

CLINICAL STUDY

Interdependence of lean body mass and total body water, but not quality of life measures, during low dose GH replacement in GH-deficient adults

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Abstract

Lean body mass (LBM) and total body water (TBW) are reduced in GH-deficient (GHD) adults and alter with GH replacement. Whether these parameters are interdependent and whether alterations in their homeostasis contribute to the perceived quality of life (QOL) deficit in GHD remains unclear. In this study, IGF-I, body composition by whole-body dual-energy X-ray absorptiometry, TBW by deuterium dilution (D₂O) and two validated QOL instruments - psychological general well-being schedule (PGWB, generic, 6 domains; lower score worse QOL) and assessment of GH deficiency in adults (AGHDA, disease orientated; higher score worse QOL) were studied at baseline and after 3 and 6 months of GH replacement in thirty GHD adults. Patients with diabetes insipidus, and cardiac and renal failure were excluded. Median age-adjusted IGF-I standard deviation score increased from -3.40 (-6.40 to -1.60) to -0.2 (-1.88 to 0.78) ($P < 0.0001$) at a median daily GH dose of 0.4 mg. During treatment, LBM increased from 47.4 ± 10.7 kg at baseline to 49.5 ± 10.8 kg at 6 months ($P = 0.0008$), and fat mass decreased from 28.0 ± 12.1 kg at baseline to 27.2 ± 12.6 kg at 6 months ($P = 0.0004$). A non-significant trend towards an increase in TBW was observed (mean 1.7 kg, $P = 0.08$). The PGWB score increased from 62.9 ± 20.6 to 73.7 ± 21.7 ($P = 0.0006$). The AGHDA score decreased from 13.7 ± 7.3 to 8.75 ± 7.75 ($P = 0.0002$). At each time point, a linear correlation between LBM and TBW was demonstrated, defined by $TBW = (0.972 \times LBM) - 10.6$. However, only a weakly positive correlation existed between the percentage changes in these variables ($R = 0.40$, $P = 0.04$). No correlations were demonstrated between QOL measures and body composition. The change in LBM with physiological GH replacement correlates weakly with change in TBW, therefore factors other than TBW may also contribute to the LBM changes. Improved QOL with GH replacement is not explained by favourable changes in body composition.

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Introduction

Growth hormone deficiency (GHD) in adults is associated with reduced lean body mass (LBM), and following growth hormone (GH) replacement this has been shown to increase by a mean of 2 to 5.5 kg (1). Total body water (TBW) has also been shown to increase with GH replacement (2–4). Whether or not changes in LBM and TBW during GH replacement are interdependent is unclear. Impairment in quality of life (QOL) is a prominent feature of adult GHD (1). The areas of QOL most likely to be affected by GHD are energy and vitality (5) and the degree of improvement is proportional to the deviation from normality at the outset (6). However, the mechanisms underlying these observations remain poorly understood (6). Measures

of effort-independent submaximal aerobic performance have provided novel objective determinants of functional impairment and fatigue and have been used to evaluate and predict the response to GH treatment (7). The possibility that alterations in LBM and/or TBW homeostasis could contribute to the perceived QOL deficit in GHD or whether favourable changes in these parameters may translate into clinically meaningful improvements in QOL has not been systematically studied. In the present study, measurement of TBW (by deuterium (D₂O) dilution), LBM and fat mass (FM) (by whole-body dual-energy X-ray absorptiometry (DEXA)), and QOL (by two validated QOL instruments) were performed in thirty GHD adults before and during 6 months low-dose GH replacement to address these issues.

Patients and methods

Patients

Thirty (16 female, 14 male, age range 17–65 years) severely GHD adults who had not received GH replacement for at least one year prior to commencing the study were included. Patients with diabetes insipidus or cardiovascular or renal disease requiring diuretic therapy were excluded from the study.

