

Subclinical Hypercortisolism among Outpatients Referred for Osteoporosis

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Background: Hypercortisolism is known to cause osteoporosis.

Objective: To evaluate the prevalence of subclinical hypercortisolism in participants referred for evaluation of osteoporosis.

Design: Cross-sectional study.

Setting: Two community hospitals and research institutes in Italy.

Patients: 219 patients without clinically overt hypercortisolism or other secondary causes of osteoporosis who were referred for evaluation of osteoporosis between January 2005 and December 2005.

Measurements: Bone mineral density was measured by using dual-energy x-ray absorptiometry, and hypercortisolism was assessed with serum cortisol levels after a dexamethasone suppression test. Also measured were 24-hour urinary free cortisol levels and mid-night plasma cortisol levels.

Results: Seven of 65 patients with T-scores of 2.5 or less and vertebral fractures had subclinical hypercortisolism (prevalence,

10.8% [95% CI, 3.23% to 18.31%]). This prevalence was 4.8% (CI, 1.32% to 8.20%) among patients with osteoporosis. In multivariable analyses adjusted for age, sex, and body mass index, a positive dexamethasone suppression test result was associated with the presence of osteoporosis (odds ratio, 3.37 [CI, 1.78 to 6.43]; $P < 0.001$) and vertebral fractures (odds ratio, 1.70 [CI, 1.04 to 2.79]; $P = 0.035$).

Limitations: The study was conducted in a referral setting; its findings may not apply to the general population.

Conclusions: Subclinical hypercortisolism may be more common than is generally recognized in patients with osteoporosis in whom secondary causes of osteoporosis have been excluded.

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Hypercortisolism is a frequent cause of secondary osteoporosis (1). Overt endogenous hypercortisolism (Cushing syndrome) is a well-recognized cause of osteoporosis (2), but because its prevalence in the general population is low (1 per 500 000 persons) (2), its contribution to osteoporosis in general populations is trivial. The terms *subclinical Cushing syndrome* and *subclinical hypercortisolism* describe altered adrenocorticotropic hormone (ACTH)-cortisol homeostasis without the classic signs or symptoms of the Cushing syndrome (3). Subclinical hypercortisolism is more common than overt hypercortisolism, with an estimated prevalence of about 0.8 per 1000 individuals in the general population (3); however, this prevalence is probably underreported because of the lack of symptoms or signs in these patients (3–7). Several cross-sectional and longitudinal studies have suggested that these patients are at high risk for complications of hypercortisolism, such as diabetes and osteoporosis (8–16).

Recent studies have indicated that subclinical hypercortisolism is more prevalent than previously thought in patients with type 2 diabetes (17–19). However, studies on the prevalence of subclinical hypercortisolism in patients with osteoporosis are lacking. Some evidence suggests that osteoporotic fractures may be the presenting manifestations of otherwise-asymptomatic hypercortisolism (20). Moreover, a recent paper showed a difference in cortisol secretion between healthy participants and patients with established osteoporosis, possibly due to mild autonomous cortisol hypersecretion in some individuals (21). Thus, the prevalence of subclinical hypercortisolism in patients with osteoporosis may be underestimated. We therefore designed a study to assess the prevalence of subclinical hypercortisolism in patients referred to our outpatient clinics for evaluation of osteoporosis.

METHODS

Setting and Participants

The study was done at the “Casa Sollievo della Sofferenza” Scientific Institute, San Giovanni Rotondo, Foggia, Italy, and the “San Giuseppe-Fatebenefratelli” Hospital, Fatebenefratelli Research Association, Milan, Italy, from January 2005 to December 2005. We recruited 219 consecutive patients (200 women and 19 men) referred to our outpatient clinics for prevention or diagnosis and treatment of osteoporosis and who met the following inclusion

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Context

The Cushing syndrome is a well-recognized secondary cause of osteoporosis.

