Cardiovascular Risks and Their Long-Term Clinical Outcome in Patients with Subclinical Cushing’s Syndrome

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Abstract. Although subclinical Cushing’s syndrome has been commonly experienced, details of the clinical outcome and its indication for adrenalectomy have yet to be established. In the present study, we investigated the prevalence of cardiovascular risks, their clinical outcome during long-term follow up before and after adrenalectomy in 20 patients with subclinical Cushing’s syndrome. We also correlated the hypercortisolism and age with the cardiovascular risks and the clinical outcome. The prevalence of hypertension, impaired glucose metabolism, dyslipidemia, and obesity was 45%, 65%, 65%, and 25%, respectively. In the non-operated group (n = 12), six patients (50%) showed deterioration of at least one of the cardiovascular risks. Four patients showed an increase of at least one risk, while none of the patients showed a decrease in the number of risks. One patient developed overt Cushing’s syndrome. In the operated group (n = 10) including two operated patients of the non-operated group, eight patients (80%) showed an improvement of at least one of the cardiovascular risks after surgery and five patients (50%) showed a decrease of at least one risk. The prognosis in terms of the changes of the cardiovascular risks after surgery was significantly better in the operated group than in the non-operated group (p<0.001). Neither the hypercortisolism nor age correlated to the presence and the clinical outcome of the cardiovascular risks. The present study clearly demonstrated probability of deterioration during the clinical course and improvement after adrenal surgery in patients with subclinical Cushing’s syndrome. Careful follow-up of the cardiovascular risks is therefore warranted. Adrenalectomy could be a treatment of choice despite the hypercortisolism and age of the patients, especially when the cardiovascular risks show signs of deterioration.

Key words: Cortisol, Subclinical Cushing’s syndrome, Cardiovascular risk, Adrenalectomy, Hypercortisolism

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SUBCLINICAL. Cushing’s syndrome is defined as the pathological condition of adrenal incidentaloma with autonomous secretion of cortisol but without physical findings characteristic of Cushing’s syndrome. As the prevalence of adrenal incidentaloma is increased with the spread of imaging techniques, subclinical Cushing’s syndrome commonly accounts for 2.9% to 22.2% of the adrenal incidentaloma [1, 2]. Hypertension, diabetes mellitus, dyslipidemia, and visceral obesity are the major cardiovascular risks [3, 4]. Cushing’s syndrome is frequently associated with those cardiovascular risks through hypercortisolism, leading to cardiovascular diseases as the major cause of death [5]. Since subclinical Cushing’s syndrome has also been demonstrated to be associated with hypertension, impaired glucose metabolism, hyperlipidemia, and obesity [6, 7], the cardiovascular risks could be the crucial factor for the prognosis of the patients. Details of the long-term clinical outcome of the cardiovascular risks, however, remain to be elucidated.

There is no question that adrenalectomy is absolutely indicated for the treatment of overt Cushing’s syndrome. Adrenalectomy is also indicated in patients with subclinical Cushing’s syndrome if the tumor is
suggestive of malignant nature [7]. Objective evidence justifying the adrenalectomy in patients with subclinical Cushing’s syndrome, however, has not been fully established. Only a limited number of studies have demonstrated an improvement of cardiovascular risks after adrenal surgery [2, 8]. Autonomous secretion of cortisol is inevitably suggested to have a role in the pathogenesis of the cardiovascular risks in patients with subclinical Cushing’s syndrome. We have previously demonstrated that the cortisol secretion in subclinical Cushing’s syndrome shows large diversity in its autonomy, and the extent of the excess secretion ranging between non-functioning adenoma and overt Cushing’s syndrome [9]. If there were a significant correlation between the autonomous secretion of cortisol at the time of diagnosis and the clinical outcome of the cardiovascular risks, it would be possible to predict the prognosis and to make rational decision for adrenalectomy in patients with subclinical Cushing’s syndrome.