In those who had additional pituitary hormone deficits, all were on stable conventional hormone replacement for at least six months prior to the study. Twenty patients had adult-onset and ten had childhood-onset pituitary disease. The original diagnoses were non-functioning pituitary adenoma ($n = 8$), idiopathic/isolated GHD ($n = 7$), prolactinoma ($n = 4$), Cushing's disease ($n = 2$), head trauma ($n = 1$), Sheehan's syndrome ($n = 1$), brain tumours anatomically distant from the hypothalamic–pituitary axis (HPA) (resulting in GHD due to cranial irradiation with fields which included the HPA) ($n = 6$), and nasopharyngeal carcinoma (resulting in GHD due to irradiation with fields which included the HPA) ($n = 1$). Eighteen patients had undergone surgery in the region of the HPA as part of primary treatment and in ten patients a trans-cranial approach had been used. Eighteen patients had received radiotherapy with fields that included the HPA. The number of additional anterior pituitary hormone deficits (luteinising hormone/follicle-stimulating hormone, adrenocorticotrophin, thyrotrophin, prolactin) were as follows: GHD + 0, $n = 11$; GHD + 1, $n = 8$; GHD + 2, $n = 2$; GHD + 3, $n = 7$; GHD + 4, $n = 2$. The clinical and endocrine characteristics of the patients at baseline are summarised in Table 1.

Study design

Before entering the study, all patients underwent a general physical examination and were trained in the

Table 1 Clinical and endocrine characteristics of the study subjects.

	Female $n = 16$	Male $n = 14$
Age (years)	51 (31–54.5)	30.5 (21–58)
Body mass index	29.9 ± 2.10	25.3 ± 1.58
GHD etiology		
Pituitary adenoma	10	4
Idiopathic	3	4
Sheehan's syndrome	1	–
Head trauma	1	–
Brain tumour/ALL	1	6
Treatment: surgery/irradiation/both/neither	1/3/7/5	1/-/10/3
Age of onset of GHD (AO/CO)	12/4	8/6
Peak GH response (mU/l)	1.95 (1–4.25)	3.25 (1–6.70)

ALL, acute lymphoblastic leukaemia; AO, adult-onset; CO, childhood-onset. Values in brackets indicate quartiles.

use of an automated pen device (Genotropin pen, Pharmacia) for subcutaneous self-injection of GH. The study was of open treatment design. The study was approved by the South Manchester Local Research Ethics Committee and the Christie Hospital Clinical Trials Resource Group. All patients gave informed consent after explanation of the aims and methods of the study had been provided. After recruitment, GH replacement was started using the low-dose titration method. The treatment goal was to achieve an insulin-like growth factor-I (IGF-I) concentration within the age-corrected normal range. All patients were started on 0.3 mg as a single daily subcutaneous injection at night and the GH dose was adjusted each visit as necessary. The visits for IGF-I measurement were at baseline, and then at 6 weeks, and 3 and 6 months of the study. The following variables were studied at baseline, and at 3 and 6 months of physiological GH replacement: random plasma glucose, glycated haemoglobin (HbA1c), body composition assessed by DEXA, TBW assessed by deuterium (D_2O) dilution and QOL as assessed by two self-rating questionnaires – the psychological general well-being schedule (PGWB) which is a generic QOL questionnaire, and the assessment of GH deficiency in adults (AGHDA) which is a disease orientated QOL questionnaire (see below). All patients were questioned specifically about potential side effects of over-treatment at each visit to determine the occurrence of adverse events.

Diagnosis of severe GHD

All patients were required to undergo two tests of GH reserve to confirm their GH secretory status, except in the setting of panhypopituitarism and a peak GH response to the insulin tolerance test (ITT) of less than $3 \mu\text{g/l}$ (9 mu/l) (8). GH status was assessed using ITT (soluble insulin 0.2 IU/kg i.v.), the glucagon stimulation test (GST) (glucagon 1 mg i.m.) or the arginine stimulation test (AST) (20 g/m^2 arginine *i.v.* as a 20% solution infused over 30 min). In patients with childhood-onset (CO)-GHD, re-testing of GH reserve was repeated after discontinuation of childhood GH replacement. Severe GHD was defined as a peak GH response of less than $3 \mu\text{g/l}$ to all stimulation tests undertaken.

Methods

Body composition Whole body scanning was performed on an Hologic 4500 Acclaim scanner (Hologic Inc. Bedford, MA, USA), using software version 9.03. All jewellery and outer clothing were removed and the patients were scanned wearing a cotton gown. Patients were positioned supine on the scanning table, with arms internally rotated and hands prone on the scanning table with fingers together. The legs were positioned straight on the table with the feet taped together and

extended as much as possible. Before commencing the scan it was ensured that all parts of the body were inside the boundary of the scanning field that is marked out on the mattress of the scanning table. The short-term precision (% coefficient of variation) of whole body DEXA in the Unit is 1.75% for fat mass and 0.56% for lean (muscle) mass (9).

