Metabolic Disorders in Adult Growth Hormone Deficiency: A Study of 110 Patients at a Single Institute in Japan

EMINA ITOH, NAOMI HIZUKA, IZUMI FUKUDA AND KAZUE TAKANO

Department of Medicine, Institute of Clinical Endocrinology, Tokyo Women’s Medical University, Tokyo 162-8666, Japan

Abstract. The purpose of this study carried out at a single institute in Japan was to investigate the clinical characteristics and complications of patients with adult growth hormone deficiency (GHD). Clinical and biochemical data of 110 patients (50 males, 60 females; mean age 42 ± 17 yr) with adult GHD who attended Tokyo Women’s Medical University between 1990 and 1999 were analyzed retrospectively from medical records. This retrospective analysis demonstrated that 109 patients had multiple pituitary hormone deficiencies, with 98 patients having a deficiency of more than three hormones. Sixty-one patients had childhood onset GHD (COGHD) while the remaining 49 patients had adulthood onset GHD (AOGHD). Body mass index (BMI) ranged from 16.9 to 35.9 with a mean of 23.9 ± 4.1 (kg/m^2), with BMI being ≥25 kg/m^2 in 38 patients (31% of COGHD and 38% of AOGHD). Forty-one percent of the patients had hypercholesterolemia, 41% had hypertriglyceridemia, 47% had decreased levels of HDL cholesterol and 48% had increased levels of LDL cholesterol. Intima-media thickness (IMT) of the carotid arteries was investigated in 33 patients, with abnormal findings including increased IMT or plaque being observed in 4 of 18 COGHD patients and 4 of 15 AOGHD patients. Diabetes mellitus and impaired glucose tolerance was found in 4 COGHD patients and 16 AOGHD patients. Insulin resistance was assessed in 36 patients by the homeostasis model insulin resistance index (HOMA-R) and ranged from 0.65 to 10.58 with a mean of 2.80 ± 0.37. This mean value of HOMA-R was significantly greater than that measured in normal subjects (1.58 ± 0.05: P<0.05). These data suggest that abnormal lipid and glucose metabolism, and atherosclerotic changes occur frequently in adult patients with GHD. Insulin resistance may play a role in glucose and lipid metabolism disorders associated with GHD.

Key words: Adult GHD, Metabolic disorders, Insulin resistance, IMT

ADULT growth hormone deficiency (GHD) is now recognized as a clinical entity that is characterized by an increase in total fat mass, a reduction in lean body mass, reduced exercise capacity, decreased bone mass, abnormal lipid profile, increased prevalence of cardiovascular disease and reduced quality of life [1–3]. Epidemiological studies suggest that patients with adult GHD are at increased risk of cardiovascular and cerebrovascular mortality. On the other hand, GH therapy in adult GHD has been shown to normalize body composition, increase bone density and cardiac function, improve physical and health-related quality of life, and have beneficial effects on lipid metabolism [4]. Although the clinical findings, complications, and prognosis of adult GHD in Japan have been surveyed using a questionnaire [5, 6], the clinical characteristics of adult patients with GHD at a single institute have not been reported. In the present study, we undertook a retrospective evaluation of patients with adult GHD at Tokyo Women’s Medical University.

Subjects and Methods

Subjects

The study included 110 patients with adult GHD (61 with childhood onset GHD, 35 males and 26 females; 49 with adulthood onset GHD, 15 males and 34 females) who had attended the Department of Medicine,
Institute of Clinical Endocrinology, at Tokyo Women’s Medical University Hospital between 1990 and 1999. Adulthood onset GHD (AOGHD) was defined as the onset of GHD after 18 years of age. The mean age of patients with COGHD or AOGHD was approximately 32 yr and 50 yr, respectively, with a range of 18–81 yr. The GH provocative test (insulin-induced hypoglycemia (ITT), arginine, or L-dopa test) confirmed the peak GH response was <3 µg/L in 77 patients (ITT n = 68, arginine n = 8, and L-dopa n = 1). The remaining 33 patients had peak GH levels in response to GRH of <3 µg/L, a low serum IGF-I level (11–82 µg/L), and a clinical history of organic pituitary disease. On the basis of these results we considered that all 110 patients had adult GHD [7]. Deficient hormones, with the exception of GH, were replaced and were at stable levels at the start of this study.

