Cortisol Secretion and Rate of Bone Loss in a Population-Based Cohort of Elderly Men and Women

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Abstract. Although excessive glucocorticoids are a well-recognized cause of osteoporosis, little is known about the role of endogenous glucocorticoids in determining skeletal mass. We have performed a detailed study of the hypothalamic–pituitary–adrenal (HPA) axis to explore the relationships between cortisol secretion and adult bone mass in 151 healthy men and 96 healthy women aged 61 to 73 years. At baseline and 4-year follow-up, bone mineral density (BMD) was measured by dual energy X-ray absorptiometry (DXA) at the lumbar spine and proximal femur; a lifestyle questionnaire was completed; and height, weight, and waist and hip circumferences were measured. At follow-up subjects underwent a very low-dose (0.25 mg) dexamethasone suppression test, a low-dose (1 µg) short synacthen test, and a 24-hour urine collection for measurement of cortisol and its metabolites. In men, elevated peak plasma cortisol was associated with accelerated loss of mineral density in the lumbar spine ($r = 0.16$, $P = 0.05$). This relationship remained significant after adjustment for testosterone, estradiol, 25-hydroxyvitamin D, and parathyroid hormone levels ($r = 0.22$, $P = 0.01$) and after additional adjustment for age, (BM), activity, cigarette and alcohol consumption, and Kellgren/Lawrence score ($r = 0.19$, $P = 0.03$). In contrast in women, elevated peak plasma cortisol was associated with lower baseline BMD at the femoral neck ($r = -0.23$, $P = 0.03$) and greater femoral neck loss rate ($r = 0.24$, $P = 0.02$). There was no association between plasma cortisol concentrations after dexamethasone or urinary total cortisol metabolite excretion and bone density or bone loss rate at any site. These data provide evidence that circulating endogenous glucocorticoids influence the rate of involutional bone loss in healthy individuals.

Key words: Glucocorticoids — HPA axis — Osteoporosis

Excessive glucocorticoids have long been associated with increased risk of developing osteoporosis. There is now increasing evidence that there are interindividual variations in hypothalamic–pituitary–adrenal (HPA) axis activity, which result in differences in circulating cortisol levels between individuals and may play a role in the pathogenesis of other conditions such as diabetes, hypertension, and depression [1]. We have previously shown that endogenous cortisol secretion is associated with both bone mineral density (BMD) and rate of involutional bone loss [2, 3]. Here we have performed a detailed study using dynamic testing of the HPA axis to further explore the relationships between cortisol secretion and adult bone mass in a sample of healthy elderly men and women.

Experimental Subjects and Methods

We studied 151 men and 96 women aged 61 to 73 years who were born in and are still resident in Hertfordshire, UK. The selection procedure for these individuals has been described in detail previously [3]. In brief, individuals who had participated in a population-based longitudinal study that examined the relationship between birthweight and subsequent risk of osteoporosis [3, 4] were approached to participate in a substudy that focused on the relationship between birthweight and adult cortisol secretion and metabolic syndrome [5, 6]. Individuals who were taking drugs that might alter calcium metabolism, or might act to influence bone density or loss in some other way (hormone replacement therapy; tamoxifen; bisphosphonates; and systemic, oral, or topical glucocorticoids), or with endocrine abnormalities that influence calcium metabolism or bone density (vitamin D deficiency, hyperthyroidism, and hyperparathyroidism), were excluded. Ethical committee approval and written informed consent were obtained.

Clinical Measurements

The subjects completed an interviewer-administered questionnaire at baseline and at follow-up 4 years later. Information about medical and drug history, current alcohol intake, cigarette smoking, current physical activity (including time spent walking, gardening, doing housework, carrying loads, and other leisure activities), and dietary calcium intake, was recorded. None had a history of endocrine disease or were receiving prescribed systemic or topical glucocorticoid therapy.

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At baseline and at follow-up, subjects' heights were measured with a portable stadiometer and weights with a portable SECA scale. Waist and hip circumferences were measured with a steel tape measure at the level of the umbilicus and greater trochanter, respectively.

