Bone Mineral Density and Bone Turnover before and after Surgical Cure of Cushing’s Syndrome*

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ABSTRACT

We measured bone mineral density (BMD) using dual-energy x-ray absorptiometry in 20 patients with Cushing’s syndrome (CS) (14 pre- and 2 postmenopausal women, 4 men) before and in 18 of them also at regular intervals after surgical cure (median duration of follow-up, 36 months). In addition, in the premenopausal women with CS, fasting blood samples and 2-h fasting urine samples for measurement of biochemical parameters of bone and collagen metabolism were collected before and in 9 of them also at regular intervals during the first 2 yr after surgery. Marked osteopenia was present in most patients with active CS (Z-scores: lumbar spine -1.45 ± 1.44 and femoral neck -1.50 ± 1.02; mean ± SD). No consistent change in BMD was observed at 3 and 6 months after surgery. Thereafter BMD increased considerably in almost all patients. For the 15 patients with a follow-up of at least 1 yr, Z-scores at the last evaluation were -0.65 ± 1.27 for the lumbar spine and -0.98 ± 1.02 for the femoral neck (both P < 0.002 compared with pretreatment values). In the premenopausal patients, the increase in BMD both in the lumbar spine and in the femoral neck at 24 months was inversely correlated with age (r = -0.703, P < 0.03, and r = -0.667, P < 0.05, respectively). Serum levels of osteocalcin, bone alkaline phosphatase, carboxyterminal propeptide of type I procollagen, aminoterminal propeptide of type III procollagen, and the cross-linked telopeptide of type I collagen, and the urinary hydroxyproline/creatinine ratio increased considerably between 0 and 3 months (from 1.04 ± 0.20 to 3.82 ± 0.30 nmol/mmol) (mean ± SEM, P < 0.0001), indicating a prompt increase of osteoblast activity. Also serum levels of carboxyterminal propeptide of type I procollagen, aminoterminal propeptide of type III procollagen, and cross-linked telopeptide of type I collagen, and the urinary hydroxyproline/creatinine ratio increased significantly between 0 and 3 months. Thereafter these levels decreased gradually. We conclude that marked osteopenia in the lumbar spine and femoral neck is present in most patients with active Cushing’s syndrome. Bone density does not consistently change in the first 6 months after cure, despite an apparently rapid restoration of osteoblast activity. Thereafter remarkable improvement of bone density can be observed in almost all patients. (J Clin Endocrinol Metab 80: 2859–2865, 1995)
daily, which was tapered off in the year after surgery and stopped between 8 and 12 months postoperatively.

Six patients (6, 10-12, 15, and 20) with pituitary-dependent Cushing’s syndrome were cured by bilateral adrenalectomy via the transperitoneal route. This operation caused transient hypocortisolism in patients 6, 10-12, and 15, necessitating substitution therapy with cortisone acetate for 8–16 months, but did not induce other endocrine deficiencies. Patients 12 and 20 were also hypocortisolemic after pituitary microadenomectomy, but the short follow-up after surgery does not permit conclusions with regard to permanent postoperative endocrine deficiencies. Patients 17–19 with pituitary-dependent Cushing’s syndrome were cured by (sub)-total adenohypophysectomy via the transsphenoidal route. This operation caused permanent secondary hypocortisolism and hypothyroidism, necessitating substitution therapy with cortisone acetate and L-thyroxine. Postoperative secondary hypogonadism was present in patients 18 and 19, necessitating treatment with im injections of testosterone esters. In addition, postoperative growth hormone deficiency was present in all three patients. In patient 19 substitution therapy with recombinant human growth hormone was started daily, which was tapered off in the year after surgery and stopped between 8 and 12 months postoperatively.

The patients were fractures of lumbar vertebrae seen on radiographs made before and 24 months after surgery.

BMD measurements are expressed in g/cm². Moreover, for each BMD measurement a Z-score was calculated according to the formula:

\[ Z = \frac{\text{patient's value (g/cm}^2\text{)} - \text{mean of a reference group of age- and sex-matched healthy individuals (g/cm}^2\text{)} + \text{sd reference group (g/cm}^2\text{)}}{\text{sd reference group (g/cm}^2\text{)}} \]

Results of BMD measurements before and during the first 2 yr after surgical treatment in patients 1, 2, 3, 4, 5, and 6 have been reported earlier (6).

