Low-dose GH replacement improves the adverse lipid profile associated with the adult GH deficiency syndrome

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Summary
OBJECTIVE Adult growth hormone deficiency (AGHD) is associated with an adverse lipid profile. The majority of previous studies of GH replacement have used supraphysiological doses and reported favourable changes in the lipid profile. Whether this beneficial effect is the result of pharmacological GH therapy, or occurs in response to low-dose GH replacement aimed at normalization of the serum IGF-I, has not been fully elucidated.

STUDY DESIGN We studied 67 patients with GH deficiency using a low-dose individualized GH replacement regimen. GH was commenced at a dose of 0.27 mg/day and the GH dose titrated until the serum IGF-I was normalized. Serum lipids were assessed at baseline, 12 and 24 months.

RESULTS A reduction in total cholesterol (TC) was observed at 12 (6.01 vs. 5.77 mmol, \( P = 0.04 \)) and 24 months (6.01 vs. 5.56, \( P = 0.09 \)). The reduction in LDL cholesterol (LDLC) failed to reach significance at 12 months (3.97 vs. 3.8, \( P = 0.09 \)), but was significant at 24 months (3.97 vs. 3.50, \( P = 0.02 \)). Levels of HDLC did not change significantly at 12 or 24 months. Significant improvements in the TC/LDLC ratio were observed at both 12 (5.68 vs. 5.29, \( P = 0.01 \)) and 24 months (5.68 vs. 4.86, \( P = 0.007 \)). A significant fall in triglycerides (TG) was present at 12 months (2.07 vs. 1.83, \( P = 0.01 \)), and was maintained at 24 months, but was no longer significant (2.07 vs. 1.89, \( P = 0.28 \)). At 12 months there was no correlation between improvements in lipid parameters and either the change in IGF-I SD score or the GH dose. Using multivariate analysis the change in TC, LDLC and the TC/LDLC ratio with 12 months GH replacement were determined by the baseline TC, LDLC and TC/LDLC levels (\( R^2 = 0.18, P = 0.004; R^2 = 0.20, P = 0.006; \) and \( R^2 = 0.33, P = 0.0001 \)), respectively.

CONCLUSIONS Low-dose individualized GH replacement aimed at normalization of the serum IGF-I is associated with significant improvements in TC, LDLC, TGs and the TC/LDLC ratio. The greatest improvements are observed in patients with the most adverse lipid profiles at baseline. Improvements are independent of changes in the IGF-I SDS and GH dose.

Introduction
Hypopituitarism is associated with an increase in mortality, with a relative risk of between 1.2 and 2.17 (Rosen & Bengtsson, 1990; Bates et al., 1996; Bulow et al., 1997; Tomlinson et al. 2001). It has been proposed that GH deficiency is in part responsible for this excess (Rosen & Bengtsson, 1990). The adult growth hormone deficiency (AGHD) syndrome is a recognized clinical entity characterized by an increase in fat mass, reduced muscle mass, osteopenia, an adverse lipid profile and impaired quality of life (de Boer et al., 1995; Carroll et al., 1998). A number of cardiovascular risk factors are present in the adult GH deficiency syndrome, including an increased waist-to-hip ratio, adverse lipid profile, insulin resistance, increased procoagulant factors and impaired endothelial function and integrity (Markussis et al., 1992; Johannson et al., 1994; Weaver et al., 1995; Hew et al., 1996; Colas et al., 1998; Evans et al., 1999; Prezler et al., 1999).

The adverse lipid profile is characterized by a raised total cholesterol (TC) and low-density lipoprotein cholesterol (LDLC); Markussis et al., 1992; Cuneo et al., 1993; de Boer et al., 1994). A raised triglyceride (TG) level and reduced high-density lipoprotein cholesterol (HDL) have been reported, but less consistently (Cuneo et al., 1993; Rosen et al., 1993). The majority of short-term studies of GH replacement observed favourable changes in the lipid profile. The most frequent finding being a reduction in TC and LDLC, with no significant change in either HDLC or TG levels. A reduction is also observed in the LDLC/TG ratio and apolipoprotein B levels (Salomon et al., 1989; Whitehead et al., 1992; Cuneo et al., 1993; Russell Jones et al., 1994; Garry et al., 1996).

