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Spinal Volumetric Bone Mineral Density and Vertebral Fractures in Female Patients with Adrenal Incidentalomas: The Effects of Subclinical Hypercortisolism and Gonadal Status

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Although adrenal incidentalomas (AI) are not associated with clinically evident syndromes, some patients display biochemical features of subclinical hypercortisolism (SH). Previous studies indicated a negative effect of SH on bone in AI patients, but the prevalence of vertebral fractures and the roles of SH and gonadal status in volumetric bone mineral density are unknown. In 70 female AI patients and 84 controls, the prevalence of vertebral fractures and spinal bone mineral density (by quantitative computed tomography) were evaluated. Subjects were subdivided according to menopausal status into groups Pre (21 patients and 23 controls) and Post (49 patients and 61 controls); there were 14 and 35 patients without SH (SH^-) and 7 and 14 patients with SH (SH^+) in groups Pre and Post, respectively. The prevalence of fractures was higher in SH^+ than in controls and in SH^- subjects in both groups Pre [SH^+, 42.9%; controls, 0% ($P = 0.001$); SH^-, 7.1% ($P = 0.049$)] and post [SH^+, 78.6%; controls, 37.7% ($P = 0.006$); SH^- 42.9% ($P = 0.024$)]. In group Post, the mean z-score quantitative computed tomography values were lower in SH^+ patients (-0.78 ± 0.29) than in controls (0.06 ± 0.14; $P = 0.011$) and SH^- patients (0.02 ± 0.19; $P = 0.034$). Evaluation of spinal bone is indicated in female AI patients with SH. (*J Clin Endocrinol Metab* 89: 2237–2241, 2004)

INCIDENTALLY DISCOVERED ADRENAL masses [adrenal incidentalomas (AI)] have been frequently detected in recent years, because of the increasing use of abdominal imaging techniques (1–4). Endocrinological work-up shows that the great majority of these lesions are adrenocortical adenomas, and some of these patients present a subtle degree of cortisol hypersecretion (5–11), which is commonly defined as subclinical hypercortisolism (SH). Several previous studies suggested that SH lead to several complications, including bone loss (12–19).

However, several issues remain unresolved about bone involvement in SH. First, the effect on bone mass of gonadal status in SH patients, particularly, volumetric trabecular bone mass, which is the one mainly affected by both SH and hypogonadism, should be assessed. Second, the prevalence of fractures, which is the outcome of SH and hypogonadism on bone, should be evaluated.

We investigated the volumetric trabecular bone mineral density (BMD) of lumbar spine (L1–L4) by single energy quantitative computed tomography (QCT) as well as the prevalence of vertebral fractures in a relatively large sample of female AI patients, looking for the relative influence of gonadal status and SH.

Abbreviations: BMD, Bone mineral density; CI, confidence interval; OR, odds ratio; QCT, quantitative computed tomography; ROI, region of interest; SH, subclinical hypercortisolism; UFC, urinary free cortisol.

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Subjects and Methods

Subjects

Only female subjects were studied, to avoid gender-related confounding effects on the skeleton (20). Ninety-three AI female patients, referred to our center between September 1997 and November 2002, were retrospectively evaluated. Twenty-three patients receiving treatments known to affect bone or affected by diseases known to interfere with skeletal or mineral metabolism were excluded from the study. Data analysis was then performed on the remaining 70 patients. Eighty-four healthy female subjects (23 premenopausal and 61 postmenopausal) collected between January 2001 and December 2002 were selected as controls.

Diagnosis of AI was based on the presence of an unilateral adrenal mass by noninvasive abdominal imaging techniques, performed for unrelated diseases, and the lack of overt signs and/or symptoms of hormonal hypersecretion. No subject had evidence of metastatic disease. At computed tomography, all lesions were homogeneous, hypodense, and well shaped, features compatible with the diagnosis of adrenocortical adenoma (4).

