

Altered Bone Mass and Turnover in Female Patients with Adrenal Incidentaloma: The Effect of Subclinical Hypercortisolism

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ABSTRACT

The strategy of treatment for patients with adrenal incidentalomas (AI) may depend upon the presence of hormonal hypersecretion. Although alterations of bone turnover have been recently reported, data on bone mineral density (BMD) are not available in AI patients. We evaluated bone turnover and BMD in 32 female AI patients and 64 matched controls. Spinal and femoral BMD were similar in patients and controls. Serum bone GLA protein (6.8 ± 3.5 vs. 8.8 ± 3.2 ng/mL; $P < 0.005$) and PTH (48.8 ± 15.1 vs. 37.2 ± 10.9 pg/mL; $P < 0.0001$) were different in patients and controls. Patients were then subdivided into 2 groups: with ($n = 8$; group A) or without ($n = 24$; group B) subclinical hypercortisolism. PTH was higher ($P < 0.05$) in group A

than in group B and in both groups than in controls (57.1 ± 13.6 , 46.0 ± 14.8 , and 37.2 ± 10.9 pg/mL, respectively), and bone GLA protein was lower in group A than in group B and controls (3.8 ± 2.3 , 7.5 ± 3.1 , and 8.8 ± 3.2 ng/mL, respectively; $P < 0.05$). Serum type I cross-linked C telopeptide and fasting urinary deoxypyridinoline/creatinine were not different in the three groups. BMD at each site was lower ($P < 0.05$) in group A than in group B and controls. Bone mass and metabolism are altered in AI patients with subclinical hypercortisolism and should be taken into account, therefore, when addressing the treatment of choice for these patients. (*J Clin Endocrinol Metab* 84: 2381–2385, 1999)

INCIDENTALLY discovered adrenal masses [adrenal incidentalomas (AI)] have recently become a relatively common finding in patients evaluated by imaging techniques for unrelated disorders (1–5). The strategy of treatment for patients with AI is still under debate, and it may depend also upon the presence of hormonal hypersecretion. Although by definition AI are not associated with clinically evident syndromes, up to 12% of these patients, in fact, show biochemical signs of subclinical hypercortisolism (SH) (6–11). Although it is well known that overt glucocorticoid excess affects bone metabolism and mass (12–16), the effect of SH on bone tissue is still not completely understood. Bone turnover has been recently studied in AI patients with a wide range of cortical adrenal function (*i.e.* from normal to SH); bone apposition has been consistently reported to be slightly, albeit significantly, reduced (17, 18), whereas conflicting results have been reported on bone resorption (17, 18). In contrast, no data are available on bone mass in AI patients. This is not a trivial lack of knowledge, because a reduction of bone mineral density (BMD) would be an additional element to be considered when addressing the treatment for these patients. We present here data on bone turnover and mass in 32 consecutive female AI patients, either with ($n = 8$) or

without ($n = 24$) SH. Data were compared to those obtained in a group of 64 matched healthy subjects.

Subjects and Methods

Subjects

Thirty-two consecutive female patients with AI were studied. The diagnosis of AI was made on the basis of 1) unilateral adrenal mass detected during noninvasive methods of imaging of the abdomen performed for unrelated diseases, and 2) lack of signs and/or symptoms of hormonal hypersecretion. Only females were enrolled to avoid gender-related confounding effects on the skeleton (19). Patients were then subdivided into 2 groups: group A ($n = 8$) and group B ($n = 24$), with and without SH, respectively. The diagnosis of SH was made on the basis of increased 24-h urinary free cortisol (UFC) levels (>70 $\mu\text{g}/24$ h), the cut-off of both our and international (20) normal reference values. Three of 8 patients from group A showed unsuppressed morning serum cortisol levels after a 1-mg overnight dexamethasone suppression test (F after dex; >5 $\mu\text{g}/\text{dL}$). All patients from group A and 13 of 24 from group B showed low ACTH levels (<10 pg/mL). Similar data have been previously reported (21).

Age, body mass index, and menstrual status were not different between groups A and B (Table 1). In particular, mean menopause duration was not different between the two groups (9.5 ± 10.9 vs. 11.1 ± 8.7). Moreover, no patients in group A and only two patients in group B were within the first 3 yr after the last menses.

