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# Bone Demineralization and Vertebral Fractures in Endogenous Cortisol Excess: Role of Disease Etiology and Gonadal Status

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**Introduction:** The effects of endogenous cortisol (F) excess on bone mass and vertebral fractures have still not been thoroughly investigated. The aim of this cross-sectional case-control study was to investigate factors influencing bone demineralization and vertebral fractures in different conditions of F excess, *i.e.* Cushing's disease and adrenal and ectopic Cushing's syndrome.

**Materials and Methods:** Eighty consecutive patients and 80 controls were prospectively enrolled: 37 patients (21 females) with pituitary ACTH-secreting adenoma, 18 (14 females) with adrenocortical adenoma, 15 (11 females) with adrenal carcinoma of mixed secretion, and 10 (three females) with ectopic ACTH secretion. The groups had similar age. At diagnosis, bone mineral density (BMD) was determined by the dual-energy x-ray absorptiometry technique at the lumbar spine (L1–L4) and femoral neck; vertebral fractures were investigated by standard spinal radiographs.

**Results:** When comparing the groups with different etiology of F excess, the patients with ectopic ACTH secretion had higher F and lower BMD values than the other subgroups. Morning F ($P = 0.03$) and testosterone levels ($P = 0.04$) correlated with lumbar BMD. Vertebral fractures were found in 61 (76%) of the patients, were multiple in 52 (85%) of the cases, and clinically evident in 32 (52%). Only multiple fractures were more frequent in patients with ectopic ACTH hypersecretion ($P < 0.05$). Lumbar spine BMD was the best predictor of vertebral fractures ($P < 0.01$). Surprisingly, amenorrheic and eumenorrheic women had similar BMD values and fracture prevalence.

**Conclusion:** A high prevalence (76%) of vertebral fracture was revealed, regardless of the etiology of the patients' hypercortisolism. The harmful effects of F excess at the spine were partly counterbalanced by the increased androgen production but were not affected by gonadal status in women. **(*J Clin Endocrinol Metab* 91: 1779–1784, 2006)**

THE SYNDROME OF glucocorticoid excess, first described in 1932 by Harvey Cushing, is recognized as one of the most important causes of bone loss (1). Cortisol (F) exerts direct and indirect effects on bone, enhancing its resorption and inhibiting its formation (2, 3–5). Glucocorticoid excess directly inhibits the differentiation of pluripotent mesenchymal cells toward the osteoblastic lineage, directing them into the adipocytic pathway (6). It reduces the production of growth factors and bone matrix proteins and decreases calcium absorption (7). Bone fractures, the main complication of osteoporosis, are well recognized as a dose-dependent effect in patients on glucocorticoid treatment and have been described as a presenting symptom of endogenous F excess (8, 9). A high incidence of nontraumatic fractures in the period preceding the diagnosis of Cushing's syndrome was described in 104 patients in a retrospective study by Vestergaard *et al.* (10).

The negative effects of F on the bone probably depend on the degree of its excess, whereas sex steroids have anabolic effects. The relationship between F and sex steroids may be complex in patients with endogenous hypercortisolism. It is well known that F excess alone inhibits the gonadal axis in both genders (3, 5); nevertheless, the production of dehydroepiandrosterone sulfate (DHEAS) and androstenedione is generally increased in ACTH-dependent hypercortisolism and frequently high in adrenocortical carcinomas, together with the testosterone (T) levels. Androstenedione, DHEAS, and T are usually low in adrenal adenomas (11, 12). Estrogens may be increased in subjects with adrenal carcinomas but are frequently low in women with ACTH excess and adrenal adenomas (13, 14). Androgen excess has been found to exert protective effects on bone mass in women with polycystic ovary syndrome, counterbalancing the harmful effects of amenorrhea (15, 16). With regard to the effects of estrogens, corticosteroid treatment and Cushing's syndrome have been shown to cause more severe bone damage in postmenopausal than reproductive-aged women (17, 18). Nevertheless, it is still unclear whether any protective bone effects of androgens or estrogens can occur in patients with endogenous F excess. Few data are currently available on the effects of mixed F, androgen, and estrogen excess on bone mass and the prevalence of vertebral fractures.

