Hormone Replacement Therapy and Vascular Risk Disorders in Adult Hypopituitarism

HIDESUKE KAJI, KEIJI IIDA*, YUTAKA TAKAHASHI*, YASUHIKO OKIMURA** AND KAZAUO CHIHARA*

Division of Physiology/Metabolism, University of Hyogo, Akashi 673-8588, Japan
*Division of Endocrinology/Metabolism, Neurology and Hematology, Department of Clinical Molecular Medicine, Kobe University Graduate School of Medicine
**Department of Basic Allied Medicine, Kobe University School of Medicine

Abstract. Adult patients with hypopituitarism are treated by the replacement of deficient hormones, although GH has not been substituted until March 2006 in Japan except for clinical trial. This study examines which hormonal status influences the prevalence of vascular risk disorders in hypopituitary adults. A sample of 263 adult patients with hypopituitarism was studied, among whom there were various hormonal status such as no deficiency, treated or untreated deficiency of each pituitary hormone. Analysis of adult patients with hypopituitarism showed that hypertension was more prevalent in the older than in younger patients and in male than in female patients. Hypercholesterolemia and hypertriglyceridemia were more prevalent in patients with TSH deficiency even with thyroxine substitution than those without TSH deficiency. Both obesity and hypertension were less prevalent in patients with treated ACTH deficiency than those without ACTH deficiency. Obesity was more prevalent in patients with treated vasopressin deficiency than those without vasopressin deficiency. These results provide evidence that glucocorticoid substitution in ACTH deficient adults was favorable to prevent obesity and hypertension but that the thyroxine substitution in TSH deficient adults appeared rather insufficient to prevent hyperlipidemia.

Key words: Adult hypopituitarism, Vascular risk disorders, Hormone replacement, TSH deficiency, Hyperlipidemia

EPIDEMIOLOGICAL studies in Europe have demonstrated premature mortality due to cardiac and cerebrovascular disease in hypopituitarism [1–3]. Rosen and Bengtsson [1] reported that “the hazard function for vascular death was independent of age at diagnosis, sex, estimated duration of disease before diagnosis, time after diagnosis, size of the pituitary fossa, extent of suprasellar growth, type of pituitary insufficiency, conventional pituitary irradiation, or diabetes mellitus”. Bülow et al. [2] reported that the increased cardiovascular morbidity could not be explained by inadequate estrogen or thyroid hormone treatment alone. These reports suggested that unsubstituted GH deficiency (GHD) is likely to be a more important risk factor. On the other hand, Tomlinson et al. [3] reported that multiple regression analyses identified age at diagnosis, sex, a diagnosis of craniopharyngioma, and untreated gonadotropin deficiency as independent significant factors affecting mortality, although the study included too small a number of patients with GHD to analyze.

In Japan, we have previously reported that male adult patients with GHD revealed significantly higher BMI and significantly higher plasma ALT, AST and LDL cholesterol levels [4]. Irie et al. have reported the increased prevalence of cardiovascular risk factors in GHD adults [5]. We have previously reported that the intima-media thickness of carotid artery assessed by ultrasonographic scanning was significantly higher in adult GHD, especially of childhood onset, compared with those of control without pituitary disease [6]. On the other hand, we have reported the direct cause of
death in hypopituitarism by nation wide autopsy database, indicating the higher incidence of cerebral hemorrhage as a cause of death [7]. However, the precise epidemiological data of mortality in hypopituitarism are not yet available in Japan.

The aim of this study is to examine which hormonal status contributes to the prevalence of vascular risk disorders in hypopituitary adults.

**Subjects and Methods**

Table 1 shows the profile of 263 adults with hypopituitarism (132 male and 131 female) in the questionnaire survey answered by the expert physicians of endocrine and metabolic disease [4]. The questionnaire included the questions about the patient’s age, sex, life style, cause and duration of hypopituitarism, family history, physical and laboratory findings including hormonal data, complications and treatment.

