	35	85.1 ± 34.9	−3.2 ± 20.2	0.476	
Total cholesterol (mg/dL)	AO GH	51	241.6 ± 56.7	−18.6 ± 44.9	0.004	0.215
	AO placebo	45	245.2 ± 51.7	−3.2 ± 26.8	0.525	
	CO GH	30	211.3 ± 45.1	−9.9 ± 47.1	0.110	0.722
	CO placebo	32	220.5 ± 61.5	0.6 ± 39.6	0.978	
HDL cholesterol (mg/dL)	AO GH	51	30.5 ± 11.4	8.9 ± 10.9	<0.001	0.045
	AO placebo	45	32.7 ± 10.4	4.4 ± 7.4	<0.001	
	CO GH	30	33.9 ± 12.7	4.5 ± 12.4	0.015	0.119
	CO placebo	32	39.0 ± 13.3	3.3 ± 11.5	0.186	
LDL cholesterol (mg/dL)	AO GH	49	180.4 ± 61.7	−20.3 ± 49.3	0.001	0.198
	AO placebo	43	180.8 ± 56.5	−6.0 ± 32.0	0.191	
	CO GH	30	141.4 ± 46.6	−7.1 ± 51.3	0.287	0.821
	CO placebo	32	148.3 ± 53.4	−7.4 ± 57.3	0.653	
Serum IGF-I (ng/mL)	AO GH	46	73.4 ± 40.1	143.4 ± 101.4	<0.001	<0.001
	AO placebo	46	70.3 ± 31.6	2.5 ± 18.9	0.590	
	CO GH	32	60.7 ± 69.5	123.5 ± 106.8	<0.001	<0.001
	CO placebo	34	54.4 ± 45.7	1.1 ± 23.9	0.378	
Serum IGFBP-3 (ng/mL)	AO GH	46	2475 ± 993	997 ± 953	<0.001	<0.001
	AO placebo	46	2317 ± 929	−33 ± 554	0.636	
	CO GH	32	1563 ± 1042	1088 ± 822	<0.001	<0.001
	CO placebo	35	1596 ± 970	42 ± 408	0.724	

[a] Within-group comparisons; [b] between-group comparisons.

ular, and suprailiac sites and added together for each patient to give a sum of skinfolds value.

Bioelectrical-impedance was measured, and total body water and LBM calculated using the formula provided by the manufacturer of the body composition analyzer (Holtain, Dyfed, U.K.). Body fat mass was calculated from the difference between total body weight and LBM, and percent body fat calculated as a proportion of body weight.

Serum biochemistry

Total cholesterol, high density lipoprotein (HDL) cholesterol, and low density lipoprotein (LDL) cholesterol concentrations were measured by standard techniques. Insulin-like growth factor-I (IGF-I) was measured by an IGF binding protein (IGFBP)-blocked RIA (21) using a kit supplied by BioMerieux (Nurtingen, Germany). IGFBP-3 was measured by a two-site immunoassay (22). Osteocalcin concentration was measured by standard RIA.

Quality of life assessment

Quality of life was assessed from the Nottingham Health Profile (NHP) questionnaire (Galen Research, Manchester, U.K.), and the data analyzed by Galen Research for each of the subsections. NHP scores are inversely related to the patient's quality of life, *i.e.* a higher score indicates a worse quality of life. Scores from age and sex-matched control subjects are included for comparison of pretherapy data.

Statistical analyses

For baseline comparison of AO and CO patients, the analysis was performed using a model incorporating effects for onset, gender, and interactions of onset-by-gender, except where analysis of covariance indicated a significant effect of age (BMI, waist/hip ratio, IGFs, osteocalcin, total cholesterol) when the model also incorporated effects for age (SAS PROC GLM; 23). Analysis was performed on both original and rank transformed data, although only results based on