Total body water An initial background urine sample was obtained from each patient with full voiding to ensure an empty bladder. Patients then received an orally administered dose of D₂O (enrichment 99.8%) of approximately 4 g via a 5 ml syringe that was weighed to four decimal places before and after administration so that the actual dose given could be calculated accurately. A 100 ml bolus of tap water was administered after the D₂O as a mouth-rinse to swallow. No food or drink was consumed during the equilibration period of 6 h. D₂O enrichment in the body fluid was measured in the urine after this interval. All samples were then frozen in sealed tubes to prevent atmospheric contamination while awaiting mass spectrometric analysis for deuterium content.

A sample (0.3 ml) was pipetted into septum-sealed vials (in duplicate). A catalyst, platinum (5%) on alumina in glass insert vials, was also placed in the vials before they were sealed and the headspace flushed with pure hydrogen. Reference waters (including a quality control standard) were prepared in the same manner. Once all vials were flushed, they were left to equilibrate for a period of three days to ensure complete equilibration. The samples and references were then analysed by continuous flow using a Europa Scientific ANCA-GSL and Geo 20–20 IRMS. The deuterium enrichments of the samples were calibrated against our two laboratory reference waters IA-R008 (3.7‰ δ²H vs v-SMOW/v-SLAP) and IA-R012 (1017.2‰ δ²H vs v-SMOW/v-SLAP). The accuracy of the analyses was controlled by measuring laboratory standard water IA-R010 (551.8‰ δ²H vs v-SMOW/v-SLAP) as a check standard in each batch of samples. The difference in the deuterium value measured for a control water standard measured 4 months apart was less than 0.4 ppm.

The equation used for calculation of the deuterium oxide dilution space (N) was that published by Schoeller *et al.* (10):

$$N = (d/MW) \times (APE/100) \times 8.02 \times (1/(R_{std} \times \Delta\delta D)) \text{kg}$$

where d is the dose of D₂O in grams, MW is the molecular weight of the D₂O (20.0274), R_{std} is the ratio of deuterium/hydrogen in the standard (0.00015576), APE is the D₂O enrichment (99.9 atom percent excess) and ΔδD is the difference in the baseline and post dose urine samples (δD vs V-SMOW values).

The final total body water value was calculated as N/1.03 to account for the overestimation of total body water by exchange of D₂O with 'non-body water' hydrogen pools.

Growth hormone The GH assays were performed by a two-site immunoradiometric assay. All assays were measured against the reference preparation NIBSC 80/505.

IGF-I IGF-I assays were performed by a chemiluminescence immunoassay (Nichols Advantage System, Nichols Institute Diagnostics, San Clemente, CA). The reference range of the assay was calculated using reference values based on Brabant *et al.* (11).

Glucose Glucose assays were performed using the Advia 1650 system using the glucose oxidation method.

HbA1c HbA1c was measured using the Menarini HA-8140 HPLC method with values Diabetes Control and Complications Trial aligned.

Quality of life

PGWB This is a generic self-assessment inventory designed to measure intrapersonal affective or emotional state (12). It contains 22 items that are scored on a scale of 0–5, a value of 0 being the most negative and 5 the most positive. The score range for the PGWB is 0–110.

AGHDA This is a self-assessment questionnaire designed for use in adults with GHD (13). 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.

Statistical analysis

Data are presented as means ± standard deviation for normally distributed data and medians (quartiles) for non-normally distributed data. The paired *t*-test and Wilcoxon signed rank test were used when evaluating a treatment effect. The strength of correlations was sought using Pearson Product Moment Correlation or Spearman Rank Order Correlation. The Friedman repeated measures ANOVA was used to determine treatment effects at different time points during the study. A *P* value of <0.05 was accepted as significant.

Results

Thirty patients were recruited and baseline studies were completed in all patients. Of these, one patient did not start GH replacement and a second patient discontinued treatment after 3 months.

