The effects of two doses of replacement growth hormone on the biochemical, body composition and psychological profiles of growth hormone-deficient adults

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Abstract

This study examined the effects of growth hormone (GH) replacement on the insulin-like growth factor-I (IGF-I), body composition and psychological profiles of GH-deficient adults. We assessed whether two doses of GH produced different effects on these variables and whether patients who, at the end of the study chose to remain on long-term GH replacement responded differently to those who chose to abandon therapy. Forty-two adults (aged 42.9 ± 1.9 years (mean ± S.E.M.)) with documented GH deficiency entered two studies (24 in study 1, 18 in study 2). Biochemical, body composition and psychological profiles were assessed at baseline, and after 6 months and 1 year. Psychological assessments were performed using well-established, independent, validated ‘Quality of Life’ questionnaires (Nottingham Health Profile (NHP) and the Psychological General Well-Being Schedule (PGWB)). The study protocols differed only in the doses of growth hormone (0.024 mg/kg per day and 0.012 mg/kg per day respectively). Comparison between studies and between patients eventually continuing and abandoning GH therapy was performed.

GH replacement was associated with significant changes in IGF-I levels (P < 0.001), body composition (P < 0.01) and self-perceived well-being (NHP, P < 0.01; PGWB, P < 0.01). The higher dose of GH produced a greater IGF-I response than the lower dosage (44.6 ± 7.3 vs 26.2 ± 3.6 nmol/l, P < 0.05), but no better psychological response (NHP, P = 0.22; PGWB, P = 0.23). Those deciding to continue replacement therapy did not respond differently to those choosing to abandon therapy with respect to IGF-I (P = 0.72), body composition (P = 0.38) and psychological assessment (NHP, P = 0.29; PGWB, P = 0.24).

GH replacement in GH-deficient adults was associated with significant improvements in self-perceived well-being as well as changes in body composition and other variables. This improvement was similar at two different doses of replacement GH. Those patients electing to continue on long-term replacement did not achieve a demonstrably different psychological, body composition or biochemical benefit to those patients deciding to discontinue replacement.

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Introduction

The availability of recombinant human growth hormone (GH) has led to an increase in both clinical and research uses of this anabolic hormone. The effects of GH replacement on metabolism and body composition in GH-deficient adults are well established (1), with increases occurring in lean tissue, bone mineral density and reduction in fat mass. Many of the actions of GH are mediated through insulin-like growth factor-I (IGF-I) (2, 3), and GH replacement is associated with an increase in the circulating level of serum IGF-I.

Decreased psychological well-being has been reported in hypopituitary adults despite replacement of all hormone deficiencies with the exception of GH (4, 5). Evidence suggests that the severity of psychological distress experienced by these patients is associated with the duration of GH deficiency (6). Several studies have addressed the effects of GH replacement on the psychological profiles of adults with GH deficiency (6–11). These studies have produced inconsistent results with improvements in subjective well-being occurring in some studies but no benefit reported in others (7, 9–11).

In many endocrine units GH-deficient adults are now offered a short trial of GH replacement following which the patient and clinicians make a decision as to whether continuing GH replacement is appropriate. The factors

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which influence this decision are many. A self-perceived psychological benefit is considered one of the most important influencing features (9). Methods of assessment of patients’ psychological profiles are thus important and may further our understanding of who may benefit from long-term GH replacement and which patients are likely to wish to continue on long-term treatment. As GH replacement is expensive, there are strong health economic reasons to find the lowest effective dose.

We have completed a retrospective analysis of two consecutive double-blind placebo-controlled trials of GH replacement in GH-deficient adults (12–18). The trials ran consecutively with study 2 beginning immediately on completion of study 1. No patients were included in both trials. Inclusion criteria were: age 18–55 years, GH deficiency (defined as a peak serum GH <3 mU/l on insulin tolerance testing, producing a nadir plasma glucose <2.2 mmol/l), and stable replacement of all other pituitary deficiencies (including sex steroids). All patients were in good general health. The studies were double-blind placebo-controlled for the first six months and ‘open label’ with all patients receiving GH for the second six months. GH (Genotropin, Pharmacia Ltd, Milton Keynes, Bucks, UK) or placebo was administered as a nightly subcutaneous injection. The studies differed in the GH dosage used with patients receiving either 0.024 mg/kg per day (0.50 U/kg per week, study 1) or 0.012 mg/kg per day (0.25 U/kg per week, study 2). The patients in each study were similar in terms of age, weight and height, as well as duration of GH deficiency and baseline circulating IGF-I concentration. The studies were approved by the Ethics Committee, Guys and St Thomas’ NHS Trust and all patients provided written informed consent.