BMD was measured in each subject at baseline and follow-up by dual energy X-ray absorptiometry (DXA) at the lumbar spine and proximal femur. Measurements in the baseline study were performed on a QDR 1000 instrument (Hologic, Inc., Waltham, MA, USA), and by a new QDR 4500 instrument at follow-up. To ensure comparability between readings, 23 individuals underwent two follow-up bone density scans, one on each instrument, permitting calculation of a conversion algorithm that was linear across the bone mineral values studied [2]. Annual rates of bone loss were expressed both as absolute values and as a percentage of the original bone density. Measurement precision, expressed as coefficient of variation (CV), was 1.8% for femoral neck BMD and 1.1% for lumbar spine BMD. Lateral thoracolumbar spine radiographs were obtained using a standard protocol and osteoarthritic changes assessed using the Kellgren/Lawrence system [7]. This uses a standard radiographic atlas to characterise the extent of disc narrowing, uncovertebral and apophyseal joint osteophyte, sclerosis, and cyst formation on a 5-point scale (none, minimal, mild, moderate, and severe).

In order to assess bone expansion and strength, DXA scan images were first converted into bone mass images using the automated Hip Strength Analysis (HSA) program developed by Beck et al. and described elsewhere [8]. A single operator manually placed four cursers to define the limits of the femoral neck region. The software, using the algorithm, then automatically demarcated the linear axes of the femoral neck and shaft as well as three cross-sectional analysis regions: the narrow neck (measured across the narrowest width of the femoral neck) the intertrochanteric (IT) region (along the bisector of the neck-shaft angle) and the femoral shaft, located 2 cm distal to the user-defined midpoint of the lesser trochanter along the shaft axis. For each region, cross-sectional measurements are derived from the distribution of bone mass across the bone within the region using the method described by Martin and Burr [9]. Fifty scans were duplicated and the CV was derived for the femoral neck length (5.1%), femoral width (0.83%), and cross-sectional moment of intertia (CSMI) (1.7%) at the IT area.

In the same year as the 4-year follow-up DXA, subjects also underwent dynamic suppression and stimulation tests of the HPA axis. On the night before clinic, subjects ingested 0.25 mg dexamethasone at 2200 hours and fasted overnight. At 0830 hours, a 21-gauge butterfly cannula was inserted in an antecubital fossa vein and after 30 minutes rest a baseline blood sample was obtained before 1.0 µg of freshly diluted tetracosactrin (ACTH$_{1-24}$) (Synacthen, Alliance Pharmaceutical LTD, Chippenham, UK) was injected. Venous blood was sampled through the cannula at 20, 30, 40, and 60 minutes post synacthen administration. Samples were centrifuged immediately and plasma was stored at −80°C. Finally, subjects collected a 24-hour urine sample at least a week before or after the dexamethasone/ACTH$_{1-24}$ test.

Dexamethasone (0.25 mg) and ACTH$_{1-24}$ (1 µg) doses were selected to provide an average 50% to 75% of maximal suppression or stimulation, respectively, with a wide range [10, 11]. The reproducibility of both of these tests has previously been demonstrated [12, 13]. More conventional doses (e.g., 1 mg dexamethasone or 250 µg ACTH$_{1-24}$) would be expected to produce maximal effects in all of these otherwise healthy participants and would not detect subtle alterations in the control of cortisol secretion.

Laboratory Analyses

Cortisol was measured in plasma by radioimmunoassay using Guildhay antisera (interassay CV 7.4% to 10.3%) [14]. Corticosteroid-binding globulin (CBG) was measured with a commercial assay (Medgenics Diagnostics, Fleurus, Belgium; CV 4.5% to 5%). Cortisol, cortisone, and their metabolites were measured in urine by gas chromatography/electron impact mass spectrometry [15]. Total cortisol metabolite excretion was calculated as tetrahydrocortisols + tetrahydrocortisone + cortols + cortolones. Measurements of 25-hydroxyvitamin D, parathyroid hormone, estradiol, testosterone, and osteocalcin have been reported previously [3].

Statistical Analyse

Because the distributions of cortisol measurements were skewed, log$_e$-transformed values were used in all analyses, and geometric means and standard deviations (SDs) are, therefore, presented. The associations between plasma cortisol concentrations post dexamethasone, peak cortisol concentrations following ACTH$_{1-24}$, total urinary cortisol metabolites, and BMD and bone loss rate at the lumbar spine and femoral neck were analyzed using Pearson's correlation and partial correlation coefficients. Relationships were explored initially without adjustment for any other factor, but were then adjusted for the potential confounding effects of "hormonal variables" including testosterone, estradiol, 25-hydroxyvitamin D, parathyroid hormone, and osteocalcin and then with adjustment for these factors and "lifestyle variables" including age, body mass index (BMI) activity, alcohol, smoking and Kellgren/Lawrence score. *P*-values refer to analyses using continuously distributed variables. In a power calculation for this sample size of 151 men and 96 women, the minimal detectable change in bone loss rate per SD change in cortisol was 0.30% per year in men and 0.35% per year in women at the lumbar spine, and 0.33% per year in men and 0.40% per year femoral neck. All statistical analysis was carried out using STATA, release 8 (Statacorp 2003, College Station, TX, USA).