TSH was not deficient in 64 patients but deficient in 199 patients among whom thyroxine (L-T\textsubscript{4}) was replaced in 198 patients. ACTH was not deficient in 56 patients but deficient in 207 among whom glucocorticoid was replaced in 206. In 136 patients with age below 50 years, gonadotropin was deficient in 102, among whom sex steroids or gonadotropins were replaced in 91. GH was not deficient in 69 but deficient in 194, all of whom were not replaced by GH. Each pituitary hormone deficiency was diagnosed by conventional methods. Diagnosis of GHD was based upon peak plasma GH values less than 3 ng/ml measured by WHO 66/217 or 80/505 as references (=1.8 ng/ml when measured by human recombinant GH as references) after GH stimulation tests (mostly insulin hypoglycemia, L-DOPA, and arginine test). ADH was not deficient in 218 patients but deficient in 45 patients among whom all patients were replaced with desmopressin.

Logistic regression analysis was performed for assessing the association among the presence of each vascular risk disorders (impaired glucose tolerance/diabetes, hypercholesterolemia, hypertriglyceridemia, obesity, fatty liver and hypertension) as dependent variables, and age, sex or hormonal status as independent variables. \(\chi^2\) test was used to analyze whether doses, numbers, or combinations of replacement hormone contribute to each vascular risk disorders. \(P<0.05\) was considered to denote statistical significance.

Impaired glucose tolerance was defined as plasma fasting glucose more than 110 mg/dl but less than 126 mg/dl or random glucose more than 140 mg/dl but less than 200 mg/dl. Diabetes was defined as plasma fasting glucose more than 126 mg/dl, or random plasma glucose or plasma glucose 2 h after oral 75 g glucose tolerance test more than 200 mg/dl. Hypercholesterolemia was defined as plasma total cholesterol more than 220 mg/dl or as LDL cholesterol more than 140 mg/dl. Hypertriglyceridemia was defined as plasma triglyceride levels more than 150 mg/dl. Obesity was defined as BMI more than 25 kg/m\textsuperscript{2}, which was a criterion of obesity in Japan. Fatty liver was diagnosed by abdominal echo. Hypertension was defined as a systolic blood pressure higher than 140 mmHg and/or a diastolic blood pressure higher than 90 mmHg.

**Results**

As shown in Table 2, hypertension was more prevalent in older than younger patients and in male than female patients. Either hypercholesterolemia or hypertriglyceridemia was more prevalent in patients with
VASCULAR RISK DISORDERS IN HYPOPITUITARISM 241

TSH deficiency replaced by L-T₄ than those without TSH deficiency. Either obesity or hypertension was less prevalent in patients with ACTH deficiency replaced by glucocorticoid than those without ACTH deficiency. Obesity was more prevalent in patients with vasopressin deficiency replaced by desmopressin than those without vasopressin deficiency.

The prevalence of vascular risk disorders did not differ between patients with replaced gonadotropin deficiency and those without gonadotropin deficiency under age 50 plus those over age 50. The prevalence of vascular risk disorders did not differ between patients with untreated GHD and those without GHD.

As shown in Table 3, χ² test was performed for assessing the association between the presence of each vascular risk disorders and doses or number of hormone replacement. There were no differences between thyroxine doses not only for prevalence of hypercholesterolemia but also for hypertriglyceridemia. There were no differences between glucocorticoid doses not only for prevalence of obesity but also for hypertension. Fatty liver was more prevalent in patients replaced with more than 3 hormones than those with less than 3. Hypertension was less prevalent in patients replaced with more than 3 hormones than those with less than 3.

As shown in Table 4, 21 of 25 combinations of 2–4 treated or untreated pituitary hormone deficiency influenced the prevalence of vascular risk disorders compared with those without any combined deficiency. In particular, treated TSH deficiency plus untreated GHD caused higher prevalence of hypercholesterolemia, obesity, and fatty liver. Treated deficiencies of TSH plus gonadotropin caused higher prevalence of hypercholesterolemia and fatty liver. Treated deficiencies of TSH plus Gonadotropin plus untreated GHD caused