In the present study, we investigated the prevalence of the cardiovascular risks, the long-term clinical outcome in 20 patients with subclinical Cushing’s syndrome. We also investigated the correlation between hypercortisolism and cardiovascular risks.

**Subjects and Methods**

Twenty patients (6 males and 14 females, median age of 59.7 yr, range 43–74 yr) with subclinical Cushing’s syndrome treated at the Department of Medicine of the Tokyo Women’s Medical University from 1995 to 2006 were retrospectively studied. Patients who were followed up for at least six months were included in the study. The diagnosis of subclinical Cushing’s syndrome was made by the diagnostic criteria of the Research Committee of the Japanese Ministry of Health, Labor and Welfare for adrenal diseases [10]. The criteria includes as the essential conditions 1) presence of adrenal incidentaloma, 2) a lack of characteristic features for Cushing’s syndrome, 3) normal basal serum cortisol levels, and 4) serum cortisol levels higher than 3 µg/dl after 1 mg dexamethasone and higher than 1 µg/dl after 8 mg dexamethasone, respectively. The diagnosis was defined based upon the presence of all these essential conditions and at least one of the following additional criteria: 1) suppression of plasma ACTH (basal plasma ACTH levels less than 10 pg/ml and/or decreased response of ACTH after CRH stimulation test, 2) loss of cortisol diurnal rhythm, 3) decreased serum DHEA-S levels, and 4) unilateral uptake in the adrenal scintigraphy.

**Prevalence of cardiovascular risks**

Twelve patients (patient no. 1 to no. 12) who were followed up for more than 6 months (15–69 months, average 27.3 ± 15.2 months) without being subjected to adrenalectomy were classified as the non-operated group (4 men, 8 women; mean age 60 ± 10 yr) (Table 1). Eight patients (patient no. 13 to no. 20) in addition to the 2 patients (no. 11, no. 12) underwent surgical treatment after follow-up of more than 6 months were classified as the operated group (2 men, 8 women; mean age 59 ± 10 yr) (Table 1). The follow-up period after adrenalectomy ranged from 7 to 19 months (average 13.8 ± 3.8 months). The diagnosis was confirmed by the histological analysis of the resected tumor and the loss of autonomous secretion of cortisol after adrenal surgery.

Presence of hypertension, impaired glucose metabolism, dyslipidemia, and obesity were evaluated as cardiovascular risks based upon respective definition. Hypertension was defined according to the guidelines of Japan Society of Hypertension 2004 [11] if the systolic blood pressure higher than 140 mmHg and/or diastolic pressure higher than 90 mmHg. Glucose metabolism was classified according to the World Health Organization 1999 criteria [12]: 1) normoglycemia with fasting plasma glucose (FPG) lower than 110 mg/dl or 2-h plasma glucose lower than 140 mg/dl, 2) impaired glucose regulation (IGR) with FPG 110–125 mg/dl (IFG) and/or 2-h plasma glucose between 140–199 mg/dl on 75 g OGTT (IGT), and 3) diabetes mellitus with FPG higher than 126 mg/dl and/or 2-h plasma glucose higher than 200 mg/dl on 75 g OGTT. Dyslipidemia was defined if total cholesterol (TC) level was higher than 220 mg/dl. Body-mass index (BMI) was calculated as weight in kg divided by the square of height in m. Obesity was defined as a BMI of 25.0 kg/m² or greater, according to the criteria of Society for the Study of Obesity [13]. Patients who were under medication for hypertension, diabetes mellitus, and dyslipidemia were defined as having respective risks.
OUTCOME OF SUBCLINICAL CUSHING’S SYNDROME

Evaluation of the clinical outcome of cardiovascular risks

Changes in the blood pressure were defined as follows: 1) improvement in patients with systolic blood pressure decreased below 140 mmHg and diastolic blood pressure decreased below 90 mmHg and with antihypertensive agents discontinued or decreased in number and 2) deterioration in patients with systolic blood pressure elevated above 140 mmHg and/or diastolic blood pressure elevated above 90 mmHg and with antihypertensive agents started or increased in number, respectively.

