0013-7227/02/$15.00/0
Printed in U.S.A.

The Journal of Clinical Endocrinology & Metabolism 87(1):129–135

GH-Deficient Survivors of Childhood Cancer: GH Replacement during Adult Life

R. D. MURRAY, K. H. DARZY, H. K. GLEESON, AND S. M. SHALET

Department of Endocrinology, Christie Hospital, Manchester, M20 4BX, United Kingdom

Childhood survivors of cancer are prone to a number of adverse sequelae related to the therapeutic interventions undertaken to achieve remission. The endocrine system is frequently affected; hypothalamo-pituitary dysfunction, in particular GH deficiency, is common after cranial irradiation. It is unclear to what extent GH deficiency contributes to the abnormalities observed in adult survivors of childhood cancer, and whether GH replacement reverses these anomalies. We compared 27 GH-deficient survivors of childhood cancer with 27 adult age- and sex-matched controls and went on to replace GH in the patient group to determine whether GH resulted in improvements of the baseline abnormalities.

The GH-deficient survivors of childhood cancer had an adverse lipid profile (total cholesterol, 5.4 *vs.* 4.6 mM, $P = 0.004$; high-density lipoprotein cholesterol, 1.05 *vs.* 1.6 mM, $P < 0.001$; and triglycerides, 1.3 *vs.* 1.0 mM, $P < 0.001$) and were osteopenic (lumbar spine z-score, −1.53 *vs.* −0.31 SD score, $P < 0.001$; femoral neck z-score, −1.23 *vs.* −0.27 SD score, $P = 0.02$); additionally, the female subgroup had an increased percentage body fat (43.6 *vs.* 32.8%, $P = 0.016$). In keeping with the selection criterion, quality of life in the patient cohort, relative to the healthy controls, was severely impaired [adult GH-deficiency assessment (AGHDA), 15.5 (range, 8–25) *vs.* 1 (range, 0–19), $P < 0.0001$; psychological general well-being schedule, 67.5 (range, 18–86) *vs.* 89.0 (range, 51–104), $P < 0.0001$].

After 12 months of GH replacement, small (but significant) improvements were observed in body composition in the male subgroup (waist-hip ratio, 0.871 *vs.* 0.863, $P < 0.05$); and in the female cohort, total cholesterol (6.0 *vs.* 5.2 mM, $P = 0.01$) and triglyceride (2.1 *vs.* 1.4 mM, $P = 0.01$) levels fell. Bone mineral density improved in only one of the four sites studied (ultradistal radius, −1.21 *vs.* −1.09, $P = 0.048$) after a median duration of GH therapy of 18 months. Quality of life improved dramatically by 3 months (AGHDA, 15.5 *vs.* 10.0, $P < 0.001$), and the improvement was maintained at 12 months (AGHDA, 15.5 *vs.* 9.0, $P < 0.001$). Importantly, there was no clinical suggestion of tumor recurrence during the 12 months of GH replacement.

The minor improvements observed in body composition, the lipid profile, and bone mineral density in GH-deficient adult survivors of childhood cancer after 12–18 months of physiological GH replacement suggest that GH deficiency may not be the major etiological factor in their pathogenesis; the converse seems to be true for the quality of life status of these individuals. We propose that, as in patients with hypopituitarism caused by pituitary disease, the main indication for GH replacement in GH-deficient survivors of childhood cancer should be severe impairment of quality of life. (*J Clin Endocrinol Metab* 87: 129–135, 2002)

SURVIVAL RATES FOR certain childhood malignancies have increased dramatically over the last 20 yr, with 5-yr survival rates in many common childhood malignancies in excess of 70% (1). As a consequence of the complex treatment regimens employed to achieve such remarkable cure rates, significant detrimental effects on the endocrine system, growth, and fertility are well recognized (2–8). Additionally, survivors of childhood cancer are at increased risk of subsequent malignant neoplasms and show increased mortality from nonmalignant disease (9, 10).

Endocrine sequelae of cancer therapy include thyroid dysfunction, thyroid nodules, thyroid carcinoma, hyperparathyroidism, hypogonadism, and hypopituitarism (3, 11). GH secretion is recognized to be the most vulnerable of the hypothalamo-pituitary axes to radiation-induced damage (12, 13). Over the last decade, the abnormalities that result from GH deficiency have been well defined in the hypopituitary adult: increased fat mass, reduced lean body mass (14, 15), reduced bone mineral density (BMD) (16, 17), an adverse lipid profile (14, 18), and impaired quality of life (19, 20). Furthermore, hypopituitary adults on conventional pituitary replacement, but not GH replacement, have an increased mortality rate (21, 22). Similarly, young adult survivors of cancer who received cranial irradiation show an increased prevalence of obesity (23, 24), reduced BMD (25, 26), an adverse lipid profile (27, 28), impaired academic achievement, and reduced quality of life (29).

The relative contribution of GH deficiency toward these abnormalities noted in childhood survivors of cancer has not been disentangled from the direct effects of the primary pathology, irradiation, chemotherapy, high-dose corticosteroids, and insufficient exercise and excessive caloric intake. Furthermore, whether GH replacement therapy has any role in reversing the abnormalities described in these patients has not been investigated. We therefore undertook an open treatment study of GH replacement, in addition to comparing the baseline characteristics of the patient group with an age- and sex-matched control group of healthy volunteers.

Abbreviations: AGHDA, Adult GH-deficiency assessment; ALL, acute lymphoblastic leukemia; BMD, bone mineral density; BMI, body mass index; DXA, dual-energy x-ray absorptiometry; HbA1C, hemoglobin-A1C; HDL, high-density lipoprotein; LDL, low-density lipoprotein; PGWB, psychological general well-being schedule; SDS, SD score; TC, total cholesterol; TG, triglyceride; WHR, waist to hip ratio.