Study design

Using medical records for each patient we obtained data on body mass index (BMI) and the prevalence of hyperlipidemia, impaired glucose tolerance, hypertension and liver dysfunction. We also investigated insulin resistance in 36 patients and atherosclerotic changes in the carotid arteries of 30 patients. Total cholesterol, triglyceride and HDL-cholesterol levels were determined by standard techniques in our hospital laboratory. In the cases whose serum triglyceride levels were <200 mg/dl, serum LDL-cholesterol levels were calculated as follows: (Total cholesterol mg/dl) – (HDL-cholesterol mg/dl) – (triglyceride mg/dl × 0.2). Hypercholesterolemia was defined as a serum cholesterol level >220 mg/dl, hypertriglyceridemia as a fasting serum triglyceride level >150 mg/dl, increased LDL-cholesterol level as a concentration >140 mg/dl, and decreased HDL-cholesterol level as a concentration <40 mg/dl for female patients and <35 mg/dl for male patients.

For the diagnosis of diabetes mellitus (DM), either fasting or non-fasting plasma glucose levels were measured in all the patients while HbA1c was measured in 68 patients. The diagnosis of impaired glucose tolerance (IGT) was based on plasma glucose levels during a 75 g oral glucose tolerance test (OGTT).

Insulin resistance was investigated by calculating HOMA-R (homeostasis model insulin resistance index) using fasting plasma glucose and insulin levels according to the following equation: Glucose (mmol/l) × insulin (µU/ml)/22.5 [8]. HOMA-R was also calculated in 30 normal subjects (BMI<25) none of whom had abnormal lipid and glucose metabolism. Liver function was evaluated using serum AST/ALT levels from the medical records.

Ultrasonographic assessment of IMT

We assessed atherosclerosis of the carotid arteries by measuring intima-media thickness (IMT) or plaque using high resolution B-mode ultrasound system (GE-Yokogawa LOGIQ 500) with a 7.5-MHz linear array transducer. Bilateral common carotid arteries were scanned longitudinally 1, 2 and 3 cm below the bifurcations. The image was focused on the posterior walls. These three values were then averaged and the highest mean value used as the representative IMT. All measurements were carried out by the same operator. The IMT values for each patient were compared to the values reported for the normal Japanese population grouped according to decades of age [9].

Hormonal assays

Serum GH concentration was measured with a commercially available immunoradiometric assay (IRMA) kit (Eiken Chemical Co., Ltd.). Serum IGF-I and IGFBP-3 were measured by immunoradiometric assay (IRMA) kits (Daiichi Radioisotope Laboratories, Tokyo, Japan). The intra- and inter-assay coefficients of variation for IGF-I were 2.4 and 2.6%, respectively, and for IGFBP-3 were 5.1 and 5.0%, respectively. As the serum concentrations of IGF-I and IGFBP-3 are dependent on gender and age we used the normal reference values for age-matched controls supplied in the kits [10]. Serum insulin levels were measured by an enzyme immunoassay (EIA).

Statistics

All statistical analyses were carried out using StatView (version 5.0, SAS Institute Inc., NC). All data are expressed as mean ± SD. Differences between groups were analyzed by Student’s t-test, while differences in the prevalence of variables between COGHD and AOGHD were analyzed by the chi-square test. Correlation coefficients were calculated using Spearman’s rank test. A P value <0.05 was considered as statistically significant.
Results

Clinical characteristics

The clinical characteristics of the patients with adult GHD are summarized in Table 1. The mean estimated duration of COGHD was 26 yr compared to 16 yr for AOGHD (P<0.01). Obesity (BMI ≥ 25 kg/m²) was found in 38% of male patients and 32% of female patients. Mean BMI was not significantly different between the COGHD and AOGHD groups for either males (24.0 ± 4.2 vs 25.3 ± 4.9) or females (23.6 ± 3.5 vs 23.5 ± 4.2). However, the prevalence of obesity was higher in male patients aged 30–39 yrs or over 50 yr and in female patients aged 20–39 yrs or 59–69 yrs compared to similar aged groups in the general Japanese population [11]. Fifty-three percent of male AOGHD patients were obese with the prevalence of impaired glucose tolerance and ischemic heart disease, but not hyperlipidemia, being significantly higher than in non-obese male patients with AOGHD. Mean IGF-I SD score (SDS) and IGFBP-3 SDS were −2.6 ± 0.2 and −4.6 ± 0.4, respectively. In patients with COGHD, IGFBP-3 SDS was significantly lower than in patients with AOGHD (−5.1 ± 0.4 vs −3.2 ± 0.8, P<0.05). There was no difference in IGF-I SDS between the two groups.