In each study 50% of the patients were randomized to receive placebo for the first 6 months. Data are not available for four patients in study 1. All analyses refer to the 38 patients who completed the studies. Of these there were 21 men and 17 women, aged 42.9±1.9 (mean±SEM) years. At the end of the trials, patients were given the option to continue or abandon GH replacement. Eighteen (48%) of 38 decided to continue on long-term GH replacement (8 from study 1, 10 from study 2). Of these 18, 10 (55%) received GH in the first 6 months of the study.

The patients’ responses to two well-established questionnaires that assess general self-perceived well-being, the Nottingham Health Profile (NHP) and the Psychological General Well-Being Schedule (PGWB) were performed at baseline, and again following 6 months placebo or GH, and finally 6 months after commencement of the open label phase of GH replacement. The NHP is designed to measure perceived health problems and the extent to which such problems affect daily activities. It asks about physical, emotional and social distress (19). It yields both an overall score and sub-section scores. The sub-sections assess subjects’ perception of their sleep, energy, emotional reaction, social isolation, physical mobility and pain. Subjects answer yes or no to statements concerned with each category. The questions are weighted, a score of zero indicates that the subject perceives no problem in that category. The total score is 600, with 100 the maximum score for each subset. The PGWB is a measure of mood or emotional state reflecting subjective well-being (20). Six affective states are analysed as subsets: anxiety, depressed mood, positive well-being, self-control, general health and vitality. Response options for questions in each subset are scored on a scale of 0 to 5. A sense of well-being is given the score 5, with a sense of distress receiving the lowest score, 0. The score range is thus 0–110 overall and varies in the sub-sections from 0 to 15, 20 or 25.

Body composition was assessed in all patients at baseline, with measurement of height, weight, abdominal skin-fold thickness and waist/hip ratio. Measurements of these variables were repeated after 6 months and 1 year. Serum total IGF-I was measured by radioimmunoassay after an ethanol-hydrochloric acid extraction (21) (within assay coefficient of variation, 7%) at baseline and thereafter at 6 months and 1 year.

**Patients and methods**

A total of 42 adults entered two studies (24 in study 1, 18 in study 2) of GH replacement conducted in St Thomas’ Hospital between 1989 and 1993. The trials ran consecutively with study 2 beginning immediately on completion of study 1. No patients were included in both trials. Inclusion criteria were: age 18–55 years, GH deficiency (defined as a peak serum GH <3 mU/l on insulin tolerance testing, producing a nadir plasma glucose <2.2 mmol/l), and stable replacement of all other pituitary deficiencies (including sex steroids). All patients were in good general health. The studies were double-blind placebo-controlled for the first six months and ‘open label’ with all patients receiving GH for the second six months. GH (Genotropin, Pharmacia Ltd, Milton Keynes, Bucks, UK) or placebo was administered as a nightly subcutaneous injection. The studies differed in the GH dosage used with patients receiving either 0.024 mg/kg per day (0.50 U/kg per week, study 1) or 0.012 mg/kg per day (0.25 U/kg per week, study 2). The patients in each study were similar in terms of age, weight and height, as well as duration of GH deficiency and baseline circulating IGF-I concentration. The studies were approved by the Ethics Committee, Guys and St Thomas’ NHS Trust and all patients provided written informed consent.

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**Statistical analyses**

Statistical analyses were performed using personal computer spreadsheet software (Microsoft Excel 5.0, Microsoft Corporation, Redmond, WA, USA). Simple statistical analysis is presented with means±SEM. Paired analysis between groups for psychological assessment was performed using the Mann–Whitney U test. P values of less than 0.05 were considered significant. IGF-I and body composition data were analysed using two-tailed t-tests and P values of less than 0.05 were considered significant.
Results

The results are summarized in Figs 1–4 and Tables 1 and 2. Analyses refer to the initial 6 months of active GH replacement, whether this period was during the randomized or open label phase of the study. Absolute values at baseline were compared with those after 6 months GH treatment and, where appropriate, changes in values over the 6-month period were compared between groups.

