An Assessment of Bone Mineral Density in Patients with Addison’s Disease and Isolated ACTH Deficiency Treated with Glucocorticoid

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Abstract. Glucocorticoid replacement therapy needs to be tailored to individual patient’s requirements in order to avoid risk of over or under medication. We measured bone mineral density (BMD) of lumbar spine using dual X-ray absorptiometry in 10 patients with Addison’s disease and 5 patients with isolated ACTH deficiency receiving glucocorticoid replacement therapy. We also examined the effect of glucocorticoid replacement on BMD. Decreased %BMD (less than 80% of age-matched controls) was found in 2 female patients who had received hydrocortisone at a dose of 14.8 and 15.4 mg/m²/day. In contrast, no patient receiving a hydrocortisone dose of less than 12.4 mg/m²/day had decreased %BMD. There was no correlation between %BMD and hydrocortisone dose (mg/m²), duration of therapy, or cumulative hydrocortisone dose when treated with appropriate dose of hydrocortisone (<13.6 mg/m²). There was also no statistically significant difference in %BMD with age. We concluded that long-term glucocorticoid replacement therapy does not induce bone loss in patients with glucocorticoid deficiency unless an excessive dose of hydrocortisone is given.

Key words: Glucocorticoid, Addison’s disease, Isolated ACTH deficiency, Bone mineral density, Dual X-ray absorptiometry

(Patients with primary and secondary adrenal insufficiency require lifelong glucocorticoid replacement therapy. Inadequate replacement of glucocorticoids can lead to malaise, hypotension, electrolyte disturbance and poor response to stress. Conversely, excessive glucocorticoid replacement may lead to Cushingoid features and associated metabolic disturbances of glucose intolerance, hypertension, protein catabolism and osteoporosis [1, 2]. Glucocorticoid replacement in adrenocortical insufficiency is achieved conventionally by oral administration of hydrocortisone. Recent studies have shown that minor increases in hydrocortisone dose over many years can produce osteoporosis [3, 4]. However, there is conflicting evidence regarding the long term effects of hydrocortisone on bone mass in patients with Addison’s disease. Studies in postmenopausal woman showed a reduction in bone mass [3, 5], while other investigations found this decrease occurred only in males [4], or not at all in either sex [6–9].

In primary adrenal failure (Addison’s disease), simultaneous measurement of cortisol and ACTH levels throughout the day provides an insight into the adequacy of replacement therapy [10]. Unfortunately there are no good objective tests for assessing secondary adrenal failure and therefore the treatment of this condition is based mainly on clinical experience.

The primary purpose of this study was to assess bone mineral density in patients with primary and secondary adrenocortical insufficiency, and to derive recommendations for optimum maintenance replacement

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therapy with hydrocortisone in Japanese people. In addition, we analyzed the data to determine whether BMD is impaired even if patients with adrenal insufficiency are carefully managed to avoid glucocorticoid excess. Since growth hormone, thyroid stimulating hormone, and gonadotropins are all known to affect bone mass, we studied isolated ACTH deficiency as secondary adrenocortical insufficiency in order to exclude the effects of these hormones on bone mass.

**Subjects & Methods**

**Patients and treatment**

The study group was comprised of 10 patients with primary Addison’s disease (3 males, 7 females) and 5 patients with secondary adrenocortical insufficiency (isolated ACTH deficiency; 4 males, 1 female), with a mean age of 54.9 ± 4.3 yr with a range of 21–83 yrs. The clinical details of individual patients are summarized in Table 1. As shown in Table 1, the study group was treated with glucocorticoids for a mean of 104.8 months with a range of 8–363 months. They were carefully managed with glucocorticoids at the lowest dose (<22.5 mg hydrocortisone/day). No signs or symptoms of hypercortisolism were observed in any of these patients. Nearly one-half of the patients were treated with hydrocortisone alone, 6 patients (No. 1, 2, 3, 8, 9, 10) with hydrocortisone and dexamethasone, and 2 patients (No. 11 and 12) with prednisolone. For calculating dosages, glucocorticoid dose was converted to milligrams of hydrocortisone with 30 mg hydrocortisone being equivalent to 7.5 mg prednisolone or 1 mg dexamethasone. All patients were Japanese and were fully mobile outpatients with normal renal function and no major medical illness apart from adrenocortical insufficiency. No patient was taking vitamin D or any other drug known to interfere with bone metabolism. Six patients (No. 8, 9, 10, 11, 13, 14) were postmenopausal and had never received estrogen replacement therapy, with the exception of one patient (No. 10) who had been taking 1 mg of estriol daily for 5 years. The remaining two female patients had normal menstrual cycles. Mean plasma ACTH was determined in at least 3 samples from each subject collected in the morning. Plasma ACTH value was determined by a radioimmunometric assay (Allegro ACTH kit, Nichols Institute Diagnostics, Los Angeles, CA) that had a limit of sensitivity of 3 pg/ml.