Current practice has moved away from the use of weight- and surface area-based dosing regimens that have resulted in...
supraphysiological IGF-I levels, and towards the individual optimization of the GH dose according to the serum IGF-I level. With one exception (Florakis et al., 2000), all of the current studies in the literature demonstrating beneficial effects of GH therapy on the lipid profile, have used weight-based GH replacement regimens. These dosing regimens have resulted in a mean GH dose (range 0.67–1.63 mg/day) that is far higher than that associated with an individually optimized dosing regimen. Whether GH retains the beneficial effects on serum lipids with this low-dose regimen, and which patient characteristics best predict outcome, are not fully clarified. We therefore undertook an open treatment study in adults with GH deficiency, and examined the effect of individualized GH dosing on the lipid profile.

Subjects and methods

Patients

The study cohort comprised 67 GH-deficient adults of mean age 37.5 ± 14.7 years (37 were female, with a mean BMI of 29.5 ± 7.8 kg/m²). Thirty-five patients were diagnosed as GH-deficient during childhood (childhood-onset, CO), and 32 acquired GH deficiency during adult life (adult-onset, AO). GH deficiency was diagnosed on the basis of provocative tests of GH reserve. All patients with isolated GH deficiency underwent two provocative tests. All but seven of the patients were subject to insulin induced hypoglycaemia (ITT), the arginine and glucagon stimulation test were used if the ITT was contraindicated, or a second test required. A peak GH response of less than 9 mU/l was regarded as consistent with GH deficiency. Twenty-three patients had isolated GH deficiency and the remaining 44 varying degrees of hypopituitarism. The latter patients were on stable replacement with corticosteroids, thyroxine and sex steroids for the duration of the study. In the female cohort, 19 patients were gonadotrophin-deficient, 16 of whom were on oestrogen replacement therapy. The cohort included only one post-menopausal female who was gonadotrophin replete who did not take oestrogen replacement therapy. The cohort included only one post-menopausal female who was gonadotrophin replete who did not take oestrogen replacement therapy. The cohort included only one post-menopausal female who was gonadotrophin replete who did not take oestrogen replacement therapy. The cohort included only one post-menopausal female who was gonadotrophin replete who did not take oestrogen replacement therapy. The cohort included only one post-menopausal female who was gonadotrophin replete who did not take oestrogen replacement therapy. The cohort included only one post-menopausal female who was gonadotrophin replete who did not take oestrogen replacement therapy.

Study protocol

The design of the study was an open treatment trial of GH replacement. Before commencing GH replacement the patients underwent a physical examination and blood was drawn for measurement of IGF-I, and a serum sample stored at –80°C for analysis of the lipid profile subsequently. Approximately 50% of the samples, at each of the three time points (0, 12 and 24 months), were fasting. The patients were taught to self-inject GH using an automated pen device (Genotropin pen, Pharmacia & Upjohn, Milton Keynes, UK), and when competent were commenced on GH at a dose of 0.27 mg/day. 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 standard deviations (SD) of the age adjusted mean in the absence of GH-related side-effects. Further serum samples were stored at 12 months in all patients, and 24 months in the 32 patients who had completed 2 years of GH therapy. Serum samples from all subjects, at all three time points were analysed in a single batch for TC, HDLC, LDLC, TGs, Apo-AI and Apo-B. An additional measure of body fat mass was obtained at baseline and 12 months in a subset of patients (n = 44) using a bioelectrical impedance monitor (Tanita TBF-305, Uxbridge, UK). Ethical approval for this study was granted by the South Manchester Local Research Ethics Committee and written consent was obtained from each subject.

Assays

Cholesterol, triglycerides and direct HDLC, apoA1 and apoB assays were carried out on a Bayer ADVIA 1650 chemistry analyser (Bayer Diagnostics, Newbury, Berks, UK) using proprietary methods. The cholesterol and triglyceride methods, respectively, employ cholesterol oxidase and lipoprotein lipase/glycerol kinase. The HDLC method measures cholesterol by polyethylene glycol (PEG)-linked cholesterol esterase and oxidase after serum incubation with sulphated cyclodextin buffer. LDL was calculated using the Friedewald equation. LDL was not determined if serum TGs were greater than 4 mmol/l. ApoA1 and apoB were determined by endpoint immunoturbidimetry, analytical coefficients of variation (CV%) = 4.0% at 920 mg/l for apoA1 and 3.9% at 970 mg/l for apoB. Serum samples were analysed for IGF-I, using a radioimmunoassay (RIA), following separation of IGF-I from IGF-BPs by acid/albumin extraction. Dow(-1)-3)-IGF-I was used as radioligand to minimize interference of IGF-BPs in the extract. The intra- and interassay coefficients of variation were 10% and 3%, 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.

