Introduction

The clinical features of adult hypopituitarism and growth hormone deficiency (GHD) and its long-term consequences have been thoroughly described in Caucasian subjects (1), and the efficacy of growth hormone (GH) replacement is now well established in Western countries (2, 3). In Japanese subjects, the assessment of the adult GHD syndrome and its implications should take into account their different genetic and environmental backgrounds; for example, the overall incidence of atherosclerosis, one of the major postulated consequences of adult GHD, is considerably lower in Japan than in Western countries (4).

The clinical relevance of the adult GHD syndrome and its complications in Japan has recently been investigated by epidemiological surveys sponsored by the Japanese government. According to the 2001 Annual Report of the Study Group on the Epidemiology of Pituitary Diseases (5), it was estimated that in the year 2000 there were approximately 7000 adult patients with hypopituitarism who had been referred to clinicians for treatment. It was also estimated (6) that up to 1995 there were nearly 29 000 Japanese short stature children registered for paediatric GH treatment, some of whom will require further GH replacement as adults.

In a study of adult Japanese patients with hypopituitarism, the 507 patients established to be GHD had higher prevalence of angina pectoris, myocardial infarction, hypertension and hyperlipidaemia compared with the 362 who had non-GHD hypopituitarism (7). Although there was no significant difference between...
the two groups in number and cause of death, the mean age at death of patients with GHD was a decade younger than that of non-GHD patients (7). One very recent study showed that Japanese patients with childhood onset (CO) or adult onset (AO) GHD had an increased intima-media thickness of the carotid artery (8), a finding consistent with data reported in adult Caucasians with GHD (9).

These reports indicate that the adult GHD syndrome is a relevant clinical entity in Japanese subjects and, similar to Caucasians, its consequences have a significant impact on health outcomes and public health consumption. On the other hand, few studies of GH treatment in adult Japanese GHD subjects have been performed (10). In the present paper we report the results of a study carried out in Japanese patients suffering from the adult GHD syndrome. An interpretation of the baseline clinical data of the patients using criteria validated for the Japanese population is presented in addition to efficacy data under GH replacement.

Patients and methods

This was a 24-week, randomised, placebo-controlled, double-blind study performed in 25 Japanese study centres. All patients gave informed consent and the study was performed with appropriate ethical approval and according to the Declaration of Helsinki. Japanese patients aged 18–64 years, with organic or idiopathic, isolated or multiple, CO as well as AO GHD were recruited. AO patients were defined as having onset of GHD at 18 years or older and CO patients as having onset before 18 years of age; 29 of the 37 CO patients enrolled in the study had been treated with GH during childhood. For diagnosis of GHD, patients had to have a serum GH peak < 3.0 μg/l in a GH stimulation test (insulin tolerance, arginine or glucagon test). Replacement therapy for other missing hormones was stable and adequate for thyroid, vasopressin, and glucocorticoid during the 3 months prior to entering the study and throughout the study. For diagnosis of GH deficiency, patients had to have a serum GH peak < 3.0 μg/l in a GH stimulation test (insulin tolerance, arginine or glucagon test). Replacement therapy for other missing hormones was stable and adequate for thyroid, vasopressin, and glucocorticoid during the 3 months prior to entering the study and throughout the study. In hypogonadal females, oestrogen replacement had to be adequate for at least 3 months and was continued during the study if they were younger than 40 years of age; if between 40 and 55 years of age no change in previous oestrogen replacement was permitted for 3 months prior to commencing the study and for those of 55 years or more oestrogen was discontinued at least 3 months before starting the study. Androgen replacement in males was stable throughout the study and was performed according to the physician’s judgement and patients’ acceptance, conforming to current medical practice in Japan; two males (CO 39 years, AO 59 years) in the GH group and five males in the placebo group (CO 18 years, CO 32 years, AO 48 years, AO 59 years, AO 63 years) were not on androgen replacement during the study. Malignancy, diabetes, severe organ dysfunction and severe hypertension were major exclusion criteria.

