Osteoporosis Is More Prevalent in Adrenal than in Pituitary Cushing’s Syndrome

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Abstract. Osteoporosis is the most common complication of Cushing’s syndrome. We retrospectively examined the prevalence and risk factors for osteoporosis in 42 female patients with Cushing’s syndrome. Osteoporosis and atraumatic fractures were assessed by bone mineral density of the lumbar vertebral spine (L2-L4) using dual energy X-ray absorptiometry (DXA) and X-ray examination. The prevalence of osteoporosis and fracture were 54.8% and 21.4%, respectively. The prevalence of osteoporosis (69.6% vs. 37.8%) and atraumatic bone fracture (26.1% vs. 15.8%) were significantly higher in patients with adrenal Cushing’s than those with pituitary Cushing’s. AP and lateral BMD was significantly higher in patients with pituitary origin than in those with adrenal origin. Among several variables examined by multiple logistic regression, the etiology of Cushing’s syndrome (adrenal vs. pituitary origin) was a significant factor affecting the prevalence of osteoporosis. Neither age, body mass index, duration of amenorrhea, nor extent of hypercortisolism were significant factors in this analysis. Plasma DHEA-S and urinary 17-KS excretion were significantly higher in pituitary Cushing’s than in adrenal Cushing’s. The present study shows that the prevalence of osteoporosis in patients with Cushing’s syndrome is influenced by its etiology. A factor associated with pituitary Cushing’s syndrome, such as adrenal androgen, may protect these patients from glucocorticoid-induced osteoporosis.

Key words: Osteoporosis, Pituitary Cushing’s syndrome, Adrenal Cushing’s syndrome, Bone mineral density


IN 1932, Cushing first reported osteoporosis or atraumatic fractures induced by glucocorticoid excess [1]. Hypercortisolism decreases bone formation and increases bone absorption, resulting in decreased bone mineral density and osteoporosis [2-4]. Osteoporosis is now recognized as a major complication of Cushing’s syndrome. The prevalence of osteoporosis in Cushing’s syndrome has been estimated at approximately 50% in the United States and Europe [5, 6] and 70% in Japan [7]. However, because these estimates are dated, prevalence should be reevaluated with more sophisticated, modern methods. Cushing’s syndrome can be due to different etiologies but the primary causes include ACTH-producing pituitary adenoma (i.e. pituitary Cushing’s syndrome) and cortisol-producing adrenal adenoma (i.e. adrenal Cushing’s syndrome). These subtypes of Cushing’s syndrome have relatively equal prevalence in Japan [8]; however, adrenal Cushing’s syndrome is rare among Caucasians [9]. Adrenal and pituitary Cushing’s syndrome have different hormonal characteristics and may thus be associated with different incidence of osteoporosis.

In this study, we examine whether the prevalence of osteoporosis is different between pituitary and
adrenal Cushing's syndrome, and, if so, what factors contribute to this difference.

**Subjects and Methods**

The present study design is an observational and retrospective case-series. We enrolled 55 patients with Cushing's syndrome who had been diagnosed in our department from 1993 to June 2001. Among them, 46 patients (83.6%), all of whom their gave informed consent, were evaluated for their bone status as described later. There were four male patients in this sample (one with pituitary Cushing's and three with adrenal Cushing's); however, because they represented such a small sample size, we did not include them in this study. Our final sample included 42 female patients (23 with adrenal Cushing's syndrome due to adrenal adenoma and 19 with pituitary Cushing's syndrome due to pituitary adenoma). All patients had chronic hypercortisolism as indicated by morning and midnight serum cortisol and plasma ACTH levels, urinary-free cortisol excretion, and serum cortisol levels during an overnight low-dose dexamethasone suppression test.

All patients were evaluated either by adrenal CT scan or pituitary MRI. They were all treated surgically, either by resection of the adrenal gland bearing an adenoma, or by resection of a pituitary adenoma using a transsphenoidal approach. Their surgically resected tissues were diagnosed as either cortisol-secreting adenoma or ACTH-secreting adenoma. All patients suffered transient hypocortisolism after surgery, which was subsequently resolved.

The diagnosis of osteoporosis was based on two diagnostic methods: measuring bone mineral density (BMD) of the lumbar vertebral spine (L3) at the lateral view based on the report that lateral spine densitometry was a more sensitive indication of glucocorticoid-induced bone loss [11], and of one (L2–L4) at the AP view using dual energy X-ray absorptiometry (DXA) (QDR-2000 apparatus, Hologic Inc., Waltham, MA) and X-ray examination of the vertebral spine with the atraumatic fracture and radiographic osteopenia. We resulted predominantly lateral view of DXA, this is a very reliable tool for estimating BMD and has been available in our hospital for this purpose since 1993.