This cross-sectional, case-control study aimed at investigating the risk factors for bone demineralization and verte-

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Abbreviations: ALP, Alkaline phosphatase; BMD, bone mineral density; BMI, body mass index; DHEAS, dehydroepiandrosterone sulfate; $E_2$, 17-$\beta$-estradiol; F, cortisol; iPTH, intact PTH; T, testosterone; UFF, urinary free F.

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bral fractures in endogenous glucocorticoid excess of different etiologies.

## Subjects and Methods

### *Study design*

In this cross-sectional, case-control study, we have analyzed determinants of bone demineralization and vertebral fractures in glucocorticoid excess of different etiologies. We took into consideration the gender, anthropomorphic features, estimated disease duration, serum F, T, androstenedione, DHEAS, and 17-$\beta$-estradiol ($E_2$) levels, and the ratios among serum F, androgens, and $E_2$. All determinations were performed at the diagnosis of Cushing's syndrome. The study was performed according to the procedures indicated by the Helsinki II Declaration. All enrolled subjects gave their informed consent to participate in the study.

### *Subjects*

From January 1996 to June 2003, 80 consecutive patients with endogenous F excess were referred to our department and prospectively enrolled in this study. The diagnosis of F excess was made on the basis of the typical clinical signs and symptoms and inappropriately elevated values of serum F and urinary free F (UFF) excretions. Additional investigations included assays of circulating ACTH, FSH, LH, and prolactin levels, a low-dose 2-mg dexamethasone suppression test in all cases, and a high-dose 8-mg dexamethasone suppression test in all patients with ACTH-dependent Cushing's syndrome; pituitary magnetic resonance imaging or adrenal computed tomography was performed as appropriate. A whole-body scintigraphy with $^{111}$In-DTPA-D-phe1-octreotide was performed in patients with suspected ectopic ACTH hypersecretion; areas of abnormal uptake were then evaluated by computed tomography scan to confirm the presence of lesions. Among the 80 patients, histology confirmed the diagnosis of pituitary ACTH-secreting adenoma in 37 (microadenoma in 30 and macroadenoma in seven) of them, F-secreting adrenocortical adenoma in 18, mixed F- and androgen-secreting adrenocortical adenoma in four, mixed secreting carcinoma in 11, and ectopic ACTH excess due to bronchial carcinoid in eight patients. In the remaining two patients, a diagnosis of ectopic ACTH syndrome was suspected, but the tumor site is still unknown. Disease duration was estimated around the interval between the symptom onset mentioned by the patients when specifically asked (*i.e.* weight gain, appearance of striae rubrae, increase in blood pressure, *etc.*) and the diagnosis. Patients were considered to have hyperandrogenism when at least one of the androgens (T, DHEAS, or androstenedione) was 2 SD above the mean of the controls. Women were considered amenorrheic when menstrual cycles did not occur at regular intervals and $E_2$ levels were below the normal range for the early follicular phase.

For each patient enrolled, a control subject matched for age, gender, and body mass index (BMI) was selected and included in the data analysis. Eighty subjects with eucortisolism were recruited among the patients with euthyroid goiter (TSH, 1–2.5 U/liter). Age was matched within 1 yr of the birth date, and BMI was matched within $\pm 1.5$ kg/m$^2$. None of the 160 subjects had previously taken drugs known to interfere with bone metabolism, oral contraceptive, or hormonal replacement therapy, nor used to drink more than four cups of coffee per day and/or two alcohol-containing beverages per day.