Contributions

The researchers looked for hypercortisolism in asymptomatic patients referred for osteoporosis testing. They identified 7 patients with the condition. Six had functioning adrenal masses and 1 had an adrenocorticotrophic hormone–secreting pituitary adenoma. The prevalence of subclinical hypercortisolism among patients with T-scores of -2.5 or less and vertebral fractures was 10.8%.

Caution

The findings come from a referral setting and might not apply to patients in the community.

Implication

Subclinical hypercortisolism may be more common than is generally recognized in patients with osteoporosis.

—The Editors

criteria: 1) absence of any known secondary causes of osteoporosis (that is, past or current thyrotoxicosis, bowel disease, precocious or surgical menopause, chronic renal failure, chronic hepatic disease, eating disorders, or rheumatologic or hematologic disease); 2) absence of depression and alcoholism, which may enhance cortisol secretion; 3) no administration of drugs influencing bone, cortisol, and dexamethasone metabolism or cortisol secretion; and 4) no signs or symptoms of cortisol excess, including moon facies, striae rubrae, skin atrophy, or buffalo hump.

All participants signed consent forms, and local ethical committees approved the study in accordance with the second Declaration of Helsinki.

Testing Sequence

The **Figure** shows the study flow diagram. All patients had spinal and femoral dual-energy x-ray absorptiometry and spinal radiography. They had outpatient testing for secondary causes of osteoporosis (general chemistry profile, calcium homeostasis measurements [serum calcium, phosphorus, alkaline phosphatase total activity, 24-hour urinary calcium], thyroid-stimulating hormone, anti-gliadin antibodies, and serum testosterone in men) and blood for cortisol measurement drawn at 8:00 a.m. after a 1-mg overnight dexamethasone suppression test. Participants with altered thyroid-stimulating hormone levels were tested for free thyroxine, antithyroglobulin, and antithyroperoxidase antibodies; those with high serum calcium levels were tested for serum parathyroid hormone. In patients with normal anti-gliadin antibodies but clinical suspicion of celiac disease, antiendomysial antibodies were also measured.

Participants with serum cortisol levels greater than

50.0 nmol/L after the 1-mg overnight dexamethasone suppression test were hospitalized for further diagnostic investigations (case participants). Those with cortisol levels less than 50.0 nmol/L had no further evaluation, but anti-osteoporotic therapy was started in those with osteoporosis. Among hospitalized patients, catheters were inserted in the forearm vein on the day of admission, and blood testing began the day after to avoid stress-related hypopituitary–adrenal axis activation due to venipuncture. Because inpatient status can in theory increase cortisol secretion (19), a control group of inpatients was recruited to estimate the prevalence of subclinical hypercortisolism in hospitalized participants (control participants). This group comprised 56 age- and sex-matched inpatients without diabetes, osteoporosis, or vertebral fractures who were consecutively hospitalized from January 2005 to December 2005.