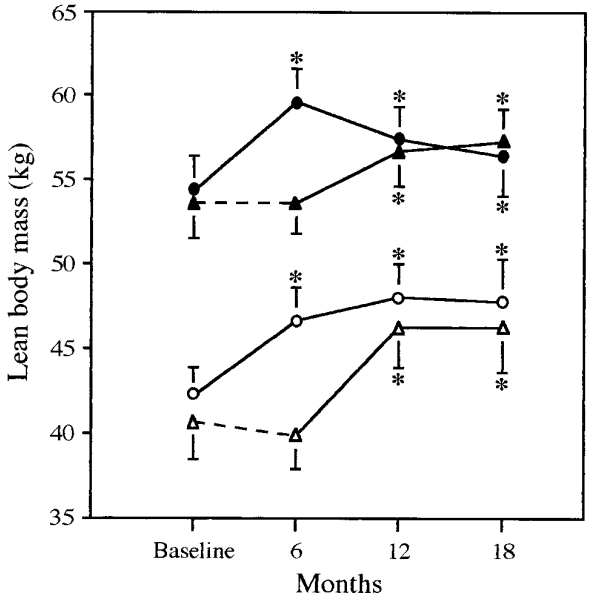

FIG. 1 Long-term changes in LBM of adult patients treated with GH. Adult GH-deficient patients were treated for 18 months with either placebo for 6 months followed by GH (▲, △) or with GH throughout (●, ○). Patients had GH deficiency arising either during adult life (●, ▲) or during childhood (○, △). *, $P < 0.02$ *vs.* baseline values and, at 6 months, *vs.* placebo treated. Values are mean ± SE; number of patients at 18-month endpoint: AO, GH/GH (n = 37); placebo/GH (n = 36); CO, GH/GH (n = 20); placebo/GH (n = 21).

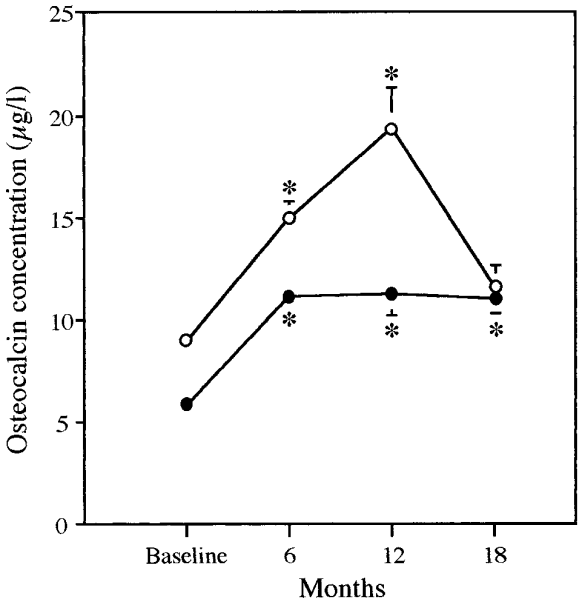

FIG. 2 Long-term changes in serum osteocalcin concentration of patients treated with GH. Patients had GH deficiency arising either during adult life (●) or during childhood (○) and received GH therapy throughout the 18-month study (GH/GH). *, $P < 0.02$ *vs.* baseline values. Values are mean ± SE; number of patients at 18-month endpoint: AO, n = 41; CO, n = 20.

rank transformed data are presented. Spearman correlation coefficients were used to examine the linear relationship between two variables.

Efficacy results were analyzed for between-treatment comparisons of change from baseline to endpoint (last visit in the double-blind period) using ANOVA incorporating effects for treatment, investigator, and treatment-by-investigator interactions using rank transformed data. Within-treatment analyses were performed using a sign test.

Results

Baseline data

Demographic, anthropometric, and body composition. The spectrum of causes of GH deficiency (Table 1) was entirely different between the two patient groups. Idiopathic GH deficiency was recorded for 89.5% of CO patients. Concomitant medications in this group were thyroxine (54%), cortisol (28%), sex steroids (60%), and vasopressin (9%). In AO subjects, the predominant cause of GH deficiency was surgical intervention for (peri-)pituitary tumors (82%), mainly adenomas. Concomitant medications were thyroxine (83%), cortisol (79%), sex steroids (86%), and vasopressin (23%). The highest reported peak GH values in the stimulation tests were 4.3 and 4.6 μg/L in AO and CO patients, respectively.

Baseline demographic and anthropometric data are presented in Table 2. CO patients were significantly ($P < 0.001$) younger than AO patients and, although full-grown, were significantly ($P < 0.001$) shorter. Comparison with an adult height reference standard (23) indicated that for the CO group approximately 50% of both males and females had height values below the 2 SD normal range, whereas the distribution for AO subjects was almost identical to the reference standard. There was a significant correlation with age for BMI and waist/hip ratio. However, after correction for age, mean values were significantly ($P < 0.001$) higher in AO than in CO patients. Correlations of waist/hip ratio with weight and BMI were very strong in AO males (weight: r = 0.45, $P < 0.001$; BMI: r = 0.60, $P < 0.001$) but less strong in CO males (weight: r = 0.22, $P = 0.106$; BMI: r = 0.40, $P = 0.002$).