**Biochemical measurements.** Before surgical therapy in the 14 premenopausal women with Cushing’s syndrome, blood samples were drawn (between 0830 and 0930 h) and 2-h urine samples were collected (between 0800 and 1000 h) after an overnight fast for measurement of biochemical parameters of bone and collagen metabolism. In 9 of these premenopausal patients (1–9), the parameters (except for bone alkaline phosphatase) were also determined at 3, 6, 12, 18, and 24 months after definitive surgical treatment. Data were compared with those of a group of 18 age-matched healthy premenopausal women in the early follicular phase of the menstrual cycle.

Blood samples for measurement of serum bone alkaline phosphatase, osteocalcin, carboxyterminal propopdeptide of type I procollagen (PICP), amino terminal propeptide of type III procollagen (P1NP) and the cross-linked telopeptide of type I collagen (ICTP) were centrifuged immediately after collection. Thereafter, samples were kept at —20°C until analyzed. All samples were run in duplicate. Serum bone alkaline phosphatase was assayed by a direct immunoradiometric assay (Ostase, Hybritech, San Diego CA) using two monoclonal antibodies directed against the bone isoenzyme and with bone alkaline phosphatase purified from human osteosarcoma cells as a standard. Intra- and interassay CVs were 5% and 7.5%, respectively. Serum osteocalcin was measured by RIA (OSTK-PR, CIS, Gif-sur-Yvette Cedex, France; intraassay CV 6%, interassay CV 7%). Serum PICP was measured by RIA (PICP RIA-kit, Orion Diagnostica, Espoo, Finland). Intra- and interassay CVs using a reference serum sample were 4% and 6%, respectively. Serum ICTP was measured by RIA (ICTP RIA-kit, Orion Diagnostica; intraassay CV 4.5%, interassay CV 6%).

Urines were not acidified before analysis. Urinary creatinine was measured on a Cobas Bio automatic analyzer system (Roche, Basel, Switzerland). Urinary hydroxyproline was measured with the Hypronostic kit (Organon Teknika, Bostel, The Netherlands).

### Methods

**BMD measurements.** BMD was measured two times before (on 2 consecutive days) and at 3, 6, 12, 18, 24, 36, 48, and 60 months after definitive surgical treatment. BMD was measured in the lumbar spine (L1-L4; anterior-posterior) and the left femoral neck using dual-energy x-ray absorptiometry (Hologic Inc, Waltham MA, model QDR-1000). The coefficient of variation (CV) for repeat measurements in our hospital is 1.0% in the lumbar spine and 1.7% in the femoral neck (5). In none of the patients were fractures of lumbar vertebrae seen on radiographs made before and 24 months after surgery.

BMD measurements are expressed in g/cm². Moreover, for each BMD measurement a Z-score was calculated according to the formula:

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Urines were not acidified before analysis. Urinary creatinine was measured on a Cobas Bio automatic analyzer system (Roche, Basel, Switzerland). Urinary hydroxyproline was measured with the Hypronostic kit (Organon Teknika, Bostel, The Netherlands).
Statistical analyses

Statistical analyses were performed using the Wilcoxon signed rank test for paired observations (P values denoted as P), the Mann-Whitney U test for unpaired observations (P = P*) and the Spearman rank correlation test (P = P**). Unless otherwise stated, the mean values ± 1 sd are given.

Results

BMD in patients with active Cushing's syndrome

Marked osteopenia was present in most patients with active Cushing's syndrome (Table 2). The decrease in BMD was equally severe in the lumbar spine and femoral neck (Z-scores: lumbar spine -1.56 ± 1.32 and femoral neck -1.76 ± 0.85) and those with an adrenal adenoma (Z-scores: lumbar spine -1.19 ± 1.80 and femoral neck -1.39 ± 1.09).