No subject had evidence of neoplastic disease. At computed tomography, all lesions were homogeneous and hypodense and had regular margins; these features are compatible with the diagnosis of adrenocortical adenoma (5). The diameter of incidentalomas was not different between group A and group B (mean \pm sd, 2.4 ± 1.2 vs. 2.7 ± 1.2 cm; range, 0.9–4.0 and 1.0–5.5 cm, respectively). Three patients (no. 5, 7, and 19 from group B in Table 2), who displayed diameters of AI greater than 4 cm, had previously refused surgery. In all patients, no increase in adrenal mass was observed in a 12-month follow-up. Pheochromocytoma and aldosteronoma were excluded by appropriate hormonal measurements (24-h urinary catecholamines

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TABLE 1. Clinical characteristics of patients and controls

	Controls (n = 64)	Patients		
		All (n = 32)	Group A (n = 8)	Group B (n = 24)
Age (yr)	56.4 ± 12.3 (22–76)	56.5 ± 12.4 (26–76)	54.0 ± 18.4 (26–75)	57.3 ± 10.0 (38–76)
BMI (kg/m ²)	29.7 ± 4.8 (21.5–45.0)	29.1 ± 4.3 (21.9–40.0)	28.4 ± 4.0 (21.9–33.2)	29.3 ± 4.5 (22.3–40.0)
Gonadal status (pre/postmenopausal)	16/48	8/24	4/4	4/20

Data are expressed as the mean ± SD (range). Patients are presented either all together (All) or subdivided according to the presence (group A) or the absence (group B) of subclinical hypercortisolism (see *Materials and Methods*).

TABLE 2. Biochemical indexes of adrenal function in patients with adrenal incidentalomas

Patient no.	F at 0800 h (μg/dL)	F after dex (μg/dL)	UFC (μg/24 h)	ACTH (pg/mL)
Group A				
1	6.2	0.7	102.8	7.1
2	14.5	1.0	113.0	7.7
3	10.4	2.5	86.5	5.7
4	11.6	1.7	73.6	4.4
5	24.0	9.9	104.0	8.8
6	16.8	7.4	317.0	1.7
7	17.8	13.3	73.0	3.0
8	16.0	1.4	95.0	9.0
Mean ± SD	14.7 ± 5.4	4.8 ± 4.8	120.6 ± 80.6 ^a	5.9 ± 2.7 ^b
Group B				
1	6.4	0.8	55.5	14.8
2	7.7	2.1	40.8	6.0
3	8.5	1.1	61.7	7.5
4	10.0	4.0	38.0	1.2
5	15.9	1.7	67.1	13.0
6	17.6	0.9	35.0	28.8
7	17.0	1.0	44.4	27.1
8	14.9	2.0	44.0	8.7
9	14.5	2.0	28.2	6.9
10	31.2	2.7	49.0	8.5
11	22.7	1.2	24.0	12.5
12	8.1	2.4	63.0	8.6
13	8.6	2.2	29.0	4.5
14	28.3	2.8	36.8	9.6
15	23.8	2.0	37.7	8.3
16	8.3	1.7	19.7	12.6
17	10.0	1.6	32.3	6.7
18	19.2	1.0	44.0	26.1
19	18.9	3.7	54.3	11.0
20	12.8	3.7	32.5	5.4
21	20.1	1.8	29.1	12.0
22	28.7	0.9	37.2	34.2
23	6.8	1.0	11.9	14.1
24	7.1	2.5	29.1	3.6
Mean ± SD	15.3 ± 7.6	2.0 ± 0.9	40.6 ± 17.4	12.1 ± 8.5

Group A, Patients with subclinical hypercortisolism. Group B, Patients without subclinical hypercortisolism. F, Serum cortisol; normal values: 7–25 μg/dL at 0800 h; F after dex, Serum cortisol at 0800 h after overnight 1 mg dexamethasone; normal values, less than 5 μg/dL. UFC, Urinary free cortisol; normal values, less than 70 μg/24 h. ACTH, mean of three determinations at 0800; normal values, above 10 pg/mL.

^a *P* < 0.0001 vs. group B.

^b *P* < 0.05 vs. group B.

and PRA and aldosterone in the recumbent position and after 3 h of orthostatic posture). Sixty-four healthy women, matched for age, body mass index, and menstrual status, served as controls (Table 1). Premenopausal women were studied in the early follicular phase (days 3–7) of the menstrual cycle.

All subjects gave their witnessed informed consent before the study. None of them was given medications known to affect bone metabolism, including estrogen replacement therapy. Vertebral fractures were excluded in all subjects by lateral x-ray of the spine.