LBM was not age dependent for the age range of the patients in this study. The mean value for LBM (Table 2) was significantly ($P < 0.001$) less in CO than AO patients, and in each group males had significantly ($P < 0.001$) higher values than females. Comparison with reference values (1, 3, 24, 25) from an age- and sex-matched normal population assessed with the same methodology showed that LBM was decreased ($P < 0.01$) in CO but not in AO individuals. The mean body fat mass was less in CO than AO ($P < 0.001$) patients, although the percentage body fat was very similar between the two groups. In comparison with reference standards (1, 3, 24, 25), both CO and AO patients had significantly greater fat mass and percentage body fat. The sum of skinfold measurements confirmed the bioimpedance data because there was no statistically significant difference between the mean values for the AO and CO groups.

Hormone and clinical chemistry measurements. Mean baseline values for serum concentrations of IGF-I, IGFBP-3, and osteocalcin are presented in Table 2. IGF-I levels were significantly ($P < 0.001$) lower in CO patients than in AO patients, although the mean concentration in each group was below the normal adult reference range (21). In the AO but not in the CO group, the values for males were significantly higher than those for female patients. IGFBP-3 values in AO patients were within the normal range but were significantly ($P <$

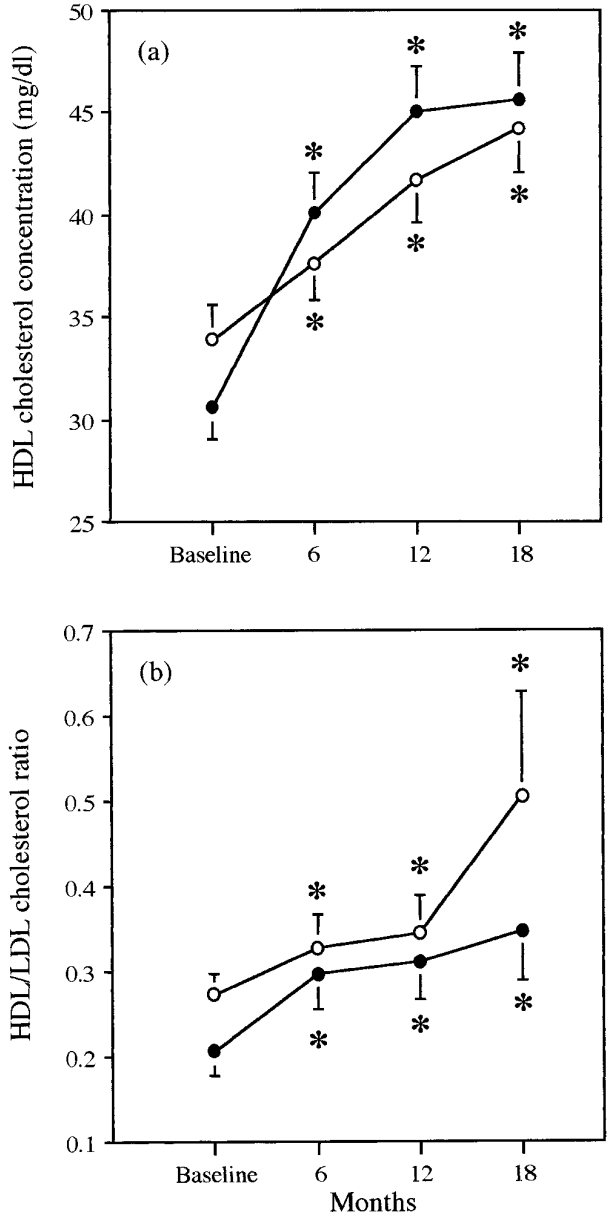

FIG. 3 Long-term changes in HDL cholesterol concentration (a) and in ratio of HDL/LDL cholesterol (b) in adult patients treated with GH. Patients had GH deficiency arising either during adult life (●) or during childhood (○) and received GH therapy throughout the 18 month study (GH/GH). *, $P < 0.02$ *vs*. baseline values. Values are mean ± SE; numbers of patients at 18-month endpoint: AO, n = 41; CO, n = 18.

0.001) greater than in CO patients, which were below the normal range. The correlation of IGFBP-3 with IGF-I values was not as strong in AO (r = 0.58) as in CO (r = 0.93) patients. Osteocalcin concentration was within the normal adult range in AO, whereas it was elevated in CO patients and significantly ($P < 0.001$) greater than that of AO patients.