### *Assessment of bone density and turnover*

Serum calcium, phosphorus, creatinine, alkaline phosphatase (ALP), albumin, intact PTH (iPTH), and osteocalcin were determined after at least 8 h fasting, whereas urinary calcium and hydroxyproline excretion were measured in 24-h urine collection and corrected for creatinine excretion. Bone mineral density (BMD) at the lumbar spine (L1–L4 in anteroposterior scan) and femoral neck was determined by dual-energy x-ray absorptiometry using Hologic QDR 1000 densitometer (Hologic, Inc., Waltham, MA). Because of mixed (male and female) population, individual BMD values were expressed as Z scores. The coefficient of variation for the dual-energy x-ray absorptiometry technique was less than 1.5% for the lumbar spine and less than 1.8% for the femoral neck. The reference population adopted in this study was the international pooled sample provided by the manufacturer; their data, however, did not differ significantly from those obtained on a local sample in a study performed when the device was set up (19). Quality control was maintained by daily scanning of an anthropomorphic spine phantom. A systematic review of each BMD was performed, and artifacts from fractured vertebral bodies, kyphosis, and scoliosis were excluded from the evaluation. No patient had imbedded metal at the lumbar vertebrae or severe joint disease at the L1–L4 segments.

### *Assessment of vertebral fractures*

All patients were evaluated for back pain and height changes as clinical symptoms of vertebral fractures. Potential asymptomatic vertebral compression fractures were investigated in all patients by standard spinal radiographs in anterior-posterior and lateral positions of the vertebrae Th4–L4. A prevalent fracture was defined in accordance with previous studies, with a 20% difference in anteroposterior, middle-posterior, or posterior-posterior adjacent ratio (20, 21). Vertebral collapse was defined as wedge-shaped, biconcave, or completely collapsed bodies (20, 21). Because most patients had a very severe demineralization of the vertebral bodies, it was impossible to use the digitalized technique for vertebral body measurement. An analysis of radiographic films was independently performed in chronological order by two operators: a skeletal radiologist (L.C.) and an endocrinologist trained in osteoporosis management (L.T.). They were blind to the status of case/control and origin of F excess. The validity of each finding was established by both operators for the detection of the presence and number of fractures; the interobserver agreement was calculated using $k$ statistics, and results were good ($k = 0.87$).

### *Assays*

Hormone determinations were performed with the same commercial kits for the whole study period: F, T, $E_2$, and DHEA-S by Immulite and solid-phase chemoluminescent enzyme immunoassay (Diagnostic Products Corp., Los Angeles, CA); androstenedione by RIA Diagnostic Systems Laboratories (Webster, TX); FSH and LH by RIA using Biodata kits (Rimini, Italy); and prolactin by RIA using Radim kits (Pomezia, Italy). iPTH and serum osteocalcin levels were measured by RIA (Nichols Institute Diagnostics, San Clemente, CA). Hydroxyproline excretion was measured with HPLC. Blood chemistry profile, including levels of calcium, phosphorus, ALP, 24-h urinary calcium excretion, and creatinine, were analyzed using a standard autoanalyzer.

### *Statistical analysis*

The statistical analysis was performed by the SPSS Inc. (Chicago, IL) package (release 13.0) and StatsDirect statistical software (release 2.5.2, StatsDirect Ltd., Cheshire, UK). Data distribution was analyzed by the Kolmogorov-Smirnov test. To compare data for continuous variables, ANOVA followed by Bonferroni test as *post hoc* test or Kruskal-Wallis H test followed by Dwass-Steel-Chritchlow-Fligner test (22) were used, according to the data distribution. Categorical variables were compared by using the Pearson's $\chi^2$ test. The data were compared between patients and controls, between patients with and without fractures, and between subgroups of patients with different etiology of F excess. Age, BMI, estimated disease duration, urinary F excretion, and circulating levels of F, androgens, and $E_2$ were considered as potential predictive factors for BMD by the linear regression analysis. All these parameters plus BMD were included in the evaluation of risk factors for vertebral fractures by the logistic regression. The step-wise forward selection was used for both procedures. Predictive factors of vertebral fractures have been evaluated by the receiver operating characteristic analysis on the different parameters considering the value associated with the maximal diagnostic accuracy (maximal sum of sensitivity and specificity). Statistical significance was set at 5%.