Subjects and Methods

Patients

We studied 27 (14 female) severely GH-deficient adults who had survived childhood cancer. The primary diagnoses were medulloblastoma (n = 6), astrocytoma (n = 5), germinoma (n = 4), pinealoma (n =

4), glioma (n = 3), acute lymphoblastic leukemia (ALL) (n = 3), and ependymoma (n = 2). Mean age at diagnosis of the primary pathology was 9.9 ± 4.3 yr; and at the time of the study, 24.2 (range, 16–40) yr. Therapy for the primary pathology included transcranial surgery in 13 patients; and all 27 patients received cranial irradiation, 17 of whom also received spinal irradiation. In addition, 14 patients received chemotherapy, the majority (n = 8) receiving a regimen of 1-(2-chloroethyl)-3-cyclohexyl-1-nitrosourea and procarbazine; other regimens included a combination of etopiside, carboplatin, and either vincristine (n = 1) or bleomycin (n = 1), and 1 patient received iv thiotepa. The 3 patients with ALL were treated with combination chemotherapy using the UKALL IV intensive, UKALL X, and Memphis total 5 protocols.

Severe GH deficiency (a peak GH response of less than 9 mU/L) was confirmed during adult life by the use of provocative tests of GH secretion. All patients with isolated GH deficiency were subject to two provocative stimuli. Twenty-two patients underwent insulin-induced hypoglycemia (insulin tolerance test, glucose nadir less than 2.0 mM); 25, the arginine stimulation test; and 6, the glucagon stimulation test. During childhood and adolescence, 17 patients received GH therapy to facilitate growth. Childhood GH therapy was discontinued between 8 months and 14 yr before the start of the current study. In addition to GH deficiency, 7 patients were gonadotrophin deficient, 7 were TSH deficient, 5 were ACTH deficient, and 3 were ADH deficient. Replacement with sex steroids, T_4, hydrocortisone, and DDAVP was optimized before the study and was not altered during the study period.

Our control group consisted of 27 normal volunteers (14 female); mean age, 29.1 (range, 17–50) yr.

Study protocol

The design of the study was an open-treatment trial of GH replacement. An active bias in selection of patients occurred (GH replacement was only offered to those patients with subjectively impaired quality of life). During the study, no dietary restrictions were placed on the patients. Before commencing GH replacement, the patients underwent a physical examination, and blood was drawn between 0930 and 1200 h for measurement of IGF-I, glucose, and hemoglobin-A1C (HbA1C). Additional serum was stored at −80 C for further analyses. Body composition was estimated from measurement of height, weight, waist and hip circumference, allowing calculation of the body mass index (BMI) and waist to hip ratio (WHR). An additional measure of body fat mass was obtained using a bioelectrical impedance monitor (Tanita TBF-305; Tanita/Stellar Innovations, Inc., Uxbridge, UK). BMD was assessed using dual-energy x-ray absorptiometry (DXA) at the lumbar spine and femoral neck, and by single energy x-ray absorptiometry at the distal and ultradistal radius. Quality of life was assessed objectively using two self-rating questionnaires, the psychological general well-being schedule (PGWB) (30) and the adult GH-deficiency assessment (AGHDA) (31, 32). The patients were then taught to self-inject using an automated pen device (Genotropin pen, Pharmacia & Upjohn, Inc., Milton Keynes, UK) and, when competent, were commenced on GH at a dose of 0.27 mg/d. The GH dose was subsequently adjusted at intervals of 4–6 weeks, to normalize the serum IGF-I within the range of +2 to −2 SD in the absence of GH-related side-effects. All measures undertaken at baseline were repeated after 3 and 12 months on GH replacement therapy, except BMD (which was reassessed after at least 1 yr of GH replacement therapy). Serum stored at the baseline and 12-month visit was used to analyze changes in the lipid profile. Formal ethical approval was obtained from South Manchester Local Research Ethics Committee.

Quality of life measures

The PGWB is a generic self-assessment inventory designed to measure intrapersonal affective or emotional state. It contains 22 items that are scored on a scale of 0–5, a value of 0 being the most negative response, and 5 the most positive. The score range for the PGWB is 0–110. The AGHDA is a self-assessment questionnaire designed specifically for use in adults with GH deficiency. The format consists of 25 statements to which a 'yes' or 'no' response is requested. The score range for the AGHDA is 0–25, a score of 25 representing the greatest morbidity.

BMD measurement

DXA measurements of integral (mixed cortical and trabecular) bone were performed at the lumbar spine (L1–L4) and the left proximal femur (femoral neck), unless fracture or joint replacement on that side meant that the right hip had to be scanned. This region was scanned using either a DPX-L (Lunar Corp., Madison, WI) or a QDR 4500 Acclaim fan beam scanner (Hologic, Inc., Bedford, MA). Coefficients of variation are 0.5 and 1.09% in the lumbar spine and 2.5 and 3.29% in the femoral neck, respectively. In all patients, the follow-up scan was performed using the same scanner as used for the baseline scan. Single-energy x-ray absorptiometry BMD was measured in the nondominant forearm using an Osteometer DTX-100 scanner (Osteometer A/S, Roedovre, Denmark). Scanning was performed at the distal site, giving measurements predominantly (87%) of cortical bone, and in an ultradistal site in which trabecular bone predominates (65%). Precision is 1% at the distal site and 2.5% in the ultradistal site. The BMD was measured in grams per square centimeter, and values are expressed as Z-scores derived from comparison with appropriate normal reference data matched for age and sex, provided by the manufacturer of the relevant bone density scanner.

Assays

Serum samples were analyzed for IGF-I, using a RIA, after separation of IGFs from IGF-I binding proteins by acid/alcohol extraction. Des(1–3)-IGF-I was used as radioligand to minimize interference of IGF-I binding proteins in the extract. The intra- and interassay coefficients of variation were 10% and 3.1%, respectively. The normal range of the assay was adjusted for age and was constructed using normative data from 400 healthy Swedish individuals equally distributed across the age-range.

Cholesterol, triglycerides (TGs), and direct high-density lipoprotein (HDL) cholesterol assays were carried out on an ADVIA 1650 chemistry analyzer (Bayer Corp. Diagnostics, Newbury, Berkshire, UK) using proprietary methods. The cholesterol and TG methods, respectively, employ cholesterol oxidase and lipoprotein lipase/glycerol kinase. The HDL cholesterol method measures cholesterol by polyethylene glycol-linked cholesterol esterase and oxidase after serum incubation with sulfated cyclodextrin buffer. The lipid assays were carried out in two batches, both of which contained a random mix of patient and control samples.