Statistics

Analysis of the data was performed on an intention to treat basis. The data are presented as median and ranges, or mean ± SD.
Differences between paired data were examined using the paired t-test or Wilcoxon signed rank test for parametric and non-parametric data, respectively. Non-paired data were compared using the t-test or the Mann–Whitney rank sum test for parametric and non-parametric data, respectively. Changes in data over the three time points were examined using the Friedman repeated measure analysis of variance on ranks. Comparison of the number of patients with values above, and below, the 5th and 95th percentiles was performed using the Chi-squared test. Correlations were sought using Pearson’s test. Stepwise multiple regression was used to examine determinants of the observed changes in lipid parameters. A P-value of < 0.05 was deemed significant.

Results

GH treatment

The IGF-I SDS at baseline, 12 and 24 months was –2.47 ± 2.06, respectively. At baseline, 12 and 24 months, only 14.9 and 15.6% of patients, respectively, had IGF-I SD values of less than –2 at 12 and 24 months, respectively. The mean GH replacement dosage at 12 and 24 months was 0.36 ± 0.18 mg/day (P = 0.005). Similar, but non-significant differences were observed for LDLC (4.23 ± 1.24 mmol/l, P = 0.016) and HDLC levels (1.17 ± 0.95 mmol/l, P = 0.019) compared with baseline. As a result of the higher LDLC and HDLC levels in females, the TC/HDLC ratio was not significantly different between males and females (5.76 ± 5.62; P = 0.72). Comparison with age-related reference ranges revealed 56.8% of females and 20% of males to have a total cholesterol level greater than the 95th percentile (F vs. M; P = 0.005). Similar, but non-significant differences were observed for HDLC (F vs. M, 4.86 ± 2.66; P = 0.11) and TG (F vs. M, 4.86 ± 23.3%; P = 0.06). No significant difference in the proportion of patients of each gender with HDLC values below the 5th percentile was detected (F vs. M, 10.8 ± 16.7%; P = 0.50).

Body composition

No significant changes in either body mass index (BMI; 29.5 ± 7.8 vs. 28.5 ± 5.8 vs. 28.5 ± 7.7 kg/m²) or WHR (0.89 ± 0.08 vs. 0.88 ± 0.082 vs. 0.889 ± 0.094) occurred during the 24 months of GH replacement. There was no significant difference in BMI between the female and male subgroups at baseline, 12, or 24 months (data not shown). In the subset of patients with bioimpedence data (n = 44) no significant change in fat mass (FM; 31.8 ± 17.8 vs. 32.6 ± 16.8 kg; P = 0.25), percentage fat mass (%FM, 38.0 ± 15.6 vs. 38.2 ± 14.5%; P = 0.30), or lean body mass (LBM; 47.6 ± 17.5 vs. 48.2 ± 16.8 kg; P = 0.22) was observed between baseline and 12 months. Analysis after stratification for gender and onset of GH deficiency revealed no significant changes in the body composition of females, males, or adult-onset patients (data not shown). A small, but significant increase in FM (22.0 ± 12.5 vs. 24.6 ± 13.1 kg; P = 0.04), but not %FM or LBM, was detected in the childhood-onset patients at 12 months.

Baseline lipids (Table 1)

At baseline, females were observed to have significantly higher TC (6.29 ± 5.47 mmol/l, P = 0.009), LDLC (4.23 ± 3.6 mmol/l, P = 0.016) and HDLC levels (1.17 ± 0.95 mmol/l, P = 0.019) than males. As a result of the higher LDLC and HDLC levels in females, the TC/HDLC ratio was not significant different between males and females (5.76 ± 5.62; P = 0.72). Comparison with age-related reference ranges revealed 56.8% of females and 20% of males to have a total cholesterol level greater than the 95th percentile (F vs. M; P = 0.005). Similar, but non-significant differences were observed for LDLC (F vs. M, 4.86 ± 2.66; P = 0.11) and TG (F vs. M, 4.86 ± 23.3%; P = 0.06). No significant difference in the proportion of patients of each gender with HDLC values below the 5th percentile was detected (F vs. M, 10.8 ± 16.7%; P = 0.50).