A total of 64 eligible patients were enrolled and baseline assessments were carried out during the following 4 weeks. Patients were then assigned to treatment with either recombinant human GH (Humatrope, Eli Lilly and Company, Indianapolis, IN, USA) or placebo by a randomly stratified method using onset of GHD as the stratifying factor, and was further balanced by gender and age with a minimisation method (11). The GH was administered by cartridge pens and placebo was matched by giving excipient solution using the same number of clicks of the pen. By this means, both the investigating physician and the patients were blinded to study treatment. GH was started at 0.021 mg/kg/week (3.0 μg/kg/day) for the first 4 weeks and then increased stepwise to 0.042 mg/kg/week for 8 weeks and a final dose of 0.084 mg/kg/week (12.0 μg/kg/day) for the last 12 weeks. In the event of GH-induced side effects, dose reduction by 25–50% was permitted at the physician’s discretion.

Patients attended for clinic visits at the time of starting GH treatment and then at weeks 4, 8, 12 and 24. At the baseline and 24-week visits, lean body mass (LBM) and fat mass (FM) were measured by dual-energy X-ray absorptiometry (DXA). All DXA measurements performed in each investigative centre were evaluated centrally in a blinded fashion (Dept. of Radiology, Kawasaki Medical School, Kurashiki-city, Okayama, Japan). Serum insulin-like growth factor (IGF)-I and IGF binding protein (IGFBP)-3 concentrations as well as triglycerides and total, high- and low-density lipoprotein (HDL and LDL)-cholesterol levels were measured centrally (BML Inc., Shibuya-ku, Tokyo, Japan). IGF-I and IGFBP-3 were determined by standard immunoradiometric assays; cholesterol concentrations were determined by enzymatic methods.

Safety was assessed by the recording of treatment-emergent adverse events (TEAEs), coded according to the MedDRA system, and by evaluation of laboratory test values and blood pressure. Laboratory determinations were performed centrally and included measurements of liver and kidney function, thyroid hormones and glycosylated haemoglobin concentrations.

Standard deviation scores (S.D. scores) were calculated from serum IGF-I and IGFBP-3 concentrations by comparison with age- and gender-matched subjects, and from height at baseline by comparison with 18-year-old gender-matched subjects, from a Japanese healthy reference population (12). All results were analysed on an intent-to-treat basis and assessed at a 2-sided significance level of 5%. Baseline comparisons between placebo and GH treatment were carried out using Wilcoxon tests or chi-square tests. A paired t-test or Wilcoxon signed-rank test was used to assess the difference between baseline and the end of the study for each treatment group. Student’s t-test or Wilcoxon rank sum
test was used to test differences between the two groups. Examinations of gender and onset effects and interaction with treatment were carried out using ANOVA. SAS version 8.2 (SAS Institute Inc., Cary, NC, USA) was used for all statistical analyses.

Results

Baseline data

The baseline demographic, anthropometric, diagnostic and body composition data of the patients is presented in Table 1. AO patients were older than CO patients and the duration of GHD was longer in CO than in AO patients. All except one AO patient had multiple pituitary hormone deficiencies. Hypopituitarism was due to tumours for most of the patients and an idiopathic cause only occurred in the CO patients. Height S.D. scores were comparable between AO and CO patients but only 13.5% of CO patients. The IGF-I and IGFBP-3 S.D. scores were also lower in females than males (Table 2). The mean peak GH values in the stimulation tests ranged from 0.1 to 2.7 μg/l and overall were slightly higher in the AO (0.5±0.7 μg/l) compared with the CO (0.3±0.3 μg/l; P=0.053) group. The GH and placebo groups were well balanced within both AO and CO patients for all parameters.