Mean serum total cholesterol levels (Table 2) were elevated for both AO and CO groups when compared with age- and sex-matched normal ranges from the central laboratory. Mean HDL cholesterol levels were lower than normal in AO but not in CO patients, although 72% of AO and 54% of CO patients had abnormal HDL cholesterol values.

Quality of life assessment. Baseline NHP scores (Table 3) showed that both CO and AO patients had scores that were higher (worse) than a normal population matched for age and sex. However, CO patients generally had lower scores (a lower level of distress) than AO patients. For the dimensions of physical mobility and energy level the differences between AO and CO patients were statistically significant ($P < 0.01$).

Efficacy analysis

Double-blind comparison at 6 months. The mean values at baseline and changes from baseline at the 6-month endpoint for primary efficacy variables are shown in Table 4. For both the AO and CO groups there was a significant increase in LBM and decrease in percent body fat in the GH-treated patients in comparison with baseline values and with placebo-treated patients. Total cholesterol concentration was significantly decreased from baseline only in AO patients, but in neither group was the GH-induced change significant by comparison with placebo treatment. HDL cholesterol concentration was increased from baseline by GH in both AO and CO patients, but only in AO patients was the increase significant in comparison with placebo treatment. There was a significant change from baseline in LDL cholesterol concentration in the AO but not in the CO group. GH therapy increased IGF-I and IGFBP-3 concentrations within 6 months, and the increases were maintained to the 18-month endpoint.

Within-group changes with long-term treatment. There was no significant change in body weight or BMI for either the AO or CO groups. LBM (Fig. 1) showed parallel significant ($P < 0.001$) increases at 6 months with little change thereafter. The sum of skinfolds was significantly decreased by GH therapy at each time point ($P < 0.001$ at 6-, 12-, and 18-month endpoints) in both AO and CO patients. Waist/hip ratio was significantly decreased at 12 and 18 months only in the AO group (change from baseline to: 12 months, -0.012 ± 0.055, $P = 0.024$; 18 months, -0.019 ± 0.048, $P = 0.005$) and was not changed throughout treatment in the CO patients.

There was a significant increase in serum osteocalcin concentration (Fig. 2) in AO patients at 6 months, with no further change throughout treatment. In CO patients there was a steep increase up to 12 months of GH therapy but then a sharp decrease.

Total cholesterol concentration was significantly ($P = 0.004$) decreased in AO patients at 6 months but not at later time points, and there was no significant change in the CO group at any time point. In contrast, the HDL cholesterol concentration (Fig. 3a) was significantly increased from baseline at each time point for both groups. The ratio of HDL cholesterol to LDL cholesterol (Fig. 3b) was also significantly increased throughout the 18 months of GH therapy.

Quality of life. During the double-blind therapy phase, changes in NHP scores showed significant improvements in the placebo- as well as the GH-treated patients in both groups. However, the treatment effect was significantly ($P < 0.01$) different from placebo for the social isolation and phys-

TABLE 5. GH therapy side effects in AO and CO groups during the 18-month study

	AO				CO			
	GH/GH		Placebo/GH		GH/GH		Placebo/GH	
	n	%	n	%	n	%	n	%
6-month endpoint								
Edema, peripheral edema	15	28.8	2	4.3	2	6.3	0	
Arthralgia, myalgia, joint disorder	12	23.1	3	6.5	2	6.3	0	
Paresthesia, hypesthesia	3	5.8	2	4.3	2	6.3	0	
Hypertension	0		1	2.2	0		0	
18-month endpoint[a]								
Edema, peripheral edema	17	32.7	13	28.3	3	9.4	3	10.0
Arthralgia, myalgia, joint disorder	19	36.5	11	23.9	4	12.5	2	6.7
Paresthesia, hypesthesia	10	19.2	6	13.0	3	9.4	0	
Hypertension	4	7.7	2	4.3	0		0	

[a] GH treatment only; throughout 18 months of study for GH/GH and from 6-month baseline to 18-month endpoint for placebo/GH.

ical mobility domains in AO but not in CO patients. In AO patients these improvements persisted with GH therapy, and at 18 months physical mobility and energy level were significantly ($P < 0.01$ for each) improved from baseline. For the CO group at 12 and 18 months no significant effects of GH therapy were seen for any of the NHP scores.

Safety parameters. There were no serious adverse events related to therapy for either group. In the AO group, therapy was discontinued in four patients (4.1%) because of adverse events; one because of recurrence of craniopharyngioma, one because of hypertension and arthralgia, one because of abnormal glucose tolerance, and the last because of a viral illness. In the CO group, therapy was discontinued in three patients (4.5%) because of adverse events; one becaues of hepatitis, one from the same study center because of increased liver enzyme levels, and the third because of joint disorder. Expected side effects of GH therapy were reported throughout the study, and events reported at a frequency of ≥5% are shown in Table 5. Treatment-emergent adverse events were mainly reported in AO patients, with very few reported by CO patients.