Table 1 Changes in serum lipids with low-dose GH replacement in the cohort overall and in a subset with values at all three time points

<table>
<thead>
<tr>
<th></th>
<th>All patients</th>
<th>Subset</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Baseline</td>
<td>12 months</td>
<td>24 months</td>
<td>Baseline</td>
</tr>
<tr>
<td></td>
<td>(n = 67)</td>
<td>(n = 67)</td>
<td>(n = 32)</td>
<td>(n = 32)</td>
</tr>
<tr>
<td>TC</td>
<td>6.01 ± 1.29</td>
<td>5.77 ± 1.28*</td>
<td>5.56 ± 1.07</td>
<td>5.76 ± 1.25</td>
</tr>
<tr>
<td>LDLC</td>
<td>3.97 ± 1.07</td>
<td>3.80 ± 1.04</td>
<td>3.50 ± 0.89*</td>
<td>3.97 ± 1.07</td>
</tr>
<tr>
<td>HDLC</td>
<td>1.10 ± 0.27</td>
<td>1.13 ± 0.50</td>
<td>1.20 ± 0.31</td>
<td>1.12 ± 0.33</td>
</tr>
<tr>
<td>TC/HDLC ratio</td>
<td>5.68 ± 1.48</td>
<td>5.29 ± 1.35*</td>
<td>4.86 ± 1.25*</td>
<td>5.38 ± 1.47</td>
</tr>
<tr>
<td>Triglycerides</td>
<td>2.07 ± 1.25</td>
<td>1.83 ± 1.08*</td>
<td>1.89 ± 1.17</td>
<td>1.82 ± 0.91</td>
</tr>
<tr>
<td>Apolipoprotein A1</td>
<td>155 ± 38</td>
<td>150 ± 38</td>
<td>160 ± 33</td>
<td>165 ± 45</td>
</tr>
<tr>
<td>Apolipoprotein B</td>
<td>108 ± 29</td>
<td>109 ± 29</td>
<td>104 ± 25</td>
<td>105 ± 29</td>
</tr>
</tbody>
</table>

*P ≤ 0.05 compared with baseline. LDLC, low-density lipoprotein cholesterol; HDLC, high-density lipoprotein cholesterol; TC, total cholesterol.

Values in mmol/l, except apolipoproteins measured in mg/dl.

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correlate with either the serum IGF-I level or IGF-I SD and any of the lipid parameters at baseline (data not shown).

Effect of GH on the lipid profile (Table 1)

Total cholesterol (TC) When analysing the data for the cohort as a whole, GH replacement resulted in a significant fall in TC levels at 12 months (6·01 vs. 5·77 mmol/l, \( P = 0·04 \)), maintained at 24 months but no longer significant (6·01 vs. 5·56 mmol/l, \( P = 0·09 \)). The mean fall in TC, from baseline, was 0·24 and 0·45 mmol/l at 12 and 24 months, respectively. A significant correlation was observed between the change in TC at 12 months (\( \Delta TC_{12} \)) and the baseline TC value (\( R = -0·38, P = 0·001 \)). No correlation was observed between \( \Delta TC_{12} \) and either the change in IGF-I SD (\( \Delta GFI_{12} \)) or maintenance GH dose.

LDLC levels fell from 3·97 mmol/l at baseline to 3·80 (\( P = 0·09 \)) and 3·50 (\( P = 0·02 \)) mmol/l at 12 and 24 months, respectively, in the cohort as a whole. A significant correlation was demonstrated between the change in LDL-C levels at 12 months (\( \Delta LDLC_{12} \)) and the baseline LDL-C level (\( R = -0·39, P = 0·001 \)). In the subset of 32 patients with available data at all three time points, changes in LDL-C were of a similar degree, reaching significance at 12 months (\( P = 0·04 \)), but not at 24 months (\( P = 0·06 \)).

HDLC Overall, HDLC increased with GH therapy from a baseline value of 1·10 mmol/l to 1·13 (\( P = 0·63 \)) and 1·20 (\( P = 0·14 \)) mmol/l at 12 and 24 months, respectively. Non-significant changes of similar magnitude were observed in the cohort (\( n = 32 \)) with data at all time points.

TC/HDLC ratio A beneficial effect on the TC/HDLC ratio was observed with GH replacement. In the whole study cohort a significant fall from 5·68 at baseline to 5·29 (\( P = 0·01 \)) at 12 months, and 4·86 (\( P = 0·007 \)) at 24 months occurred. No significance difference in the TC/HDLC ratio occurred between 12 and 24 months of treatment. The change in the TC/HDLC ratio following 12 months of GH replacement (\( \Delta TC/HDLC_{12} \)) did not correlate with either the \( \Delta GFI_{12} \) or the maintenance GH dose; however, a strong correlation with the baseline TC/HDLC ratio was observed (\( R = -0·51, P < 0·001 \)). Significant changes in the TC/HDLC ratio were present at 12 (\( P = 0·026 \)) and 24 (\( P = 0·05 \)) months in the subgroup with data at all three time points.