Changes in the glucose metabolism were defined as follows: 1) improvement in patients with glucose levels became normoglycemia on OGTT, HbA1c decreased by more than 0.3%, or antidiabetic agents discontinued or decreased in number and 2) deterioration in patients with IGR or diabetes mellitus if HbA1c increased by more than 0.3% or antidiabetic agents started or increased in number and in patients with normoglycemia if glucose levels became IGR or diabetes mellitus on OGTT, respectively.

Changes in dyslipidemia were defined as follows: 1) improvement in patients with plasma total cholesterol levels became normal (TC<220 mg/dl) or antihyperlipidemic agents discontinued or decreased in number and 2) deterioration in patients with plasma total cholesterol levels increased above 220 mg/dl or antihyperlipidemic agents started or increased in number.

Changes in body weight were defined as improvement if body weight decreased by 3 kg or more and deterioration if body weight increased by 3 kg or more.

Changes in tumor size

The size of the adrenal tumor was evaluated by adrenal CT scan with 3-mm thick sections at an interval of 6 months or more. The size was determined as the average of the maximum diameter.

Correlation of hypercortisolism, age, and BMI with cardiovascular risks and their clinical outcome

Hypercortisolism, age, and BMI were compared between the patient groups divided in terms of the presence and absence of the cardiovascular risks and the clinical outcome both in the non-operated and operated groups. The markers for the hypercortisolism used

Table 1. Clinical characteristics and cardiovascular risks of the patients with subclinical Cushing’s syndrome

<table>
<thead>
<tr>
<th>Case</th>
<th>Gender</th>
<th>Age (yrs)</th>
<th>Tumor size (mm)</th>
<th>Plasma ACTH (pg/ml)</th>
<th>Plasma cortisol (µg/dl)</th>
<th>Cardiovascular risk</th>
<th>Adrenalectomy</th>
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<tbody>
<tr>
<td>1</td>
<td>M</td>
<td>65</td>
<td>30</td>
<td>13.5</td>
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<td>DM</td>
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<tr>
<td>2</td>
<td>F</td>
<td>47</td>
<td>30</td>
<td>3.8</td>
<td>9.5</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>3</td>
<td>F</td>
<td>70</td>
<td>40</td>
<td>4.4</td>
<td>17.5</td>
<td>+</td>
<td>IGR</td>
</tr>
<tr>
<td>4</td>
<td>M</td>
<td>74</td>
<td>22</td>
<td>12.3</td>
<td>10.8</td>
<td>+</td>
<td>–</td>
</tr>
<tr>
<td>5</td>
<td>F</td>
<td>67</td>
<td>25</td>
<td>24.3</td>
<td>13.8</td>
<td>–</td>
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<tr>
<td>6</td>
<td>F</td>
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<td>17</td>
<td>11.8</td>
<td>9.0</td>
<td>–</td>
<td>–</td>
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<td>7</td>
<td>F</td>
<td>51</td>
<td>32</td>
<td>8.9</td>
<td>14.4</td>
<td>–</td>
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<tr>
<td>8</td>
<td>M</td>
<td>53</td>
<td>28</td>
<td>13.9</td>
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<td>9</td>
<td>M</td>
<td>66</td>
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<tr>
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<td>F</td>
<td>73</td>
<td>32</td>
<td>14.6</td>
<td>15.5</td>
<td>+</td>
<td>IGR</td>
</tr>
<tr>
<td>11</td>
<td>F</td>
<td>54</td>
<td>25</td>
<td>&lt;3.0</td>
<td>15.6</td>
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<tr>
<td>12</td>
<td>F</td>
<td>58</td>
<td>25</td>
<td>7.5</td>
<td>10.9</td>
<td>–</td>
<td>IGR</td>
</tr>
<tr>
<td>13</td>
<td>F</td>
<td>69</td>
<td>45</td>
<td>11.4</td>
<td>11.2</td>
<td>+</td>
<td>DM</td>
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<tr>
<td>14</td>
<td>F</td>
<td>55</td>
<td>20</td>
<td>6.4</td>
<td>14.1</td>
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<td>IGR</td>
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<tr>
<td>15</td>
<td>F</td>
<td>47</td>
<td>29</td>
<td>&lt;3.0</td>
<td>18.4</td>
<td>+</td>
<td>IGR</td>
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<tr>
<td>16</td>
<td>M</td>
<td>59</td>
<td>38</td>
<td>&lt;5.0</td>
<td>7.1</td>
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<td>17</td>
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<td>72</td>
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<td>DM</td>
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<td>19</td>
<td>F</td>
<td>71</td>
<td>45</td>
<td>6.0</td>
<td>13.0</td>
<td>+</td>
<td>IGR</td>
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<tr>
<td>20</td>
<td>F</td>
<td>56</td>
<td>47</td>
<td>&lt;5.0</td>
<td>14.4</td>
<td>–</td>
<td>IGR</td>
</tr>
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</table>