Discussion

Previous studies of GH therapy in adult patients (9–17) have focused on efficacy outcome measurements. The assumption has been that abnormalities caused by GH deficiency are present in all GH-deficient adults and respond homogeneously to therapy. However, the pathogenesis and disease history leading to adult GH deficiency differs depending on whether the deficiency has existed since childhood or has been acquired during adult life. The concept of a pediatric disease that affects developmental outcome, and therefore adult life, should apply to GH deficiency in a similar way to other hormone deficiency syndromes such as hypothyroidism and hypogonadism.

Baseline anthropometric and body composition measurements describe the clinical presentation of the adult GH deficiency syndrome and are indicative of its heterogeneity. In terms of height and body shape, CO patients differed significantly from AO patients. CO patients were somatically underdeveloped and retained typical features of hypopituitary dwarfism. This was despite the previous treatment of all of the CO patients with GH, which was pituitary derived in the majority of cases. These patients therefore may not have benefited from modern optimized therapy with recombinant GH (26), which has significantly improved final height outcome during the last decade. However, the emphasis for treatment of pediatric patients remains final height and other maturational aspects, and their impact on later adult life are still poorly understood.

In CO patients, both IGF-I and IGFBP-3 levels were significantly lower than in AO patients and were strongly correlated, similar to the relationship found in childhood (21). In AO patients, IGF-I and IGFBP-3 values did not correlate as strongly, and IGFBP-3 levels were within the normal range. Baseline data therefore indicated that in AO patients the regulation of IGFBP-3 is different, and that IGFBP-3 measurements cannot be used for diagnosis of AO GH deficiency, as established in CO patients. GH therapy increased IGF-I and IGFBP-3 concentrations into the normal range, but did not change the relationships.

Differences in serum osteocalcin levels at baseline and in response to GH therapy indicates that bone biology also differs between AO and CO patients. Withdrawal of GH therapy in hypopituitary dwarfs at epiphyseal closure may prevent full maturation of the bones in these patients. Some studies, although not prospective, have provided indirect evidence that in CO adult GH-deficient patients the bone mineral density is lower than in GH-deficient AO subjects (27, 28), and that their response to GH therapy may be better (28).

Assessing body composition by bioelectrical impedance has shortcomings (2) but is the most feasible method in a large multicenter trial and detects therapy effects with significant power. During the 6-month double-blind period, significant and comparable increases in LBM and decreases in body fat were observed in both AO and CO patients. The significant increases in LBM persisted to 18 months of therapy. However, the waist/hip ratio was decreased only in AO patients, indicating a preferential decrease in intraabdominal fat.

GH treatment also caused a significant long-term increase in HDL cholesterol concentration and HDL/LDL cholesterol ratio. Adult patients with CO deficiency have previously been reported to have normal HDL cholesterol levels (5), which were not altered by GH therapy (29), consistent with

the smaller alteration in lipid values in the CO than the AO patients in the present study.

The heterogeneity between the AO and CO patients was confirmed by the changes in the quality of life and by treatment-related adverse events. AO patients showed a significant improvement in quality of life, whereas CO patients showed no long-term changes. AO patients would have previously experienced a normal adult quality of life and therefore conceivably have suffered more from the GH deficiency than the CO patients who had grown up with and adapted to it. The NHP results in the AO group demonstrate the specific therapy effect and are indicative of the high motivation of these patients. The differences in GH-induced side effects between AO and CO patients primarily may reflect the disposition of the patients to therapy (30). Reported events could reflect real differences in responsiveness, or that CO patients accept any problems whereas AO patients report everything.

In conclusion, this study indicates that there are two distinct entities to the adult GH deficiency syndrome. AO deficiency is a relatively clear clinical/biochemical entity in which the symptoms and their correction by therapy correlate well with the biological actions of GH. CO GH deficiency is more complex because it has both pediatric/developmental and adult/metabolic components, in agreement with the different functions of GH during these two stages of life. It is possible that the CO patients in the present study had not yet developed the full clinical picture of the adult GH deficiency syndrome. However, the treatment rationale in adult GH-deficient patients will differ to correct the symptoms of the syndrome in AO patients but to prevent development of the symptoms of GH deficiency in CO patients.

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