Glucose was determined by a glucose oxidase-based method in which hydrogen peroxide reacts with 4-aminophenazone and phenol to form a colored indicator quinone imine dye. Typical between-batch analytical coefficients of variation were 3.4% and 2.9% at 5.0 and 15.8 mM glucose, respectively. HbA1C was determined by an in-house-developed HPLC method (Pharmacia & Upjohn, Inc.), typical between-batch coefficients of variation were 3.8% and 4.2% at 5.1% and 8.5% HbA1C, respectively.

Statistics

The data are presented as mean ± SD if normally distributed, or as median and ranges if the data were skewed. Differences between paired data were examined using the paired *t* test or Wilcoxon signed-rank test for parametric and nonparametric data, respectively. Nonpaired data were compared using the *t* test or the Mann-Whitney rank-sum test for parametric and nonparametric data, respectively. Data at different time points, in the same individual, were analyzed using a one-way repeated-measures ANOVA or Friedman repeated-measures ANOVA on ranks, for parametric and nonparametric data, respectively. A P value < 0.05 was deemed to be significant.

Results

Baseline

The median age of the patient (23 yr; range, 16–40 yr) and control groups (26 yr; range, 17–50 yr) was not significantly different ($P = 0.09$). After subgrouping by gender, no difference was detected in the age of the patient and control groups in either the female or male cohorts ($P = 0.15$ and $P = 0.57$). The healthy controls were significantly taller than the patients (1.71 ± 0.09 *vs.* 1.59 ± 0.14 m, $P < 0.001$); however,

the two groups did not differ significantly with respect to weight (68.6 *vs.* 62.7 kg, $P = 0.11$) (Table 1). Stratifying for gender revealed the controls to be significantly taller than the patients in both the female and male subgroups ($P < 0.001$ and $P = 0.03$, respectively, data not shown), with no significant difference in weight. Systolic and diastolic blood pressure were not significantly different between patients and controls (systolic, 123 ± 14.0 *vs.* 117 ± 9.4 mm Hg, $P = 0.08$; and diastolic, 75.3 ± 8.6 *vs.* 72.0 ± 9.2 mm Hg, $P = 0.21$). The mean serum IGF-I SD score (SDS) in the patient group was −1.91 ± 2.34; 14 of the 27 patients had an IGF-I SDS score of less than −2.0.

Body composition (Table 1). In the cohort overall, no significant difference was observed between the patients and controls with respect to BMI, waist circumference, WHR, or percentage fat mass measured by bioimpedance. A further analysis was performed after stratification by gender. No significant differences were demonstrated in any of the measures of body composition in the male subgroup. The female patients were shown to have a significantly greater percentage fat mass, relative to the female controls (43.6 ± 12.2 *vs.* 32.8 ± 7.6%, $P = 0.016$); though differences in the less sensitive measures of fat mass, BMI (26.2 ± 4.7 *vs.* 23.1 ± 3.5, $P = 0.06$), and WHR (0.817 ± 0.78 *vs.* 0.775 ± 0.75, $P = 0.057$) just failed to reach significance.

Metabolic parameters. No differences were observed in fasting glucose levels between the patients and controls. However, the median HbA1C level was significantly lower in the patients (4.0 *vs.* 4.5, $P = 0.002$) (Table 2). The GH-deficient survivors of childhood cancer were found to have an adverse lipid profile, with significantly higher total cholesterol (TC) (5.38 *vs.* 4.6 mM, $P = 0.004$), low-density lipoprotein (LDL) cholesterol (3.5 *vs.* 3.2 mM, $P < 0.001$), and TG levels (1.3 *vs.* 1.0 mM, $P = 0.01$). Additionally, highly significant differences in the serum HDL (1.05 *vs.* 1.6 mM, $P < 0.001$) and the LDL/HDL ratio were observed between the patient and control groups (3.0 *vs.* 1.8 mM, $P < 0.001$).

BMD. BMD, measured at the lumbar spine, femoral neck, ultra distal and distal radius, was significantly lower at all sites than that in the control group ($P < 0.001$, $P = 0.02$, $P = 0.001$, and $P = 0.003$, respectively) (Table 3). The percentage of patients with BMD z-scores less than −2.0 at the lumbar spine, femoral neck, and ultradistal and distal radii was 33, 26, 17, and 33%, respectively.

Quality of life. Comparison of total scores derived from both the AGHDA (range, 0–25; high values represent greater morbidity) and PGWB (range, 0–110; low values represent greater morbidity) self-rating questionnaires demonstrated the patients to have severe impairment of their quality of life, relative to the healthy controls [AGHDA, 15.5 (range, 8–25) *vs.* 1 (range, 0–19), $P < 0.0001$; PGWB, 67.5 (range, 18–86) *vs.* 89.0 (range, 51–104), $P < 0.0001$].

Post-GH replacement

Three months of GH replacement increased the mean serum IGF-I SDS value to within the normal range (0.41 ± 1.92, $P < 0.001$), requiring a mean GH dose of 0.34 ± 0.09 mg/d. At 12 months, the mean serum IGF-I SDS and maintenance GH dose were 0.49 ± 1.38 ($P < 0.001$) and 0.39 ± 0.16 mg/d, respectively.

During the 12-months study, the median weight of the cohort increased from 59.6 to 62.6 kg ($P = 0.02$). Despite this gain in weight, there was no significant adverse change in any of the measures of body composition, in the 12-months treatment period, for the cohort overall (Table 1). Subanalysis by gender revealed both females and males to have gained a similar amount of weight (female, 1.46 ± 2.2 kg; male, 1.81 ± 3.3 kg), although this reached significance in the female cohort only ($P = 0.02$ and $P = 0.09$, respectively). Despite a gain in weight in the male cohort, a significant reduction in WHR was recorded at both 3 (0.871 ± 0.05 *vs.* 0.854 ± 0.04, $P < 0.05$) and 12 (0.871 ± 0.05 *vs.* 0.863 ± 0.04, $P < 0.05$) months, compared with baseline. None of the additional measures of fat mass changed significantly in either the male or female subgroups with GH therapy.