GH treatment was well tolerated in all patients and no subject withdrew from either study as a result of adverse effects. Fluid retention did occur in many patients, particularly at the higher replacement dose. No relationship was seen between adverse events and the desire to continue GH, neither was the overall perceived psychological well-being influenced by the occurrence of adverse events.

In addition, no relationship existed between the underlying disease responsible for GH deficiency and the baseline psychological score for either the NHP or PGWB. Analysis of the placebo phase data demonstrated that placebo treatment had no significant effect on body composition or IGF-I levels. There was a trend towards a ‘trial effect’ of improvement in the patients’ self-perceived well-being during the placebo phase only in the PGWB assessment (overall score 75.6 ± 4.1 at baseline vs 86.1 ± 2.6 at 6 months, *P* <0.05).

Table 1 Baseline characteristics of those eventually continuing compared with those not-continuing long term GH replacement on completion of the trials.

<table>
<thead>
<tr>
<th></th>
<th>Patients continuing</th>
<th>Patients not-continuing</th>
<th><em>P</em> value</th>
</tr>
</thead>
<tbody>
<tr>
<td>IGF-I (nmol/l)</td>
<td>15.3 ± 2.1</td>
<td>14.8 ± 1.7</td>
<td>NS</td>
</tr>
<tr>
<td>Abdominal skin fold (cm)</td>
<td>41.9 ± 2.4</td>
<td>40.2 ± 4.9</td>
<td>NS</td>
</tr>
<tr>
<td>Waist/hip ratio</td>
<td>0.96 ± 0.002</td>
<td>0.95 ± 0.002</td>
<td>NS</td>
</tr>
<tr>
<td>NHP (average)</td>
<td>16.4 ± 4.1</td>
<td>13.5 ± 2.7</td>
<td>NS</td>
</tr>
<tr>
<td>PGWB (overall)</td>
<td>80.6 ± 2.9</td>
<td>70.4 ± 4.1</td>
<td>&lt;0.05</td>
</tr>
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</table>

NS, not significant.
average NHP score was not significantly altered following 6 months placebo (12.4±2.6 vs 8.9±1.9, baseline vs 6 months).

The baseline IGF-I concentrations were similar in the two studies (12.8±3.0 and 16.2±1.2 nmol/l, P=0.22, for study 1 and study 2 respectively). Twenty percent of the patients in study 1 and 11% of those in study 2 had a baseline serum IGF-I below the lower limit of the range for healthy subjects in our hospital (18.3–98.8, 14.6–73.2, 12.8–62.2 and 11.0–43.9 nmol/l for age ranges 17–20, 21–30, 31–40 and 41–60 years respectively). GH replacement resulted in an increase in IGF-I levels in all patients, and after 6 months the IGF-I concentrations were 57.4±9.1 vs 42.4±3.4 nmol/l (studies 1 and 2 respectively). These increases resulted in circulating IGF-I concentrations above the control range in 45% and 24% of patients (studies 1 and 2 respectively). Similarly, the baseline IGF-I levels were similar in those ultimately continuing and those not-continuing long-term GH (Table 1). Following 6 months GH treatment, the IGF-I levels were similarly increased in patients opting to continue and those discontinuing therapy (50.5±4.5 and 45.2±6.3 nmol/l respectively). Thirty-three percent of those who elected to continue and 30% of subjects who abandoned GH replacement had an IGF-I level in excess of the aged-matched range following GH therapy.

GH replacement resulted in the expected significant changes in body composition, decreases occurring in waist/hip ratio and skin fold thickness (Table 2). In addition, GH therapy was associated with an improvement in self-perceived well-being as assessed using both the NHP and the PGWB. The average score in the NHP assessment decreased (14.9±2.3 vs 4.9±1.1, P<0.01) and the overall PGWB score increased significantly (74.9±2.6 vs 85.8±2.2, P<0.001) following 6 months GH treatment. Values in most sub-categories of both psychological assessments also changed, with scores indicating improvement in self-perceived quality of life (Figs 1 and 2).