The etiologies of hypopituitarism in the COGHD group were 32 (52.5%) idiopathic, 11 (18%) craniopharyngiomas and 11 (18%) germinomas and in the AOGHD group, 21 (42.9%) non-functioning pituitary adenomas, 13 (26.5%) Sheehan’s syndrome, and 5 (10.2%) craniopharyngiomas. Multiple pituitary hormone deficiencies were found in 109 patients, while the remaining patient had an isolated GH deficiency. Ten percent of the patients with GHD had one additional pituitary hormone deficiency, 19% had 2 additional hormone deficiencies, while 71% had more than 3 additional hormone deficiencies. There was no correlation between the number of hormone deficiencies and the GH peak measured in the GH provocative test. An LH/FSH deficiency was found in 97% of the patients, while deficiencies of TSH, ACTH, and anti-diuretic hormone (ADH) were found in 82%, 72%, and 29% of the patients, respectively. In these patients with TSH, ACTH or ADH deficiencies, adequate replacement therapy had been carried out. Of the 37 female patients aged <50 yr, 36 had gonadotropin deficiency with 31 receiving replacement therapy. Nine of the 23 female patients aged >50 yr were taking estrogen. In the 50 male patients, 49 were hypogonadal with 41 patients receiving replacement therapy. There were no deaths in our patient group during the study period from 1990 to 1999.

Lipid profile

The percentage of patients with an abnormal lipid profile is shown in Table 2. Forty-one percent were hypercholesterolemic, 44% hypertriglyceridemic, 47% had decreased levels of HDL cholesterol and 85% had increased levels of LDL cholesterol. Thirty-three (30%) patients had one lipid abnormality while 61 (55%) patients had more than two abnormalities.

Table 1. Clinical characteristics of patients with adult GHD

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Total</th>
<th>COGHD</th>
<th>AOGHD</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients</td>
<td>110</td>
<td>61</td>
<td>49</td>
</tr>
<tr>
<td>Gender (m/f)</td>
<td>50/60</td>
<td>35/26</td>
<td>15/34</td>
</tr>
<tr>
<td>Age (yr)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>M</td>
<td>39.1 ± 2.2 (18–77)</td>
<td>32.8 ± 1.8</td>
<td>53.8 ± 4.1</td>
</tr>
<tr>
<td>F</td>
<td>45.4 ± 2.3 (20–81)</td>
<td>31.3 ± 1.5</td>
<td>56.2 ± 2.7</td>
</tr>
<tr>
<td>Duration of GHD</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>M</td>
<td>24.4 ± 4.4</td>
<td>26 ± 11</td>
<td>16 ± 10</td>
</tr>
<tr>
<td>F</td>
<td>23.6 ± 3.9</td>
<td>23.6 ± 3.5</td>
<td>23.5 ± 4.2</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>M</td>
<td>38</td>
<td>31</td>
<td>53</td>
</tr>
<tr>
<td>F</td>
<td>32</td>
<td>31</td>
<td>32</td>
</tr>
<tr>
<td>% of BMI ≥ 25</td>
<td>−2.7 ± 1.1</td>
<td>−2.7 ± 1.0</td>
<td>−2.3 ± 1.3</td>
</tr>
<tr>
<td>IGF-I SDS</td>
<td>−4.7 ± 2.7</td>
<td>−5.1 ± 2.5</td>
<td>−3.4 ± 3.1</td>
</tr>
<tr>
<td>IGFBP-3 SDS</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table 2. Clinical complications in adult patients with GHD

<table>
<thead>
<tr>
<th></th>
<th>Total</th>
<th>COGHD</th>
<th>AOGHD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abnormal lipid profile</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total cholesterol</td>
<td>45/110 (41)</td>
<td>23/61 (38)</td>
<td>22/49 (45)</td>
</tr>
<tr>
<td>Triglyceride</td>
<td>27/62 (44)</td>
<td>12/21 (57)</td>
<td>15/41 (37)</td>
</tr>
<tr>
<td>HDL cholesterol</td>
<td>52/110 (47)</td>
<td>25/61 (41)</td>
<td>27/49 (55)</td>
</tr>
<tr>
<td>LDL cholesterol</td>
<td>53/62 (85)</td>
<td>17/21 (80)</td>
<td>36/41 (87)</td>
</tr>
<tr>
<td>Glucose metabolism</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IGT</td>
<td>14/110 (13)</td>
<td>8/61 (13)</td>
<td>6/49 (12)</td>
</tr>
<tr>
<td>DM</td>
<td>7/110 (6)</td>
<td>3/61 (5)</td>
<td>4/49 (8)</td>
</tr>
<tr>
<td>Cardiovascular disease</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>14/110 (13)</td>
<td>3/61 (5)</td>
<td>11/49 (22)</td>
</tr>
<tr>
<td>IHD*</td>
<td>10/110 (9)</td>
<td>3/61 (5)</td>
<td>7/49 (14)</td>
</tr>
<tr>
<td>Liver dysfunction</td>
<td>44/110 (40)</td>
<td>23/61 (38)</td>
<td>21/49 (43)</td>
</tr>
</tbody>
</table>