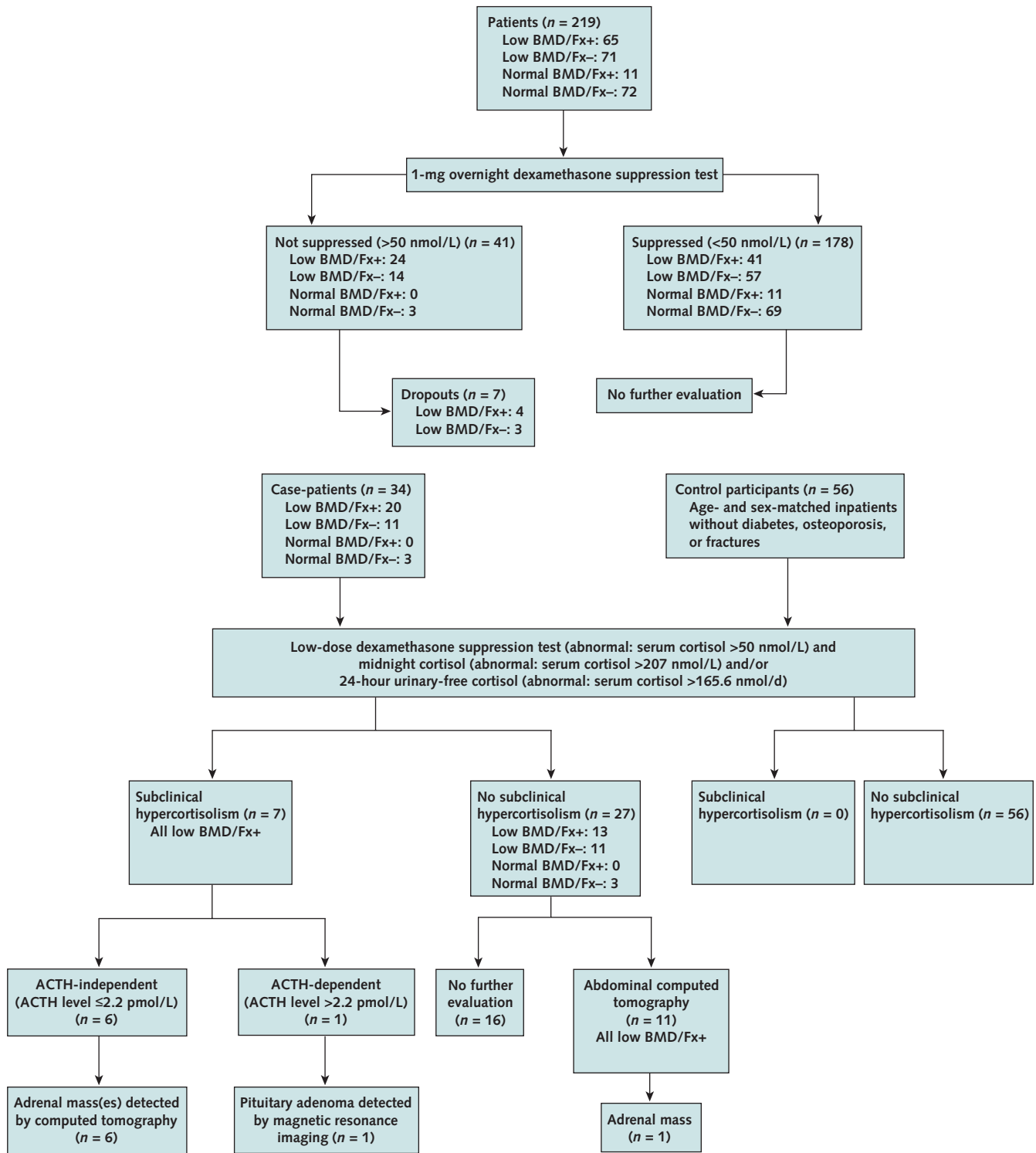
All hospitalized participants had serum cortisol levels measured at 9:00 a.m. after 2 days of low-dose (0.5 mg every 6 hours) dexamethasone suppression and at midnight, 2 measurements of 24-hour urinary free cortisol, and measurement of ACTH at 8:00 a.m.

Subclinical hypercortisolism was diagnosed if participants had incomplete suppression of cortisol (>50.0 nmol/L) after the low-dose dexamethasone suppression test and a 24-hour urinary free cortisol level greater than 165.6 nmol/d (normal range, 22.2 to 165.6 nmol/d) and/or midnight cortisol level greater than 207 nmol/L (normal range, 0.0 to 138.5 nmol/L) (3, 7, 8, 21–23). The cutoff value of 165.6 nmol/d for urinary free cortisol corresponds to the 97th percentile value of 70 healthy control participants (20 men and 50 women; age, 35 to 65 years; body mass index, 20 to 40 kg/m²) who were recruited in our center as a reference population for urinary free cortisol. The cutoff value of 207.0 nmol/L for midnight cortisol is the standard for diagnosing hypercortisolism when overt Cushing syndrome is clinically suspected (2). Terzolo and colleagues (24) proposed a cutoff value of 148.8 nmol/L for diagnosing subclinical hypercortisolism, but we used the greater value because we lack reference midnight cortisol values in our center and wanted to increase specificity.