The median age-adjusted IGF-I standard deviation score (SDS) increased significantly from –3.40

(−6.40 to −1.60) at baseline to −0.40 (−2.85 to 0.50) at 3 months and to −0.2 (−1.88 to 0.78) at 6 months ($P < 0.0001$) at a median daily GH dose of 0.4 mg. IGF-I scores for each patient at the three time points during the study are shown in Fig. 1. The change in age-adjusted IGF-I SDS and the GH dose requirement were not significantly different between genders.

Median random plasma glucose increased from 4.5 to 4.7 ($P < 0.0001$), and HbA1c increased from 5.3 to 5.6 ($P < 0.0001$) within the first 3 months of the study, levels that remained unchanged at 6 months.

Body composition changes

Weight increased during the study from 75.1 ± 20.6 to 77.9 ± 20.4 kg ($P = 0.004$). Statistical significance for weight gain was only reached after 6 months of GH replacement. The change in weight during treatment was not significantly different between males and females.

Assessment of body composition by DEXA demonstrated a significant increase in LBM from 47.4 ± 10.7 kg at baseline to 48.8 ± 10.9 at 3 months and 49.5 ± 10.8 kg at 6 months ($P = 0.0003$). The difference between the values for the two follow-up assessments did not, however, reach statistical significance. Individual results of lean body mass expressed as a percentage of body weight at baseline and after 6 months of GH replacement are shown in Fig. 2.

A significant decrease in FM occurred from 28.0 ± 12.1 kg at baseline to 27.4 ± 12.3 at 3 months and to 27.2 ± 12.6 kg at 6 months ($P < 0.0001$). Again, the difference between the values for the two follow-up assessments did not reach statistical significance.

The difference in LBM between genders did not reach statistical significance at any of the three time points of the study. However, the percentage change in LBM was significantly greater in males than females, 2.65 ± 1.36 and 0.96 ± 1.57 respectively ($P = 0.005$). FM was

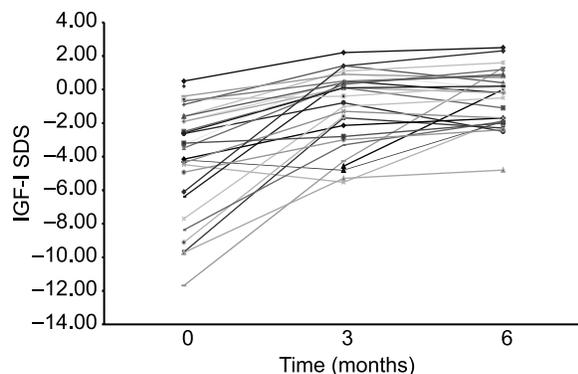


Figure 1 Individual IGF-I SDS at baseline (0) and after 3 and 6 months of low dose GH replacement.

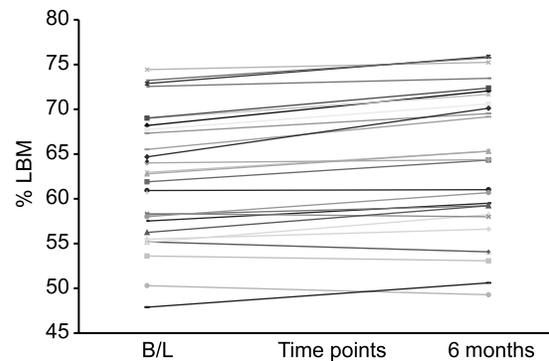


Figure 2 Individual results for lean body mass expressed as a percentage of body weight (% LBM) at baseline (B/L) and after 6 months of GH replacement.

significantly greater in females compared with males at all time points; baseline: females 32.3 ± 13.2 kg, males 23.1 ± 8.8 ($P = 0.04$); 3 months: females 32.8 ± 13.0 kg, males 21.7 ± 8.5 kg ($P = 0.01$); 6 months: females 33.1 ± 13.7 kg, males 21.2 ± 8.05 ($P = 0.01$). Furthermore, the percentage decrease in FM between baseline and 6 months of GH replacement was significantly greater in males than females, 2.61 ± 1.4 and 1.0 ± 1.6 respectively ($P = 0.009$).

D₂O dilution demonstrated a non-significant trend towards an increase in TBW of 1.7 kg ($P = 0.08$). The change in TBW as a percentage of body weight, shown in Fig. 3, and TBW as a percentage of LBM, also failed to reach statistical significance. The difference between genders in absolute TBW, TBW as a percentage of body weight and TBW as a percentage of LBM did not reach statistical significance at any of the time points studied.