Diagnosis of SH was based on the presence of at least two out of the following three alterations of the hypothalamic-pituitary-adrenal axis (11): 1) urinary free cortisol (UFC) levels above 70.0 μg/24 (193.1 nmol/24 h), the cut-off of both our own and international (21) normal reference values; 2) serum cortisol levels after a 1-mg overnight dexamethasone suppression test above 3.0 μg/dl (82.8 nmol/liter); and 3) ACTH levels below 10 pg/ml (2.2 pmol/liter). No patient with SH showed clinical features compatible with Cushing's syndrome (*i.e.* striae rubrae, moon face, buffalo hump, or hirsutism); moreover, no patients reported acute back pain.

The whole sample was subdivided on the basis of gonadal status in group Pre (21 premenopausal AI patients and 23 control subjects) and group Post (49 postmenopausal AI patients and 61 control subjects). The two groups of AI patients were further separated according to SH was concerned: in group Pre, seven patients were affected by SH (SH^+), whereas 14 were not (SH^-); in group Post, 14 patients were SH^+, and 35 were SH^-. The sample's characteristics, such as age, years since menopause, estradiol levels, height, weight, and body mass index, are shown in Table 1. Estradiol levels were higher than 40 pg/ml (146.8 pmol/liter) in all premenopausal subjects and were lower than 20 pg/ml (73.4 pmol/liter) in all postmenopausal subjects, without any difference among SH^-, SH^+, and control subjects.

The diameter of incidentalomas was not different between SH^- and SH^+ patients in both group Pre (SH^-: mean ± SE, 2.9 ± 0.4 cm; range, 1.0–8.0; SH^+: mean ± SE, 2.9 ± 0.6 cm; range, 0.9–5) and group Post (SH^-: mean ± SE, 2.9 ± 0.2; range, 1.0–5.5; SH^+: mean ± SE, 3.2 ± 0.3; range, 1.5–5.5 cm). Pheochromocytoma and aldosteronoma were excluded by appropriate hormonal measurements (24-h urinary catecholamines and plasma renin activity and aldosterone in the recumbent position and after 3 h of upright position).

The study was approved by local ethical committee and in accordance with Helsinki Declaration II.

Methods

In all AI patients, serum and urinary samples were collected at 0800 h. Serum cortisol and UFC levels (after dichloromethanol extraction) were determined immunofluorimetrically by TDX-FLX kits (Abbott Diagnostika, Wiesbaden-Delkenheim, Germany); serum ACTH levels (mean of three determinations at 20-min intervals) were measured by immunoradiometric assay (BRAHMS Diagnostica, Berlin, Germany).

In all subjects, spinal L1–L4 BMD was measured by single energy QCT using a CT 600S scanner (Toshiba Medical System Division, Tokyo, Japan; *in vivo* precision, 1.8%) and a nonsimultaneous calibration system (Lumbar Reference Simulator, CIRS, Norfolk, VA). The region of interest (ROI) in the axial plane was carried out by manually placing an elliptical ROI in the trabecular part of the vertebral body. After performing the scan, the average attenuation in the ROI was measured in the image, compared with the attenuation values of the reference standard, and finally expressed in mineral equivalents in milligrams per cubic centi-