The plasma glucose level remained unaffected by GH replacement; however, the HbA1C level was significantly elevated in comparison with baseline levels at 12 months, but not at 3 months (Table 2). Serum HbA1C also increased significantly between 3 and 12 months; and at 12 months, it was not significantly different from the control group ($P = 0.92$). Overall changes in the serum lipid values were small and failed to reach significance (Table 2). When stratified for gender, no significant changes were observed in the males; however, a significant reduction occurred in the TC (6.0 ± 1.0 *vs.* 5.2 ± 1.1 mM, $P = 0.01$) and TG levels (2.1 ± 1.4 *vs.* 1.4 ± 0.6, $P = 0.01$) in the female cohort.

Repeat BMD scans were performed after a median duration of GH replacement of 18 months. The BMD z-score was observed to increase significantly at the ultradistal radius, although it was unaltered at the additional three sites (Table 3). Quality of life, as recorded by the AGHDA and PGWB, improved significantly at 3 months, compared with the respective baseline values of the patients [AGHDA, 15.5 (range, 8–25) *vs.* 10.0 (range, 1–23), $P < 0.001$; PGWB, 67.5 (range, 18–86) *vs.* 83.0 (47–105), $P < 0.001$], and this im-

TABLE 1. Measures of body composition in GH-deficient (GHD) survivors of childhood cancer at baseline and after 3 and 12 months of GH-replacement therapy (data for the healthy age- and sex-matched controls are also provided)

	Controls	GHD patients baseline	GHD patients (3 months)	GHD patients (12 months)
Weight (kg)	68.6 ± 12.2	62.7 ± 14.9	62.9 ± 14.4	64.3 ± 15.2[a]
BMI (kg/m^2)	23.6 ± 3.9	24.8 ± 4.3	24.8 ± 4.1	25.4 ± 4.4
Waist (cm)	80.0 ± 10.8	81.6 ± 10.0	81.8 ± 9.8	82.5 ± 10.7
WHR	0.826 ± 0.07	0.859 ± 0.07[b]	0.852 ± 0.06	0.858 ± 0.06
% Fat mass	25.4 ± 11.1	29.8 ± 15.7	31.8 ± 16.4	32.3 ± 15.8

[a] $P = 0.02$ compared with baseline.
[b] $P = 0.08$ compared with controls.

TABLE 2. Metabolic measures in 27 GH-deficient survivors of childhood cancer at baseline and after 3 and 12 months of GH-replacement therapy (data for 27 healthy age- and sex-matched controls are also provided, expressed as median and ranges)

	Controls	GHD patients baseline	GHD patients (3 months)	GHD patients (12 months)
Glucose (mM)	4.3 (3.4–5.8)	4.5 (3.1–7.5)	4.8 (4.0–6.5)	4.8 (3.4–7.7)
HbA1c (%)	4.5 (3.8–5.5)	4.0 (3.6–6.4)[a]	4.3 (3.5–6.8)	4.6 (3.3–6.0)[b]
Total cholesterol (mM)	4.60 (3.70–6.40)	5.38 (3.80–7.23)[c]	N/A	5.15 (3.0–7.58)
HDL cholesterol (mM)	1.60 (0.90–2.30)	1.05 (0.50–1.88)[d]	N/A	1.08 (0.70–1.80)
LDL cholesterol (mM)	2.60 (1.40–4.60)	3.65 (2.30–5.80)[d]	N/A	3.40 (1.40–6.12)
LDL/HDL ratio	1.80 (0.70–4.00)	3.09 (1.28–6.44)[d]	N/A	3.61 (1.60–6.31)
Triglycerides (mM)	1.00 (0.60–1.90)	1.34 (0.63–5.05)[e]	N/A	1.31 (0.56–4.83)

N/A, Not available.
[a] $P = 0.001$, compared with controls, [b] $P < 0.05$, compared with baseline, [c] $P = 0.004$, [d] $P < 0.001$ compared with controls and [e] $P = 0.01$.

TABLE 3. Measures of BMD at four sites in GH-deficient survivors of childhood cancer at baseline and after 18 months of GH-replacement therapy (data for the healthy age- and sex-matched controls are also provided, expressed as Z-scores)

	Controls	GHD patients (baseline)	GHD patients (18 months)
Lumbar spine	−0.31 ± 1.06	−1.53 ± 1.17[a]	−1.55 ± 1.11
Femoral neck	−0.27 ± 1.29	−1.23 ± 1.36[b]	−1.39 ± 0.98
Ultradistal radius	−0.07 ± 1.14	−1.21 ± 1.06[c]	−1.09 ± 1.00[d]
Distal radius	−0.70 ± 1.13	−1.65 ± 0.91[c]	−1.70 ± 0.80

[a] $P < 0.001$ compared with controls, [b] $P = 0.02$, [c] $P < 0.01$.
[d] $P = 0.048$, compared with baseline.

provement was maintained at 12 months [AGHDA, 15.5 (range, 8–25) *vs.* 9.0 (range, 0–24), $P < 0.001$; PGWB, 67.5 (range, 18–86) *vs.* 83.0 (range, 34–103), $P < 0.001$] (Fig. 1A and B). No significant change in the quality of life scores occurred between 3 and 12 months.

Importantly, during the 12–18 months of GH replacement therapy, there was no clinical suggestion of tumor recurrence.