Corticosteroid-induced osteoporosis is prominent in sites that are rich in trabecular bone such as the lumbar spine [4, 10] and thus this area was evaluated with more sensitivity by lateral scanning than with the AP view. We diagnosed osteoporosis according to the criteria proposed for primary osteoporosis of the Japanese Society for Bone Mineral Research in 1996 [12], but these cases were not applied to its criteria for steroid-induced osteoporosis. A diagnosis of osteoporosis was classified into presence or absence of non-traumatic vertebral fracture. The diagnosis of the osteoporotic fractures by X-ray examination are bone loss of more than Grade I on radiographic osteopenia or lumbar BMD of less than 80% of the mean value (T-score) of healthy, young, Japanese, adult women at our hospital, bone mineral density serious loss of trabeculae without fractures or ghost-like thoracic and lumbar vertebrae. Atraumatic fracture was diagnosed based on past history of fractures, chest X-ray (anterior-posterior) and lateral views, and/or X-ray of thoracic and lumbar vertebrae base on the criteria of the Japanese Society for Bone and Mineral Research. Briefly, this method was measured by the posterior central, and anterior height of each vertebrae. A compression fracture was considered to be present when the central/anterior height or central/posterior height ratio was less the 0.8, or the anterior/posterior vertebral height was less than 0.8 on the lateral radiograph. Osteoporosis and fractures were evaluated by two orthopedists and radiologists who were not informed of the DXA result. On the other hand, the patients without fracture was diagnosed with lumbar BMD, as estimated by DXA of less than 70% previously, or radiographic osteopenia was more than Grade II.

Plasma cortisol and urinary-free cortisol were measured by RIA (Amerlex Cortisol kit, Ortho Clinical Diagnostics Co., Tokyo). Urinary-free cortisol was measured in most patients several times during hospital admission and the average value was used in this analysis. Normal urinary-free cortisol is less than 100 μg/day. Plasma DHEA-S was measured by a specific RIA (DPC-DHEA-S kit, Tokyo Mitsubishi Chemical Co., Tokyo). Normal DHEA-S is between 15 and 519 μg/dl. Urinary 17-OHCS and 17-KS were measured by colorimeter (Tokyo Mitsubishi Chemical Co., Tokyo). Normal values for 17-OHCS are between 1.6 and 8.8 mg/day. Normal values for 17-KS are between 2.4 and 11.3 mg/day.
Logistic regression, Student’s t-test, Pearson’s correlation coefficient, the chi-square test, and Fisher’s exact test were used to statistically analyze the data. The computer software package StatView J-5.0. (Abacus Concepts, Inc., Berkeley, CA) was used for these analyses. Data were presented as mean ± SD. Statistical significance was set at p<0.05.

Results

Prevalence of osteoporosis in Cushing’s syndrome

Of the 42 females examined, 19 patients had pituitary Cushing’s and 23 had adrenal Cushing’s. The overall prevalence of osteoporosis and fracture was 54.8% and 21.4%, respectively (Table 1). The prevalence of osteoporosis in patients with adrenal origin was 69.6% and 36.8% for those with pituitary origin. Patients with adrenal origin thus suffered from osteoporosis more frequently (P = 0.034). The prevalence of fracture was also significantly higher in patients with adrenal origin (26.1%) compared to those with pituitary origin (15.8%) (p<0.0005; Table 1). Lateral BMD, as indicated by T scores, was significantly higher in patients with pituitary origin (n = 13, 75.1 ± 12.9%) than in those with adrenal origin (n = 17, 64.8 ± 13.9%; p = 0.049; Fig. 1). Moreover, AP view BMD, as indicated by T scores, was significantly higher in patients with pituitary origin (n = 13, 83.8 ± 9.9%) than in those with adrenal origin (n = 17, 73.9 ± 15.0%; p = 0.048).

Risk factors for osteoporosis analyzed by multiple logistic regression

Factors contributing to osteoporosis in Cushing’s syndrome were then evaluated by multiple logistic regression analysis. Age, duration of amenorrhea, body mass index (BMI), etiology of Cushing’s syndrome (adrenal vs. pituitary origin) and urinary-free cortisol excretion were examined as potential risk factors. Patients who were still menstruating were assigned a value of zero periods for the amenorrhea variable. Among the factors tested, etiology was the only significant factor (p = 0.016; Table 2). Osteoporosis was more prevalent in adrenal Cushing’s syndrome than in pituitary Cushing’s syndrome with an odds ratio of 6.5 : 1 (95% confidence interval: 1.2–35.7).