Results

Table 1 summarizes the characteristics of the participants. Over the 4-year follow-up, subjects had increased in BMI (men: 26.8 SD 3.4 vs. 27.1 SD 3.7, *P* = 0.002; women: 26.8 SD 4.4 vs. 27.5 SD 4.0, *P* < 0.0001), but had not changed in smoking habits or alcohol consumption. Women lost bone at all sites, ranging from 0.27% per year (SD 1.23) at the lumbar spine to 1.21% per year (SD 1.39) at the femoral neck. In contrast, men lost only 0.25% per year (SD 1.45) at the femoral neck but gained bone at a rate of 0.46 SD 1.32) %/year at the lumbar spine. Forty one men (27%) and 22 women (23%) had a Kellgren/Lawrence score at the lumbar spine of grade 4, indicating severe osteoarthritis. There was a statistically significant (*P* < 0.001) positive relationship between rising Kellgren/Lawrence score and greater lumbar spine BMD in men and women. Femoral and intertrochanteric neck widths and cross-sectional moments of inertia were significantly lower in women than men (*P* < 0.0001).

There was no association between peak plasma cortisol concentrations following ACTH$_{1-24}$ and basal lumbar spine bone density in either men or women. However, in men but not in women, elevated peak plasma cortisol was significantly associated with accelerated lumbar spine loss (Fig. 1, r = 0.16, *P* = 0.05). This relationship remained significant after adjustment for testosterone, estradiol, 25-hydroxyvitamin D, and

Table 1. Summary characteristics of participants

Mean (SD) or n (%)	Men (n = 151)	Women (n = 96)
Age at baseline (yr)	66.0 (3.1)	65.8 (2.6)
Age at follow-up (yr)	70.9 (3.1)	71.0 (2.6)
BMI at baseline (kg/m^2)	26.8 (3.4)	26.8 (4.4)
BMI at follow-up (kg/m^2)	27.1 (3.7)	27.5 (4.0)
Daily calcium intake (mg/day)	729 (263)	660 (216)
Alcohol intake		
Men <8 units per week; women nondrinkers	86 (57.0%)	44 (45.8%)
Men 8–18 units; women 1–7 units; per week	30 (19.9%)	46 (47.9%)
Men >18 units; women >7 units; per week	35 (23.2%)	6 (6.3%)
Smoking status		
Never	28 (18.5%)	58 (60.4%)
Ex	97 (64.2%)	31 (32.3%)
Current	26 (17.2%)	7 (7.3%)
Active	68 (45.0%)	58 (60.4%)
BMD (g/cm^2)		
Lumbar spine	1.07 (0.18)	0.92 (0.17)
Femoral neck	0.81 (0.13)	0.71 (0.10)
Bone loss rate (%/yr)[a]		
Lumbar spine	−0.46 (1.32)	0.27 (1.23)
Femoral neck	0.25 (1.45)	1.21 (1.39)
Kellgren/Lawrence score		
Grade 0	10 (6.6%)	7 (7.3%)
Grade 1	24 (15.9%)	17 (17.7%)
Grade 2	34 (27.2%)	28 (29.2%)
Grade 3	41 (27.2%)	22 (22.9%)
Grade 4	41 (27.2%)	22 (22.9%)
Hip strength[b]		
Femoral neck width (cm)	3.7 (0.3)	3.1 (0.2)
Femoral neck CSMI (mm^4)	3.5 (1.3)	5.5 (0.3)
Intertrochanteric width (cm)	6.2 (0.4)	1.9 (1.2)
Intertrochanteric CSMI (mm^4)	19.1 (1.3)	11.6 (1.2)
[c]Peak plasma cortisol post ACTH$_{1\text{-}24}$ (nmol/L)	429.4 (1.2)	605.2 (1.2)
[c]Plasma cortisol post dexamethasone (nmol/L)	180.5 (1.8)	109.6 (2.4)
[c]Total urine cortisol metabolites (mg/24 hour)	17.0 (2.2)	4.7 (1.7)

[a] A negative value for bone loss rate implies gain over the follow-up period
[b] Data on femoral and intertrochanteric width and CSMI (cross-sectional moment of inertia) available for 120 men and 84 women
[c] Geometric mean and SD
ACTH, adrenocorticotropic hormone; BMI, body mass index; BMD, bone mineral density; SD, standard deviation

parathyroid hormone levels (r = 0.22, P = 0.01) and after additional adjustment for age, BMI, activity, cigarette and alcohol consumption, and Kellgren/Lawrence score (r = 0.19, P = 0.03).