Discussion

The results of this study support the hypothesis that GH deficiency is not a major contributor toward the abnormalities of body composition, adverse lipid profile, and osteopenia in survivors of childhood cancer. However, to consider the findings of this study in context, one must first assess the degree of GH deficiency in these patients. The severity of GH deficiency can be judged by the peak response to provocative tests of GH secretion, the number of additional pituitary hormone deficits, and the serum IGF-I level (33–35). By definition, all the patients in this study were severely GH deficient to provocative tests of GH secretion, *i.e.* a peak GH response of less than 9 mU/L (34). Many of the previous studies demonstrating the beneficial effects of GH have been undertaken with hypopituitary adults with no residual GH secretion. In contrast, 9 of our patients had a peak GH response of greater than 5 mU/L to at least 1 provocative test of GH reserve. Additionally, although the mean serum IGF-I level for the patient group was low in comparison to the controls, only 14 (52%) had an IGF-I level of at least 2 SD below the age-related mean. In contrast, De Boer *et al.* (36) (1994) found 96% of adult hypopituitary patients with GH deficiency of childhood-onset to have an IGF-I value below the normal range. The difference in the prevalence of subnormal serum IGF-I levels between our study and that of De Boer *et al.* may, in part, be explained by the severity of GH

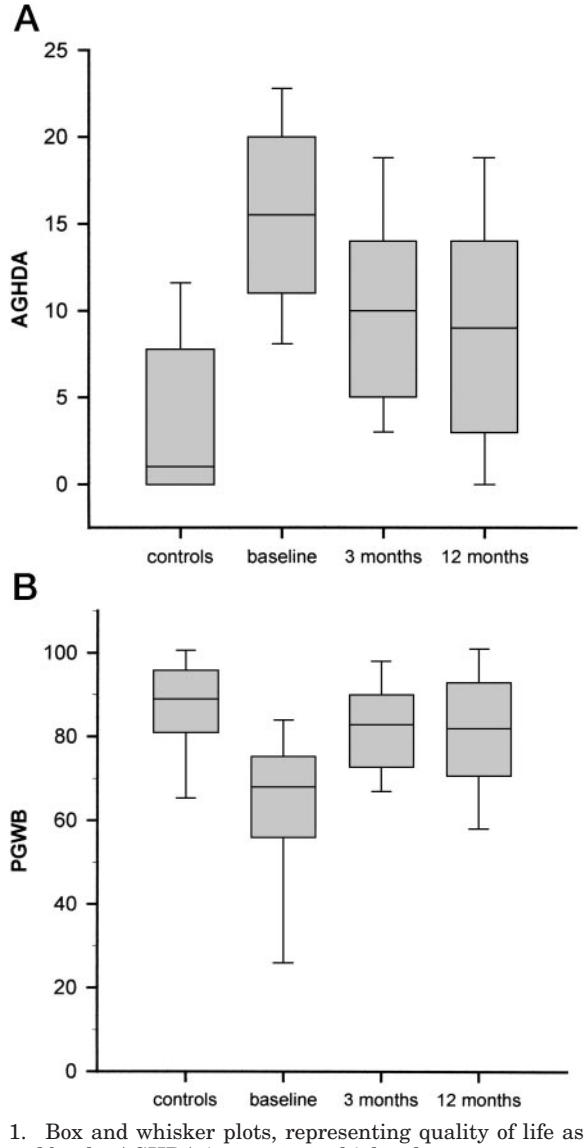

FIG. 1. Box and whisker plots, representing quality of life as represented by the AGHDA (range, 0–25; high values represent greater morbidity) (A) and the PGWB (range, 0–110; low values represent greater morbidity) (B), in GH-deficient survivors of childhood cancer during 12 months GH treatment and in healthy control subjects. The *lower boundary of the box* indicates the 25th percentile, a *line within the box* marks the median, and the *upper boundary of the box* indicates the 75th percentile. *Error bars above and below the box* indicate the 90th and 10th percentiles.

deficiency as judged by the provocative tests of GH secretion. An alternative hypothesis is that cranial irradiation affects the neuroregulatory control of GH secretion such that the pulsatile component is affected much more than the tonic component (37), resulting in less reduction of the serum IGF-I level. Further support for our patients having less severe GH deficiency is derived from the observation that 15 of the patients have no additional pituitary hormone deficits (35).

Obesity is well recognized in both survivors of childhood cancer (23, 24, 38) and GH-deficient adults (39–41). The degree of deviation from normal body composition in adults with childhood-onset GHD is recognized to be less than that seen in patients with adult-onset GH deficiency (18). Despite a significant difference between the heights of the patient and control groups, no difference was detected in the weight of the two groups. No differences were found in any of the measures of body composition unless the data were stratified for gender, the female patients having a greater percentage body fat than the female controls.

Didi *et al.* (23) (1995) reported that survivors of childhood ALL who had received cranial irradiation, had an increased prevalence of obesity; however, they found no relationship between BMI at final height and any auxological parameter. The authors went on to suggest that GH deficiency was unlikely to be a major etiological factor in the pathogenesis of the observed obesity. Unfortunately, GH status was not formally assessed in this cohort. Sklar *et al.* (24) (2000) described changes in BMI in 126 survivors of childhood ALL. An increase in BMI was noted to occur predominantly in those patients who received cranial irradiation; they also demonstrated a temporal association with the 24–36 months active treatment phase during which they received chemotherapy, with no further increases in BMI occurring after completion of treatment. GH status was not assessed in these patients; however, the authors argued that the increase in BMI started before GH deficiency could have resulted from the cranial irradiation. In the current study, our patients gained a significant amount of weight during the 12 months physiological GH replacement. Despite this, none of the measures of body composition were adversely affected; in fact, WHR fell in the male patients. The majority, if not all, of the beneficial effect of GH on body composition would be expected to have occurred by 12 months. The minor improvements in body composition, with GH replacement, observed in this study, support the proposal of Didi *et al.* (23), that GH deficiency is not a major etiological factor in the obesity of survivors of childhood cancer.

Interestingly, before GH replacement, we observed the patients to have a significantly lower HbA1c level than the controls. Hypoglycemia is a recognized presenting feature of GH deficiency in the first 2 yr of life (42); however, the majority of studies in adults infer that GH deficiency results in insulin resistance (43–46). Impaired glucose tolerance is also reported in survivors of childhood cancer and may result, in part, from obesity and GH deficiency (28). Our baseline HbA1c results are difficult to explain, and they require confirmation in further studies of adult survivors of childhood cancer.