## Results

### *Anthropometrical and endocrine profiles (Table 1)*

Age was similar in all groups of patients, whereas the estimated disease duration was shorter in patients with ectopic ACTH secretion and adrenal carcinomas when compared with the other subgroups ($P < 0.01$). BMI was higher in the patients with isolated F excess due to adrenal adenoma

**TABLE 1.** Clinical features of patients and controls

| Variable | ACTH-secreting pituitary adenoma | Adrenal adenoma | Adrenal carcinoma | Ectopic ACTH excess | Controls |
|---|---|---|---|---|---|
| No. of subjects | 37 | 18 | 15 | 10 | 80 |
| Female/male | 21/16 | 14/4 | 11/4 | 3/7 | 49/31 |
| Age (yr) | 38 (18–58) | 38 (22–66) | 41.5 (27–58) | 42 (29–52) | 39 (18–66) |
| BMI (kg/m$^2$) | 26.9 (21–40.2) | 28.3 (21.3–40.4) | 28.2 (21–33) | 27 (21.6–33.7) | 27 (21–40) |
| Estimated disease duration (months) | 19 (8–26)[a] | 21 (7–25)[a] | 8.3 (5–13) | 8.1 (4–11) | |
| No. of amenorrheic women | 9/21 (42.8%) | 6/14 (42.8%) | 4/11 (36.4%) | 2/3 (66%) | 6/49 (12%) |
| F 0800 h (nmol/liter) | 725.6 (276–1,344)[b,c] | 619 (544–1,173)[d] | 560 (328–957)[b] | 690 (469–1,724)[b,c] | 364 (260–482) |
| UFF excretion (nmol/24 h) | 1,504 (326–9,290)[a,c] | 1,496 (306–4,139)[d] | 1,847 (323–6,208)[c] | 5,132 (1,270–14,987)[b,c] | 423 (179–331) |
| DHEAS ($\mu$mol/liter) | 8.3 (2.6–18)[b] | 1.6 (1.3–5.8)[b,e] | 20 (4.3–99)[b,e] | 9 (5.9–19.5)[b] | 6.5 (4.3–8.4) |
| Androstenedione (nmol/liter) | 12.2 (3.5–34.9)[b] | 3.14 (0.34–19.2)[e] | 27 (3.8–58)[b] | 23 (6.8–69)[b] | 4.0 (1–7.7) |
| Male T (nmol/liter) | 7.7 (4.1–13)[d] | 5.5 (3.2–7.8)[b,e] | 18 (12–36) | 9 (5–14.5)[d] | 19.4 (12–35) |
| Female T (nmol/liter) | 6.1 (3.2–10)[b] | 0.9 (0.3–1.3)[b,e] | 5 (1.4–52)[d] | 6.8 (3.1–13)[b] | 2.42 ± 0.52 |
| Female $E_2$ (pmol/liter)[f] | 124 (55–191) | 159 (53–716) | 352 (132–1,534)[be] | 121 (55–147) | 147 ± 18.8 |

Data are expressed as median and range. Reference ranges: F, 140–680 nmol/liter; UFF excretion, 55–300 nmol/24 h; DHEAS, 1.3–6.7 $\mu$mol/liter; androstenedione, 3.0–6.0 nmol/liter; male T, 10–35 nmol/liter; female T, less than 3.5 nmol/liter; $E_2$, 70–220 pmol/liter.

[a] $P < 0.01$ *vs.* groups with adrenal carcinoma and ectopic ACTH excess.

[b] $P < 0.001$ *vs.* controls.

[c] $P < 0.05$ *vs.* groups with Cushing's syndrome due to adrenal adenoma or carcinoma.

[d] $P < 0.05$ *vs.* controls.

[e] $P < 0.05$ *vs.* all other groups of patients.

[f] Determined in early follicular phase in women with cycles.

($P < 0.05$ *vs.* all other groups). Women were more frequently affected by F excess than men in all subgroups except for the ectopic ACTH secretion, where men were more frequently represented. The ratio of amenorrheic *vs.* eumenorrheic women in each subgroup was similar.

Higher serum and urinary F levels, serum androstenedione, and DHEAS levels were found in ectopic and pituitary ACTH hypersecretion than in adrenal adenomas and carcinomas. Androstenedione and DHEAS were lower in adrenal adenomas than in the other subgroups ($P < 0.05$). DHEAS and $E_2$ were higher in adrenal carcinomas than in the other groups ($P < 0.05$); $E_2$ was similar among men and women with carcinomas, indicating that most adrenal malignancies produce small to large amounts of $E_2$. T was lower in men with Cushing's disease, adrenal adenoma, and ectopic ACTH secretion than in those with adrenal carcinoma ($P < 0.05$). The latter one was similar to controls. Women with adrenal carcinoma, pituitary, and ectopic ACTH hypersecretion had T levels significantly higher ($P < 0.05$) than controls, whereas those with adrenal adenoma had lower values ($P < 0.05$).