TABLE 1. Clinical characteristics of patients

	Group Pre			Group Post		
	Controls (n = 23)	SH^- (n = 14)	SH^+ (n = 7)	Controls (n = 61)	SH^- (n = 35)	SH^+ (n = 14)
Age (yr)	41.7 ± 2.0 (21–54)	39.3 ± 2.2 (24–52)	42.9 ± 3.5 (26–50)	60.8 ± 0.9 (44–75)	61.5 ± 1.4 (48–80)	63.9 ± 2.2 (46–79)
YSM				14.6 ± 1.0 (4–34)	13.6 ± 1.2 (4–32)	14.9 ± 2.0 (4–32)
Estradiol (pmol/liter)	225.2 ± 13.6 (154.1–444.8)	226.5 ± 21.0 (157.8–411.0)	237.1 ± 32.1 (151.9–359.7)	23.1 ± 2.4 (0.0–72.7)	26.4 ± 3.7 (0.0–72.3)	19.3 ± 4.4 (0.0–51.0)
Weight (kg)	71.6 ± 3.3 (46–110)	80.1 ± 5.5 (43–121)	74.9 ± 3.1 (63–84)	71.8 ± 1.9 (43–107)	77.7 ± 2.6 (53–134)	67.1 ± 1.7[a] (59–79)
Height (m)	1.59 ± 0.01 (1.48–1.68)	1.59 ± 0.04 (1.47–1.68)	1.58 ± 0.03 (1.51–1.68)	1.54 ± 0.01 (1.41–1.70)	1.54 ± 0.01 (1.39–1.66)	1.52 ± 0.01 (1.46–1.61)
BMI (kg/m^2)	28.3 ± 1.35 (18.0–45.2)	31.7 ± 2.3 (17.1–47.3)	30.1 ± 1.5 (23.1–36.0)	30.5 ± 0.8 (19.1–47.3)	32.5 ± 1.0 (24.5–50.4)	29.1 ± 0.7 (24.6–32.9)

Data are the mean ± SE (range). Group Pre, Premenopausal females; Group Post, postmenopausal females; SH^-, patients without SH; SH^+, patients with SH; YSM, years since menopause.

[a] $P < 0.05$ *vs.* Pre SH^-.

TABLE 2. Biochemical parameters of cortisol secretion, volumetric vertebral bone mineral density, and prevalence of patients with vertebral fractures

	Group Pre			Group Post		
	Controls (n = 23)	SH^- (n = 14)	SH^+ (n = 7)	Controls (n = 61)	SH^- (n = 35)	SH^+ (n = 14)
F-Dex (μg/dl)		1.85 ± 0.35 (0.70–5.70)	4.40 ± 1.57[a] (0.70–12.60)		1.96 ± 0.16 (0.70–4.50)	6.6 ± 1.40[b] (1.70–19.90)
ACTH (pg/ml)		12.72 ± 1.81 (5.90–24.54)	6.36 ± 0.90[a] (0.90–10.00)		13.60 ± 1.18 (3.18–34.10)	6.36 ± 0.60[b] (3.18–10.0)
UFC (μg/24 h)		50.02 ± 3.70 (26.28–69.01)	74.84 ± 10.51[a] (44.40–113.05)		41.1 ± 4.09 (11.90–144.03)	61.2 ± 6.48[c] (23.99–104.02)
QCT (z-values)[d]	0.13 ± 0.26 (−1.95–2.33)	0.57 ± 0.34 (−1.64–2.57)	−0.11 ± 0.48 (−1.91–1.77)	0.06 ± 0.14 (−1.96–2.20)	−0.02 ± 0.19 (−1.69–2.21)	−0.78 ± 0.29[e,f] (−2.49–1.24)
No. of patients with fractures (%)	0 [0.0]	1 [7.1]	3[a,g] [42.9]	23 [37.7]	15 [42.9]	11[e,h] [78.6]

Data are the mean ± SE (range). The prevalence in the group is in *brackets*. Group Pre, Premenopausal females; Group Post, postmenopausal females; SH^-, patients without SH; SH^+, patients with SH; UFC, normal values less than 70.0 μg/24 (193.1 nmol/24 h); ACTH, mean of three determinations at 0800 h, normal values above 10 pg/ml (2.2 pmol/liter); F-Dex, serum cortisol at 0800 h after 1 mg overnight dexamethasone, normal values less than 3.0 μg/dl (82.8 nmol/liter) (conversion factors: F-Dex, 27.59; ACTH, 0.22; UFC, 2.759); QCT, vertebral trabecular volumetric L1–L4 BMD.

[a] $P < 0.05$ *vs.* SH^- in group Eu.

[b] $P < 0.0001$ *vs.* SH^-.

[c] $P < 0.01$ *vs.* SH^-.

[d] Adjusted for weight and height.

[e] $P < 0.05$ *vs.* SH^-.