Triglycerides (TGs) In the whole cohort a small, but significant fall in TGs was observed at 12 months (2·07 vs. 1·83 mmol/l, \( P = 0·01 \)). This reduction was maintained at 24 months, but was no longer significant (2·07 vs. 1·89 mmol/l, \( P = 0·28 \)). Changes in serum TG levels within the subgroup with data at all three time points did not reach significance.

Apolipoproteins In the cohort overall, no significant change was observed in the level of Apo-AI or Apo-B. Analysis of the subgroup with data available for all three time points revealed a significant fall in both Apo-AI (165 vs. 156 mg/dL, \( P = 0·05 \)) and Apo-B (105 vs. 102 mg/dL, \( P = 0·05 \)) levels at 12 months. These values then tended to increase such that no statistical difference was present between the baseline and 24 month values (Table 1).

Subgroup analysis of patients with normalized IGF-I values At the 12 months time point we performed a subgroup analysis of the changes in lipid parameters in those patients in whom the serum IGF-I was within the target range of -2.0 to +2.0 SD of the age-related mean (\( n = 54 \)). A significant fall in LDL-C (4·09 ± 1·02 vs. 3·85 ± 1·05 mmol/l, \( P = 0·05 \)), and the TC/ HDLC ratio (5·56 ± 1·57 vs. 5·21 ± 1·44 mmol/l, \( P = 0·03 \)) was observed. A trend towards a reduction in TC (6·11 ± 1·33 vs. 5·86 ± 1·34 mmol/l, \( P = 0·08 \)) and TG (1·94 ± 1·00 vs. 1·83 ± 1·18, \( P = 0·08 \)) also occurred. There was no significant change in HDLC levels (1·14 ± 0·27 vs. 1·17 ± 0·31, \( P = 0·75 \)).

Variation in response to treatment Differences in the response to 12 months GH replacement between genders, adult- and childhood-onset patients, and between patients with MPHD and IGHD were sought using univariate analysis. In the male subgroup no significant change with treatment was observed in TC, LDLC, HDLC, TG, or the TC/HDLC ratio. A significant improvement in LDL-C (\( P = 0·04 \)) and the TC/HDLC ratio (\( P = 0·006 \)), in addition to a trend towards significant improvement in TC (\( P = 0·06 \)) and TG (\( P = 0·08 \)) was observed in the female cohort (Table 2). No significant changes in any of the lipid parameters measured occurred in the childhood-onset subgroup after 12 months of GH replacement. Within the adult-onset patients, significant improvements were demonstrated in TC (\( P = 0·05 \)), LDL-C (\( P = 0·01 \)) and the TC/HDLC ratio (\( P < 0·001 \); Table 3). In the patients with IGHD (\( n = 23 \)), no significant changes occurred in any of the lipid parameters measured. However, a significant improvement in TC (6·11 vs. 5·73 mmol/l, \( P = 0·003 \)), LDL-C (4·01 vs. 3·67 mmol/l; \( P = 0·002 \)) and TG levels (2·37 vs. 2·07 mmol/l, \( P = 0·03 \)), as well as the TC/HDLC ratio (5·97 vs. 5·35, \( P < 0·0001 \)) was observed in the patients with MPHD (Table 4).

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Changes in serum lipids with low-dose GH replacement when subgrouped according to gender

Table 2

<table>
<thead>
<tr>
<th>Gender</th>
<th>Baseline (n = 37)</th>
<th>12 months (n = 37)</th>
<th>Baseline (n = 30)</th>
<th>12 months (n = 30)</th>
</tr>
</thead>
<tbody>
<tr>
<td>TC</td>
<td>6.29 ± 1.21</td>
<td>6.01 ± 1.24</td>
<td>5.67 ± 1.32</td>
<td>5.47 ± 1.28</td>
</tr>
<tr>
<td>HDLc</td>
<td>1.37 ± 0.38</td>
<td>1.21 ± 0.32</td>
<td>1.02 ± 0.24</td>
<td>1.02 ± 0.23</td>
</tr>
<tr>
<td>TC/HDL</td>
<td>4.87 ± 1.35</td>
<td>4.80 ± 1.32</td>
<td>4.71 ± 1.15</td>
<td>4.70 ± 1.14</td>
</tr>
<tr>
<td>Triglycerides</td>
<td>1.96 ± 1.03</td>
<td>1.80 ± 1.03</td>
<td>2.20 ± 1.57</td>
<td>1.86 ± 1.16</td>
</tr>
</tbody>
</table>

*P ≤ 0.05 compared with baseline: LDLc, low-density lipoprotein cholesterol; HDLc, high-density lipoprotein cholesterol; TC, total cholesterol. Values in mmol/l.