An adverse lipid profile, characterized by a high TC, LDL-cholesterol, and TGs, in association with a low HDL-cholesterol level, was present in the patients. These abnormalities are characteristic of those observed in GH-deficient adults (47–49) but are not uncommon in other medical conditions affecting the lipid profile. Abnormalities of the lipid profile, in keeping with those observed in this study, have been described in survivors of childhood cancer (27, 28), although the underlying etiology is unclear. GH deficiency has been implicated as a contributing factor (28); however, an adverse lipid profile in survivors of childhood cancer is recognized in the absence of cranial irradiation (27). The finding of an adverse lipid profile is clearly of importance, because it may place survivors of childhood cancer at increased risk of premature cardiovascular disease. We observed only small improvements in the lipid profile after GH replacement therapy, and these were confined to the female subgroup. This is in keeping with previous data showing improvements in the lipid profile of childhood-onset GH-deficient adults with low-dose GH replacement to be minor (50).

BMD was significantly lower than the control population at all four sites studied and is a well-recognized finding in childhood cancer survivors (25, 51, 52). How much GH deficiency contributes to the etiology of this osteopenia is unclear. Brennan *et al.* (26) (1999) quantified BMD in 31 young adult survivors of ALL, using both DXA and QCT, and correlated this with GH status assessed from provocative tests of GH reserve. BMD was reduced at all sites measured; however, no correlation was observed between the degree of osteopenia and GH status. This finding indicates that there are a number of different mechanisms including the disease process itself and the therapeutic interventions that may additionally have affected bone accretion. In our study, after a median time of 18 months of GH therapy, BMD improved only at the ultradistal radial site, which is comprised predominantly of trabecular bone. Improvements in BMD after GH replacement are reported to occur in trabecular bone before those observed in cortical bone. The lumbar spine is, to a large extent, comprised of trabecular bone, and improvements at the lumbar spine may, therefore, also have been expected. However, the effect of spinal irradiation, which 17 (63%) of our cohort had received for treatment of their primary pathology, may have influenced the response to GH therapy (53).

The most dramatic effect of GH replacement was the improvement in quality of life. Quality of life improved significantly after 3 months of GH therapy, and the improvement was maintained at 12 months. One may expect patients that have had a diagnosis of cancer, with all the intensive treatment and follow-up that this entails, to have a reduced quality of life, whether GH deficient or not. The changes we have observed are dramatic and equal in magnitude to those previously observed with physiological GH replacement in cohorts comprising predominantly patients treated for pituitary disease (19, 54). Clearly, some of the improvement may relate to placebo effect, and also to regression toward the mean, because the cohort was selected on the basis of impaired quality of life. We have previously estimated the maximum effect of these confounders and found them not to explain this improvement (19). However, interpretation of the exact contribution of GH replacement on quality of life in these patients remains difficult in the absence of a placebo-

treated control group. Recently, concerns over the specificity of the AGHDA in detecting improvements in quality of life in hypopituitary patients have been raised (55). The beneficial effects of GH replacement on quality of life detected by the AGHDA in the current study have been mirrored by changes in the PGWB, confirming this to be a real finding. Impaired quality of life remains the main indication for GH-replacement therapy in GH-deficient hypopituitary adults in the United Kingdom (56).

Importantly, we observed no clinical evidence to suggest tumor recurrence in these patients while on GH therapy. Although the numbers included in this study are relatively small, and duration of treatment was only 12–18 months, the findings are in keeping with the observations of Swerdlow *et al.* (57) (2000). In this latter study, recurrence rates for brain tumors were examined in 1071 children who had received cranial irradiation for treatment of a primary brain cancer. A total of 180 children who received GH were compared with 891 children who did not. Those who received GH therapy were not found to be at an increased risk of recurrence (relative risk 0.6) after a mean follow-up of 6.4 yr since the first GH injection was administered.

In summary, we have confirmed GH-deficient survivors of childhood cancer to have a number of adverse sequelae, including abnormal body composition, an adverse lipid profile, and osteopenia. Physiological GH replacement in these individuals resulted in minor improvements, in terms of body composition, serum lipids, and BMD, but a dramatic improvement in quality of life that was maintained throughout the year follow-up. The exact contribution of GH deficiency to the adverse changes in body composition, lipid status, and bone mass is difficult to disentangle from the effect of the disease process itself and the various therapeutic interventions. However, the minor improvements after GH replacement suggest that GH is not a major etiological factor in their pathogenesis. We propose that, as in adults rendered GH-deficient as a consequence of pituitary disease, the main indication for GH replacement in GH-deficient survivors of childhood cancer should be severe impairment of quality of life.

Acknowledgments

We thank Pharmacia & Upjohn, Inc. for its support.

Received June 29, 2001. Accepted October 1, 2001.

Address all correspondence and requests for reprints to: Prof. S. M. Shalet, Department of Endocrinology, Christie Hospital NHS Trust, Wilmslow Road, Manchester, M20 4BX, United Kingdom.