[f] $P < 0.05$ *vs.* controls in group Hypo.

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

[h] $P < 0.01$ *vs.* controls in group Hypo.

TABLE 3. Predictive values of gonadal status and/or SH on volumetric trabecular spinal BMD, the prevalence of fractured patients, and the prevalence of fractured patients after adjustment for age

	Volumetric trabecular spine BMD[a]		Prevalence of fractured patients		Prevalence of fractured patients adjusted for age	
	F	*P*	Odds ratio (95% CI)	*P*	Odds ratio (95% CI)	*P*
Gonadal status (pre- or postmenopausal)	4.76	0.033	6.88 (1.71–27.59)	0.007	6.04 (0.84–43.29)	0.073
SH (presence or absence)	5.90	0.018	5.88 (1.67–20.72)	0.006	5.79 (1.62–20.62)	0.007
Interaction between gonadal status and SH	0.06	0.811	0.50 (0.03–9.19)	0.642	0.51 (0.03–9.26)	0.640

CI, Confidence interval.
[a] Weight and height were included as covariates.

meter. Individual BMD values were expressed as SD units (z-values) in relation to reference population of our center, which includes 382 healthy female subjects (22).

Conventional spinal radiograph in lateral (T4–L4) and anteroposterior (L1–L4) projections were obtained in all subjects using a standardized technique. Two trained radiologists, who were blinded to the individual's status (patient or control subject), BMD, and hormonal results, reviewed the radiographs independently. The two radiologists discussed questionable cases to agree on a diagnosis. Vertebral fractures were diagnosed on visual inspection using the semiquantitative method previously described by Genant *et al.* (23, 24). According to this technique, fractures assessed on lateral thoracolumbar spine radiographs were defined as reductions of more than approximately 20% in anterior, middle, or posterior vertebral height and were graded by severity.

Statistical analysis

Descriptive statistics are expressed as the mean ± SE. For each variable, after testing normality of distribution by Kolmogorov-Smirnov test, univariate ANOVA was used to compare BMD data of controls, SH^-, and SH^+ patients in groups Pre and Post. Multivariate linear regression analysis was then used to evaluate the influence on BMD of the categorical variables SH and gonadal status. A χ^2 test was used to compare the prevalence of vertebral fractures in controls, SH^-, and SH^+ patients in groups Pre and Post. Agreement between the two radiologists was calculated using κ statistics.

Finally, logistic regression analysis was performed to evaluate the influence of either SH and gonadal status or BMD on the prevalence of fractures. A value of $P < 0.05$ was considered significant.

Results

Descriptive statistics of patients and controls are reported in Table 1. Data regarding pituitary-adrenal axis function (*i.e.* serum cortisol levels after a 1-mg overnight dexamethasone suppression test, ACTH, and UFC) were consistent with the diagnostic criteria of SH previously mentioned. In addition, in group Post, but not in group Pre, bone mass, after adjustment for weight and height, was significantly lower in SH^+ than in controls and SH^- patients (Table 2). The same results were observed without adjusting BMD for height and weight or without considering subjects with BMI greater than 40 kg/m^2 (data not shown).

The multivariate linear regression analysis, after correction for weight and height, showed that although both SH and gonadal status were independent significant predictors of BMD, they did not interact with each other in influencing bone mass (Table 3A).

In the whole sample, 30 patients (42.8%) and 23 controls (27.3%) showed at least one vertebral fracture. The severity degree was mild (grade 1) in 27 patients and in 22 controls, and moderate (grade 2) in three patients and one control