Table 3

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>Baseline (n = 32)</th>
<th>12 months (n = 32)</th>
<th>Baseline (n = 35)</th>
<th>12 months (n = 35)</th>
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</thead>
<tbody>
<tr>
<td>Adult-onset</td>
<td>6.30 ± 1.56</td>
<td>5.98 ± 1.56*</td>
<td>5.75 ± 0.94</td>
<td>5.57 ± 0.93</td>
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<tr>
<td>Childhood-onset</td>
<td>4.12 ± 1.24</td>
<td>3.79 ± 1.21*</td>
<td>3.89 ± 0.82</td>
<td>3.80 ± 0.88</td>
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<tr>
<td>TC/HDL ratio</td>
<td>5.97 ± 1.65</td>
<td>5.32 ± 1.51*</td>
<td>5.42 ± 1.29</td>
<td>5.26 ± 1.20</td>
</tr>
<tr>
<td>Triglycerides</td>
<td>2.37 ± 0.77</td>
<td>2.21 ± 1.24</td>
<td>1.79 ± 1.35</td>
<td>1.48 ± 0.79</td>
</tr>
</tbody>
</table>

*P ≤ 0.05 compared with baseline: LDLc, low-density lipoprotein cholesterol; HDLc, high-density lipoprotein cholesterol; TC, total cholesterol. Values in mmol/l.

Multivariate analysis was performed incorporating the baseline lipid value, gender, timing of onset of GH deficiency, number of additional anterior pituitary hormone deficits and WHR as independent variables, and the change in the lipid value following 12 months GH replacement as the dependent variable. ΔTC, ΔLDLC, and ΔTC/HDL were found to be dependent only on the baseline TC, LDLc and ΔTC/HDL levels (R^2 = 0.18, P = 0.004, R^2 = 0.20, P = 0.006, and R^2 = 0.33, P = 0.0001), respectively. The effect of gender, timing of onset of GH deficiency, or additional anterior pituitary hormone deficits did not have an effect on either ΔTC, ΔLDLC, or ΔTC/HDL above that of the respective baseline values. The greatest improvements in TC, LDLc and TC/HDL occurred in patients with the highest TC, LDLc and TC/HDL levels at baseline.

A further multiple regression analysis was performed as previously, but including only those patients with bioimpedence data at baseline and 12 months (n = 44), and replacing WHR with ΔSDM. ΔTC/HDL was found to be dependent only on the baseline ΔTC/HDL levels (R^2 = 0.25, P = 0.0006). However, ΔTC, ΔLDLC, and ΔSDMc were dependent on both the baseline lipid value and the ΔSDM (ΔTC, R^2 = 0.33; ΔLDLC, R^2 = 0.23). For ΔTC/HDL, the relative contributions of the ΔSDM and baseline TC level were R^2 = 0.18, P = 0.002 and R^2 = 0.13, P = 0.01, respectively. The relative contributions of the ΔSDM and baseline TC level towards explaining ΔLDLCc were R^2 = 0.10, P = 0.02 and R^2 = 0.13, P = 0.03, respectively. The greatest improvements in the lipid profiles of this subgroup were in patients with the highest baseline lipid values and those with the greatest improvement in %FM during GH replacement.

Table 4

<table>
<thead>
<tr>
<th>GH Deficiency</th>
<th>Baseline (n = 23)</th>
<th>12 months (n = 23)</th>
<th>Baseline (n = 44)</th>
<th>12 months (n = 44)</th>
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<tbody>
<tr>
<td>TC</td>
<td>5.82 ± 1.04</td>
<td>5.84 ± 1.21</td>
<td>5.73 ± 1.32</td>
<td>5.73 ± 1.32*</td>
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<tr>
<td>LDLc</td>
<td>3.98 ± 0.82</td>
<td>4.05 ± 0.94</td>
<td>3.67 ± 1.07*</td>
<td>3.67 ± 1.07*</td>
</tr>
<tr>
<td>HDLc</td>
<td>1.17 ± 0.23</td>
<td>1.16 ± 0.22</td>
<td>1.12 ± 0.33</td>
<td>1.12 ± 0.33</td>
</tr>
<tr>
<td>TC/HDL ratio</td>
<td>5.13 ± 1.19</td>
<td>5.16 ± 1.28</td>
<td>5.35 ± 1.39*</td>
<td>5.35 ± 1.39*</td>
</tr>
<tr>
<td>Triglycerides</td>
<td>1.49 ± 0.78</td>
<td>1.37 ± 0.95</td>
<td>2.07 ± 1.08*</td>
<td>2.07 ± 1.08*</td>
</tr>
</tbody>
</table>