average M6/F14 59.7 ± 10.4* 31.7 ± 8.5* 9.5 ± 5.4* 12.6 ± 3.0* 23.1 ± 3.7*  

* Values are shown by the mean ± SD. DM: diabetes mellitus, IGR: impaired glucose regulation
were as follows: basal plasma levels of adrenocorticotropic hormone (ACTH), cortisol, and dehydroepiandrosterone sulfate (DHEA-S) determined in the early morning, nocturnal plasma levels of cortisol determined at 2300 h, plasma ACTH in response to corticotrophin-releasing factor (CRH) administration (peak levels, fold increase), and plasma levels of cortisol after 1 mg dexamethasone suppression.

Hormone assay

Plasma ACTH, cortisol, and DHEA-S levels were determined by radioimmunoassay in the consigned commercial laboratories. Radioimmunoassay kits used were as follows: Amerlex RIA (Ortho-clinical Diagnostics Co., Tokyo) for cortisol, Allegro ACTH kit (Nichols Institute Diagnostics, Los Angeles, CA) for ACTH, and DPC-DHEA-S kit (Tokyo Mitsubishi Chemical Co., Tokyo) for DHEA-S, respectively.

Statistical analysis

Results were expressed as the mean ± SD. Differences between the means were assessed by the Mann-Whitney U test. Fisher’s exact probability test was used for comparison of the changes in cardiovascular risks between the non-operated and operated groups. P values of less than 0.05 were considered statistically significant.

Results

Prevalence of cardiovascular risks

The clinical and endocrine characteristics and cardiovascular risks in 20 patients with subclinical Cushing’s syndrome are shown in Table 1. At the time of diagnosis, the prevalence of hypertension, impaired glucose metabolism, dyslipidemia, and obesity was 45% (9/20), 65% (13/20) (diabetes mellitus: 25%; IGR: 40%), 65% (13/20), and 25% (5/20), respectively (Fig. 1).

Clinical outcome of cardiovascular risks

In the non-operated group, the prevalence at the time of diagnosis of hypertension, impaired glucose metabolism, dyslipidemia, and obesity was 33% (4/12), 50% (6/12) (diabetes mellitus: 17%; IGR: 33%), 50% (6/12), and 25% (3/12), respectively (Table 2).