Participants with subclinical hypercortisolism and an ACTH level of 2.2 pmol/L or less (normal range, 1.1 to 11.0 pmol/L) had abdominal computed tomography. Patients with subclinical hypercortisolism and ACTH levels greater than 2.2 pmol/L had abdominal computed tomography, nuclear magnetic resonance of the pituitary region, and additional biochemical tests (serum cortisol measurement after 8-mg overnight dexamethasone suppression and serum ACTH and cortisol measurement after stimulation with corticotropin-releasing hormone). Whole-body computed tomography was done when an ectopic source of ACTH hypersecretion was suspected (25).

Subclinical hypercortisolism in patients with type 2 diabetes can be attributed mainly to adrenal masses (19). Because incidentally discovered adrenal lesions (adrenal in-

Figure. Study flow diagram.



All patients were subdivided on the basis of bone mineral density (*BMD*) (T-score of -2.5 or less [low *BMD*] or greater than -2.5 [normal *BMD*]) and vertebral fractures. ACTH = adrenocorticotropic hormone; Fx+ = presence of vertebral fractures; Fx- = absence of vertebral fractures.

Table 1. Characteristics of Patients with Subclinical Hypercortisolism and Its Relation to Osteoporosis*

Characteristic	Participants with Low BMD		Participants with Normal BMD		P Value	Participants with Osteoporosis* (n = 147)	Participants without Osteoporosis (n = 72)	P Value
	With Fractures (n = 65)	Without Fractures (n = 71)	With Fractures (n = 11)	Without Fractures (n = 72)				
Mean age (SD), y	65.8 (9.6)	61.7 (9.6)	64.4 (12.2)	57.4 (9.6)	<0.001	63.7 (9.9)	57.4 (9.6)	<0.001
Mean BMI (SD), kg/m ²	26.7 (4.4)	26.4 (4.5)	30.0 (3.8)	27.1 (3.9)	0.064	26.8 (4.5)	27.1 (3.9)	0.57
Women, n	58	65	8	69	0.071	131	69	0.127
Mean T-score (SD)								
Lumbar spine	-3.20 (1.04)	-2.83 (0.91)	-1.29 (1.04)	-1.37 (1.09)	<0.001	-2.88 (1.08)	-1.37 (1.09)	<0.001
Total femur	-2.30 (0.92)	-1.78 (0.75)	-1.12 (0.52)	-0.99 (0.97)	<0.001	-1.96 (0.88)	-0.99 (0.97)	<0.001
Femoral neck	-2.28 (0.90)	-1.90 (0.81)	-1.34 (0.66)	-1.13 (0.90)	<0.001	-2.03 (0.88)	-1.13 (0.90)	<0.001
Subclinical hypercortisolism, n (%) [95% CI]	7 (10.8 [3.23–18.31])	0	0	0	0.001	7 (4.8 [1.32–8.20])	0	0.099
Grade of fracture (I/II/III), n/n/nt	46/11/8	–	8/3/0	–	–	54/14/8	–	–

* Osteoporosis was defined as T-score of -2.5 or less and/or presence of vertebral fracture. BMD = bone mineral density; BMI = body mass index. † 10 patients with low BMD and fractures and 2 patients with normal BMD and fractures had multiple fractures.

cidentalomas) are frequently found in otherwise-healthy persons (4), we performed abdominal computed tomography in a subset of patients who tested positive after the 1-mg overnight dexamethasone suppression test but were classified as having no subclinical hypercortisolism.