Baseline values for serum total cholesterol and LDL-cholesterol concentrations were similar in the AO and CO patients (Table 3) and mean values were close to or above the upper limits of the normal ranges. Serum total cholesterol values were >240 mg/dl for 10 (37.0%) AO patients and 8 (21.6%) CO patients.

Efficacy data

The average GH doses at 4 weeks and 8 weeks were as described in the methodology, at 0.021 and 0.042 mg/kg/week respectively. At the end of the 24-week study period, the mean dose in the GH-treated patients was 0.078±0.015 mg/kg/week (range 0.021–0.085). The median doses were the same for AO and CO patients at endpoint although the mean was slightly lower in AO patients (0.071±0.022 mg/kg/week) owing to dose reductions due to adverse events in four patients.

For all patients combined, a statistically significant (P < 0.001) increase in LBM was seen after 24 weeks in the GH-treated patients compared with almost no change in the placebo-treated group (4.7±3.9% versus −0.5±4.1%; P < 0.001; Fig. 1). In parallel, a significant decrease in FM was observed for GH compared

Table 1 Baseline characteristics of Japanese adult onset (AO) and childhood onset (CO) GH deficient patients, by assigned treatment group (means±S.D.).

|                  | GH (n = 14) | Placebo (n = 13) | GH (n = 19) | Placebo (n = 18) | P-value*
|------------------|------------|-----------------|------------|-----------------|--------
| Age (years)      | 48.7±11.5  | 53.0±7.2        | 28.6±8.1   | 28.9±6.7        | <0.001
| Age at onset (years) | 33.9±10.0 | 43.4±10.8       | 12.2±7.7   | 10.7±4.8        | <0.001
| Male/female      | 5/9        | 4/9             | 11/8       | 11/7            | —      
| Isolated/multiple | 0/14       | 1/12            | 0/19       | 0/18            | —      
| Diagnosis        | —          | —               | —          | —               | —      
| Idiopathic       | —          | —               | 6          | 9               | —      
| Tumour           | —          | —               | 11         | 9               | —      
| Sheehan syndrome | 2          | 2               | —          | —               | —      
| Empty sella      | —          | 1               | 1          | —               | —      
| Trauma           | —          | —               | —          | —               | —      
| Height S.D. score| −0.25±0.89 | −0.46±1.25      | −0.17±1.21 | −0.45±0.85      | 0.870  
| BMI (kg/m²)      | 24.3±3.6   | 23.6±3.8        | 24.9±5.1   | 23.2±4.7        | 0.683  
| LBM (kg)         | 39.4±10.0  | 36.9±8.3        | 41.4±9.7   | 40.5±11.3       | 0.348  
| FM (kg)          | 21.5±7.4   | 20.9±6.0        | 22.9±8.0   | 19.1±7.7        | 0.654  
| Peak GH (μg/l)   | 0.5±0.7    | 0.5±0.8         | 0.2±0.2    | 0.3±0.4         | 0.053  
| IGF-I (μg/l)     | 39.5±54    | 95±47           | 48±30      | 58±48           | <0.001 
| IGF-I S.D. score | −1.2±1.15  | −0.73±0.93      | −3.37±1.69 | −2.98±1.24      | <0.001 
| IGFBP-3 (mg/l)   | 2.5±1.1    | 2.5±1.0         | 1.6±0.7    | 1.7±0.9         | <0.001 
| IGFBP-3 S.D. score | −1.84±2.83 | −1.58±2.73      | −5.15±3.16 | −4.52±3.21      | <0.001 

* P-value for AO vs CO patients for combined treatment groups; b isolated GHD or multiple pituitary deficiencies; c includes pituitary adenoma, cranio-phyaryngioma, glioma, germ cell cancer; d in standard stimulation tests.
Table 2 Changes in IGF-I and IGFBP-3 S.D. score values after 24 weeks of GH or placebo in Japanese GHD patients (means±S.D.).