In the group of 14 premenopausal women, BMD (Z-score) in the lumbar spine was significantly correlated with BMD in the femoral neck (r = 0.553, P** < 0.05). BMD in the lumbar spine was also significantly correlated with the body mass index (kg/m²) (r = 0.644, P** < 0.02) in the group of premenopausal women, whereas there was no significant correlation between BMD in the femoral neck and body mass index (r = 0.355, P** > 0.10). There was also no significant correlation between BMD (Z-scores) at either site and age, duration of symptomatic glucocorticoid excess, duration of amenorrhea, or mean 24-h plasma cortisol in the group of premenopausal patients.

BMD after surgical cure of Cushing's syndrome

After surgery no consistent change in BMD was observed at 3 and 6 months (Fig. 1). In fact, BMD was lowered by 2% or more in comparison with pretreatment values at one or both time points in 6 of 17 patients at the lumbar spine and in 11 of 16 patients at the femoral neck. In the group of premenopausal women, there was a highly significant inverse correlation between age and increase in BMD in the lumbar spine in the first 6 months after surgery (r = -0.925, P** < 0.0005).

From 6 months onward BMD increased considerably in most patients (Fig. 1). For the 15 patients with a duration of follow-up of at least 1 yr, Z-scores at the time of the last evaluation are given in Table 2. At the last evaluation Z-scores in these 15 patients were -0.65 ± 1.27 for the lumbar spine and -0.98 ± 1.02 for the femoral neck (both P < 0.002 compared with pretreatment values). When compared with pretreatment values, BMD at the last measurement had increased in the lumbar spine in 12 of 15 patients (in 7 of them by more than 15%; increase 22.0% ± 4.0%, n = 5). However, at the last measurement, BMD in the lumbar spine was still lower than -1 sd in 6 of 15 patients and in the femoral neck in 7 of 15 patients. In the group of premenopausal patients, the in-

### Table 2. Bone mineral density (BMD; g/cm²) in the lumbar spine (L1-L4) and left femoral neck in 20 patients with Cushing's syndrome before and after surgical cure

<table>
<thead>
<tr>
<th>Patient number</th>
<th>BMD lumbar spine in g/cm² (Z-score in sd)</th>
<th>BMD femoral neck in g/cm² (Z-score in sd)</th>
<th>Time between definitive surgery and last measurement of BMD (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Before definitive surgery</td>
<td>Last measurement after definitive surgery</td>
<td>Before definitive surgery</td>
</tr>
<tr>
<td>1</td>
<td>0.700 (−3.18)</td>
<td>0.861 (−1.57)</td>
<td>0.638 (−2.54)</td>
</tr>
<tr>
<td>2</td>
<td>0.791 (−2.08)</td>
<td>0.989 (−0.41)</td>
<td>0.661 (−2.31)</td>
</tr>
<tr>
<td>3</td>
<td>1.024 (−0.10)</td>
<td>1.288 (2.22)</td>
<td>0.684 (−2.12)</td>
</tr>
<tr>
<td>4</td>
<td>0.937 (−0.70)</td>
<td>0.933 (−0.63)</td>
<td>0.664 (−1.77)</td>
</tr>
<tr>
<td>5</td>
<td>0.723 (−2.70)</td>
<td>0.931 (−0.89)</td>
<td>0.731 (−1.64)</td>
</tr>
<tr>
<td>6</td>
<td>0.918 (−0.99)</td>
<td>0.866 (−0.11)</td>
<td>0.737 (−1.15)</td>
</tr>
<tr>
<td>7</td>
<td>0.949 (−0.79)</td>
<td>0.927 (−1.06)</td>
<td>0.722 (−1.78)</td>
</tr>
<tr>
<td>8</td>
<td>0.708 (−3.07)</td>
<td>0.707 (−0.88)</td>
<td>0.546 (−3.44)</td>
</tr>
<tr>
<td>9</td>
<td>0.869 (−1.48)</td>
<td>1.031 (−0.09)</td>
<td>0.811 (−0.83)</td>
</tr>
<tr>
<td>10</td>
<td>1.014 (−0.15)</td>
<td>1.067 (0.26)</td>
<td>0.815 (−0.80)</td>
</tr>
<tr>
<td>11</td>
<td>0.800 (−1.90)</td>
<td>0.942 (0.67)</td>
<td>0.790 (−1.76)</td>
</tr>
<tr>
<td>12</td>
<td>1.061 (0.39)</td>
<td>0.779 (−0.66)</td>
<td>0.673 (−2.09)</td>
</tr>
<tr>
<td>13</td>
<td>0.757 (−2.62)</td>
<td>0.811 (−0.37)</td>
<td>0.673 (−2.09)</td>
</tr>
<tr>
<td>14</td>
<td>0.934 (0.80)</td>
<td>0.811 (−0.37)</td>
<td>0.673 (−2.09)</td>
</tr>
<tr>
<td>15</td>
<td>0.671 (−2.50)</td>
<td>0.771 (−1.25)</td>
<td>0.637 (−1.43)</td>
</tr>
<tr>
<td>16</td>
<td>1.120 (1.60)</td>
<td>0.783 (−0.15)</td>
<td>0.637 (−1.43)</td>
</tr>
<tr>
<td>17</td>
<td>0.743 (−3.17)</td>
<td>0.863 (−2.07)</td>
<td>0.623 (−2.98)</td>
</tr>
<tr>
<td>18</td>
<td>0.828 (−2.40)</td>
<td>0.925 (−1.51)</td>
<td>0.802 (−1.40)</td>
</tr>
<tr>
<td>19</td>
<td>1.130 (1.74)</td>
<td>1.158 (1.04)</td>
<td>0.955 (0.99)</td>
</tr>
<tr>
<td>20</td>
<td>0.710 (−3.05)</td>
<td>0.649 (−1.75)</td>
<td>0.689 ± 0.147</td>
</tr>
</tbody>
</table>