**Bone densitometry**

Bone mineral density (BMD gm/cm²) of the lumbar spine (L2 to L4) was measured by dual X-ray absorptiometry using a Hologic QDR-2000 or S/N 2210 apparatus (Hologic Inc., Waltham, MA, USA). The results of the measurements were compared with age-matched references provided by the manufacture (%BMD) that were obtained from the normal Japanese

**Table 1. Characteristics of 15 patients with adrenocortical insufficiency**

<table>
<thead>
<tr>
<th>No.</th>
<th>Sex</th>
<th>Age (yrs)</th>
<th>Disease</th>
<th>Dose (mg/day)</th>
<th>Dose (mg/m²/day)</th>
<th>Duration (months)</th>
<th>Total dose (mg X m²)</th>
<th>BMD (gm/cm²)</th>
<th>%BMD (%YAM)</th>
<th>plasma ACTH (pg/ml)</th>
<th>Eosinophils (mm³) (% WBC)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>M</td>
<td>56</td>
<td>Addison</td>
<td>18.9</td>
<td>11.8</td>
<td>77</td>
<td>909</td>
<td>0.987</td>
<td>101 (94)</td>
<td>18.4</td>
<td>29.5 (0.5)</td>
</tr>
<tr>
<td>2</td>
<td>M</td>
<td>21</td>
<td>Addison</td>
<td>15.0</td>
<td>8.8</td>
<td>88</td>
<td>774</td>
<td>1.032</td>
<td>101 (98)</td>
<td>6.9</td>
<td>88.2 (1.6)</td>
</tr>
<tr>
<td>3</td>
<td>M</td>
<td>57</td>
<td>Addison</td>
<td>18.1</td>
<td>11.7</td>
<td>8</td>
<td>94</td>
<td>1.269</td>
<td>130 (121)</td>
<td>9.7</td>
<td>98.6 (1.8)</td>
</tr>
<tr>
<td>4</td>
<td>M</td>
<td>64</td>
<td>ACTH</td>
<td>20.8</td>
<td>11.5</td>
<td>19</td>
<td>213</td>
<td>1.347</td>
<td>141 (129)</td>
<td>&lt;3.0</td>
<td>227.5 (1.5)</td>
</tr>
<tr>
<td>5</td>
<td>M</td>
<td>36</td>
<td>ACTH</td>
<td>16.0</td>
<td>9.4</td>
<td>9</td>
<td>85</td>
<td>0.927</td>
<td>92 (90)</td>
<td>&lt;3.0</td>
<td>162.0 (4.4)</td>
</tr>
<tr>
<td>6</td>
<td>M</td>
<td>62</td>
<td>ACTH</td>
<td>20.0</td>
<td>12.4</td>
<td>244</td>
<td>3025</td>
<td>1.046</td>
<td>109 (100)</td>
<td>&lt;3.0</td>
<td>106.5 (0.6)</td>
</tr>
<tr>
<td>7</td>
<td>M</td>
<td>62</td>
<td>ACTH</td>
<td>15.0</td>
<td>8.6</td>
<td>23</td>
<td>198</td>
<td>1.079</td>
<td>112 (103)</td>
<td>&lt;3.0</td>
<td>50.9 (1.6)</td>
</tr>
<tr>
<td>8</td>
<td>F</td>
<td>75</td>
<td>Addison</td>
<td>22.4</td>
<td>15.4</td>
<td>363</td>
<td>5583</td>
<td>0.379</td>
<td>*52 (37)</td>
<td>21.9</td>
<td>17.2 (0.2)</td>
</tr>
<tr>
<td>9</td>
<td>F</td>
<td>69</td>
<td>Addison</td>
<td>15.8</td>
<td>11.2</td>
<td>174</td>
<td>1943</td>
<td>0.702</td>
<td>107 (67)</td>
<td>35.9</td>
<td>72.8 (0.8)</td>
</tr>
<tr>
<td>10</td>
<td>F</td>
<td>47</td>
<td>Addison</td>
<td>21.3</td>
<td>14.8</td>
<td>119</td>
<td>1761</td>
<td>0.596</td>
<td>*66 (57)</td>
<td>39.0</td>
<td>28.8 (4.4)</td>
</tr>
<tr>
<td>11</td>
<td>F</td>
<td>63</td>
<td>Addison</td>
<td>18.4</td>
<td>11.5</td>
<td>130</td>
<td>1495</td>
<td>0.671</td>
<td>85 (66)</td>
<td>13.0</td>
<td>94.9 (1.4)</td>
</tr>
<tr>
<td>12</td>
<td>F</td>
<td>31</td>
<td>Addison</td>
<td>13.8</td>
<td>8.3</td>
<td>53</td>
<td>434</td>
<td>1.055</td>
<td>103 (104)</td>
<td>24.3</td>
<td>41.7 (0.8)</td>
</tr>
<tr>
<td>13</td>
<td>F</td>
<td>53</td>
<td>Addison</td>
<td>17.1</td>
<td>12.4</td>
<td>45</td>
<td>558</td>
<td>0.770</td>
<td>85 (76)</td>
<td>18.8</td>
<td>403.0 (4.4)</td>
</tr>
<tr>
<td>14</td>
<td>F</td>
<td>83</td>
<td>Addison</td>
<td>19.6</td>
<td>12.2</td>
<td>175</td>
<td>2129</td>
<td>0.704</td>
<td>102 (70)</td>
<td>57.6</td>
<td>104.2 (1.8)</td>
</tr>
<tr>
<td>15</td>
<td>F</td>
<td>45</td>
<td>ACTH</td>
<td>20.0</td>
<td>15.2</td>
<td>48</td>
<td>730</td>
<td>0.866</td>
<td>87 (86)</td>
<td>&lt;3.0</td>
<td>33.2 (0.5)</td>
</tr>
</tbody>
</table>