Testing Procedures

In all patients, bone mineral density (BMD) was measured by dual-energy x-ray absorptiometry (Hologic Discovery, Bedford, Massachusetts) at the spine (in vivo precision at L1 to L4, 1.0%) and total and femoral neck (in vivo precision, 1.8% and 2.3%, respectively). Individual BMD values were expressed as SD units (T-scores) relative to the reference population of our center, which included 382 healthy female participants (26). Conventional spinal radiographs in lateral (T4 to L4) and anteroposterior (L1 to L4) projections were obtained in all participants by using a standard technique. Two trained radiologists who were blinded to BMD and hormonal data independently reviewed the radiographs. Vertebral fractures were diagnosed on visual inspection by using the semiquantitative method described by Genant and colleagues (27), in which fractures assessed on lateral thoracolumbar spine radiographs were defined as a reduction of more than approximately 20% in anterior, middle, or posterior vertebral height. Fractures were graded by severity and were graded as I, II, or III on the basis of the height reduction (20% to 25%, 25% to 40%, or >40%, respectively). The radiologists discussed questionable cases for consensus on a diagnosis; the interrater reliability between the 2 radiologists was good ($\kappa = 0.85$).

The 2-day, low-dose dexamethasone suppression test was done after ACTH, 24-hour urinary free cortisol, and midnight cortisol levels were measured. Every 6 hours, 0.5 mg of dexamethasone was administered orally, and serum cortisol was measured at 9:00 a.m., 48 hours after the first dose. Serum cortisol and 24-hour urinary free cortisol levels

(after dichloromethane extraction) were measured immunofluorimetrically (TDX-FLX kits, Abbott Diagnostika, Wiesbaden-Delkenheim, Germany). Serum ACTH levels (mean of 3 determinations at 20-minute intervals) were measured by immunoradiometric assay (Brahms Diagnostica, Berlin, Germany). The intra- and interassay coefficients of variation for all assays were less than 5%.

At “San Giuseppe-Fatebenefratelli” Hospital, adrenal imaging was done by using a Tomoscan AVE1 (Philips Medical Systems, Cleveland, Ohio) spiral computed tomography scanner, and nuclear magnetic resonance imaging was done by using the 1.5-Te NMR NT-Intera with software, release 8 (Philips Medical Systems) device. At “Casa Sollievo della Sofferenza” Hospital, adrenal imaging was done by using the Pro Speed Sx power spiral computed tomography scanner (General Electric, Milwaukee, Wisconsin); pituitary imaging was done by using the 1.5-Te nuclear magnetic resonance Sigma Advantage device (General Electric). Both computed tomography scanners used 5-mm slices, resulting in a 2-mm resolution, whereas both nuclear magnetic resonance imaging devices used 3-mm slices, also with a resolution of 2 mm.

Statistical Analysis

Patients were categorized into 4 groups: low BMD and fractures (spinal or femoral BMD T-score of -2.5 or less and vertebral fractures), low BMD without fractures (spinal or femoral BMD T-score of -2.5 or less and no vertebral fractures), normal BMD with fractures (spinal or femoral BMD T-score greater than -2.5 and vertebral fractures), and normal BMD without fractures (spinal or femoral BMD T-score greater than -2.5 and no vertebral fractures) (Table 1). Because patients with nontraumatic vertebral fractures are commonly considered to have osteoporosis regardless of BMD (28), we also analyzed our data in categories of patients with osteoporosis (defined as spi-

Table 2. Odds Ratios for Osteoporosis and Vertebral Fracture*

Risk Factor	Odds Ratio for Osteoporosis (95% CI)*†	P Value	Odds Ratio for Vertebral Fracture (95% CI)‡	P Value
Cortisol level after 1-mg overnight dexamethasone suppression test (per 1- μ g/dL increase)	3.37 (1.78–6.43)	<0.001	1.70 (1.04–2.79)	0.035
Age (per 1-year increase)	1.06 (1.02–1.10)	<0.001	1.06 (1.02–1.10)	0.002
Sex (male vs. female)	2.52 (0.74–8.48)	0.138	3.40 (1.18–9.71)	0.023
BMI (per 1-kg/m ² increase)	0.945 (0.88–1.02)	0.121	1.02 (0.95–1.11)	0.614
BMD at spine (L1 to L4) (per 1-unit decrease in T-score)	–	–	1.79 (2.40–1.34)	0.001

* Osteoporosis was defined as T-score of -2.5 or less and/or vertebral fractures. BMD = bone mineral density; BMI = body mass index.