Quality of life

The PGWB score increased from 62.9 ± 20.6 to 73.3 ± 21.7 ($P = 0.0006$). The AGHDA score decreased from 13.7 ± 7.3 to 8.75 ± 7.8 ($P = 0.0002$). There was no significant difference between genders for PGWB or AGHDA scores at any time point during the study.

Correlations

At baseline and at 3 and 6 months, a highly significant linear correlation between LBM and TBW was demonstrated (Fig. 4). The regression equation at baseline was $(1.02 \times \text{LBM}) - 11.9$, after 3 months of GH replacement it was $(0.96 \times \text{LBM}) - 10.5$, and after 6 months GH replacement it was $(0.953 \times \text{LBM}) - 9.94$.

Positive correlations were also demonstrated between LBM and FM, and between TBW and FM at the three time points studied. As expected, weight correlated with LBM, TBW and FM (data not shown). In addition, a positive correlation was demonstrated between the percentage changes in LBM and TBW, and a negative

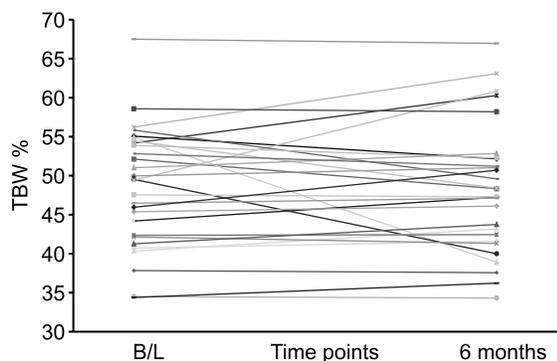


Figure 3 Individual results for total body water expressed as a percentage of body weight (% TBW) at baseline (B/L) and after 6 months of GH replacement.

correlation was demonstrated between percentage changes in FM and TBW during the study (Fig. 5).

At baseline, no correlations were demonstrated between body composition variables and IGF-I SDS. At 6 months, IGF-I SDS correlated positively with LBM ($r = 0.49, P = 0.01$), weakly positively with weight ($r = 0.4, P = 0.04$) and showed a trend towards a weak positive correlation with TBW ($r = 0.37, P = 0.055$).

No correlations were demonstrated between QOL scores with any body composition variables or IGF-I at any time point during the study.

No correlations were evident between change in IGF-I SDS and changes in LBM, FM, TBW or QOL measures during the study.

Adverse events

GH replacement was generally well tolerated and compliance was good, as evidenced by significant increases in IGF-I levels. No patients withdrew from the study due to an adverse event. One patient declined GH replacement for personal reasons and one patient withdrew from the study after 3 months because of difficulty in attending appointments. In total, 6 of the 29 patients treated (20.7%) complained of adverse symptoms, 4 (13.8%) of whom required dose reduction. Three patients suffered symptoms of transient swelling of the fingers suggesting mild fluid retention, which reversed rapidly with dose reduction. No patient developed clinical evidence of fluid overload indicated by peripheral or pulmonary oedema. One patient complained of excessive weight gain and one (male patient) complained of mild scalp hair loss.

Discussion

In this study, efficacy of treatment as judged by significant improvements in LBM, FM and QOL were observed with GH replacement, in line with previous data (14–17). However, TBW did not increase significantly,