IHD; Ischemic heart disease
Glucose metabolism

Diabetes mellitus and impaired glucose tolerance was found in 13% and 6% of patients, respectively (Table 2). Two patients were diagnosed with IGT by OGTT, while 3 patients had an increased HbA1c level (>6.5%). There was no significant difference in the prevalence of abnormal glucose metabolism between the COGHD (18%) and AOGHD (20%) groups.

Insulin resistance

Insulin resistance was assessed in 36 patients by calculating HOMA-R, which ranged from 0.65 to 10.58 with a mean of 2.80 ± 0.37 (Fig. 1). These values were significantly higher than in normal subjects (1.58 ± 0.05; P<0.05). Furthermore, when the BMI of the patients and control subjects were matched, the difference remained significant (P<0.009). There was a statistically significant positive correlation between HOMA-R and BMI (R = 0.53, P<0.01, Fig. 2a) and triglyceride (R = 0.40, P<0.05, Fig. 2b), and a significant inverse correlation between HOMA-R and HDL cholesterol (R = –0.42, P<0.05, Fig. 2c). However, there was no correlation between HOMA-R and either total cholesterol or LDL cholesterol.

Cardiovascular disease

The prevalence of patients with cardiovascular disease is shown in Table 2. Hypertension was found in 3 (5%) patients with COGHD and 11 (22%) patients with AOGHD, while ischemic heart disease was present in three (5%) of the COGHD patients, and seven (14%) of the AOGHD patients. Twenty-five percent of patients had more than two overlapping complications that included hypertension, abnormal lipid or glucose metabolism and obesity.

Intima-media thickness (IMT)

The IMT of the carotid arteries was investigated in 30 patients (Fig. 3), with increased thickness being observed in 4 (33%) of 12 patients with COGHD and 4 (22%) of 18 patients with AOGHD. Plaque formation was found in 2 (17%) of the COGHD patients and 5

Fig. 1. HOMA-R in adult patients with GHD and control subjects. The solid lines indicate the mean values of each group.

Fig. 2. The correlation between HOMA-R and (a) BMI, (b) triglyceride, and (c) HDL cholesterol.
(27%) of the AOGHD patients. Of the COGHD patients with increased IMT or plaque, 60% were hyperlipidemic while 40% had IGT. In patients with an increased IMT the estimated duration of GH deficiency ranged between 20–38 yrs in the COGHD group and 20–40 yrs in the AOGHD group.

Liver dysfunction

There was no significant difference in the prevalence of liver dysfunction in the two groups, with dysfunction being found in 23 (38%) of the patients with COGHD and in 21 (43%) patients with AOGHD (Table 2). Thirty-two (72%) of the 44 patients in whom lipid profiles were measured were hyperlipidemic.

Discussion

Epidemiological data indicate that adults with hypopituitarism have a reduced life expectancy compared with healthy controls, mainly as a consequence of a two-fold increase in mortality from cardiovascular disease [12]. A deficiency in GH has been proposed as the variable that may account for this increase in mortality. The present study suggests that a longstanding GH deficiency during adulthood predisposes to the development of premature atherosclerosis. We also showed an increase in the prevalence of diabetes mellitus and impaired glucose tolerance in our study cohort. However, as the number of subjects investigated by an oral glucose tolerance test was limited it is possible that our data may not reflect the exact prevalence of impaired glycemic control. The percentage of patients with obesity (BMI ≥ 25) was also increased in our study, with 38% of males and 32% of females being overweight. Interestingly, 53% of male AOGHD patients were obese, with the prevalence of impaired glucose tolerance and ischemic heart disease in these patients being significantly greater than in non-obese male patients with AOGHD. Furthermore, the increased prevalence of obesity in young adult GHD patients was a notable characteristic and appeared to contribute to the development of cardiovascular risk factors.

Toogood et al. reported that the greater the number of pituitary hormone deficits the more severe the GH deficiency [13]. On the other hand, there was no correlation between the number of hormone deficiencies and the GH peak measured in the GH provocative test in this study. The different results might be due to the difference in criterion of GH deficiency between the two studies, as Toogood et al. chose a peak GH of less than 20 mIU/l during ITT as their screening definition of GH deficiency.