*P ≤ 0.05 compared with baseline: IGHD, isolated GH deficiency; MPHD, multiple pituitary hormone deficits; LDLc, low-density lipoprotein cholesterol; HDLc, high-density lipoprotein cholesterol; TC, total cholesterol. Values in mmol/l.

Discussion

In agreement with previous studies of GH replacement in patients with the AGHD syndrome, we have demonstrated a significant reduction in TC and LDLc, and an improvement in the TC/HDLC ratio. HDLC tended to increase, however, the changes were small and did not reach significance. TG levels were significantly reduced by 12 months, and the degree of reduction was maintained at 24 months, but no longer reached significance. We additionally identified the greatest improvement in lipid values to occur in those patients with the highest levels at baseline. Female patients, patients with adult-onset GHD, and MPHD were demonstrated to have a significantly more adverse lipid profile at baseline than males, childhood onset (CO) patients, and patients with IGHD, respectively. Beneficial changes in the lipid profile with GH replacement were confined to the former subgroups. Changes in body composition contributed towards the observed reductions in TC and LDLc.

Analysing the 12- and 24-month data together, the absolute reductions in both the TC and LDLc level equated to approximately 0.3 mmol/l. Previous studies have reported either no significant
effect (Whitehead et al., 1992; Bengtsson et al., 1993; Baum et al., 1996; Leese et al., 1998), or a reduction in TC with GH replacement (Salomon et al., 1988; Cuneo et al., 1993; Russell Jones et al., 1994; Beshyah et al., 1995; Weaver et al., 1995; Burman et al., 1997; Al Shoumer et al., 1998). In those studies reporting a beneficial effect on serum TC levels the degree of reduction lies in the range of 0.5–1.1 mmol/l. As in our study, the beneficial effect on TC in these studies results predominantly from a reduction in LDLc; an action which is believed to be mediated through induction of hepatic LDLc receptors by a direct action of GH (Cuneo et al., 1993; Florakis et al. (2000)) used a similar GH titration regimen to that used in the current study and demonstrated a reduction in TC of around 0.4 mmol/l. Again, this resulted primarily from a reduction in LDLc.

The smaller reduction in TC reported in our patients may relate to differences in the GH replacement regimens or patient characteristics. Although there was no significant change in BMI, WHR, or bioimpedence measures of fat mass, smaller improvements in fat mass, in particular visceral fat mass during this study cannot be excluded. In the subgroup of patients with bioimpedence data, body composition changes may partly explain the beneficial effect of GH replacement on the serum lipids. This subtle change in body composition with low-dose GH replacement may go towards explaining the smaller overall change in serum lipids compared with previous studies.

In our study the GH dose has been individually optimized according to the IGF-I level; this has resulted in much lower maintenance GH doses than in previous studies using weight-based regimens (range 0.67–1.63 mg/day) which are associated with supraphysiological IGF-I levels. Nonetheless we found no correlation between the improvement in the lipid profile and the maintenance GH dose or change in the IGF-I SD when values are kept within the physiological range. This observation is not unexpected when using a GH dosing regimen aimed at normalization of GH-dependent markers, including IGF-I and the serum lipids. The greatest improvement in lipid values with GH replacement is thus seen in patients with abnormal lipid values at baseline, presumably resulting from GH deficiency. Whereas in those patients where GH deficiency has not significantly influenced the baseline lipid values, GH replacement results in only minimal improvement in the lipid profile. The patients in which GH deficiency results in an adverse lipid profile at baseline are not necessarily the same patients in whom GH deficiency induces the lowest IGF-I values, as shown by the lack of correlation between IGF-I and lipid value.