Methods

Serum and urinary samples were collected and stored at –70 C until assayed. Serum total calcium (Ca), phosphorous (P), creatinine (Cr), and

alkaline phosphatase total activity were determined by a multichannel autoanalyzer. Serum intact PTH levels were measured by a two-site immunochemiluminometric assay (Chiron Diagnostics, East Walpole, MA). Serum bone GLA protein (BGP) was assayed by immunoradiometric assay for the intact molecule [ELSA-OST-NAT, Cis Biointernational, Gif-sur-Yvette, France; intra- and interassay coefficients of variation (CVs), 3.8% and 4.7%, respectively]. Serum type I cross-linked C telopeptide (ICTP) was measured by RIA (Orion Diagnostica, Espoo, Finland; intra- and interassay CVs, 4.8% and 6.5%, respectively). Total deoxypyridinoline on fasting spot urine corrected for creatinine excretion (D-Pyr/Cr) was assessed, after reverse phase high performance liquid chromatography, fluorometrically by kits from Bio-Rad Labora-

TABLE 3a. PTH and bone turnover markers in group A, group B, and controls

	Group A (n = 8)	Group B (n = 24)	Controls (n = 64)
PTH (pg/mL)	57.1 ± 13.6 ^a	46.0 ± 14.8 ^a	37.2 ± 10.9
AP (U/L)	207 ± 104	190 ± 70	167 ± 43
BGP (ng/mL)	3.8 ± 2.3 ^a	7.5 ± 3.1	8.8 ± 3.2
ICTP (μg/L)	4.08 ± 1.29	3.90 ± 2.39	4.01 ± 1.57
D-Pyr/Cr (pmol/pmol)	28.6 ± 12.8	24.6 ± 7.9	24.6 ± 6.8

Data are expressed as the mean ± SD. PTH, Serum intact PTH; AP, serum alkaline phosphatase total activity; BGP, serum bone Gla protein; ICTP, serum type I cross-linked C telopeptide; D-Pyr/Cr, urinary deoxypyridinoline/creatinine.

^a $P < 0.05$ vs. the other two groups.

TABLE 3b. BMD at different skeletal sites in group A, group B, and controls

	Group A (n = 8)	Group B (n = 24)	Controls (n = 64)
QCT (L1–L4)	−1.02 ± 1.29 ^a	0.15 ± 1.04	−0.20 ± 0.86
DXA (L2–L4)	−1.37 ± 1.26 ^a	0.41 ± 1.24	−0.03 ± 1.07
WT	−1.31 ± 1.16 ^a	0.13 ± 1.18	0.00 ± 1.00
TR	−0.99 ± 1.16 ^a	0.50 ± 1.27	0.15 ± 1.00
FN	−1.34 ± 1.08 ^a	0.20 ± 1.12	0.07 ± 1.05

Data are the mean ± SD of z-values. QCT, Lumbar vertebral trabecular spine L1–L4 bone mineral density. DXA, Lumbar vertebral integral spine L2–L4 bone mineral density. WT, Ward's triangle bone mineral density. TR, Femoral great trochanter bone mineral density. FN, femoral neck bone mineral density. No statistically significant difference was found among the affected skeletal sites in group A.

^a $P < 0.05$ vs. the other two groups.

tories, Inc. (Segrate, Italy; intra- and interassay CVs, 6.6% and 12.3%, respectively).

In all patients the following serum hormonal determinations were performed at 0800 h: ACTH (mean of three determinations at 20-min intervals), cortisol (F), and dehydroepiandrosterone sulfate (DHEAS). F and UFC levels (after dichloromethanol extraction) were measured immunofluorometrically by TDX-FLX Abbott GmbH Diagnostika kits (Wiesbaden-Delkenheim, Germany); serum ACTH and DHEAS levels were measured by immunoradiometric assay (BRAHMS Diagnostica GmbH, Berlin, Germany) and RIA (Diagnostics Systems Laboratories, Inc., Webster, TX), respectively.