In contrast, higher peak plasma cortisol concentrations following ACTH$_{1\text{-}24}$ were associated with lower basal femoral neck bone density (r = −0.23, P = 0.03) and a greater rate of bone loss at this site (r = 0.24, P = 0.02) in women, but not in men (Fig. 1). The relationships remained significant after adjustment for testosterone, estradiol, 25-hydroxyvitamin D, and parathyroid hormone levels (r = 0.25, P = 0.02) and after additional adjustment for age, BMI, activity, cigarette and alcohol consumption, and Kellgren/Lawrence score (r = 0.23, P = 0.04). A further analysis including only subjects with a Kellgren/Lawrence score of less than 2 revealed correlations or similar magnitude to the whole group between peak cortisol and lumbar spine loss rate in men, although these were no longer signifi-

cant owing to smaller sample size (n = 34, r = 0.18, P = 0.31). Associations between peak cortisol and femoral neck loss in women remained significant in this smaller group without significant osteoarthritis (n = 23, r = 0.50, P = 0.01).

There were no associations between plasma cortisol concentrations post dexamethasone and basal bone density or rate of bone loss at the proximal femur or lumbar spine in either men or women. CBG was neither associated with bone density at any site nor was it associated with bone loss rate (data not shown). Furthermore, there were no associations between cortisol measurements and bone strength at any site in both men and women. In men, there were no associations between urinary total cortisol metabolite excretion and basal BMD or rate of bone loss at any site. In women, lower urinary total cortisol metabolite excretion tended to be associated with lower basal BMD at the lumbar spine (r = 0.22, P = 0.05; r = 0.12, P = 0.31 after adjust-

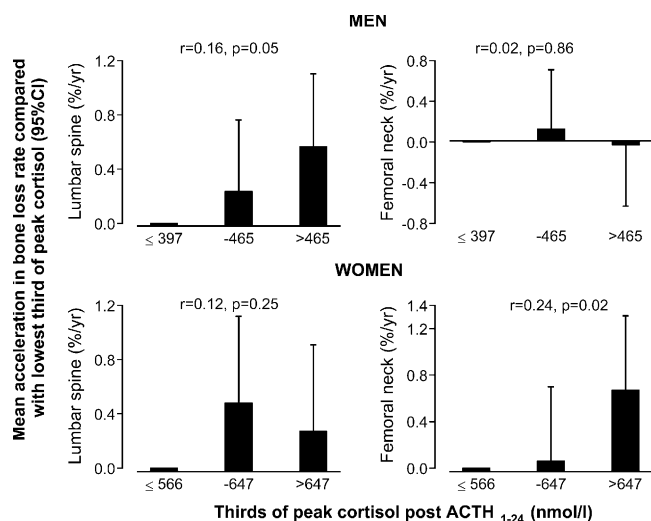**Fig. 1.** Peak plasma cortisol following $ACTH_{1-24}$ and lumbar spine and femoral neck bone loss rate in men and women. (**a.**) Values are mean + 95% confidence intervals (CIs) for accelerations in bone loss rate in men and women in the middle and upper tertiles of the distribution of peak plasma cortisol compared with a baseline group of those in the lowest third. (**b.**) For men: Lumbar spine: r = 0.16, P = 0.05 unadjusted; r = 0.22, P = 0.01 after adjustment for testosterone, estradiol, 25-hydroxyvitamin D, and parathyroid hormone levels; r = 0.19, P = 0.03 after also adjusting for age, BMI, activity, cigarette and alcohol consumption, and Kellgren/Lawrence score. Femoral neck: r = 0.02, P = 0.86 unadjusted; r = 0.01, P = 0.87 after adjustment for testosterone, estradiol, 25-hydroxyvitamin D, and parathyroid hormone levels; r = −0.01, P = 0.91 after also adjusting for age, BMI, activity, cigarette and alcohol consumption, and Kellgren/Lawrence score. (**c.**) For women: Lumbar spine: r = 0.12, P = 0.25 unadjusted, r = 0.11, P = 0.31 after adjustment for testosterone, estradiol, 25-hydroxyvitamin D, and parathyroid hormone levels; r = 0.18, P = 0.13 after also adjusting for age, BMI, activity, cigarette and alcohol consumption, and Kellgren/Lawrence score. Femoral neck: r = 0.24, P = 0.02 unadjusted, r = 0.25, P = 0.02 after adjustment for testosterone, estradiol, 25-hydroxyvitamin D, and parathyroid hormone levels; r = 0.23, P = 0.04 after also adjusting for age, BMI, activity, cigarette and alcohol consumption, and Kellgren/Lawrence score.

ment), but there were no associations between urinary total cortisol metabolite excretion and bone loss at any site.