The baseline IGF-I and body composition during initial 6 months of GH therapy (n =38). These are combined data and include all patients from both studies.

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>6 months</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>IGF-I (nmol/l)</td>
<td>15.0 ± 1.3</td>
<td>47.6 ± 4.0</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Abdominal skin fold (cm)</td>
<td>41.0 ± 2.8</td>
<td>32.0 ± 2.2</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Waist/hip ratio</td>
<td>0.96 ± 0.01</td>
<td>0.93 ± 0.01</td>
<td>&lt;0.01</td>
</tr>
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</table>

Comparison of the two studies (Fig. 3) demonstrated the expected difference in IGF-I response to the two doses of GH but no significant differences were seen in the body composition changes. Similarly no significant
Figure 3 Comparison of the changes in IGF-I concentration, body composition and psychological profile between the two studies during the first 6 months of GH therapy. Study 1: GH at 0.024 mg/kg per day (open bars). Study 2: GH at 0.012 mg/kg per day (solid bars). *P<0.05, unpaired two-tailed t-test. Note: waist/hip ratio amplified 10-fold.

Figure 4 Comparison of the changes in IGF-I concentration, body composition and psychological profile between those continuing (open bars) and those not-continuing (solid bars) GH treatment on completion of the studies. Note: waist/hip ratio amplified 10-fold.
differences were observed in the changes in the overall psychological assessments (nor in any of their sub-
categories) between the two replacement dosages.

No relationship existed between the underlying cause of GH deficiency and the desire to either continue or abandon long-term GH replacement. At the end of the 12-month trials, there was no evidence that those electing to continue on GH replacement differed in their responses (IGF-I level, body composition or psychological profile) from those deciding to stop therapy (Fig. 4). The baseline characteristics of those continuing and those discontinuing GH replacement were similar with respect to all variables with the exception of the average PGWB score, which was significantly higher \((P<0.05; \text{indicating perceived better quality of life})\) in those finally deciding to continue GH therapy (Table 1).

Discussion
The case for GH replacement in adults has not yet been unequivocally established. Some ‘purchasers’ of health care are questioning the benefits, and the costs remain high. The physical benefits of such replacement are now established without question (1): less well-defined, however, are the effects on well-being, the patient’s psychological profile and perceived quality of life. These features may be influential in the patient’s and the physician advisor’s decision to continue with long-term GH replacement.

The psychological assessment of patients undergoing GH replacement in a true double-blind placebo-controlled fashion is difficult. Both the patient and physician may associate the occurrence of recognised features of GH replacement, such as peripheral oedema and joint pain, with ‘active’ GH treatment. In addition all patients are aware that during the second 6-month period of the trials, they are receiving GH. These features may bias the psychological assessment and must be taken into account when interpreting the results from such trials.

By combining the results from two independent trials using identical protocols, these data provide strong statistical evidence of an improvement in self-perceived psychological well-being (quality of life) associated with GH replacement (as assessed using standardized questionnaires). Not surprisingly, a modest ‘trial’ effect was seen in the placebo group when scoring quality of life with the PGWB (but not the NHP).

The improvements for those on GH occurred over a 6-month period. The perceived psychological benefits were observed in almost all sub-categories of both independent quality-of-life instruments, with the exception of pain, self control and sleep. The trend was for an improvement in score in the latter two categories with a worsening in the pain category, probably reflecting the joint and muscle discomfort which is a feature of GH therapy used at these doses. The largest improvements in quality of life were in the categories of vitality, general health, emotional reaction, energy and social isolation (similar to the findings of McGauley (9) and Holmes & Shalet (22)).

These trials were conducted consecutively and were designed to record the psychological changes seen with GH replacement as well as to quantitate any placebo effect. Although the studies were not specifically structured to assess the effects of the different doses of GH, we feel that the otherwise identical double-blind placebo-controlled parallel-group protocols using objective well-validated questionnaires, identical surroundings and similar research personnel, allow valid comparison of the results. The psychological benefits recorded were similar despite different doses of GH. This is important from a health economic view as the lower dose was half the higher dose. These data suggest that an improvement in self-perceived well-being and quality of life may not be dose dependent, or may occur at a dose lower than 0.012 mg/kg per day, with higher doses contributing no additional benefit. It is also possible that current methods of psychological assessment in studies such as these (NHP, PGWB) are not sufficiently sensitive to detect subtle but important changes in perceived well-being between the doses. The remaining possibility is that the demonstrated psychological benefit is an all-or-nothing effect associated with GH replacement, and independent of replacement dosage.