Factors contributing to the differential prevalence of osteoporosis between adrenal and pituitary Cushing’s syndrome

In order to identify factors that mediate the differential prevalence of osteoporosis between adrenal and pituitary Cushing’s syndrome, we compared clinical and hormonal characteristics of patients with adrenal and pituitary Cushing’s syndrome (Table 3). Age, BMI, the frequency and duration of amenorrhea, urinary excretion of free cortisol, 17-OHCS and 17-KS, and serum DHEA-S levels were examined. Although the data were only available in a limited number of patients, serum DHEA-S levels and urinary 17-KS excretion were significantly higher in patients with pituitary origin than in those with adrenal origin. BMI was also significantly higher in patients with pituitary origin compared to those with adrenal origin. Extremely low BMI (i.e., lower than 15 kg/m²) was not observed. No significant differences were seen in age, the frequency or duration of amenorrhea, and urinary excretion of free cortisol and 17-OHCS.

<table>
<thead>
<tr>
<th></th>
<th>Patients examined</th>
<th>Patients with osteoporosis</th>
<th>Patients with fracture</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pituitary Cushing’s syndrome</td>
<td>19</td>
<td>7 (36.8%)</td>
<td>3 (15.8%)</td>
</tr>
<tr>
<td>Adrenal Cushing’s syndrome</td>
<td>23</td>
<td>16 (69.6%)</td>
<td>6 (26.1%)</td>
</tr>
<tr>
<td>Total</td>
<td>42</td>
<td>23 (54.8%)</td>
<td>9 (21.4%)</td>
</tr>
</tbody>
</table>

Prevalence of osteoporosis was significantly higher in adrenal than in pituitary Cushing’s syndrome (p = 0.034 by Chi-square test). Prevalence of atraumatic fractures was also significantly higher in adrenal compared to pituitary Cushing’s syndrome (p<0.0005 by Fisher’s exact test).
Fig. 1. Bone mineral density in pituitary and adrenal Cushing’s syndrome. A T score lower than 70% (dashed line) indicates osteoporosis. The bar represents the mean T score.

Table 2. Risk factors for osteoporosis estimated by multiple logistic regression analysis

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>Odds ratio (95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>0.961 (0.892–1.036)</td>
<td>NS</td>
</tr>
<tr>
<td>BMI</td>
<td>0.375 (0.02–7.114)</td>
<td>NS</td>
</tr>
<tr>
<td>Duration of amenorrhea*</td>
<td>1.014 (0.997–1.030)</td>
<td>NS</td>
</tr>
<tr>
<td>Etiology (adrenal vs. pituitary)</td>
<td>6.510 (1.188–35.66)</td>
<td>0.016</td>
</tr>
<tr>
<td>Urinary excretion of free cortisol</td>
<td>1.002 (0.999–1.005)</td>
<td>NS</td>
</tr>
</tbody>
</table>

*Patients with menstruation were counted as zero for duration of amenorrhea.

BMD did not correlate with urinary free cortisol (N = 30, r = −0.03, p = 0.88), urinary 17-OHCS (N = 36, r = −0.03, p = 0.89), DHEA-S (N = 21, r = 0.17, p = 0.48) or urinary 17-KS excretion (N = 25, r = 0.07, p = 0.74) by Pearson’s correlation coefficient.

Discussion

In our study, 54.8% of female patients with Cushing’s syndrome had osteoporosis. This prevalence in a single institution was slightly lower than that (70%) reported in a Japanese nationwide survey in 1988 [7]. However, as data from the nationwide survey were based on physician responses to questionnaires and not on defined diagnostic criteria, our finding is likely to be more valid and reliable. Our results also demonstrate a two-fold higher prevalence of osteoporosis in adrenal Cushing’s syndrome (69.6%) than in pituitary Cushing’s (36.8%). The prevalence of osteoporosis in Caucasians was estimated to be about 50% in old reports [5, 6]. Pituitary Cushing’s syn-
Table 3. Characteristics of patients with Cushing’s syndrome of adrenal and pituitary origin

<table>
<thead>
<tr>
<th>Patient profiles</th>
<th>Pituitary CS (N = 19)</th>
<th>Adrenal CS (N = 23)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years old</td>
<td>40.3 ± 17.1</td>
<td>47.3 ± 15.0</td>
<td>NS</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>25.0 ± 4.1</td>
<td>22.3 ± 2.9</td>
<td>0.015</td>
</tr>
<tr>
<td>Amenorrhea, case (%)</td>
<td>16 (84.2%)</td>
<td>16 (69.6%)</td>
<td>NS</td>
</tr>
<tr>
<td>Amenorrhea, period (months)</td>
<td>66.4 ± 70.9</td>
<td>77.8 ± 104.6</td>
<td>NS</td>
</tr>
<tr>
<td>Urinary free cortisol excretion (µg/day)</td>
<td>456.4 ± 328.4</td>
<td>348.2 ± 268.5</td>
<td>NS</td>
</tr>
<tr>
<td>Urinary 17-OHCS excretion (µg/day)</td>
<td>13.3 ± 4.4</td>
<td>12.7 ± 4.6</td>
<td>NS</td>
</tr>
<tr>
<td>(N = 15)</td>
<td>(N = 21)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Urinary 17-KS excretion (µg/day)</td>
<td>12.3 ± 6.4</td>
<td>7.2 ± 6.4</td>
<td>0.017</td>
</tr>
<tr>
<td>(N = 15)</td>
<td>(N = 20)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Serum DHEA-S (µg/l)</td>
<td>253.6 ± 136.8</td>
<td>80.0 ± 84.8</td>
<td>0.0004</td>
</tr>
<tr>
<td>(N = 7)</td>
<td>(N = 19)</td>
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Means ± SD are shown. Urinary excretion of 17-OHCS and 17-KS and serum DHEA-S were measured in a limited number of patients as shown.