In agreement with the findings of two previous studies, we have demonstrated the greater beneficial effect of GH in the patients with the highest TC and LDLc levels at baseline (Garry et al., 1996; Florakis et al., 2000). Furthermore, improvements with GH replacement were confined to females, adult-onset patients, and those with MPHD. These subgroups were noted to have the more adverse lipid profile at baseline than males, childhood-onset and patients with IGHD, respectively. In our study around half the cohort was comprised of patients with CO GH deficiency. The studies demonstrating benefits to the lipid profile in GH deficiency have been undertaken in cohorts of AO patients, or mixed cohorts amongst whom CO patients represent only a minority of cases. The smaller reduction in TC and LDLc in our cohort may result in part, from the high proportion of CO patients. Relative to the AO patients, CO patients have been shown to have less adverse body composition, which may in turn impact less on the baseline lipid profile (Attanasio et al., 1997). A further factor that likely influenced the differences between AO and CO patients at baseline, and the response of the serum lipids to GH replacement in this study, is the higher percentage of patients with IGHD (51%) in the CO subgroup compared with AO patients (16%). The less adverse lipid changes observed in patients with IGHD may reflect the degree of severity of GH deficiency, rather than an effect of additional pituitary hormone deficits on the lipid profile of patients with MPHD.

The effect of GH replacement on HDLC has been variable, with studies showing a significant increase (Eden et al., 1993; Beshyah et al., 1995), a non-significant increase (Cuneo et al., 1993; Garry et al., 1996; Al Shoumer et al., 1998), no change (Russell Jones et al., 1994; Baum et al., 1996; Burman et al., 1997), or a decrease (Leese et al., 1998). We observed only minor increases in HDLC levels which failed to reach significance despite a larger number of patients than in the above studies. It remains possible that GH increases HDLC levels, but, if so, the effect is small and a larger number of patients are required to substantiate this suggestion. The TC/HDLC ratio is a method of comparing the relative amounts of atherogenic and cardio-protective cholesterol present to help ascertain vascular risk. The individualized low-dose GH replacement regimen used in this study resulted in beneficial and highly significant reductions in this ratio at both 12 and 24 months. The greatest degree of improvement was observed to be in patients with the highest ratio before initiation of GH therapy.

In our study the reduction in TGs observed at 12 months returned to baseline values at 24 months. No significant change was observed in the Apo-AI or Apo-B levels with treatment of the whole cohort, but when analysing the 24-month data (n = 32) both Apo-AI and Apo-B levels fell significantly at 12 months but returned to baseline values at 24 months. Apo-AI is present predominantly in HDLC, and would not be expected to change significantly in view of the absence of a significant change in HDLC levels with GH replacement. Apo-B is present in lipoproteins of the very-low-density lipoprotein (VLDL) cascade, which is comprised of VLDL, intermediate density lipoprotein (IDL) and LDL. The absence of a change in Apo-B levels, in the setting of a significant reduction in LDL levels, may reflect an increase in VLDL or IDL, or a change in the composition of LDL.
Hypopituitary patients have an increased mortality rate (Rosen & Bengtsson, 1990; Bates et al., 1996; Tomlinson et al., 2001), and it has been suggested that this may in part relate to GH deficiency. A notable observation from these studies is that the relative increase in mortality is greater in females than males (Rosen & Bengtsson, 1990; Bulow et al., 1997; Nilsson et al., 2000). Compared with normal controls, hypopituitary females on conventional replacement, but not GH, have more marked abnormalities of TC and LDL-C than hypopituitary males (Al Shoumer et al., 1997). This may explain why females experience greater improvements in their lipid profile with GH replacement. In keeping with the above observations and those from the current study, Abdu et al. (2001) calculated coronary risk in growth hormone-deficient hypopituitary adults using the Framingham Heart Study equation, and demonstrated the increase in relative risk of coronary events to be confined to women (Abdu et al., 2001).

In summary, we have demonstrated that the beneficial effects of GH replacement are retained when using an individually optimized GH replacement regimen aimed at normalization of the IGF-I level. The mean reduction in TC and LDL-C was 0.3 mmol/l, and was maintained during 2 years of GH replacement. This improvement in the lipid profile is less than reported in earlier studies and may relate to differences in the GH replacement regimen and demographic characteristics of the cohort. The TC/HDL-C ratio, a marker of atherogenic potential, improved significantly. Changes in TC, LDL-C and the TC/HDL-C ratio were greater in females and patients with AO-GHD and MPHD relative to males, CO patients, and those with IGHD, respectively. The greatest improvements in the serum lipids were, however, best predicted from the baseline levels. Patients who achieved the greatest improvement in body composition with GH replacement were also observed to experience the more beneficial changes in the lipid profile. Taking the lipid profile as a surrogate marker, these findings provide further insight into which patients are likely to gain the greatest benefit from GH replacement, in terms of reduced mortality risk.

Acknowledgements
We would like to thank Pharmacia & Upjohn for their support.

References

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