Discussion

The results of this study support the hypothesis that the HPA axis plays a role in the pathogenesis of age-related osteoporosis. We found that activation of the HPA axis, as evidenced by an elevated peak plasma cortisol response to $ACTH_{1-24}$, was associated with greater bone loss at the lumbar spine in men and with lower BMD at the femoral neck and greater bone loss at this site in women. Urinary cortisol metabolite excretion was not associated with bone loss at any site in either men or women.

Although exogenous glucocorticoids are well recognized as a cause of osteoporosis [16], little is known of the effect of endogenous circulating glucocorticoids on bone mass. Previous studies have suggested that the effects may differ in men and women. We found endogenous cortisol secretion (measured as "integrated 24-hour cortisol level") was associated with BMD and rate of bone loss in men but not in women [2, 3]. Weak associations between serum cortisol and lumbar spine BMD have been described in men [17] but not in women [18]. The current data suggest that sensitivity of the HPA axis also influences BMD and the rate of involutional bone loss in healthy individuals, with differing effects at cortical and trabecular sites in men and women. These differences were not accounted for by differences in bone strength. Our findings of differing relationships between cortisol production and bone mass at the two sites measured according to sex may reflect a true pattern of sexual dimorphism, or may reflect the difficulties associated with assessment of bone loss at the lumbar spine in this age group, where osteoarthritic changes are common.

We did not find any associations between urine cortisol metabolite excretion and bone loss at any site in either men or women. This may be because of the relatively small sample size and the imprecision of measurements in 24-hour urine samples given that in a larger group of 684 men and women aged 70 to 79 years over a 7-year period, increasing quartiles of urinary free cortisol were associated with increasing risk of fracture, an effect that was seen primarily in men [19].

The mechanism for the increased sensitivity to adrenocorticotropic hormone (ACTH), which associates with measurements of bone density is unclear. It appears not to be associated with altered negative feedback control of the HPA axis, since we found, no associations between plasma cortisol following suppression with dexamethasone and either baseline bone density or loss at any site. It is likely that it reflects a subtle degree of adrenocortical hypertrophy. This may result from enhanced endogenous ACTH secretion but, in the absence of increased 24-hour urine cortisol metabolite excretion, we cannot confirm that there is a primary increase in central "drive" to the HPA axis in subjects who lose the greatest amount of BMD. We have not examined this population for polymorphisms in the glucocorticoid receptor gene, which affect glucocorticoid sensitivity, and which have been associated with differences in body composition and BMD [20]. In our studies of the relationship between birthweight and adult HPA axis function, we have found the $ACTH_{1-24}$ stimulated cortisol level to be the most sensitive marker of HPA-axis dysfunction [6]. It may be that the abnormalities are too subtle to be detected by other techniques. Nonetheless, even small differences in glucocorticoid exposure cumulatively over time might plausibly contribute to a loss of bone density.

There were a number of limitations to this study. Although subjects were all born in Hertfordshire and still lived there in adult life, they are known to be representative of national norms with respect to smoking and alcohol consumption [21]. The participants were also known to be representative of the larger group from which they were selected with regard to their height, weight, and BMI, and their BMD values fell within the normal range provided by the manufacturer of the DXA scan instrument. The findings could not be explained by changes in BMI or lifestyle factors. Another limitation of the study is the change in densitometer model between baseline and follow-up. To ensure standardization we calculated a conversion algorithm by performing repeat examinations of 23 individuals from within the study sample using both instruments, which were models produced by the same manufacturer. Interpretation of results at the lumbar spine was made more difficult by the high prevalence of osteoarthritis at this site, which may have artificially elevated bone density values [22]. However, the associations remained after adjustment for Kellgren and Lawrence grade of osteoarthritis and analyses of only subjects without significant osteoarthritis revealed correlations of peak cortisol and bone loss rates of similar magnitude to the whole group. The sample size for this study was moderate, and the observed effects were of the same magnitude as the estimated minimal detectable effects from our power calculation suggesting the positive findings were not due to chance.

In conclusion, in addition to the well-recognized deleterious effects of exogenous glucocorticoids, these data provide further evidence that circulating endogenous glucocorticoids and HPA-axis activity may also influence the rate of involutional bone loss in healthy elderly individuals. Larger studies with more prolonged follow-up are now justified to clarify the importance of these associations.

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