![Fig. 1. Prevalence of cardiovascular risks in 20 patients with subclinical Cushing’s syndrome. IGR: impaired glucose regulation, DM: diabetes mellitus.](image)

Table 2. Prevalence and clinical outcome of each cardiovascular risk in the non-operated and operated groups of subclinical Cushing’s syndrome

<table>
<thead>
<tr>
<th></th>
<th>Non-operated group (n = 12)</th>
<th>Operated group (n = 10)</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>Before</td>
<td>Outcome after long-term follow up</td>
</tr>
<tr>
<td>Hypertension</td>
<td>+ 4 (33)</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>- 8 (67)</td>
<td>0</td>
</tr>
<tr>
<td>Impaired glucose metabolism</td>
<td>+ 6 (50)</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>- 6 (50)</td>
<td>0</td>
</tr>
<tr>
<td>Dyslipidemia</td>
<td>+ 6 (50)</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>- 6 (50)</td>
<td>0</td>
</tr>
<tr>
<td>Obesity</td>
<td>+ 3 (25)</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>- 9 (75)</td>
<td>0</td>
</tr>
</tbody>
</table>
After the long-term follow-up period, hypertension, impaired glucose metabolism, dyslipidemia, and obesity showed deterioration in 2 patients, 3 patients, 2 patients, and 2 patients, respectively. None of the patients showed any improvement of the cardiovascular risks during the follow-up period (Table 2). On the whole, six of 12 patients showed a deterioration of at least one of the cardiovascular risks along the clinical course (Fig. 2). In addition, one female patient developed overt Cushing’s syndrome. The patient showed clinical features of Cushing’s syndrome including central obesity and moon face after the follow-up period of 69 months and presented weight gain of 3 kg and worsening of hypertension and diabetes mellitus. Clinical outcome of the cardiovascular risks were further ascertained in terms of changes in the number of risks. While eight patients did not show any change in the number of risks, two each of the patients showed an increase of one risk and two risks, respectively. None of the patients showed a decrease in the number of risks (Fig. 3a). By contrast to the changes in the cardiovascular risks, there was no significant change in the mean size of the adrenal tumor between at the time of diagnosis (28.0 ± 5.8 mm) and after the follow-up period (27.8 ± 5.2 mm).

In the operated group, the prevalence before surgery of hypertension, impaired glucose metabolism, dyslipidemia, and obesity was 60% (6/10), 90% (9/10) (diabetes mellitus: 30%; IGR: 60%), 90% (9/10), and 30% (3/10), respectively (Table 2). After adrenalectomy, hypertension, impaired glucose metabolism, and dyslipidemia showed an improvement in 5 patients, 2 patients, and 6 patients, respectively (Table 2). Obesity did not show a significant change. On the whole, eight of 10 patients showed an improvement of at least one of the cardiovascular risks along the clinical course (Fig. 2). While five patients did not show a change in the number of risks, 4 patients showed a decrease of one risk and one patient showed a decrease of two risks (Fig. 3b).

In addition, prognostic difference between the non-operated and operated groups was investigated in terms of the changes of the cardiovascular risks using Fisher’s exact probability test. The clinical outcome was defined as an improvement and deterioration/no changes, respectively. The prognosis of the cardio-

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**Fig. 2.** Clinical outcome of the cardiovascular risks in the non-operated and operated groups of the patients with subclinical Cushing’s syndrome. Two patients in the non-operated group were subjected to unilateral adrenalectomy after long-term follow-up period.

**Fig. 3.** Changes in the number of the complicated cardiovascular risks in the non-operated group (a) and the operated group (b). Two patients in the non-operated group subjected to adrenalectomy are shown by dotted and broken lines, respectively.
vascular risks was significantly better in the operated group than in the non-operated group (p<0.001).

**Correlation of hypercortisolism, age, and BMI with cardiovascular risks and their clinical outcome**

There was no significant difference in any of the markers for hypercortisolism between the patient groups without and with hypertension (Fig. 4), impaired glucose metabolism, dyslipidemia, or obesity (data not shown). In addition, hypercortisolism was compared between the patient groups divided by the outcome of cardiovascular risks both in the non-operated and operated groups. There was, however, no significant difference in any of the markers between the patient groups without and with deterioration of risks in the non-operated group and the patient groups with and without improvement of the risks in the operated group (not shown).