† Hosmer–Lemeshow goodness of fit $P = 0.67$, and c-statistic = 0.74.

‡ Hosmer–Lemeshow goodness of fit $P = 0.75$, and c-statistic = 0.76.

nal or femoral BMD T-score of -2.5 or less, vertebral fractures, or both; 131 women and 16 men) or without osteoporosis (defined as spinal and femoral BMD T-score greater than -2.5 without vertebral fractures; 69 women and 3 men).

Comparison of continuous variables among groups was done by using 1-way analysis of variance and Bonferroni post hoc analysis. Categorical variables were compared by using the Fisher exact test. Associations between variables were tested by using Pearson product moment correlation coefficient.

We created 2 logistic regression models. One assessed the association between the presence of osteoporosis (dependent categorical variable) and independent variables, including results of the 1-mg overnight dexamethasone suppression test, age, sex, and body mass index. The other assessed the association between the presence of fractures (dependent categorical variable) and the 1-mg overnight dexamethasone suppression test, age, sex, body mass index, and spinal BMD expressed as a T-score. Results of logistic regression models are expressed as odds ratios and 95% CIs, and goodness of fit and predictive accuracy were assessed by using the Hosmer–Lemeshow test and the c-statistic, respectively.

Results are expressed as means (SDs), and P values less than 0.05 are considered significant. Statistical analyses were done by using SPSS software, version 12.0 (SPSS, Chicago, Illinois).

Role of the Funding Source

The study did not receive funding.

RESULTS

Table 1 reports patient characteristics. In an evaluation for secondary causes of osteoporosis, no patient had celiac or thyroid disease, 1 male patient (0.5%) with osteoporosis had hypogonadism, and 3 female patients (1.3%) had primary hyperparathyroidism. One hundred thirty-six patients (62.1%) had a BMD T-score less than -2.5 , and

76 patients (34.7%) had vertebral fractures. All vertebral fractures were asymptomatic and were not clinically evident before testing.

Patients with normal BMD and no fractures were younger than patients in other groups, and patients with low BMD who had fractures had lower BMDs than did patients with low BMD and no fractures (**Table 1**).

Patients with osteoporosis were older (63.7 years [SD, 9.9] vs. 57.4 years [SD, 9.6]) and had lower BMD T-scores (L1 to L4, -2.88 [SD, 1.09] vs. -1.36 [SD, 1.09]; total neck, -1.96 [SD, 0.88] vs. -0.99 [SD, 0.97]; femoral neck, -2.02 [SD, 0.87] vs. -1.12 [SD, 0.91]) than patients without osteoporosis ($P < 0.001$ for all comparisons).

Forty-one patients (18.7%) had serum cortisol levels greater than 50 nmol/L after a 1-mg overnight dexamethasone suppression test. Seven (17.1%) declined further investigations. The remaining 34 patients were hospitalized; of these, 27 did not have subclinical hypercortisolism (serum cortisol level <50.0 nmol/L after a 2-day, low-dose dexamethasone suppression test, 24-hour urinary free cortisol level <165.6 nmol/d, and midnight cortisol level <207.0 nmol/L) and 7 (3.3% of the 212 patients who completed the study) had subclinical hypercortisolism (cortisol level >50.0 nmol/L after a 2-day, low-dose dexamethasone suppression test and 24-hour urinary free cortisol level >165.6 nmol/d or midnight cortisol levels >207.0 nmol/L) (**Figure**). No patient in the control group had subclinical hypercortisolism.