<table>
<thead>
<tr>
<th></th>
<th>IGT/DM OR (95%CI)</th>
<th>HC OR (95%CI)</th>
<th>HTG OR (95%CI)</th>
<th>Obesity OR (95%CI)</th>
<th>Fatty liver OR (95%CI)</th>
<th>HT OR (95%CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age (n)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;50 (136)</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>≥50 (126)</td>
<td>1.12 (0.199–1.25)</td>
<td>2.38 (0.992–5.69)</td>
<td>1.48 (0.58–3.75)</td>
<td>1.08 (0.451–2.59)</td>
<td>0.889 (0.369–2.14)</td>
<td>14.1</td>
</tr>
<tr>
<td><strong>Sex (n)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male (132)</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Female (131)</td>
<td>0.498 (0.199–1.25)</td>
<td>1.13</td>
<td>0.951 (0.544–1.79)</td>
<td>0.766 (0.544–1.79)</td>
<td>1.089 (0.369–2.14)</td>
<td>232</td>
</tr>
<tr>
<td><strong>Hormonal status (n)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No TSHD (64)</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Treated TSHD (198)</td>
<td>2.59 (0.705–9.53)</td>
<td>2.96 (1.24–7.10)</td>
<td>3.78 (1.39–10.3)</td>
<td>2.30 (0.961–5.51)</td>
<td>1.48 (0.995–70.1)</td>
<td>1.13</td>
</tr>
<tr>
<td>No ACTHD (56)</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Treated ACTHD (206)</td>
<td>0.715 (0.226–2.26)</td>
<td>1.45</td>
<td>1.41 (0.586–3.41)</td>
<td>0.346 (0.162–0.739)</td>
<td>0.959 (0.346–3.71)</td>
<td>231</td>
</tr>
<tr>
<td>No GnD or age ≥50 (160)</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Treated GnD (age &lt;50) (91)</td>
<td>0.289</td>
<td>1.32</td>
<td>1.41 (0.586–3.41)</td>
<td>0.346 (0.162–0.739)</td>
<td>0.959 (0.346–3.71)</td>
<td>231</td>
</tr>
<tr>
<td>No GHD (69)</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Untreated GHD (194)</td>
<td>1.21 (0.39–3.75)</td>
<td>0.848</td>
<td>0.493 (0.233–1.04)</td>
<td>1.10 (0.517–2.34)</td>
<td>0.889 (0.297–2.66)</td>
<td>0.815</td>
</tr>
<tr>
<td>No VPD (218)</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Treated VPD (45)</td>
<td>0.756 (0.208–2.74)</td>
<td>0.894 (0.419–1.72)</td>
<td>0.891 (0.394–2.01)</td>
<td>2.30 (1.10–4.81)</td>
<td>0.988 (0.394–2.01)</td>
<td>0.34 (0.5–2.47)</td>
</tr>
</tbody>
</table>

a, P<0.05; b, P<0.01

IGT/DM, impaired glucose tolerance & diabetes mellitus; HC, hypercholesterolemia; HTG, hypertriglyceridemia; HT, hypertension; TSHD, TSH deficiency; ACTHD, ACTH deficiency; GnD, gonadotropin deficiency; GHD, GH deficiency; VPD, vasopressin deficiency
higher prevalence of obesity and fatty liver. All of these 3 combinations caused lower prevalence of hypertension.

Discussion

Either hypercholesterolemia or hypertriglyceridemia
was more prevalent in patients with L-T$_4$-replaced TSH deficiency than those without TSH deficiency. The inverse correlation between serum levels of cholesterol and thyroid hormone has long been clinically reported. Hyperlipidemia is commonly associated with both primary and secondary hypothyroidism. Type IIa hyperlipidemia was the most common lipid abnormality in patients with primary hypothyroidism, whereas type IIb was the most common in those with secondary hypothyroidism [8]. Our report is not only in good agreement with either hypercholesterolemia or hyperlipidemia in secondary hypothyroidism but also suggest that L-T$_4$ replacement is still insufficient to prevent hyperlipidemia. The average dose of L-T$_4$ replacement was 97.1 ± 7.2 µg/day, which does not appear to be so low of a dose. In addition, there were no differences between thyroxine doses not only for prevalence of hypercholesterolemia but also for hypertriglyceridemia. Taken together, the replacement doses of L-T$_4$ were adjusted and varied according to the sex, age, clinical symptoms, etc. but the adjusted doses were still individually insufficient, although we cannot exclude the possibility that the hyperlipidemia was caused by factors other than hypothyroidism. The mechanism of hypercholesterolemia in hypothyroidism may be explained by the reported evidence that thyroid hormone stimulates sterol regulatory element-binding protein-2 (SREBP-2) gene expression, thereby causing an increased LDL receptor gene expression to decrease serum LDL cholesterol levels [9]. The mechanism of hypertriglyceridemia by secondary hypothyroidism still remains to be clarified.