References

1. **Stiller CA** 1994 Population based survival rates for childhood cancer in Britain, 1980–91. BMJ 309:1612–1616
2. **Stevens MC, Mahler H, Parkes S** 1998 The health status of adult survivors of cancer in childhood. Eur J Cancer 34:694–698
3. **Murray RD, Brennan BM, Rahim A, Shalet SM** 1999 Survivors of childhood cancer: long-term endocrine and metabolic problems dwarf the growth disturbance. Acta Paediatr Suppl 88:5–12
4. **Adan L, Souberbielle JC, Blanche S, Leverger G, Schaison G, Brauner R** 1996 Adult height after cranial irradiation with 24 Gy: factors and markers of height loss. Acta Paediatr 85:1096–1101
5. **Davies HA, Didcock E, Didi M, Ogilvy Stuart A, Wales JK, Shalet SM** 1994 Disproportionate short stature after cranial irradiation and combination chemotherapy for leukaemia. Arch Dis Child 70:472–475
6. **Robison LL** 1993 Issues in the consideration of intervention strategies in long-term survivors of childhood cancer. Cancer 71(Suppl):3406–3410
7. **Shalet SM, Beardwell CG, Aarons BM, Pearson D, Jones PH** 1978 Growth impairment in children treated for brain tumours. Arch Dis Child 53:491–494
8. **Oeffinger KC, Eshelman DA, Tomlinson GE, Buchanan GR, Foster BM** 2000 Grading of late effects in young adult survivors of childhood cancer followed in an ambulatory adult setting. Cancer 88:1687–1695
9. **Robertson CM, Hawkins MM, Kingston JE** 1994 Late deaths and survival after childhood cancer: implications for cure. BMJ 309:162–166
10. **Neglia JP, Meadows AT, Robison LL** 1991 Second neoplasms after acute lymphoblastic leukemia in childhood. N Engl J Med 325:1330–1336
11. **Hancock SL, Cox RS, McDougall IR** 1991 Thyroid diseases after treatment of Hodgkin's disease. N Engl J Med 325:599–605
12. **Brennan BM, Rahim A, Mackie EM, Eden OB, Shalet SM** 1998 Growth hormone status in adults treated for acute lymphoblastic leukaemia in childhood. Clin Endocrinol (Oxf) 48:777–783
13. **Littley MD, Shalet SM, Beardwell CG, Robinson EL, Sutton ML** 1989 Radiation-induced hypopituitarism is dose-dependent. Clin Endocrinol (Oxf) 31:363–373
14. **Carroll PV, Christ ER, Bengtsson BA, et al.** 1998 Growth hormone deficiency in adulthood and the effects of growth hormone replacement: a review. Growth Hormone Research Society Scientific Committee. J Clin Endocrinol Metab 83:382–395
15. **de Boer H, Blok GJ, Van der Veen EA** 1995 Clinical aspects of growth hormone deficiency in adults. Endocr Rev 16:63–86
16. **Holmes SJ, Economou G, Whitehouse RW, Adams JE, Shalet SM** 1994 Reduced bone mineral density in patients with adult onset growth hormone deficiency. J Clin Endocrinol Metab 78:669–674
17. **Kaufman JM, Taelman P, Vermeulen A, Vandeweghe M** 1992 Bone mineral status in growth hormone-deficient males with isolated and multiple pituitary deficiencies of childhood onset. J Clin Endocrinol Metab 74:118–123
18. **Attanasio AF, Lamberts SW, Matranga AM, et al.** 1997 Adult growth hormone (GH)-deficient patients demonstrate heterogeneity between childhood onset and adult onset before and during human GH treatment. Adult Growth Hormone Deficiency Study Group. J Clin Endocrinol Metab 82:82–88
19. **Murray RD, Skillicorn CJ, Howell SJ, Lissett CA, Rahim A, Shalet SM** 1999 Dose titration and patient selection increases the efficacy of GH replacement in GHD adults. Clin Endocrinol (Oxf) 50:749–757
20. **McGauley GA** 1989 Quality of life assessment before and after growth hormone treatment in adults with growth hormone deficiency. Acta Paediatr Scand 356(Suppl):70–74
21. **Rosen T, Bengtsson BA** 1990 Premature mortality due to cardiovascular disease in hypopituitarism. Lancet 336:285–288
22. **Bulow B, Hagmar L, Mikoczy Z, Nordstrom CH, Erfurth EM** 1997 Increased cerebrovascular mortality in patients with hypopituitarism [see Comments]. Clin Endocrinol (Oxf) 46:75–81
23. **Didi M, Didcock E, Davies HA, Ogilvy Stuart AL, Wales JK, Shalet SM** 1995 High incidence of obesity in young adults after treatment of acute lymphoblastic leukemia in childhood. J Pediatr 127:63–67
24. **Sklar CA, Mertens AC, Walter A, et al.** 2000 Changes in body mass index and prevalence of overweight in survivors of childhood acute lymphoblastic leukemia: role of cranial irradiation. Med Pediatr Oncol 35:91–95
25. **Gilsanz V, Carlson ME, Roe TF, Ortega JA** 1990 Osteoporosis after cranial irradiation for acute lymphoblastic leukemia. J Pediatr 117:238–244
26. **Brennan BM, Rahim A, Adams JA, Eden OB, Shalet SM** 1999 Reduced bone mineral density in young adults following cure of acute lymphoblastic leukaemia in childhood. Br J Cancer 79:1859–1863
27. **Parsons SK, Skapek SX, Neufeld EJ, et al.** 1997 Asparaginase-associated lipid abnormalities in children with acute lymphoblastic leukemia. Blood 89:1886–1895
28. **Talvensaari KK, Lanning M, Tapanainen P, Knip M** 1996 Long-term survivors of childhood cancer have an increased risk of manifesting the metabolic syndrome. J Clin Endocrinol Metab 81:3051–3055
29. **Herold AH, Roetzheim RG** 1992 Cancer survivors. Prim Care 19:779–791
30. **Dupuy HJ** 1984 The psychological general well-being (PGWB) index. In: Wenger NK, ed. Assessment of quality of life in clinical trials of cardiovascular therapies. New York: Le Jacq Publishing Inc; 170–183
31. **Holmes SJ, McKenna SP, Doward LC, Hunt SM, Shalet SM** 1995 Development of a questionnaire to assess the quality of life of adults with growth hormone deficiency. Endocrinol Metab 2:63–69
32. **Hunt SM** 1994 Developing a measure of quality of life for adults with growth hormone deficiency. Drug Information J 28:3–11
33. **Hoffman DM, O'Sullivan AJ, Baxter RC, Ho KK** 1994 Diagnosis of growth-hormone deficiency in adults. Lancet 343:1064–1068
34. **Growth-Hormone-Research-Society** 1998 Consensus guidelines for the diagnosis and treatment of adults with growth hormone deficiency: summary statement of the Growth Hormone Research Society Workshop on Adult Growth Hormone Deficiency. J Clin Endocrinol Metab 83:379–381
35. **Toogood AA, Beardwell CG, Shalet SM** 1994 The severity of growth hormone deficiency in adults with pituitary disease is related to the degree of hypopituitarism. Clin Endocrinol (Oxf) 41:511–516