ACTH = isolated ACTH deficiency, BMD = bone mineral density, YAM = young adult mean
population [11]. Radiological studies were used to exclude patients with vertebral fractures and severe osteoarthritis. The percent of young adult mean (%YAM) was also calculated.

Statistical analysis

All values are expressed as mean ± SE unless stated otherwise. Differences between the groups were analyzed using Student’s t test. Linear regression analysis was used to assess the association between %BMD and daily hydrocortisone dose (mg/m$^2$/day), duration of substitution (months), and cumulative hydrocortisone dose (mg/m$^2$/day × days).

Results

Table 1 summarizes the characteristics of the 15 patients with adrenocortical insufficiency who underwent measurement of BMD. In all male patients (No. 1–7), %BMD was normal as compared to age and sex matched controls and YAM. Two female patients (No. 8 and 10) had decreased BMD defined as a value lower than 80% of the age-matched reference population (i.e. the 20% percentile). Both of these patients were postmenopausal and had received relatively high doses of hydrocortisone of 15.4 and 14.8 mg/m$^2$/day, respectively. Patient No. 15 who had received 15.2 mg/m$^2$/day hydrocortisone had a marginally normal BMD that was lower than 90% of the reference population. These results were reflected by mean %BMD being significantly lower in females compared to males (85.9 ± 6.7% vs 112.3 ± 6.6%, P = 0.015). It should be noted that BMD was decreased (<80%) in four patients (nos. 9, 11, 13, 14) when assessed by %YAM. As a result, 4 out of 8 female patients had osteoporosis.