In parentheses BMD is expressed as positive or negative standard deviations from the age- and sex-specific normal mean (Z-score, see text).  
Mean of two determinations.  
Values of patients with a duration of follow-up of at least 12 months after definitive surgery are given.
Fig. 1. Percentage change in BMD in the lumbar spine (L1-L4) and femoral neck after surgical cure of 18 patients with Cushing's syndrome. The individual values at seven time points after surgery were compared with the pretreatment value (t = 0 months; mean of two determinations). Note that the improvement of BMD in the lumbar spine in patients 7 and 8 is less than that in the other patients. Both patients used glucocorticoids in doses that were higher than the normal substitution dose, and patient 7 was treated for a malignant midline granuloma 9 months after bilateral adrenalectomy.

crease in BMD in the lumbar spine at 24 months was inversely correlated with age (\( r = -0.733, P^{**} < 0.03 \)) and positively correlated with the increase in BMD in the femoral neck at 24 months (\( r = 0.767, P^{**} < 0.03 \)) and with the increase in BMD in the lumbar spine at 6 months (\( r = 0.867, P^{**} < 0.005 \)). The increase in BMD in the femoral neck at 24 months was also inversely correlated with age (\( r = -0.667, P^{**} < 0.05 \)).

**Biochemical parameters of bone and collagen metabolism in premenopausal patients with active Cushing's syndrome**

Serum levels of parameters of osteoblast activity and collagen synthesis (osteocalcin, bone alkaline phosphatase, PICP, PIIINP) were not significantly different between the group of 14 premenopausal patients with active Cushing's syndrome and the group of 18 age-matched healthy premenopausal women (Table 3). Of the parameters of bone resorption, the urinary hydroxyproline/creatinine ratio was significantly higher in patients with Cushing's syndrome, whereas serum levels of ICTP were not different between both groups.

In the patients with Cushing's syndrome, serum osteocalcin levels were significantly correlated with those of PICP (\( r = 0.645, P^{**} < 0.03 \)) and those of bone alkaline phosphatase (\( r = 0.639, P^{**} < 0.05 \)). No other significant correlations were observed between the above-mentioned biochemical parameters in the group of premenopausal patients with Cushing's syndrome. Z-scores in the lumbar spine or the femoral neck did not correlate significantly with any of the biochemical parameters of bone and collagen metabolism.