BMD was evaluated at both axial and appendicular skeletal sites, as previously described (22). Spinal BMD was measured by both single energy quantitative computed tomography L1–L4 (QCT; Toshiba CT Xpeed, Toshiba Medical Systems Division, Tokyo, Japan), able to selectively detect trabecular true density (*in vivo* precision, 1.8%), and dual x-ray absorptiometry L2–L4 (DXA; Norland XR-26, Norland Instruments, Fort Atkinson, WI), which assesses BMD of total vertebral bodies (*in vivo* precision, 1.0%). BMD was also evaluated by dual x-ray absorptiometry at three femoral sites: neck (FN), Ward's triangle, and great trochanter (*in vivo* precision, 2.1%, 3.5%, and 2.4%, respectively). Individual BMD values were expressed as SD units (z-values) in relation to the reference population at our center (23).

Statistical analysis

The results are expressed as the mean ± SD. For each variable, normality of distribution was tested by the W statistic of Shapiro-Wilk. Data were compared by one-way ANOVA and either Bonferroni or Student-Newman-Keuls test, as appropriate. The associations between variables were tested by either Pearson or Spearman correlation, as appropriate. $P < 0.05$ was considered significant.

Results

BMD measured at each site was not different between the whole group of patients and controls (data not shown). In contrast, BGP levels were lower, and PTH levels were higher in patients than in controls [6.8 ± 3.5 vs. 8.8 ± 3.2 ng/mL ($P < 0.005$) and 48.8 ± 15.1 vs. 37.2 ± 10.9 pg/mL ($P < 0.0001$), respectively].

Hormonal data of patients from group A and B are summarized in Table 2. By selection criterion, UFC levels were

significantly higher in group A. ACTH levels were also significantly different, being lower in group A than in group B (Table 2). F, both basally and after dexamethasone suppression, (Table 2), and DHEAS (data not shown) levels were not different between the two groups.

Bone turnover data are shown in Table 3a. PTH levels were significantly higher in group A than in group B and in both groups than in controls. BGP levels were lower in group A than in group B and controls. Alkaline phosphatase total activity, ICTP, and D-Pyr/Cr (Table 3a) and serum Ca, P, and creatinine (data not shown) did not significantly differ among the three groups.

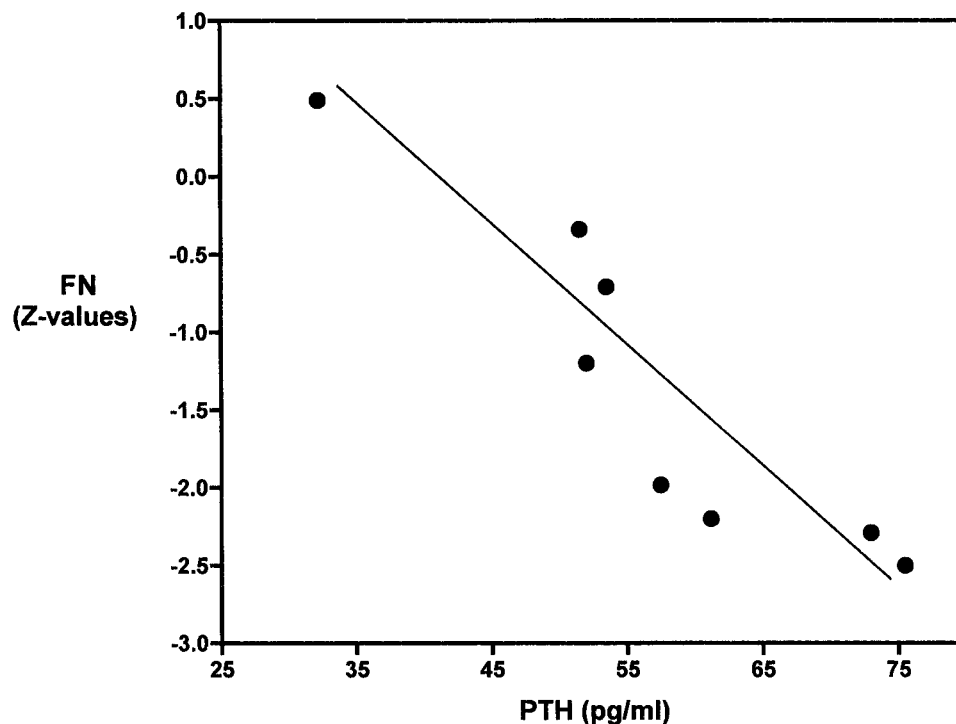
Spinal BMD, measured by both QCT and DXA, and femoral BMD at each site were significantly lower in group A than in group B and controls (Table 3b). No significant difference was found among the BMD reductions in each skeletal site in group A patients (Table 3b).