### *Assessment of bone density and turnover (Table 2)*

Calcium, phosphorus, iPTH, and vitamin D values did not differ between controls and patients of any subgroup. Serum osteocalcin levels were lower and hydroxyproline excretion

**TABLE 2.** Parameters of bone turnover, bone density, and fractures in patients and controls

| Variable | ACTH-secreting pituitary adenoma | Adrenal adenoma | Adrenal carcinoma | Ectopic ACTH excess | Controls |
|---|---|---|---|---|---|
| No. of subjects | 37 | 18 | 15 | 10 | 80 |
| Serum calcium (mmol/liter) | 2.36 ± 0.13 | 2.38 ± 0.15 | 2.34 ± 0.14 | 2.39 ± 0.16 | 2.33 ± 0.11 |
| Albumin (g/dl) | 3.99 ± 0.44 | 4.06 ± 0.36 | 3.86 ± 0.5 | 4.28 ± 0.3 | 4.1 ± 0.3 |
| Urinary calcium excretion (mg/24 h) | 182 ± 95 | 215 ± 88 | 171 ± 44 | 192 ± 62 | 166 ± 73 |
| iPTH (ng/liter) | 43.4 ± 12 | 40.2 ± 14 | 38 ± 15 | 44.5 ± 13 | 41.2 ± 16 |
| Osteocalcin (ng/ml) | 1.5 ± 0.5[a] | 2.3 ± 0.7 | 2.4 ± 0.9 | 1.2 ± 0.4[a] | 8.9 ± 2.4[b] |
| ALP (U/liter) | 153 ± 52 | 174.5 ± 58 | 185 ± 61 | 187 ± 49 | 168 ± 58 |
| Creatinine ($\mu$mol/liter) | 86 ± 8.6 | 88 ± 8.9 | 90 ± 9 | 87 ± 8.7 | 82 ± 9.8 |
| Hydroxyprolinuria ($\mu$mol/m$^2$) | 135 ± 41.5 | 129 ± 36 | 127.5 ± 32 | 137 ± 40 | 102 ± 16[b] |
| Lumbar Z score (SD) | −1.97 (−5.15 to −0.06) | −1.8 (−4 to −0.36) | −1.8 (−2.9 to 0.9) | −3.53 (−4.9 to −3.0)[c] | −0.03 ± 1.1[d] |
| Femoral Z score (SD) | −1.04 (−2.6 to 0.3) | −1.5 (−2.6 to 1.2) | −0.8 (−2.3 to 0.7) | −0.6 (−2.45 to −0.2) | 0.05 ± 0.8[b] |
| Prevalence (%) of any vertebral fracture | 29 (78%) | 12 (67%) | 10 (67%) | 10 (100%) | 1 (1.3%)[d] |
| Clinical fractures[e] | 15 (52%) | 6 (60%) | 4 (40%) | 7 (70%) | 0 (0%)[b] |
| Multiple fractures[e] | 25 (86%) | 9 (75%)[f] | 8 (80%)[f] | 10 (100%) | 0 (0%)[d] |

Data are expressed as mean ± SD or median and range, as appropriate.

[a] $P < 0.05$ *vs.* all other groups of patients.

[b] $P < 0.05$ *vs.* all groups of patients.

[c] $P < 0.01$ *vs.* all other groups of patients.

[d] $P < 0.01$ *vs.* all groups of patients.

[e] The percentage of clinical and multiple fractures was calculated as a subset of patients with any fracture. Reference ranges: calcium, 2.2–2.6 mmol/liter; ALP, 98–275 U/liter; creatinine, less than 133 $\mu$mol/liter; albumin, 3.6–5.2 g/dl; osteocalcin, 2–22 ng/ml; PTH, 10–75 ng/liter; hydroxyproline excretion, 60–190 $\mu$mol/m$^2$.