<table>
<thead>
<tr>
<th></th>
<th>AO patients</th>
<th></th>
<th>CO patients</th>
<th></th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Male (n = 9)</td>
<td>Female (n = 18)</td>
<td>Male (n = 22)</td>
<td>Female (n = 15)</td>
</tr>
<tr>
<td>IGF-I S.D. score</td>
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<td></td>
<td></td>
<td></td>
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<tr>
<td>GH Baseline</td>
<td>−0.68±1.04</td>
<td>−1.37±1.20</td>
<td>−2.59±0.81</td>
<td>−4.43±2.04</td>
</tr>
<tr>
<td>Change</td>
<td>4.56±0.47</td>
<td>2.59±2.15</td>
<td>2.75±1.56</td>
<td>3.93±2.01</td>
</tr>
<tr>
<td>Placebo Baseline</td>
<td>−0.00±0.51</td>
<td>−1.05±0.91</td>
<td>−2.51±1.38</td>
<td>−3.71±0.44</td>
</tr>
<tr>
<td>Change</td>
<td>−0.98±0.78</td>
<td>−0.19±0.54</td>
<td>−0.00±0.40</td>
<td>0.02±0.59</td>
</tr>
<tr>
<td>IGFBP-3 S.D. score</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>GH Baseline</td>
<td>−0.77±1.64</td>
<td>−2.43±3.25</td>
<td>−4.57±2.71</td>
<td>−5.96±3.73</td>
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<tr>
<td>Change</td>
<td>2.21±1.19</td>
<td>2.50±1.84</td>
<td>4.00±2.94</td>
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<tr>
<td>Placebo Baseline</td>
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<td>−4.75±1.82</td>
</tr>
<tr>
<td>Change</td>
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<td>−0.28±1.28</td>
<td>−0.20±1.68</td>
<td>−0.65±1.66</td>
</tr>
</tbody>
</table>

Table 3 Serum total and LDL-cholesterol concentrations at baseline and after 24 weeks of GH or placebo treatment in Japanese GHD patients (means±S.D.).

<table>
<thead>
<tr>
<th></th>
<th>AO patients</th>
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<th>CO patients</th>
<th></th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Male (n = 9)</td>
<td>Female (n = 18)</td>
<td>Male (n = 22)</td>
<td>Female (n = 15)</td>
</tr>
<tr>
<td>Total cholesterol (mg/dl)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>GH Baseline</td>
<td>207±34</td>
<td>237±37</td>
<td>221±54</td>
<td>209±37</td>
</tr>
<tr>
<td>24-weeks</td>
<td>171±16</td>
<td>215±28</td>
<td>210±43</td>
<td>212±43</td>
</tr>
<tr>
<td>Change</td>
<td>−36±30</td>
<td>−22±22</td>
<td>−11±40</td>
<td>4±31</td>
</tr>
<tr>
<td>Placebo Baseline</td>
<td>229±18</td>
<td>226±40</td>
<td>190±47</td>
<td>203±15</td>
</tr>
<tr>
<td>24-weeks</td>
<td>235±19</td>
<td>226±56</td>
<td>205±46</td>
<td>209±36</td>
</tr>
<tr>
<td>Change</td>
<td>7±21</td>
<td>−0±39</td>
<td>15±53</td>
<td>6±27</td>
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<tr>
<td>LDL-cholesterol (mg/dl)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>GH Baseline</td>
<td>121±31</td>
<td>142±49</td>
<td>130±35</td>
<td>112±31</td>
</tr>
<tr>
<td>24-weeks</td>
<td>97±20</td>
<td>125±41</td>
<td>126±30</td>
<td>122±36</td>
</tr>
<tr>
<td>Change</td>
<td>−24±26</td>
<td>−17±16</td>
<td>−4±29</td>
<td>11±27</td>
</tr>
<tr>
<td>Placebo Baseline</td>
<td>147±46</td>
<td>138±37</td>
<td>116±39</td>
<td>99±29</td>
</tr>
<tr>
<td>24-weeks</td>
<td>153±31</td>
<td>146±44</td>
<td>123±24</td>
<td>112±34</td>
</tr>
<tr>
<td>Change</td>
<td>6±23</td>
<td>8±33</td>
<td>7±31</td>
<td>13±20</td>
</tr>
</tbody>
</table>

Normal ranges: total cholesterol 150–219 mg/dl; LDL-cholesterol 70–139 mg/dl.