Age of the patients with hypertension or obesity was
significantly higher than those without respective risks (Fig. 5a, b). BMI of the patients with hypertension was significantly higher than those without hypertension (Fig. 5c). There was no significant difference of the age and BMI between the patient groups with and without impaired glucose metabolism or dyslipidemia (data not shown). In addition, there was no significant difference of age and BMI between the patient groups without and with deterioration of risks in the non-operated group and the patient groups without and with improvement of risks in the operated group (not shown).

Discussion

The present study clearly demonstrated that subclinical Cushing’s syndrome is frequently associated with various cardiovascular risks. The prevalence of hypertension, impaired glucose metabolism, and dyslipidemia was about 50%. The prevalence was in agreement with the previous studies [6, 7] and equivalent to that reported in patients with overt Cushing’s syndrome [2]. In addition, most of the patients were associated with multiple cardiovascular risks.

Although Rossi et al. [7] reported that no significant change was seen in 7 patients with subclinical Cushing’s syndrome, the long-term clinical outcome of the cardiovascular risks remains to be elucidated. In the present study, we investigated the clinical outcome of cardiovascular risks in 12 patients with subclinical Cushing’s syndrome over an average period of 27 months without surgical treatment. While half of the patients showed no significant change in the severity of the risks, the other half of the patients showed deterioration. In addition, 33% of the patients showed an increase in the number of cardiovascular risks. None of the patients showed an improvement in the severity of the risks and a decrease in the number of the risks. These results suggest that the cardiovascular risks in patients with subclinical Cushing’s syndrome are likely to deteriorate in terms of the severity and the number of the complicated risks along the long-term clinical course.

Erbil et al. [2] and Reincke et al. [8] demonstrated a significant improvement of hypertension, diabetes mellitus, dyslipidemia, and obesity after unilateral adrenalectomy. In the present study, we investigated the clinical outcome of the cardiovascular risks in 10 patients for an average period of 13.8 months after unilateral adrenalectomy. The severity of the risks showed an improvement in 80% and the number of the complicated risks was decreased in 50% of the patients. No patients showed a deterioration of the risks in terms of their severity and number. In addition, the prognostic difference between the non-operated and operated groups was investigated using Fisher’s exact probability test. It was shown that the prognosis in terms of the changes of cardiovascular risks was significantly better in the operated group than in the non-operated group. Taking all these results into account, removal of the adrenal tumor could result in an improvement of the cardiovascular risks, providing a rationale for a positive surgical indication of the subclinical Cushing’s syndrome.

Erbil et al. [2] and Reincke et al. [8] demonstrated a significant improvement of hypertension, diabetes mellitus, dyslipidemia, and obesity after unilateral adrenalectomy. In the present study, we investigated the clinical outcome of the cardiovascular risks in 10 patients for an average period of 13.8 months after unilateral adrenalectomy. The severity of the risks showed an improvement in 80% and the number of the complicated risks was decreased in 50% of the patients. No patients showed a deterioration of the risks in terms of their severity and number. In addition, the prognostic difference between the non-operated and operated groups was investigated using Fisher’s exact probability test. It was shown that the prognosis in terms of the changes of cardiovascular risks was significantly better in the operated group than in the non-operated group. Taking all these results into account, removal of the adrenal tumor could result in an improvement of the cardiovascular risks, providing a rationale for a positive surgical indication of the subclinical Cushing’s syndrome.

The tumor size estimated by CT scan did not show any significant increase during the average follow-up period of 27.3 months. It is well known that the size of the tumor and its enlargement are closely related to the malignant nature of the tumor. It is therefore suggested that the tumors of the patients studied in the present study are likely to be benign rather than malignant, although further follow-up is warranted.