[f] $P < 0.05$ *vs.* ectopic ACTH hypersecretion.

higher in patients than controls ($P < 0.05$). Osteocalcin was lower in patients with pituitary and ectopic ACTH secretion than in those with adrenal tumors ($P < 0.05$).

Both lumbar ($P < 0.01$) and femoral BMD ($P < 0.05$) values were significantly lower in patients than controls. Gender- and age-corrected lumbar BMD was lower in the group with ectopic ACTH secretion ($P < 0.01$ *vs.* all groups) but similar among the others.

*Assessment of vertebral fractures (Table 2)*

Vertebral fractures were found in 61 (76%) patients, with multiple involvement of thoracic and/or lumbar vertebrae in 52 (85%). Clinically symptomatic collapsed vertebrae were found in 32 (52%) patients; they were associated with pain, functional limitation, and height shortening by 3–10 cm of final stature. Twenty-nine patients (48% of those with fractures) had asymptomatic fractures, which were multiple in 22 (76%) of them. The fractures involved the thoracic vertebral bodies in 52% of patients, the lumbar vertebrae in 23% of patients, and both thoracic and lumbar bodies in 25% of cases. Seven patients with vertebral fractures (11%) had values of lumbar BMD within the normal range. The prevalence of any and clinical fractures did not differ among the groups with different disease etiology, whereas multiple fractures were more frequent in patients with ectopic ACTH hypersecretion when compared with those with adrenal tumors ($P < 0.05$).

When comparing the patients with fractures with those without fractures, the first group had decreased lumbar BMD ($0.83 \pm 0.14$ *vs.* $1.03 \pm 0.19$ g/cm$^2$; $P < 0.001$), whereas both groups presented similar age, BMI, and endocrine parameters.

*Predictive factors for bone loss and fractures*

Lumbar and femoral BMD correlated with morning F ($r = -0.36$, $P = 0.03$ and $r = -0.4$, $P = 0.02$, respectively) and total T ($r = 0.35$, $P = 0.04$ and $r = 0.58$; $P = 0.015$, respectively), whereas femoral BMD showed a trend also with DHEAS ($r = 0.47$; $P = 0.06$). There was no correlation between BMD and $E_2$ values.

By logistic regression analysis, vertebral fractures were predicted by lumbar BMD values ($\beta = 0.61$; $P < 0.001$). Among the different parameters evaluated to distinguish those with a predictive value, lumbar BMD was the only one statistically significant at receiver operating characteristic analysis with the area under the curve of $0.87 \pm 0.07$ (95% confidence interval, 0.74–1.008; $P = 0.001$). Lumbar BMD value of 0.823 g/cm$^2$ indicated the cutoff to distinguish patients with and without vertebral fractures with a sensitivity of 100% and specificity of 53%.

Surprisingly, there were no differences in lumbar BMD Z score ($-1.96 \pm 1.14$ *vs.* $-1.61 \pm 1.13$; $P = 0.367$) and prevalence of fractures [18 of 21 (86%) *vs.* 16 of 28 (57%); $P = 0.1$] between amenorrheic and eumenorrheic women. Their F and androgen levels did not differ significantly as well as those of $E_2$ ($191 \pm 209$ *vs.* $261 \pm 305$ pmol/liter; $P = 0.3$).

## Discussion

This is the first systematic evaluation of both symptomatic and nonsymptomatic vertebral fractures and their risk factors in a large population of patients with endogenous F excess. A high prevalence (76%) of vertebral fractures was revealed, regardless of the different etiology of patients' hypercortisolism. A lower lumbar BMD was a predictor for vertebral fractures.

Patients with ectopic and pituitary ACTH hypersecretion had more severe F excess than those with adrenal adenomas or carcinomas. Androgen excess (high DHEAS, androstenedione, and female T) was present in patients with pituitary and ectopic Cushing, whereas the excess of androgens plus estrogens was revealed in patients with adrenal carcinoma. F and total T correlated with both lumbar and femoral BMD in our patients, whereas Minetto *et al.* (23) showed a significant correlation between DHEAS and BMD at either lumbar spine or femoral neck.