The prevalence of subclinical hypercortisolism among patients with low BMD and fractures was 10.8% (95% CI, 3.23% to 18.31%); all patients with subclinical hypercortisolism had a BMD T-score of -2.5 or less and vertebral fractures. The prevalence of subclinical hypercortisolism in patients with osteoporosis (those with vertebral fractures and/or T-score of -2.5 or less) was 4.8% (CI, 1.32% to 8.20%). Participants without osteoporosis did not have subclinical hypercortisolism. The mean urinary calcium

Table 3. Biochemical and Imaging Data of Patients with Subclinical Hypercortisolism

Patient	Age, y	Sex	Cortisol Level after 2-Day, Low-Dose Dexamethasone Suppression Test, nmol/L	Adrenocorticotropic Hormone Level, pmol/L	24-Hour Urinary Free Cortisol Level, nmol/d	Midnight Cortisol Level, nmol/L	Imaging Findings	Diagnosis
1	72	Female	52.4	1.3	182.2	55.1	3-cm adrenal mass	Adrenal subclinical hypercortisolism
2	65	Female	52.4	1.5	248.3	151.6	2-cm adrenal mass	Adrenal subclinical hypercortisolism
3	44	Female	151.6	2.0	293.0	57.9	1-cm adrenal mass	Adrenal subclinical hypercortisolism
4	68	Female	57.9	1.8	258.5	234.3	1.8-cm adrenal mass	Adrenal subclinical hypercortisolism
5	52	Male	55.1	1.9	173.9	234.3	1-cm bilateral adrenal masses	Adrenal subclinical hypercortisolism
6	65	Female	135.0	2.1	223.5	187.4	1-cm bilateral adrenal masses	Adrenal subclinical hypercortisolism
7	71	Male	68.9	7.0	251.6	212.2	3.0-mm pituitary mass	Pituitary subclinical hypercortisolism

level was similar between patients with and those without subclinical hypercortisolism (0.073 [SD, 0.014] vs. 0.068 [SD, 0.003] mmol/kg per day; $P = 0.71$).

Among the 34 hospitalized patients who tested positive for the initial evaluation for subclinical hypercortisolism, a significant inverse correlation was observed between cortisol levels after the 2-day, low-dose dexamethasone suppression test and BMD at the total neck ($r = -0.393$; $P = 0.024$) and femoral neck ($r = -0.420$; $P = 0.015$), and a significant positive correlation was observed between body mass index and BMD at the lumbar spine ($r = 0.429$; $P = 0.011$), total femur ($r = 0.440$; $P = 0.009$), and femoral neck ($r = 0.485$; $P = 0.004$). There was no association between body mass index and the indices of cortisol secretion.

Multivariable analyses suggested that failure to suppress cortisol secretion after a 1-mg overnight dexamethasone suppression test was significantly associated with osteoporosis (adjusted odds ratio, 3.37 [CI, 1.78 to 6.43]) and with the presence of vertebral fractures (adjusted odds ratio, 1.70 [CI, 1.04 to 2.79]) (Table 2).

Table 3 and the Figure show ACTH levels and imaging results for the 7 patients with subclinical hypercortisolism. Six of these patients had ACTH levels less than 2.2 pmol/L. Computed tomography of the abdomen showed a homogeneous, hypodense, and well-shaped adrenal mass consistent with adrenocortical adenoma in 4 participants (28). Two participants had 1-cm bilateral adrenal masses. The remaining patient had normal ACTH levels and a well-defined pituitary lesion on magnetic resonance imaging. Additional investigations in this last patient were consistent with ACTH hypersecretion of pituitary origin (data not shown). Three patients (patients 1, 2, and 4) with an adrenal mass and subclinical hypercortisolism were surgically treated. In all case-patients, adrenocortical adenoma

was the pathologic diagnosis, and all participants needed steroidal replacement therapy after surgical excision because of secondary adrenal failure.

Eleven of 27 participants who initially had a positive result on overnight dexamethasone suppression testing but did not have subclinical hypercortisolism underwent abdominal computed tomography to evaluate the prevalence of an adrenal mass. These participants were similar in age to the 7 inpatients with subclinical hypercortisolism. Only 1 of the 11 patients had an adrenal mass; in this patient, further investigations after 6 and 12 months confirmed normal ACTH, urinary free cortisol, and plasma cortisol levels after a 2-day, low-dose dexamethasone suppression test.