Zelissen et al. reported that adult men with Addison’s disease, treated for at least 10 years with a dose of less than 13.6 mg/m$^2$/day hydrocortisone had normal BMD [4]. On the basis of this finding we divided our patients into 2 groups, one receiving hydrocortisone <13.6 mg/m$^2$/day and the other >13.6 mg/m$^2$/day (Table 2). No patient receiving <13.6 mg/m$^2$/day of hydrocortisone had decreased %BMD, while 2 of the 3 patients treated with higher doses of hydrocortisone had decreased BMD (Fisher’s exact probability = 0.029).

There was a significant negative relationship between %BMD and hydrocortisone dose (Fig. 1a; r = −0.526, p = 0.04). We also observed a statistically significant correlation between %BMD and duration of therapy (Fig. 1b; r = −0.532, P = 0.04), and cumulative dose of hydrocortisone (Fig. 1c; r = −0.59, P = 0.02). To address the question whether BMD is impaired even if patients with adrenal insufficiency are carefully managed to avoid glucocorticoid excess, the correlations were analyzed without the data of the three patients (nos. 8, 10, 15) receiving large dose hydrocortisone (≥13.6 mg/m$^2$). Accordingly, the significant correlation between %BMD and hydrocortisone dose (Fig. 1d; r = 0.057, p = 0.863), duration of treatment (Fig. 1e; r = −0.231, P = 0.480), and cumulative dose (Fig. 1f; r = −0.212, P = 0.519) was lost when these 3 patients were omitted from the analyses. Thus, when treated with appropriate dose of hydrocortisone (≥13.6 mg/m$^2$), there was no significant correlation between %BMD and hydrocortisone dose, duration of therapy or cumulative dose in our study. We also did not find a significant correlation between %BMD and age (r = −0.024, P = 0.93) or primary and secondary adrenocortical insufficiency (P = 0.23).

Plasma ACTH levels in patients with Addison’s disease and the number of eosinophils are thought to be biologically sensitive parameters to determine whether hypercortisolism is present or not. In this context, patients nos. 8 and 10, receiving high dose hydrocortisone, showed normal ACTH, while the number of eosinophils was slightly decreased. Percent of eosinophils was not correlated with hydrocortisone dose (r = −0.024, P = 0.933) or with %BMD (r = −0.190, P = 0.505). No correlation was found between plasma ACTH and either hydrocortisone dose (r = −0.118, P = 0.753) or %BMD (r = −0.139, P = 0.712). Thus, neither eosinophils nor plasma ACTH are sensitive markers for monitoring appropriate replacement dose of hydrocortisone.

### Table 2. Relationship between %BMD and daily hydrocortisone dose

<table>
<thead>
<tr>
<th></th>
<th>Normal %BMD</th>
<th>decreased %BMD (&lt;80% of age and sex matched control)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;13.6 mg/m$^2$</td>
<td>12</td>
<td>0</td>
</tr>
<tr>
<td>&gt;13.6 mg/m$^2$</td>
<td>1</td>
<td>2</td>
</tr>
</tbody>
</table>
Glucocorticoids are potent osteopenic agents that pro-
duce a negative calcium and bone balance. The major
pharmacological effects of these drugs are direct inhibi-
tion of matrix synthesis by osteoblasts and reduction in