drome was reported to be five to six times more common than adrenal Cushing’s in the United States [9], but relatively equal in Japan [8]. Such a different distribution of Cushing’s syndrome between Japan and Europe/United States may reflect a difference in the prevalence of osteoporosis. The prevalence of fractures was estimated at 21.4% in this study. Khanine et al. [13] collected 30 patients with Cushing’s syndrome with osteoporotic fractures including two of their own cases and 28 cases described in the literature. They reported a high distribution of adrenal Cushing’s (i.e., 20 adrenal gland lesions, 9 pituitary adenoma and a medullary thyroid carcinoma). Their findings suggested a higher risk of atraumatic fracture in adrenal origin. Our findings have now confirmed their suggestions.

A variety of risk factors for primary and secondary osteoporosis have been reported including age, female sex, Caucasian/Asian race, late menarche, early menopause, low parity, low body weight, amenorrhea, cigarette and alcohol consumption, immobilization, hyperthyroidism, corticosteroid therapy, low dietary calcium intake and malabsorption [14-17]. The effect of race, however, still remains to be confirmed [18, 19]. In this study, patients were all female and Japanese and did not suffer from hyperthyroidism, or from calcium malabsorption. Time of menarche, cigarette and alcohol consumption and dietary calcium intake were not analyzed and thus could not be investigated as mediating factors. We therefore examined the following factors: age, amenorrhea, low body weight, degree of hypercortisolism (urinary-free cortisol excretion), and etiology of Cushing’s syndrome (adrenal vs. pituitary). By multiple logistic regression, etiology of Cushing’s syndrome was identified as the only significant factor. Aging, amenorrhea, low BMI, and urinary-free cortisol excretion were not significant risk factors. Furthermore, urinary-free cortisol was not correlated with BMD. It may be argued that osteoporosis depends not only on the extent of hypercortisolism, but also on its duration. However, it is difficult to estimate the exact disease duration. In addition, glucocorticoid-induced osteoporosis is reported to begin and end within a few years after the onset of glucocorticoid administration [20]. This finding contradicts the concept that the longer the duration of hypercortisolism, the more severe the osteoporosis. Therefore, for these practical and rational reasons, the duration of the disease was not examined in this study. Although osteoporosis has been identified as a major complication of Cushing’s syndrome, interfering factors appeared to mask a direct relationship between severity of osteoporosis and degree of hypercortisolism in this study.

As to type of etiology-associated factor might modify the prevalence of osteoporosis, the possibilities include a protective factor in pituitary Cushing’s syndrome or an eliciting factor in adrenal Cushing’s syndrome. BMD is positively correlated with DHEA-S [21]. Moreover, DHEA-S treatment increases serum osteocalcin and seems to prevent osteo-
porosis [22]. Because plasma DHEA-S levels were measured in only a limited number of patients, this factor could not be evaluated as explanatory variables for osteoporosis by multiple logistic regression. Moreover, urinary 17-KS excretions were not evaluated accurately because of the small number of the patients. However, when examined by Student’s t-test, they were significantly higher in pituitary than in adrenal Cushing’s syndrome as would be expected if they are indeed protective factors. Patients with pituitary Cushing’s syndrome also had higher BMI than patients with adrenal Cushing’s. BMI lower than 15 kg/m² is considered to be a risk factor for osteoporosis [23]. Such low BMI, however, was not found in any patient in this study, suggesting that the difference in BMI did not explain the differential prevalence of osteoporosis.

Reversing hypercortisolism could cure glucocorticoid-induced osteoporosis [10, 24, 25]. Osteoporosis-induced bone fractures, however, remain even after Cushing’s syndrome is treated. Therefore, osteoporosis treatment is important in patients with Cushing’s syndrome, especially patients with adrenal Cushing’s syndrome.

In summary, the prevalence of osteoporosis in female patients with Cushing’s syndrome was 54.8%. It was lower in pituitary Cushing’s syndrome (36.8%) compared to adrenal Cushing’s syndrome (69.8%). Adrenal androgen, which was higher in patients with pituitary origin, may play a protective role in osteoporosis.

References