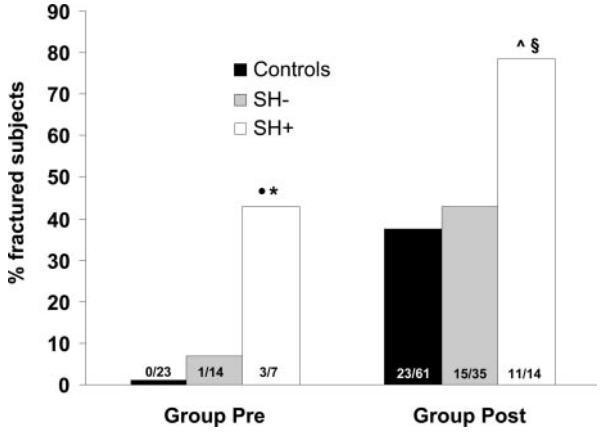

FIG. 1. ●, $P < 0.001$ *vs.* controls; *, $P < 0.05$ *vs.* SH^- (in group Pre). §, $P < 0.01$ *vs.* controls; ^, $P < 0.05$ *vs.* SH^- (in group Post). See *Subjects and Methods* for explanation of groups.

subject. In both groups Pre and Post, the prevalence of patients with fracture was higher in SH^+ than in controls and SH^- patients (Table 2 and Fig. 1). Taking into account more than one fracture in the same patient, in group Post we observed five control subjects and seven patients with two fractures (three SH^- and four SH^+). Interrater reliability between two radiologists was good ($k = 0.87$).

Logistic regression analysis showed that SH and gonadal status were significant predictors of the prevalence of fractures (Table 3B). However, gonadal status after adjusting for age was not a significant predictor of fractures ($P = 0.073$) with this sample size (Table 3C). SH and gonadal status did not interact each other in influencing fractures (Table 3, B and C). Separately analyzing Groups Pre and Post, SH significantly predicted fractures only in the latter group [group Pre: odds ratio (OR), 12.66; 95% confidence interval (CI), 0.83–192.70; $P = 0.068$; group Post: OR, 4.69; 95% CI, 1.10–20.00; $P = 0.037$]. Finally, high BMD z-values significantly predicted a low prevalence of fracture in AI patients (OR, 0.50; 95% CI, 0.31–0.80; $P = 0.004$).

Discussion

This is the first study evaluating the effect of subclinical cortisol hypersecretion and gonadal status on spinal volumetric trabecular bone density and vertebral fractures in a large sample of patients with AI. Our data clearly show that subtle hypercortisolism is associated with a high prevalence

of fractures independent of gonadal status. In addition, trabecular volumetric bone mass at the lumbar spine was affected by SH regardless of gonadal status, as indicated by multivariate analysis, although BMD was mainly affected among postmenopausal women.

Interestingly, the detrimental effect of subclinical cortisol hypersecretion on the vertebrae accounts for the very high prevalence of fractures we found in our AI patients, which exceeds the corresponding figures in the control group. It is also worth noting that the high number of vertebral fractures was clinically unexpected, because no patient reported back pain. The vast majority of the fractures were mild and were not detectable without an accurate morphological evaluation of the radiographs.

Logistic regression analysis showed a significant influence of gonadal status on fractures, even if it was lost when including age in the model. This result is probably due to the fact that age partially conceals the effect of menopause.

The higher prevalence of vertebral fractures in AI patients in the presence of SH is only partially explained by the reduced spinal BMD. We hypothesize that subtle cortisol excess may exert an integrated detrimental effect on trabecular bone quality, as previously suggested (19). The negative influence of SH on connective tissue (25) and muscle strength could also contribute to the increased fracture risk. The deleterious effect of SH on the quality of trabecular bone and on connective tissue may also explain the unexpected increased prevalence of fractures we found in premenopausal AI women with subclinical hypercortisolism; nevertheless, this finding needs to be confirmed on a larger sample of premenopausal AI patients with SH.

Our data on BMD are in line with previous results obtained by our and other groups in relatively small samples of AI patients, in which spinal areal (determined by dual energy x-ray absorptiometry) and volumetric (by QCT) bone density were cross-sectionally and longitudinally evaluated (12, 15, 18). Our current findings are interesting, because QCT directly measures the volumetric bone density of a cubic slice of trabecular vertebral tissue, whereas DXA devices only provide its indirect estimate (26, 27). Thus, as trabecular bone tissue is noticeably affected by glucocorticoid excess (28), the QCT technique, although it appears to be more apt to accurately identify the effect of SH, confirms the results obtained with DXA in a small sample (12).