The prevalence of abnormal lipid profiles, such as hypercholesterolemia, decreased HDL cholesterol, increased LDL cholesterol, and hypertriglyceridemia was also increased in our patient group. A population-based study reported that low levels of HDL cholesterol are associated with an increased risk of rupture-prone atherosclerotic plaques [14] and therefore our finding of increased IMT and plaque formation in both our study groups is of clinical relevance.

In this study we used HOMA-R as a marker of insulin resistance and found that values in patients with GHD were significantly higher than in normal subjects. This finding confirmed previous reports that GH-deficient adults may be insulin resistant [15]. As expected there were significant positive correlations between HOMA-R and BMI and serum triglyceride concentration and an inverse correlation between HOMA-R and HDL cholesterol levels. When the BMI of patients and control subjects were matched, HOMA-R remained higher in the GHD patients, a finding that suggested other factors including abnormal lipid profile are also responsible for the increase in insulin resistance. One of the main clinical features of insulin resistance includes central obesity with an increase in intra-abdominal adiposity being a characteristic that is seen frequently in patients with adult GHD. Recent reports
have suggested that insulin resistance itself is an important risk factor for atherosclerosis [16] as it decreases lipoprotein lipase activity and causes hypertriglyceridemia and decreased HDL cholesterol [17].

The metabolic syndrome is a cluster of cardiovascular risk factors that includes hyperglycemia, dyslipidemia, abdominal adiposity, insulin resistance and hypertension. In the present study, overlapping of these factors occurred in one-quarter of the patients with GHD, a finding that implies GH deficiency may contribute to the development of these factors. However, we evaluated obesity only by BMI with neither intra-abdominal fat nor the waist to hip ratio being measured.

Some GHD patients, in spite of having a normal BMI, had metabolic disorders. This finding raised the possibility that visceral fat may have been increased in these patients. Another factor that may contribute to the development of atherosclerosis in patients with hypopituitarism is an irrelevant replacement dose of hormones, especially an excess of glucocorticoids. In this study, patients with an ACTH deficiency received up to 20 mg of hydrocortisone per day. However, further evaluation as to whether or not these patients were being exposed to excessive glucocorticoids was not undertaken as it was considered to be too difficult under the conditions of this study.

Although the mechanisms responsible for the increased cardiovascular mortality in patients with adult GHD have yet to be established conclusively, carotid artery ultrasonography has demonstrated that hypopituitary adults have increased IMT and intimal plaque formation [18] and reduced arterial compliance [19]. We also found an increased prevalence of atherosclerotic changes in the carotid arteries in our subjects and it is interesting to note that IMT was increased markedly even in some of the younger patients with COGHD. This finding is in accordance with an earlier report of a similar study in GHD-deficient Japanese adults [20]. The estimated duration of GH deficiency in COGHD and AOGHD patients with increased IMT tended to be longer than in GHD patients without increased IMT. Furthermore, the prevalence of hypertension and ischemic heart disease was increased in AOGHD in spite of the longer duration of disease in COGHD. Taken together these findings demonstrate that aging is a major factor that clearly contributes to these two cardiovascular complications. There is now evidence that GH treatment of patients with GHD reverses early atherosclerotic changes in large arteries, and if maintained, may also reduce vascular morbidity and mortality [21].

It has been reported that mortality from cardiovascular diseases is higher in patients with adult GHD than in the general population [12]. However, life style factors, including dietary and genetic background, are different between Japanese and Caucasian subjects. Therefore, whether the risk of cardiovascular disease and mortality is increased in Japanese patients with GHD is an important issue that requires further elucidation.

In conclusion, the present study demonstrated that abnormal glucose and lipid metabolism and atherosclerotic changes occur frequently in patients with adult GHD. It appears likely that insulin resistance plays a role in these disorders of glucose and lipid metabolism. Furthermore, this study in 110 patients with GH deficiency at a single institute in Japan confirmed the clinical and laboratory characteristics of patients with this disorder reported from other countries. Further long-term studies are required in order to verify the increased risk of cardiovascular mortality associated with GHD and also to determine the influence of GH treatment on the complications that develop with this disorder.

Acknowledgements

This work was supported in part by Grants-in-Aid for Scientific Research (C) (No. 14571074, 16590913) from The Ministry of Education, Science and Culture, a research grant from the Foundation for the Growth Science, Japan, and a research grant from the Ministry of Health, Labour and Welfare, Japan.

References