In the group of healthy premenopausal women, serum osteocalcin levels were significantly correlated with those of PICP (\( r = 0.602, P^{**} < 0.01 \)) and of bone alkaline phosphatase (\( r = 0.783, P^{**} < 0.0001 \)), as they were in the patients with Cushing's syndrome. In the healthy women, serum PICP levels were also correlated with serum levels of bone alkaline phosphatase (\( r = 0.737, P^{**} < 0.0003 \)). Unlike the serum levels of ICTP in the patients with Cushing's syndrome, serum levels of ICTP in the healthy premenopausal women were

| TABLE 3. Serum and urine levels of parameters of bone and collagen metabolism in 14 premenopausal patients with active Cushing's syndrome and in 18 age-matched healthy premenopausal women |
|---------------------------------|-----------------|-----------------|
|                                 | Cushing's syndrome | Healthy woman |
| Serum osteocalcin (nmol/L)      | 1.05 ± 0.60      | 1.28 ± 0.42     | NS          |
| Serum bone alkaline phosphatase (µg/L) | 12.6 ± 6.5 | 9.9 ± 3.7      | NS          |
| Serum PICP (µg/L)               | 190 ± 99         | 128 ± 53        | NS          |
| Serum PIIINP (µg/L)             | 3.9 ± 2.8        | 2.6 ± 0.8       | NS          |
| Serum ICTP (µg/L)               | 3.8 ± 1.6        | 3.7 ± 1.1       | NS          |
| Urine hydroxyproline/creatinine (µmol/mmol) | 24.6 ± 9.6 | 16.2 ± 3.5     | <0.01       |

PICP, Carboxyterminal propeptide of type I procollagen; PIIINP, aminoterminal propeptide of type III procollagen; ICTP, cross-linked telopeptide of type I collagen.

* Mann-Whitney U test (NS, not significant).
significantly correlated with those of osteocalcin (r = 0.504, \( P^{**} < 0.05 \)), PICP (r = 0.608, \( P^{**} < 0.01 \)), and bone alkaline phosphatase (r = 0.740, \( P^{**} < 0.0003 \)).

Biochemical parameters of bone and collagen metabolism after surgical cure of premenopausal patients with Cushing's syndrome

In nine premenopausal patients with Cushing's syndrome we determined the above-mentioned parameters, except for bone alkaline phosphatase, at regular intervals during the first 2 yr after surgical cure (Fig. 2). In all patients, serum levels of osteocalcin increased considerably between 0 and 3 months [from 1.04 ± 0.20 to 3.82 ± 0.30 nmol/L (mean ± SEM), \( P < 0.0001 \)], indicating a prompt increase of osteoblast activity. Also serum levels of PICP and PIIINP increased significantly between 0 and 3 months [PICP from 173 ± 32 to 250 ± 35 \( \mu \)g/L (mean ± SEM), \( P < 0.05 \), and PIIINP from 3.14 ± 0.89 to 14.80 ± 1.75 \( \mu \)g/L (mean ± SEM), \( P < 0.0001 \)]. Thereafter PICP levels decreased gradually (24 months vs. 3 months, \( P < 0.05 \); 24 months vs. healthy controls, \( P^{*} > 0.10 \)). Serum osteocalcin and PIIINP levels also decreased gradually from 3 months after surgery onward (24 months vs. 3 months, \( P < 0.05 \)), but at 24 months after surgery these levels were still elevated when compared with levels in healthy women (\( P^{*} < 0.05 \)). Of the parameters of bone resorption, the urinary hydroxyproline/creatinine ratio and serum levels of ICTP increased in all patients between 0 and 3 months [ICTP: from 4.07 ± 0.65 to 14.09 ± 2.30 \( \mu \)g/L (mean ± SEM), \( P < 0.05 \); urinary hydroxyproline/creatinine ratio: from 27.36 ± 2.85 to 70.73 ± 7.45 \( \mu \)mol/mmol (mean ± SEM), \( P < 0.0001 \)]. Thereafter the urinary hydroxyproline/creatinine ratio decreased gradually (24 months vs. 3 months, \( P < 0.005 \); 24 months vs. healthy controls, \( P^{*} > 0.10 \)). Serum ICTP levels also decreased gradually from 3 months after surgery onward (24 months vs. 3 months, \( P < 0.05 \)), but at 24 months after surgery these levels were still elevated when compared with levels in healthy women (\( P^{*} < 0.05 \)).