36. **de Boer H, Blok GJ, Popp Snijders C, van der Veen EA** 1994 Diagnosis of growth hormone deficiency in adults. Lancet 343:1645–1646
37. **Achermann JC, Hindmarsh PC, Robinson IC, Matthews DR, Brook CG** 1999 The relative roles of continuous growth hormone-releasing hormone (GHRH(1–29)NH2) and intermittent somatostatin(1–14)(SS) in growth hormone (GH) pulse generation: studies in normal and post cranial irradiated individuals. Clin Endocrinol (Oxf) 51:575–585
38. **Schell MJ, Ochs JJ, Schriock EA, Carter M** 1992 A method of predicting adult height and obesity in long-term survivors of childhood acute lymphoblastic leukemia. J Clin Oncol 10:128–133
39. **Beshyah SA, Freemantle C, Thomas E, et al.** 1995 Abnormal body composition and reduced bone mass in growth hormone-deficient hypopituitary adults. Clin Endocrinol (Oxf) 42:179–189
40. **Rosen T, Bosaeus I, Tolli J, Lindstedt G, Bengtsson BA** 1993 Increased body fat mass and decreased extracellular fluid volume in adults with growth hormone deficiency. Clin Endocrinol (Oxf) 38:63–71
41. **Sartorio A, Narici M, Conti A, Giambona S, Ortolani S, Faglia G** 1997 Body composition analysis by dual energy x-ray absorptiometry and anthropometry in adults with childhood-onset growth hormone (GH) deficiency before and after six months of recombinant GH therapy. J Endocrinol Invest 20:417–423
42. **Herber SM, Milner RD** 1984 Growth hormone deficiency presenting under age 2 years. Arch Dis Child 59:557–560
43. **Weaver JU, Monson JP, Noonan K, et al.** 1995 The effect of low dose recombinant human growth hormone replacement on regional fat distribution, insulin sensitivity, and cardiovascular risk factors in hypopituitary adults. J Clin Endocrinol Metab 80:153–159
44. **Hew FL, Koschmann M, Krieger T, et al.** 1995 Insulin tolerance test in patients with anterior pituitary hormone deficiency: reduced insulin sensitivity. Endocrinol Metab 2:93–98
45. **Hew FL, Koschmann M, Christopher M, et al.** 1996 Insulin resistance in growth hormone-deficient adults: defects in glucose utilization and glycogen synthase activity. J Clin Endocrinol Metab 81:555–564
46. **Johansson JO, Fowelin J, Landin K, Lager I, Bengtsson BA** 1995 Growth hormone-deficient adults are insulin-resistant. Metabolism 44:1126–1129
47. **Cuneo RC, Salomon F, Watts GF, Hesp R, Sonksen PH** 1993 Growth hormone treatment improves serum lipids and lipoproteins in adults with growth hormone deficiency. Metabolism 42:1519–1523
48. **de Boer H, Blok GJ, Voerman HJ, Phillips M, Schouten JA** 1994 Serum lipid levels in growth hormone-deficient men. Metabolism 43:199–203
49. **Rosen T, Eden S, Larson G, Wilhelmsen L, Bengtsson BA** 1993 Cardiovascular risk factors in adult patients with growth hormone deficiency. Acta Endocrinol (Copenh) 129:195–200
50. **Murray RD, Wieringa GE, Lissett CA, Darzy KH, Smethurst LE, Shalet SM,** Low-dose GH replacement improves the adverse lipid profile associated with the adult GH deficiency syndrome. Clin Endocrinol (Oxf), in press
51. **Aisenberg J, Hsieh K, Kalaitzoglou G, et al.** 1998 Bone mineral density in young adult survivors of childhood cancer. J Pediatr Hematol Oncol 20:241–245
52. **Hoorweg-Nijman JJ, Kardos G, Roos JC, et al.** 1999 Bone mineral density and markers of bone turnover in young adult survivors of childhood lymphoblastic leukaemia. Clin Endocrinol (Oxf) 50:237–244
53. **Murray RD, Smethurst LE, Adams JE, Shalet SM,** Spinal irradiation impairs the osteo-anabolic effects of low-dose growth hormone replacement in adults with childhood-onset GH deficiency. Clin Endocrinol (Oxf), in press
54. **Drake WM, Coyte D, Camacho Hubner C, et al.** 1998 Optimizing growth hormone replacement therapy by dose titration in hypopituitary adults. J Clin Endocrinol Metab 83:3913–3919
55. **Barkan AL** 2001 The "Quality of Life-Assessment of Growth Hormone Deficiency in Adults" questionnaire: can it be used to assess quality of life in hypopituitarism? J Clin Endocrinol Metab 86:1905–1907
56. **Bengtsson BA, Johannsson G, Shalet SM, Simpson H, Sonken PH** 2000 Treatment of growth hormone deficiency in adults. J Clin Endocrinol Metab 85:933–942
57. **Swerdlow AJ, Reddingius RE, Higgins CD, et al.** 2000 Growth hormone treatment of children with brain tumours and risk of tumor recurrence. J Clin Endocrinol Metab 85:4444–4449

The 15th International Symposium of the Journal of Steroid Biochemistry & Molecular Biology

(Recent Advances in Steroid Biochemistry & Molecular Biology)

May 17–20, 2002
Munich, Germany

The main topics are: Steroid receptors, structure, gene expression, and mechanism of action; non-genomic effect of steroid hormones; steroid membrane receptors; steroids and cancer; steroids in the central and peripheral nervous systems; steroids and the menopause; enzyme modulators; steroid hormones, phyto- and xeno-estrogens, and the environment; steroids and sport.

For more information, contact Prof. J. R. Pasqualini, Steroid Hormone Research Unit, Institut de Puériculture, 26 Blvd Brune, 75014 Paris, France. Telephone: 331-4539-9109; Fax: 331-4542-6121; E-mail: Jorge.Pasqualini@wanadoo.fr.