Collectively taken, our data confirm the need to study trabecular bone mineral density at the spine at least in postmenopausal patients with AI and suggest that thoracolumbar spine radiographs should be obtained in AI patients with subtle hypercortisolism. In these subjects, indeed, the detection of glucocorticoid excess complications, such as the reduction of bone mass and/or the presence of vertebral fractures, becomes one of the pivotal criteria when deciding whether these tumors deserve surgical excision.

In conclusion, female AI patients with SH display increased fracture prevalence together with low BMD at the lumbar spine; the latter is being particularly affected in postmenopausal subjects. These findings should be taken into account when addressing the treatment of choice in patients with adrenal incidentalomas.

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References

1. **Ross NS, Aron DC** 1990 Hormonal evaluation of the patient with an incidentally discovered adrenal mass. N Engl J Med 323:1401–1405
2. **Griffing G** 1994 Editorial: A-I-D-S: the new endocrine epidemic. J Clin Endocrinol Metab 79:1530–1531
3. **Kloos RT, Gross MD, Francis IR, Korobkin M, Shapiro B** 1995 Incidentally discovered adrenal masses. Endocr Rev 16:460–484
4. **Cook DM** 1997 Adrenal mass. Endocrinol Metab Clin North Am 26:829–852
5. **Reincke M, Nieke J, Krestin GP, Saeger W, Allolio B, Winkelmann W** 1992 Preclinical Cushing's syndrome in adrenal "incidentalomas:" comparison with adrenal Cushing's syndrome. J Clin Endocrinol Metab 75:826–832
6. **Mantero F, Masini AM, Opocher G, Giovanetti M, Arnaldi G** 1997 Adrenal incidentaloma: an overview of hormonal data from the National Italian Study Group. Horm Res 47:284–289
7. **Torlontano M, Zingrillo M, D'Aloiso L, Ghiggi MR, Di Cerbo A, Scillitani A, Petracca-Ciavarella G, Liuzzi A** 1997 Pre-Cushing's syndrome not recognized by conventional dexamethasone suppression-tests in an adrenal "incidentaloma" patient. J Endocrinol Invest 20:501–504
8. **Osella G, Terzolo M, Borretta G, Margo G, Alì A, Piovesan A, Paccotti P, Angeli A** 1994 Endocrine evaluation of incidentally discovered adrenal masses (incidentalomas). J Clin Endocrinol Metab 79:1532–1539
9. **Valli N, Catargi B, Ronci N, Vergnot V, Leccia F, Ferriere JM, Chene G, Grenier N, Lurent F, Tabarin A** 2001 Biochemical screening for subclinical cortical-secreting adenomas amongst adrenal incidentalomas. Eur J Endocrinol 144:401–408
10. **Aron DC** 1998 Adrenal incidentalomas and glucocorticoid autonomy. Clin Endocrinol (Oxf) 49:157–158
11. **Terzolo M, Osella G, Alì A, Borretta G, Cesario F, Paccotti P, Angeli A** 1998 Subclinical Cushing's Sindrome in adrenal incidentaloma. Clin Endocrinol (Oxf) 48:89–97
12. **Torlontano M, Chiodini I, Pileri M, Guglielmi G, Cammisa M, Modoni S, Carnevale V, Trischitta V, Scillitani A** 1999 Altered bone mass and turnover in female patients with adrenal incidentalomas: the effect of subclinical hypercortisolism. J Clin Endocrinol Metab 84:2381–2385
13. **Osella G, Reimondo G, Peretti P, Alì A, Paccotti** 2001 The patients with incidentally discovered adrenal adenoma (incidentaloma) are not at increased risk of osteoporosis. J Clin Endocrinol Metab 86:604–607
14. **Rossi R, Tauchmanova L, Luciano A, Di Martino M, Battista C, Del Vescovo L, Nuzzo V, Lombardi G** 2000 Subclinical Cushing's syndrome in patients with adrenal incidentaloma: clinical and biochemical features. J Clin Endocrinol Metab 85:1440–1448
15. **Chiodini I, Torlontano M, Carnevale V, Guglielmi G, Cammisa M, Trischitta V, Scillitani A** 2001 Bone loss rate in adrenal incidentalomas: a longitudinal study. J Clin Endocrinol Metab 86:5337–5341
16. **Chiodini I, Tauchmanova L, Torlontano M, Battista C, Guglielmi, G, Cammisa M, Colao A, Carnevale V, Rossi R, Di Lembo S, Trischitta V, Scillitani A** 2002 Bone involvement in eugonadal male patients with adrenal incidentaloma and subclinical hypercortisolism. J Clin Endocrinol Metab 87: 5491–5494
17. **Devogelaer JP** 2001 Incidentaloma, glucocorticoid excess and low bone mineral density: a coincidence? Eur J Endocrinol 145:237–239
18. **Hadjidakis D, Tsagarakis S, Roboti C, Stakianakis M, Iconomidou V, Raptus SA, Thalassinos N** 2003 Does subclinical hypercortisolism adversely affect the bone mineral density of patients with adrenal incidentalomas? Clin Endocrinol (Oxf) 58:72–77
19. **Tauchmanova L, Rossi R, Nuzzo V, Del Puente A, Esposito-Del Puente A, Pizzi C, Fonderico F, Lupoli G, Lombardi G** 2001 Bone loss determined by quantitative ultrasonometry correlates inversely with disease activity in patients with endogenous glucocorticoid excess due to adrenal mass. Eur J Endocrinol 145:237–239
20. **Reid IR, France JT, Pybus J, Ibbertson HK** 1985 Plasma testosterone concentrations in asthmatic men treated with glucocorticoids. Br Med J 291:574
21. **Kratz A, Lewandrowsky KB** 1998 Normal reference laboratory values. N Engl J Med 339:1063–1072
22. **Guglielmi G, Giannatempo GM, Blunt BA, Grampp S, Gluer CC, Cammisa M, Genant HK** 1995 Spinal bone mineral density by quantitative CT in a normal Italian population. Eur Radiol 5:269–275
23. **Genant HK, Wu CY, van Knijk C, Nevitt M** 1993 Vertebral fracture assessment using a semi-quantitative technique. J Bone Miner Res 8:1137–1148