Figure 1 Percentage changes from baseline in lean body mass (LBM) and fat mass (FM) determined by dual-energy X-ray absorptiometry, in Japanese GHD patient treated for 24 weeks with either GH or placebo. The bottom and top edges of the boxes indicate the 25th and 75th percentiles respectively and the horizontal line shows the 50th percentile (median); the vertical lines, or whiskers, extend from the box as far as the data extend, to a distance of at most 1.5 interquartile ranges; values more extreme than this are marked with plot symbols.

with little change with placebo treatment (−9.2±11.8% versus 1.1±6.9%; P < 0.001; Fig. 1). The increases in LBM and decreases in FM were significantly greater with GH treatment compared with placebo treatment for both AO and CO patients (Table 4). Serum IGF-I levels increased significantly (P < 0.001) in the GH-treated group from 65±46 µg/l to 240±115 µg/l after 24 weeks, with very little change (−8±25 µg/l) in the placebo group. Expressed as S.D. score, the average change with GH treatment for all patients was 3.26±1.85 S.D., which resulted in a normalisation of the mean IGF-I S.D. score (from −2.42±1.85 S.D. to 0.85±2.29 S.D.; P < 0.001). When analysed by subgroup, there was no significant effect of time of onset or gender on the changes in IGF-I S.D. score (Table 2). However, the change was greatest in AO male patients and the mean endpoint value in AO males was well above the normal population. All five GH-treated AO male patients had IGF-I S.D. scores greater than +1.96 either at endpoint or at some period during the study;
in addition, three of the nine female AO patients had an IGF-I s.d. score greater than +1.96 during GH treatment. On the other hand, there were no patients who had a combination of an IGF-I exceeding +1.96 s.d. score and an IGFBP-3 below −1.96 s.d. score at any time during treatment (data not shown).

Serum total cholesterol significantly decreased from 220±43 mg/dl to 206±38 mg/dl (P = 0.025) in the GH-treated group and the difference between the groups for the change after 24 weeks was significant (GH: −14±34 versus placebo: 7±39 mg/dl; P = 0.036). Similar and parallel changes were seen in LDL-cholesterol concentrations and, although the decrease in the GH-treated group did not reach significance, the difference between the groups for the change after 24 weeks was significant (GH: −7±27 versus placebo: 9±27 mg/dl; P = 0.040). There were no significant within-group changes or between-group differences for HDL-cholesterol or triglyceride concentrations (data not shown). In a separate analysis, the GH-treatment effect was examined in patients who had serum total cholesterol values either below the upper limit of the normal range or higher than normal at baseline. This analysis (Fig. 2), showed that the GH-treatment effect occurred essentially in patients with high cholesterol levels at baseline and there was almost no change in those who had a baseline value within or below the normal range. The same trends were seen for LDL-cholesterol concentrations (data not shown).

Safety

For TEAEs occurring at a frequency of ≥5%, musculoskeletal and connective tissue disorders (including arthralgia, myalgia, back pain and limb pain) were reported at a significantly higher rate in the GH-treated group compared with the placebo group (39.4% versus 12.9%; P = 0.016). Oedema was reported at higher frequency in the GH-treated than in the placebo-treated patients, but the difference was not statistically significant (12.1% versus 6.5%; P = 0.437). There was no clinically significant change in systolic or diastolic blood pressure and no difference between treatment groups for changes from baseline.