DISCUSSION

The term *subclinical hypercortisolism* generally refers to biochemical alterations of the pituitary–adrenal axis without classic signs or symptoms of hypercortisolism. Available evidence suggests that patients with subclinical hypercortisolism are at risk for osteoporosis and vertebral fractures (8–16), cortisol secretion differs between healthy participants and patients with osteoporosis (21), and asymptomatic hypercortisolism may manifest as osteoporotic fractures (20).

In our study of outpatients referred for evaluation of osteoporosis, we found a 10.8% prevalence of subclinical hypercortisolism among those with low BMD and vertebral fractures and no secondary causes of osteoporosis. In another study, in which a higher-dose dexamethasone suppression test (3 mg overnight) was used, a prevalence of 5.0% of subclinical hypercortisolism has been reported (21). Our use of a lower-dose dexamethasone suppression test (1 mg overnight) may have increased the sensitivity for

detecting hypercortisolism, leading to higher prevalence. Our prevalence estimates are also similar to those in reports from patients with type 2 diabetes (19).

The association between cortisol secretion and vertebral fractures was independent of age and sex. This is consistent with recent data showing that circulating endogenous glucocorticoids influence the rate of involutional bone loss (29) in healthy elderly participants. The association between cortisol secretion and vertebral fractures was independent of body mass index and BMD. This finding is important because BMD at several sites is related to body mass index, and indexes of cortisol secretion could be greater in both obese and underweight participants.

Hospitalization, pain, or other physiologic stress can cause hypercortisolism. The absence of subclinical hypercortisolism in control participants without osteoporosis or diabetes suggests that the presence of the condition in our study population was not due to hospitalization. Because all patients with vertebral fractures were asymptomatic, the hypercortisolism we detected is unlikely to be due to pain and stress from spinal fractures.

The adrenal source of subclinical hypercortisolism in all patients in the study differs from that generally reported in persons with overt endogenous cortisol excess (2). Elsewhere, we reported a greater prevalence of subclinical hypercortisolism of adrenal origin than pituitary origin in patients with type 2 diabetes (19), and we speculate that subclinical hypercortisolism may more often originate in the adrenal gland than in the pituitary gland. Larger studies are needed to confirm this observation.

Our study has several limitations. We used a cross-sectional design, which shows association and not causality. Nevertheless, our findings are consistent with those of studies showing the negative influence of glucocorticoid excess (2) and subclinical hypercortisolism (12) on bone. Our findings are generalizable only to patients with osteoporosis referred for evaluation to medical centers like those in the study and not individuals with osteoporosis and fractures in the general population. We excluded participants with known or overt secondary osteoporosis, and as a result, the prevalence of subclinical hypercortisolism in patients with osteoporosis may be less than we observed. Finally, given the high prevalence of adrenal incidentalomas in the normal population (4), our findings do not suggest that adrenal masses should be considered clinically important, even in patients with possible complications of hypercortisolism, such as osteoporosis and diabetes. Intervention studies should be done to longitudinally evaluate the effect of surgical treatment on bone mass and incidence of fractures in patients with subclinical hypercortisolism due to adrenal adenomas.

In conclusion, our study suggests that subclinical hypercortisolism is a common and underrecognized finding in patients with established osteoporosis without known secondary causes who are referred for evaluation, and the

presence of subclinical cortisol hypersecretion should be considered when evaluating patients with osteoporosis.

From “San Giuseppe-Fatebenefratelli” Hospital, Fatebenefratelli Research Association, University of Milan, Fondazione Policlinico, Mangiagalli e Regina Elena, Scientific Institute, Milan, Italy; “Casa Sollievo della Sofferenza” Scientific Institute, San Giovanni Rotondo, Foggia, Italy; and University “La Sapienza,” Rome, Italy.

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