24. **Genant HK, Jergas M, Palermo L, Nevitt M, Valentin RS, Black D, Cummings SR** 1996 Comparison of semiquantitative visual and quantitative morphometric assessment of prevalent and incident vertebral fractures in osteoporosis: The Study of Osteoporotic Fractures Research Group. J Bone Min Res 11:984–996
25. **Sartorio A, Conti A, Ferrero S, Giambona S, Re T, Passini E, Ambrosi B** 1998 Evaluation of markers of bone and collagen turnover in patients with active and preclinical Cushing's syndrome and in patients with adrenal incidentaloma. Eur J Endocrinol 138:146–152
26. **Genant HK, Engelke K, Fuerst T, Gluer CC, Grampp S, Harris ST** 1996 Noninvasive assessment of bone mineral and structure: state of the art. J Bone Miner Res 11:707–730
27. **Guglielmi G, Schneider P, Lang TF, Giannatempo GM, Cammisa M, Genant HK** 1997 Quantitative computed tomography at the axial and peripheral skeleton. Eur Radiol 7(Suppl 2):S32–S42
28. **Chiodini I, Carnevale V, Torlontano M, Fusilli S, Guglielmi G, Pileri M, Modoni M, Di Giorgio A, Liuzzi A, Minisola S, Camisa M, Trischitta V, Scillitani A** 1998 Alterations of bone turnover and bone mass at different skeletal sites due to pure glucocorticoid excess: study in eumenorrheic patients with Cushing's syndrome. J Clin Endocrinol Metab 83:1863–1867

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