Surprisingly, serum androgens were similar in men and women with overt Cushing's syndrome. Moreover, in our experience, amenorrheic and eumenorrheic women had similar bone density and prevalence of fractures. Although their $E_2$ values overlapped, the lack of any relationship among $E_2$, BMD, and fractures in this study can likely be explained by the negative bony effects of overt hypercortisolism, which overwhelm the positive effects of estrogens in this particular population. Because the decrease in estrogen levels in the general population is the most important cause of bone loss and the number of women included in each patient group in this study was relatively small, some milder correlation may have been missed. As a matter of fact, Karavitaki *et al.* (18) have documented reduced forearm BMD in 16 postmenopausal but not in 13 premenopausal women with Cushing's syndrome; nevertheless, peripheral and axial skeleton may have different behavior during the F excess.

Our data suggested that among the risk factors considered for bone loss, spinal bone status worsened proportionally with the degree of F excess, being partly influenced by increased androgen levels but not directly by $E_2$.

As concerning the etiology of F excess, lower lumbar BMD and a higher frequency of multiple fractures were observed in patients with ectopic ACTH excess, whereas there was no statistical difference between subjects with pituitary or adrenal Cushing's disease. This is in contrast with a previous finding by Ohmori *et al.* (24) who reported a greater bone loss in patients with pure F excess due to adrenal adenomas compared with those with Cushing's disease and attributed this difference to the protective effect of androgens.

Concerning the fractures, the prevalence revealed by this study is not so surprising because Chiodini *et al.* (25) have recently reported a prevalence of vertebral fractures as high as 43% in premenopausal and 78% in postmenopausal women with subclinical hypercortisolism due to adrenal incidentaloma. Male patients were more frequently affected by clinically evident fractures. Thoracic vertebrae were more frequently fractured than the lumbar ones. However, there are no data on predictive factors for fractures in endogenous hypercortisolism. On the other hand, in patients with exogenous F excess, a daily dose was found to be a strong pre-

dictor of vertebral fractures by Van Staa *et al*. (26), whereas combined effects of higher doses, longer duration, and a continuous pattern of exposure increased the relative risk for vertebral and nonvertebral fractures in the study by Steinbuch *et al*. (27). Overt endogenous F excess is likely more severe than that caused by corticosteroid treatments because only some of the patients on steroid therapy develop typical symptoms of hypercortisolism.

The high prevalence of multiple vertebral fractures detected in the current study at diagnosis of F excess is of particular clinical relevance because they are irreversible. An increase in BMD ranging from 14–79% has been reported in patients successfully treated for endogenous F excess (28–30), and fracture incidence decreased after glucocorticoid treatment withdrawal (26). These findings point out the necessity of a very precocious preventive treatment to reduce, at least partially, the detrimental effects of F excess on the bone. In fact, the use of calcium, vitamin D, and bisphosphonates is recommended for the prevention of bone loss in chronic users of corticosteroids (31, 32), and we previously reported that bisphosphonate treatment counterbalanced the negative effects of hypercortisolism in patients with active Cushing's disease (33).

Although lumbar BMD was found to be a predictive factor for vertebral fractures, this study confirms that patients with either exogenous or endogenous F excess are at risk for symptomatic and nonsymptomatic vertebral fractures even at normal densitometric values, and a radiography of the spine is required to assess the morphology of vertebral bodies.

In conclusion, this study confirms and extends previous observations on the negative early and dose-dependent effects of endogenous F excess on bone density and bone turnover (10, 34–36). The harmful effects of hypercortisolism on the spine were partly counterbalanced by an increased androgen production in both genders but not by female gonadal status. Among the groups with different etiology of F excess, the patients with ectopic ACTH secretion had higher F, lower lumbar BMD values, and more frequent multiple fractures. Any vertebral fracture was present in 76% of the patients at diagnosis of Cushing's syndrome, regardless of its etiology. The best preventive intervention should include a very early diagnosis of F excess, simultaneous bone status evaluation, and a prompt preventive treatment. Unfortunately, it is not an easy task in a common clinical practice.

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All of the authors have nothing to declare.

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