Levels of free thyroxine (T₄) decreased significantly in the GH-treated group (baseline: 1.5±0.4 ng/dl, 24 weeks: 1.2±0.3 ng/dl; P < 0.001) but not the placebo group (baseline: 1.5±0.6 ng/dl, 24 weeks: 1.4±0.3 ng/dl; P = 0.586); the difference in the change from baseline was of borderline significance (P = 0.058). Glycosylated haemoglobin significantly increased in the GH group (baseline: 4.6±0.4%, endpoint: 4.8±0.4%; P < 0.001) and the difference between groups for the change from baseline to 24 weeks was statistically significant (GH: 0.2±0.3% versus placebo: 0.0±0.2%; P = 0.016). However, the maximum values remained below the upper limit of normal (5.8%) for all patients at the end of GH treatment.

Discussion

The adult GHD syndrome and its response to GH replacement are well characterised in Caucasians. In Japanese subjects the clinical presentation and the response to GH treatment is likely to be influenced by factors intrinsic to the Japanese population; for example, the prevalence of obesity, one major consequence of adult GHD in Caucasians. In Japanese GHD patients with a baseline value either below (normal) or greater than (high) the upper limit of the normal range; values are means ± s.d.; the P-value is for the difference between baseline and the 24-week endpoint using the Wilcoxon signed-rank test.

Figure 2 Serum total cholesterol levels at baseline (open bars) and after 24 weeks of GH treatment (solid bars) in Japanese GHD patients with a baseline value either below (normal) or greater than (high) the upper limit of the normal range; values are means ± s.d.; the P-value is for the difference between baseline and the 24-week endpoint using the Wilcoxon signed-rank test.

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1.4±0.3 ng/dl; P = 0.586); the difference in the change from baseline was of borderline significance (P = 0.058). Glycosylated haemoglobin significantly increased in the GH group (baseline: 4.6±0.4%, endpoint: 4.8±0.4%; P < 0.001) and the difference between groups for the change from baseline to 24 weeks was statistically significant (GH: 0.2±0.3% versus placebo: 0.0±0.2%; P = 0.016). However, the maximum values remained below the upper limit of normal (5.8%) for all patients at the end of GH treatment.

Discussion

The adult GHD syndrome and its response to GH replacement are well characterised in Caucasians. In Japanese subjects the clinical presentation and the response to GH treatment is likely to be influenced by factors intrinsic to the Japanese population; for example, the prevalence of obesity, one major consequence of adult GHD in Caucasians, has been reported to be lower in Japan than in Western countries. Using the World Health Organisation criteria for obesity, i.e. a BMI value > 30 kg/m², only 2–3% of the Japanese

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population would be considered obese, which is about 10-fold less than for Western populations (13). On the other hand, it has recently been recognised that the frequency of obesity-related complications such as hyperglycaemia, dyslipidaemia and hypertension are already increased in Japanese subjects with a BMI value ≥25 kg/m² (14, 15). Since almost a third of the GHD patients in the present study had a BMI value greater than 25 kg/m², it follows that risk-associated obesity was a relatively common feature in these patients.

The obesity of the patients was confirmed by the DXA FM values, which were on average 19 to 23 kg at baseline. For both genders, mean values were higher than the average DXA FM values reported in the normal adult Japanese population, which were 14.6 kg in males and 17.3 kg in females for the age range of 20–79 years (16). The mean FM in the present study was also somewhat higher than the baseline bioelectrical impedance FM values of 14–18 kg reported for GHD patients in a previous study of GH replacement therapy in Japanese patients (10).