To evaluate the role of estrogens on the effect of glucocorticoid excess on bone turnover and mass, BGP and BMD z-values were separately compared for premenopausal (group A, n = 4; group B, n = 4; controls, n = 16) and postmenopausal (group A, n = 4; group B, n = 20; controls, n = 48) subjects. Significant ($P < 0.05$) differences were confirmed only in postmenopausal subjects (group A vs. group B vs. controls: BGP, 2.6 ± 0.6 vs. 7.7 ± 3.3 vs. 9.3 ± 3.3 ng/mL; DXA (L2–L4), -2.37 ± 0.61 vs. 0.27 ± 0.98 vs. -0.19 ± 0.93 ; QCT (L1–L4), -1.77 ± 0.75 vs. -0.01 ± 1.08 vs. -0.3 ± 0.89 ; Ward's triangle, -1.83 ± 0.90 vs. -0.01 ± 1.19 vs. -0.11 ± 0.98 ; great trochanter, -1.80 ± 1.06 vs. 0.25 ± 1.07 vs. 0.06 ± 0.98 ; FN, -2.24 ± 0.21 vs. 0.04 ± 1.07 vs. -0.04 ± 0.87).

Correlations

In group A patients, but not in group B patients or controls, PTH was significantly correlated directly with D-Pyr/Cr (r

FIG. 1. Correlation between femoral neck BMD and PTH values in patients with subclinical hypercortisolism (group A).



= 0.72; $P < 0.05$) and inversely with BMD measured at FN ($r = -0.92$; $P < 0.002$; Fig. 1).

Discussion

The aim of this study was to investigate whether the skeleton is affected in AI patients. For this purpose, BMD and bone turnover in 32 consecutive female patients with AI were evaluated. When comparing the whole group of patients to matched controls, we found altered osteoblastic activity, as reflected by reduced BGP levels, but normal bone resorption and BMD at each site studied. After subdividing AI patients into 2 groups according to the presence/absence of SH, we found reduced BMD at each site and reduced BGP levels only in the former group (group A). The negative effect of SH on bone mass and apposition (BGP) was greater in postmenopausal than in premenopausal patients. However, due to the small number of observations, this has to be considered with great caution.

Data on bone turnover, but not on BMD, have been previously reported in AI patients (17, 18). Our present finding on bone apposition is in agreement with a recent report showing reduced BGP in AI patients with SH (18). ICTP, a marker of bone resorption, has been reported to be either increased (17) or reduced (18). In our series, ICTP levels were not different among the two groups of patients and controls. Such conflicting results are possibly due to the low sensitivity of the marker employed (24). To overcome this potential problem, we also used a more sensitive marker of bone resorption, such as D-Pyr/Cr (24), which was slightly, but not significantly, increased in group A patients. At variance with previous studies (17, 18), we also measured PTH levels in AI patients. Similar to patients with Cushing's syndrome (16), subjects with AI showed a picture of secondary hyper-

parathyroidism, the degree of which was significantly higher in group A (with SH) than in group B (without SH).

In this study, BMD was assessed in AI patients and was reduced in those with SH. In our opinion, the finding of reduced bone mass in AI patients with SH is of immediate clinical relevance; the risk of osteoporosis may be, in fact, an additional element to be considered when addressing the treatment of choice in these patients.

At variance with patients with Cushing's syndrome, in which trabecular bone at lumbar spine is predominantly affected (16), AI patients with SH showed a similar degree of BMD reduction at various skeletal sites. It can be hypothesized that, in contrast to patients with Cushing's syndrome, in whom the overt glucocorticoid excess obscures the negative effect of high PTH levels, in AI patients the effects of a low degree of glucocorticoid excess and of hyperparathyroidism on trabecular and cortical bone, respectively, are of the same degree. Moreover, a cause-effect relationship between PTH and decreased cortical bone mass in AI patients with SH is suggested by the negative correlation between PTH levels and BMD measured at FN.

After ruling out the possibility of a primary or metastatic malignant lesion, a central point in the management of AI smaller than 4–6 cm is whether such tumors deserve surgical excision (5, 25–29). This decision may depend on the presence of several variables; among others, the presence of glucocorticoid excess complications, including reduction of bone mass and altered bone metabolism, have to be considered. In this regard, our data indicate that AI patients with SH are at risk of osteoporosis. Bone mass and metabolism should, therefore, be evaluated and taken into account when addressing the treatment of choice for these patients.

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