The mechanisms responsible for the improvement in well-being remain unknown. GH replacement in GH-deficient adults has been shown to alter the levels of vasoactive intestinal polypeptide and the dopamine metabolite, homovanillic acid, as well as elevating \(\beta\)-endorphin levels in cerebrospinal fluid but whether these changes are responsible for improvement in mood and well-being is not known (23). Alternatively, GH and IGF-I may have direct effects on the nervous system but the additional increase in serum IGF-I seen at the higher dose of GH replacement in this study did not produce a greater psychological benefit.

There were no significant differences in the psychological changes between those opting to continue therapy compared with those who abandoned GH therapy. This suggests that assessment using the NHP and PGWB is not useful in the prediction of patients who ultimately opt for long-term replacement. The features affecting the patient’s decision are many and complex and it has been suggested that a perceived improvement in well-being is a major influence (9). In the patients whom we report here, the improvement in well-being following GH therapy was no greater in those deciding to continue with therapy. On the one hand this may indicate that change in well-being alone is not as powerful an influence as was previously thought, while on the other hand it may highlight deficiencies in the current methods of psychological assessment such that the NHP and PGWP questionnaires are not sufficiently
sensitive to detect changes that may influence a patient’s decision to remain on GH.

It has been suggested that those who opt to remain on long-term GH replacement are the patients with the most severe GH deficiency (22). We are unable to address this issue since in this study all patients had severe GH deficiency. The baseline characteristics (in terms of biochemical and body composition) of those abandoning treatment were similar to those continuing and it was only the baseline PGWB which in any way related to the patients’ decision, in that those continuing began with a greater sense of general well-being than those abandoning therapy. The significance of this is doubtful since, unlike most other occasions, the NHP scores were in the opposite direction.

The dose of GH (0.024 mg/kg per day) used in study 1 is higher than currently used for replacement in the GH-deficient adult. High doses of GH are recognised to result in adverse effects, including fluid retention, arthralgia, hyperinsulinaemia as well as serum IGF-I concentrations in excess of those observed in healthy aged-matched controls (24). Hyperinsulinaemia may increase the risk of cardiovascular complications (25) and ‘excessive’ GH replacement may result in the clinical features of acromegaly. Evidence suggests that those patients most at risk from adverse effects of GH replacement are older, more obese, with a greater GH response on provocative testing and the largest IGF-I rise following GH treatment (26).

The GH doses used in this study resulted in excessive serum IGF-I concentrations in approximately 50% and 25% of subjects in study 1 and study 2 respectively. If one of the aims of GH replacement is to ‘normalise’ circulating IGF-I, the higher dose was clearly excessive, whereas the lower dose resulted in a ‘normal’ circulating IGF-I level in 75% of patients. A study of GH replacement in 233 hypopituitary adults, with GH doses ranging from 0.08–0.3 IU/kg per week resulted in fluid retention (37.4%), arthralgia (19.1%) and muscle pains (15.7%) in the first 6 months of treatment (27). In this meta-analysis the authors felt that a GH dose tailored to individual patients with normalisation of IGF-I concentrations and avoidance of adverse effects is the most appropriate approach to GH replacement in the GH-deficient adult.

In summary the results from these studies of GH replacement in GH-deficient adults demonstrate that GH replacement is associated with a self-perceived improvement in well-being. This effect occurs similarly at two different doses of GH. Replacement of GH is responsible for a rise in IGF-I level which is, at least partly, dose dependent and over a 6-month period of therapy significant changes occur in body composition profiles. Patients who wish to stay on GH replacement permanently do not have a demonstrably different response in terms of IGF-I, body composition or psychological profiles, compared with those patients deciding to cease therapy; however those who opted to continue on GH had a better sense of psychological well-being, as assessed by one of the two psychological instruments used prior to commencement of GH replacement.

References
Two GH replacement doses in GH-deficient adults


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