The baseline serum cholesterol values were consistent with the body composition findings in showing elevated total and LDL-cholesterol concentrations. The Framingham risk model has recently been validated in the Japanese population (17) and epidemiological studies have reported a total cholesterol value >240 mg/dl in 7.6% of the general population. About 30% of the subjects in the present study had a total cholesterol value higher than the Framingham threshold for cardiovascular risk; this would indicate an approximately fourfold increase in risk compared with the general population and confirms our interpretation of the BMI and FM data. High total cholesterol concentrations were reported for hypopituitary patients in a national survey in Japan (18). However, it was reported that the hypercholesterolaemia was associated with untreated gonadotrophin and thyrotrophin deficiencies and not with GHD. The GH status was equivocal since more than half of the patients did not have a stimulation test and this conflicts with published data on Caucasian patients where elevated total and LDL-cholesterol levels were associated specifically with GHD patients who either had isolated GHD (19) or were adequately replaced with other pituitary hormones (20), similar to the patients in the present study.

Significant differences at presentation in AO compared with CO GHD have been described in Caucasian patients (1, 21). These differences were essentially related to body mass, body composition and IGF-I and IGFBP-3 levels. Interestingly, body mass and composition did not differ between the AO and CO Japanese patients in the present study; this discrepancy may be accounted for by aspects such as modalities of paediatric GH treatment and racial differences in stature and body shape. However, similar to results in Caucasians, IGF-I and IGFBP-3 were lower in CO than in AO patients, confirming that in Japanese subjects the inherent heterogeneity between the two entities also exists.

To date, results from one other double-blind, placebo-controlled study have been published on the effect of GH replacement in Japanese adult GHD patients (10). The duration of GH administration in that study was 4 months and significant changes in body composition, measured by bioelectrical impedance, and in lipid concentrations were observed with treatment. The present study, in which body composition was measured by DXA methodology, confirmed the efficacy of GH replacement in adult Japanese patients in increasing LBM and decreasing FM. The net changes seen in LBM and FM were quantitatively comparable to those reported in adult GHD patients of Caucasian origin (22).

With the fixed dosage regimen used in this study, IGF-I and IGFBP-3 levels were normalised for most patients. Similar to the baseline comparisons, GH-stimulated levels were higher in males than in females and in AO compared with CO patients, consistent with results in Caucasians (21, 22). The increases by gender and time of onset were similar but because CO patients started with lower s.d. scores than AO patients, and females started lower than males, the IGF-I level was elevated in the AO males and this finding may indicate higher sensitivity to GH in males as has been seen in Caucasians (23).

The response seen in serum lipids was in line with findings in Caucasians (1, 21), although the magnitude of the changes seen in total and LDL-cholesterol was limited. On the other hand, mean baseline total and LDL-cholesterol levels in the patients were within the normal range, which may explain the limited response to GH. When analysed by initial status of total cholesterol it was demonstrated that those patients with the highest baseline levels responded most to GH treatment. Because the effect of GH on lipid status has been considered critical to reduce the increased cardio- and cerebrovascular risk associated with adult GHD, it is important to confirm in Japanese patients similar GH effects on lipids as those seen in Caucasians. However, the Japanese population is not fully comparable to the Caucasian population with respect to lipid status; serum cholesterol levels are relatively low in Japan and hypercholesterolaemia as a risk factor is similarly predictive but at a lower level than in Caucasians. Recent studies have indicated that other lipid fractions, such as the very-low-density lipoprotein particles, may be better risk predictors in the Japanese population than total or LDL-cholesterol (24). This aspect should be analysed in future studies with GH replacement in Japanese adult GHD subjects.

The safety profile for the 6 months of GH treatment in these Japanese adult GHD subjects did not reveal any uncommon or unexpected event. The increase in glycosylated haemoglobin seen in the GH-treated group was within the normal range and in line with the known insulin antagonistic effects of GH.
In summary, this study has confirmed that the short term efficacy of GH replacement in Japanese patients, specifically on body composition changes, is comparable to that seen in Caucasians and has a similar safety profile. However, the study has also indicated that adequate clinical assessment of Japanese adult GHD patients requires slightly different evaluation criteria than in Caucasians. Being less obese, the thresholds for cardiovascular risk factors are lower, although still present and responsive to GH replacement.

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