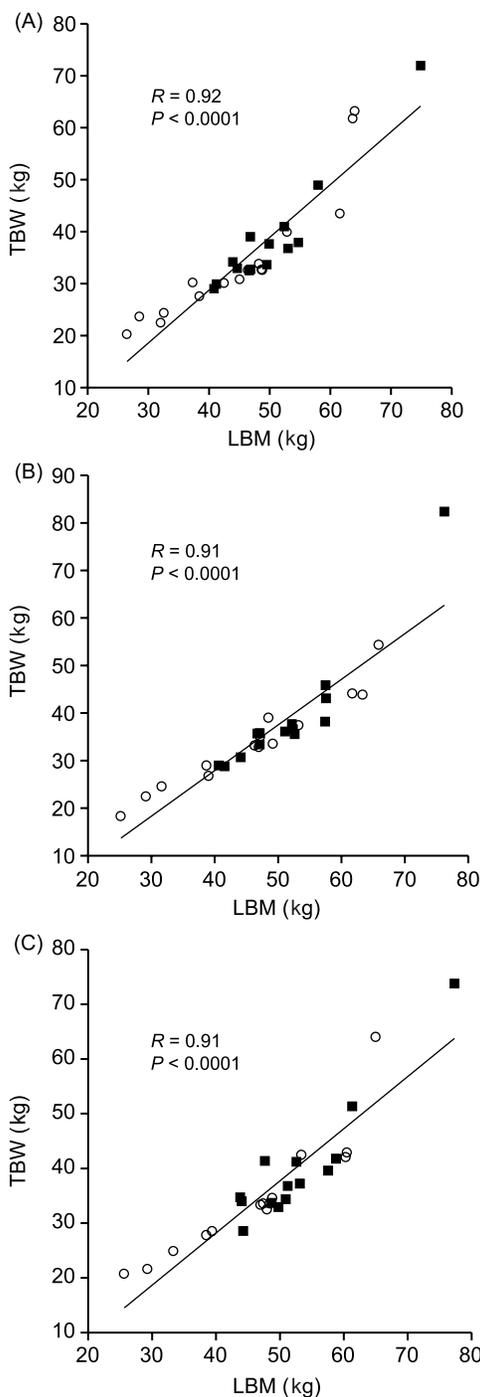


Figure 4 Relationship between lean body mass (LBM) and total body water (TBW) at baseline (A) and after 3 (B) and 6 (C) months GH replacement. ○ denotes values for females and ■ denotes values for males.

with a trend towards an increase of the order of 1.7 kg, which is less than that observed in many previous studies using weight-based GH dosing regimens (18–20). Nonetheless, other more recent studies using low-dose GH regimens have generally shown

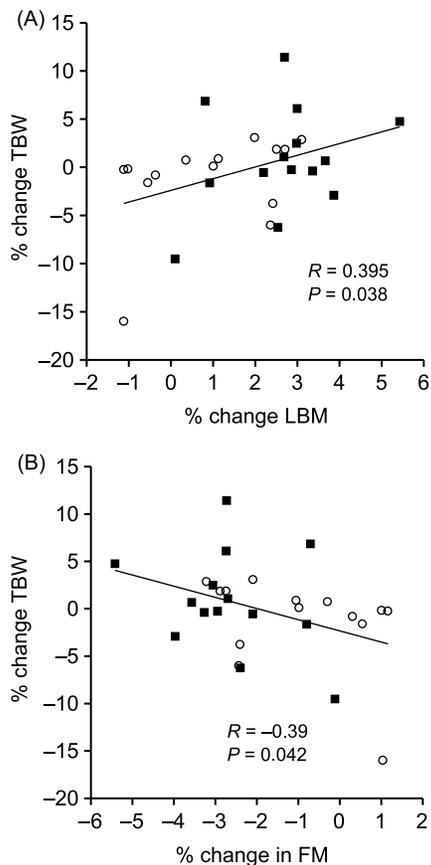


Figure 5 Relationship between (A) changes in lean body mass (LBM) and total body water (TBW), and (B) changes in fat mass (FM) and TBW after 6 months GH replacement. ○ denotes values for females and ■ denotes values for males.

only modest increments in TBW (2–4). A strong correlation was observed between TBW and LBM both before and during GH replacement suggesting that their overall relationship is proportional both in GHD and with physiological replacement of GH. Changes in these variables with treatment correlated less strongly, with, in particular, a marked heterogeneity of individual responsiveness of TBW change; this variable was reduced after treatment in some instances (Fig. 3) suggesting that factors other than TBW may also contribute to the LBM changes. None of the patients in whom TBW decreased with treatment had an identifiable explanation such as incipient cardiac or renal failure, diabetes mellitus or drug-related effects. Nonetheless, the possibility of technical problems with measurement of TBW in these individuals cannot be excluded and would provide one conceivable explanation as to why TBW did not increase significantly with treatment in this patient cohort.