**Discussion**

The correlation between %BMD and hydrocortisone dose (a, d), the duration of the treatment (b, e) and cumulative hydrocortisone dose (mg/m²/day × days) (c, f). A significant inverse correlation was found when all the patients were analyzed (a–c). This significant correlation was lost when patients no. 8, 10, 15, who had a large dose of hydrocortisone (>13.6 mg/m²), were omitted from the analyses as shown in Figs. d–f. The regression lines are shown with open circles representing females and closed circles representing males.
corticoid replacement to minimize the development of osteoporosis. The replacement dose of hydrocortisone required to mimic normal cortisol secretion rate in patients with adrenal insufficiency was thought to be approximately 25 to 30 mg/day [2]. However, studies using stable isotopes showed the normal rate of cortisol production was lower at 5.7 mg/m² compared to 12–15 mg/m²/day [15]. This lower cortisol production is equivalent to approximately 10–12 mg/m²/day of oral hydrocortisone, allowing for bioavailability and first-pass hepatic metabolism. There is evidence that conventional hydrocortisone doses of 30 mg/day may reduce BMD. Zelissen et al. [4] demonstrated male patients receiving 13.6 mg/m²/day hydrocortisone had normal BMD as compared to age and sex matched control, while those receiving 16.4 mg/m²/day hydrocortisone had decreased BMD. The findings of our study confirm the desirability of lower glucocorticoid replacement dosages, as 2 of the 3 patients receiving more than 14.8 mg/m²/day hydrocortisone had decreased %BMD, whereas no patient receiving less than 12.4 mg/m²/day had decreased %BMD of age and sex matched control. Taken together, these results indicated glucocorticoid replacement therapy does not reduce BMD unless excessive doses of hydrocortisone are given. Such a conclusion is consistent with previous reports showing normal BMD of age and sex matched control in patients with Addison’s disease [6–9].

Zelissen et al. [4] demonstrated an inverse correlation between hydrocortisone dose per kg of body weight and BMD of the lumbar spine in men receiving long-term conventional glucocorticoid replacement therapy for Addison’s disease. We found no significant relationship between %BMD and hydrocortisone dose (mg/m²/day). We also observed no relationship between %BMD and hydrocortisone dose in 55 patients with panhypopituitarism (r = –0.094, P = 0.495, unpublished data), when treated with appropriate dose of hydrocortisone (~13.6 mg/m²/day). Thus, the loss of correlation after deletion of 3 patients (Fig. 1d) may not be just due to insufficient statistical power. It appears that the daily glucocorticoid dose has no significant effect on bone mass. No relationship was found between %BMD and either duration or cumulative dose (Fig. 1e, f). These findings are consistent with other reports that were also unable to show an association between BMD and duration of steroid therapy and total cumulative glucocorticoid dose [4, 6]. The lack of significant change in BMD of patients with Addison’s disease treated during the 60 months of follow-up with DEXA also supports this notion [8]. However, a weak but significant negative correlation was observed between %BMD and the duration (r = –0.331, P = 0.013) or the cumulative dose (r = –0.290, P = 0.0315) in the patients with panhypopituitarism (n = 55, unpublished data). It needs to be determined whether the duration of hydrocortisone replacement therapy may affect bone mass in a study using a larger number of patients.

The incidence of osteoporotic fracture is about five times less in males than in females [16], with postmenopausal women considered to be the group with the highest risk of developing glucocorticoid-induced osteoporosis. In this study, %BMD was significantly lower in female than in male patients with adrenocortical insufficiency. In addition, the female patients with decreased BMD were postmenopausal. Additionally, 6 of 8 female patients had decreased BMD as assessed by %YAM. This suggests estrogen may exert a protective effect against the development of osteoporosis caused by excessive glucocorticoid replacement.

We observed no difference in BMD between primary and secondary adrenocortical insufficiency. This finding indicated that a patient with secondary adrenocortical insufficiency can be treated with the same hydrocortisone dose used in patients with Addison’s disease. Glucocorticoid-induced bone loss also appears to be unrelated to age [17, 18], and we were unable to demonstrate a correlation between %BMD and age.

In summary, our study showed that decreased %BMD of age and sex-matched control occurred only in patients receiving an excess amount of hydrocortisone replacement therapy for adrenocortical insufficiency. We found no significant correlation between %BMD and hydrocortisone dose, duration of therapy, or cumulative hydrocortisone dose. A daily hydrocortisone dose of less than 13–14 mg/m²/day may serve as a guideline for the dose of glucocorticoid replacement in patients with adrenocortical deficiency, as this dose was not associated with the development of osteoporosis in our study.
References