Discussion

In the present study, marked osteopenia, equally severe in the lumbar spine and in the femoral neck, was demonstrated by dual-energy x-ray absorptiometry in most patients with active Cushing's syndrome. In a preliminary report, Mercado-Asis et al. (7), using the same technique as that used in our study, emphasized that the decrease in BMD was more severe in pediatric than in adult patients with Cushing's syndrome (in agreement with the observation that young patients receiving glucocorticoid therapy lose bone more rapidly than do older patients (8)). In our group of 14 adult premenopausal patients with Cushing's syndrome, we could not demonstrate a significant correlation between BMD and age, nor between BMD and estimated duration of symptom-
atic glucocorticoid excess, duration of amenorrhea, and mean 24-h plasma cortisol. Interestingly, a significant positive correlation between BMD in the lumbar spine and body mass index was observed. Apparently a high body mass protects against glucocorticoid-induced bone loss in the lumbar spine.

The mechanism of the profound decrease of BMD in Cushing's syndrome cannot be derived from our study. It is, however, most likely that several factors act together, e.g. the detrimental effect of hypercortisolism on bone formation, the glucocorticoid-induced decrease of muscular strength leading to impaired physical activity, and the glucocorticoid-induced impairment of the activity of the pituitary-gonadal axis and of growth hormone secretion.

Histomorphometric studies in patients treated with glucocorticoids show a marked decrease in the thickness of osteoid seams, a low mineral apposition rate as measured by tetracycline labeling, and a reduced mean wall thickness (9, 10). These findings support the view that glucocorticoid administration decreases bone formation because of direct or indirect inhibition of osteoblast function. Histomorphometric studies in a few patients with Cushing's syndrome revealed a similar pattern (3, 9). In our group of 14 premenopausal patients with active Cushing's syndrome, we found normal serum levels of markers of osteoblast activity and collagen synthesis. In our opinion the normal serum levels of osteocalcin, bone alkaline phosphatase, and PICP indicate either that osteoblast activity would be normal in these premenopausal Cushing's patients or that these biochemical parameters lack sufficient sensitivity to detect small decreases of osteoblast activity in patients with Cushing's syndrome at the time of diagnosis. In this respect it has to be noted that the mean duration of estimated symptomatic cortisol excess in our patients was more than 2.5 yr and that in corticosteroid-treated patients bone loss seems to be most marked during the first 6–12 months of treatment, with the rate of bone loss sharply slowing down or even approaching zero thereafter (11, 12). Our data on markers of osteoblast activity are in agreement with those from Ebeling et al. (13) who found normal serum levels of bone alkaline phosphatase and PICP in a group of 25 patients with exogenous (n = 10) or endogenous (n = 15) glucocorticoid excess. Normal serum levels of PICP in patients with Cushing's syndrome were also reported by Piovesan et al. (14). In contrast to our data, decreased serum levels of osteocalcin and PICP indicate either that osteoblast activity would be normal in these premenopausal Cushing's patients or that these biochemical parameters lack sufficient sensitivity to detect small decreases of osteoblast activity in patients with Cushing's syndrome at the time of diagnosis. In this respect it has to be noted that the mean duration of estimated symptomatic cortisol excess in our patients was more than 2.5 yr and that in corticosteroid-treated patients bone loss seems to be most marked during the first 6–12 months of treatment, with the rate of bone loss sharply slowing down or even approaching zero thereafter (11, 12). Our data on markers of osteoblast activity are in agreement with those from Ebeling et al. (13) who found normal serum levels of bone alkaline phosphatase and PICP in a group of 25 patients with exogenous (n = 10) or endogenous (n = 15) glucocorticoid excess. Normal serum levels of PICP in patients with Cushing's syndrome were also reported by Piovesan et al. (14). In contrast to our data, decreased serum levels of osteocalcin in Cushing's syndrome were reported in a number of studies (3, 13–16).