Either obesity or hypertension was less prevalent in patients with glucocorticoid-replaced ACTH deficiency than those without ACTH deficiency. It is well known that the glucocorticoid excess causes obesity, hypertension, and impaired glucose tolerance/diabetes. Our results suggest that the doses of glucocorticoid substitution are not excessive but rather less than the doses to cause hypertension and obesity, although their prevalence did not differ between patients with higher and lower doses of glucocorticoid replacement. Li et al. reported that, in ectopic ACTH syndrome without identifiable source of ectopic hormone production, patients treated with bilateral or unilateral adrenalectomy and a strict steroid replacement had better outcomes than those without surgical intervention but treated with aminoglutethimide [10].

Obesity was more prevalent in patients with desmo-
but also with others report that there was no association between GHD and either hypercholesterolemia [11, 16, 17] or obesity [11]. On the other hand, some investigators reported the increased total cholesterol levels in GHD [18–20]. The discrepancy may be explained by the different controls such as normal subjects instead of hypopituitary patients without GHD or by the different method of statistics.

We and others have previously shown the increased IMT of carotid artery in adult GHD [6, 21], although Markussis et al. reported that IMT was found to be increased in patients with hypopituitarism at middle and old age, but not in patients below 40 yr of age [22]. The mechanism underlying the intimal thickening observed in GHD patients remains to be clarified. Tsukahara et al. reported the direct demonstration of insulin-like growth factor-1-induced nitric oxide production by endothelial cells [23].

We also found that very low doses of GH caused suppression of atherosclerosis-inducible cytokines or chemokines in cultured human macrophage detected by antibody array (unpublished observation). Taken together, GHD may directly but not indirectly through vascular risk disorders cause atherosclerosis to develop, less frequently advancing to acute coronary syndrome or ischemic stroke. It is still controversial whether the longevity of patients with GHD is longer or shorter. In a recent report by Laron [24], dwarfed patients with isolated GHD, patients with multiple hormone deficiencies including GH, and patients with Laron syndrome lived longer even though none had received GH/IGF-I replacement, as suggested by the higher longevity of animal models of genetic GHD such as Snell mice (Prop-1 gene mutation) or Ames mice (PROP-1 gene mutation).

Patients with more than 3 pituitary hormone deficiency with replacement had more association with fatty liver but less with hypertension. Although the reason remains unknown, patients with more than 3 pituitary hormone deficiency with replacement usually have at least both ACTH and TSH deficiency, and sometimes vasopressin deficiency, which cause less hypertension and more hyperlipidemia even if glucocorticoid, L-T₄ and vasopressin were replaced. The results shown in Table 4 suggested that the combinations of treated or untreated pituitary hormones, particularly combinations of TSH deficiency, GHD, and gonadotropin deficiency, are more likely to influence the prevalence of multiple vascular risk disorders at least when univariate but not multivariate analysis was performed.

These results provide evidence that deficient hormones even though replaced could still influence the prevalence of vascular risk disorders in hypopituitary adults. A careful adjustment of hormone replacement therapy, particularly for TSH deficiency, is required to prevent vascular risk disorders in hypopituitary adults.

Acknowledgments

We wish to thank the expert endocrinologists for their cooperation in the survey. This work was supported in part by research grants from the Japanese Ministry of Education, Culture, Sports, Science and Technology, the Japanese Ministry of Health, Labor and Welfare, and the Foundation for Growth Science in Japan.

References