Cortisol is well known to be involved in the development of hypertension, impaired glucose metabolism, and insulin resistance [14]. In the present study, 50% of the patients showed a deterioration of the risks during the long-term follow-up period and 80% of the patients showed an improvement of the risks after unilateral adrenalectomy. Therefore, if there is a direct correlation between the hypercortisolism and cardiovascular risks, endocrine data at the time of diagnosis could be the rationale for indicating adrenalectomy in individual patients. The causal relationship between the hypercortisolism and the cardiovascular risks remains to be elucidated. We used various indices as the marker for the autonomous secretion of cortisol. There was, however, no significant correlation between any of the indices of cortisol secretion and the cardiovascular risks and the clinical outcome. The findings agree with similar previous findings on Cushing’s syndrome in which there was no correlation between the complications (hypertension, dyslipidemia and body weight) and blood and urine levels of cortisol as well as plasma cortisol after 1 mg of dexamethasone suppression [5, 15]. The exact reason for the lack of direct correlation is not known. Walker et al. [14] demonstrated individual variations in the sensitivity
to cortisol. Biological actions of cortisol are mediated through diverse mechanisms including the mineral corticoid receptor, the renin-angiotensin system, and the vascular sensitivity to vasoactive substances. Biological activity is also regulated locally in the target tissues by its inactivating enzyme, 11-beta-hydroxysteroid dehydrogenase (11beta-HSD) type 2 [16, 17]. SNP of the enzyme has been shown to affect the cortisol action [18]. All these could be the factors underlying the dissociation between the indices for hypercortisolism and the prevalence and the outcome of the cardiovascular risks.

One other important factor which should be taken into account is the duration of the disease. The indices as markers for cortisol secretion are obtained by cross-sectional examination and therefore do not necessarily reflect the comprehensive, longitudinal biological effects associated with the duration of the disease. In patients with Cushing’s syndrome, there is a positive relationship between the duration exposed to the hypercortisolism and the severity of hypertension and obesity [5, 16] and postoperative hypertension [19]. There could be a certain relationship between the hypercortisolism, even though subtle, and the cardiovascular risks even in patients with subclinical Cushing’s syndrome. It is, however, not feasible to estimate precisely the duration of the disease because of the absence of specific clinical manifestations.

Subclinical Cushing’s syndrome is often experienced in the middle to elder ages [2, 8]. The patients in the present study aged from 43 to 74 yr with an average of 59.7 yr. Prevalence of hypertension, impaired glucose and lipid metabolism is generally increased as a function of age [20]. In agreement with this, the age of the patients with hypertension or obesity was higher than that of the patients without those risks. There was, however, no correlation between the age of the patient and the clinical outcome of the cardiovascular risks either in the non-operated or the operated group. That the cardiovascular risks were significantly improved after unilateral adrenalectomy even in elder patients suggests that age is not a factor for excluding a possible adrenalectomy.

One of the 12 patients in the non-operated group developed overt Cushing’s syndrome during the follow-up period of 69 months. In addition, cardiovascular risks deteriorated during the clinical course and were improved after unilateral adrenalectomy. Development of the overt Cushing’s syndrome is one of the important conditions for indicating adrenal surgery. Although not common [21, 22], cases of subclinical Cushing’s syndrome developing into overt Cushing’s syndrome have been reported in the literature [23, 24]. It is important to consider the possibility of developing overt Cushing’s syndrome during the follow-up of the patients with subclinical Cushing’s syndrome.

In conclusion, the present study clearly demonstrated the relatively high prevalence of various cardiovascular risks in patients with subclinical Cushing’s syndrome. While about half of the patients in the non-operated group showed a deterioration of the cardiovascular risks, there was a significant improvement of the risks after unilateral adrenalectomy in most of the patients. Neither the hypercortisolism nor age correlated to the presence and the clinical outcome of the cardiovascular risks. These results suggest that careful evaluation and long-term follow-up of the cardiovascular risks are warranted in patients with subclinical Cushing’s syndrome. Adrenalectomy could have a positive indication despite hypercortisolism and age, especially when the cardiovascular risks deteriorate. Further studies are required to establish the treatment of subclinical Cushing’s syndrome.

References