Histomorphometric studies, which show an increase in trabecular resorption surfaces, and calcium kinetic studies suggest that bone resorption is enhanced by glucocorticoids (9, 17, 18). This increased bone resorption is possibly attributable to secondary hyperparathyroidism, which is mediated by the negative calcium balance resulting from the inhibitory effect of steroids on both intestinal calcium absorption and renal conservation of calcium. In our study two supposed indicators of bone resorption were measured. We found that the urinary hydroxyproline/creatinine ratio was significantly higher in premenopausal patients with Cushing's syndrome than in healthy premenopausal women, whereas serum levels of ICTP were not different in both groups. However, it has to be emphasized that the first parameter is not specific for bone resorption because part of the hydroxyproline in urine could have been derived from soft tissue turnover and repair, whereas the sensitivity and specificity of the latter parameter in detecting changes in bone resorption is not yet established. Interestingly, parameters of bone formation (bone alkaline phosphatase, osteocalcin, and PICP) and those of bone resorption (ICTP) are positively correlated in healthy premenopausal women but not in our premenopausal Cushing's patients, suggesting uncoupling of bone formation and resorption in the latter.

In the first 6 months after surgery there was a highly significant inverse correlation between age and increase in BMD in the lumbar spine. At 24 months after surgery, such a significant inverse correlation between age and the increase in BMD was present for both the lumbar spine and the femoral neck. Apparently, in older premenopausal women the improvement of osteopenia after cure of Cushing's syndrome is less than that in younger women, at least during the first 2 yr after surgery.

It is of interest that in the first 6 months after surgery BMD was lowered by 2% or more in comparison with pretreatment values in 6 of 17 patients in the lumbar spine and in 11 of 16 patients in the femoral neck. In the group of premenopausal women, serum levels of osteocalcin increased considerably to above the normal range in all patients; these levels remained elevated during the whole period of observation, indicating a prompt and sustained increase of osteoblast activity. In parallel with the increase in osteocalcin levels, serum levels of PICP and PIIINP increased significantly after treatment, but their increase was not sustained. Both parameters of bone resorption (serum ICTP and urinary hydroxyproline/creatinine ratio) also increased significantly after surgery and only gradually normalized in the years thereafter. We interpret these findings as an expression of restoration of the coupling between osteoblast and osteoclast function after cure of Cushing's syndrome. It may be that in such a situation mineralization of newly formed osteoid is delayed, thus explaining the decrease in BMD occurring in a considerable number of patients after cure of Cushing's syndrome. However, interpretation of the pattern of the urinary hydroxyproline/creatinine ratio and the serum level of ICTP has to be cautious in light of the limitations of both parameters in detecting bone resorption, especially during nonsteady-state conditions. Furthermore, the increase in both parameters after treatment of Cushing's syndrome might be caused by an increase of soft tissue turnover and repair and not by an increase in bone resorption. Unfortunately, histomorphometric studies in series of patients with Cushing's syndrome after treatment are lacking.

In a cross-sectional study, Manning et al. (19) found that BMD in the lumbar spine and femoral neck in 17 patients cured earlier of Cushing's syndrome (8.6 ± 1.6 yr; mean ± SEM) was normal. These authors adduced that the regaining of bone density is gradual, probably taking approximately 10 yr to become complete. In our study (with a much shorter follow-up), BMD at the time of the last measurement was still lower than -1 sd in 6 of 15 patients in the lumbar spine and in 7 of 15 patients in the femoral neck. Additional follow-up of our patients will determine whether BMD will recover completely.

We conclude that marked osteopenia in the lumbar spine
and femoral neck is present in most patients with active Cushing’s syndrome. Bone density does not consistently change in the first 6 months after cure, despite an apparently rapid restoration of osteoblast activity. Thereafter remarkable improvement of bone density can be observed in almost all patients.

References