The low-dose GH titration against age-adjusted IGF-I approach used in this study resulted in more modest increments in IGF-I, to within +2 and –2 s.d. of the age-adjusted population mean, compared with

traditionally used weight-based GH dosing regimens. Indeed, historically, some patients with GHD receiving GH replacement may have been over-treated as evidenced by supra-physiological IGF-I levels (21). IGF-I monitoring is widely used to aid dose titration of GH replacement to minimise the risk of over-treatment. By definition, some patients will clearly have 'true normal' GH status when their IGF-I is in the lower half of the normal range. To date, no data are available to quantify risk of under-treatment of such patients. Moreover, the optimal target IGF-I during GH replacement remains unclear (22, 23). In our study, IGF-I levels rose in all patients and three of the four patients who failed to achieve IGF-I levels into the normal range nonetheless achieved substantial increments in IGF-I SDS of between +2.53 and +7.39 (Fig. 1).

The recognition that GH has antinatriuretic actions has been established for many years (24). The sodium retention and increased TBW observed in subjects with acromegaly (25) and in the early studies of GH replacement for longitudinal growth in childhood (26) demonstrated a clear pharmacological effect of GH on fluid homeostasis. Whether these antinatriuretic actions contribute physiologically to the established effects of GH on LBM are not known. Two early studies using indirect methods of measurement of body composition (27, 28) concluded that the decreased conductance during bioelectrical impedance found in GHD adults reflects reduced total and extracellular water (ECW) content out of proportion to an independent estimate of fat free mass (FFM). The indirect techniques used in these studies did not take account of components of FFM such as bone mineral content and body cell mass or reduced conductance through the skin by the reduced skin sweat content in GHD. A later study investigated the relationship between ECW and fat-free soft tissue mass (FFSTM), using direct measurement methods in GHD adults, compared with normal control subjects (29). This study demonstrated that although FFSTM was clearly reduced, the ECW proportions of FFSTM were similar in the GHD and normal groups. A further study assessed hydration state by bioelectrical impedance, and body composition by computerised tomography and DEXA in GHD adults (30). This study demonstrated normal lean tissue hydration in untreated GHD adults but also alterations in lean tissue hydration during long-term GH replacement, which they attributed to over-hydration due to supraphysiological GH dosing regimens. Our study suggests that the overall relationship between LBM and TBW is not different before compared with during low-dose GH replacement, but that the increment in LBM cannot be explained solely by TBW changes. Furthermore, these data support the suggestion that alterations in lean tissue hydration in earlier studies may have reflected supra-physiological GH dosing effects.

Impairment in QOL is a prominent feature of GHD in adulthood (1). However, a dichotomy is evident based

on the observation that in the untreated state, some GHD adults report severe impairment in QOL and some claim QOL to be normal (31). In particular, significant impairment in QOL is less frequently observed in adults with childhood-onset GHD (32). The areas of QOL most likely to be affected by GHD are energy and vitality (5). Moreover, the degree of improvement in QOL is proportional to the deviation from normality at the outset (6) and this observation is equally applicable to adults with childhood onset GHD (33) and unusual cohorts such as cancer survivors with GHD (34). Although extensive data are now available documenting the impaired QOL associated with adult GHD, the mechanisms underlying this observation remain poorly understood. These mechanisms appear to have a rapid onset of action, as most of the QOL improvement is observed to occur rapidly in affected GHD adults, within the first three months of GH replacement (16, 33). The suggestion that abnormal body composition may be responsible for the QOL deficit would fit in terms of time-scale of response to GH replacement. However, our study identified no correlation between QOL and direct measures of body composition, suggesting that improvement in body composition alone is not responsible for GH effects on QOL. Specific receptors for GH have been identified in several areas of the human brain (35) with the highest concentration being found in the choroid plexus, followed by the pituitary, hippocampus, putamen, hypothalamus and thalamus (35, 36). These represent areas of potential access into the central nervous system, and key limbic system structures known to be pivotal for the physiology of vegetative functions and in the control of behaviour, emotion and motivation, suggesting a possible central role for GH effects on QOL.

In conclusion, using low-dose titration of GH aiming for an IGF-I SDS broadly within the age-related reference range, we have demonstrated efficacy of GH replacement with significant improvements in body composition and QOL in line with previous studies. Individual changes in LBM occurring with physiologically replaced GH correlate weakly with changes in TBW suggesting that factors other than TBW contribute to the LBM changes. Improved QOL with GH replacement is not explained by favourable changes in body composition.

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