Corticosteroid-Induced Bone Loss in Men

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ABSTRACT

Lack of consistent information concerning the pathophysiology of corticosteroid-related bone loss may be due to coexisting independent factors that influence bone mineral density (BMD). For example, the disease being treated may increase bone turnover and cause bone loss, and its severity may influence the dose of corticosteroids chosen. Similarly, disease remission due to the treatment or disease progression despite treatment may influence bone turnover and the rate of bone loss. The hormonal changes purportedly responsible for reduced bone formation or increased bone resorption may be the result of the disease, not the corticosteroids.

To determine the pathophysiology of corticosteroid-related bone loss, we conducted a controlled, prospective study in men with no systemic illness treated with corticosteroids to reduce antisperm antibodies. We measured BMD using dual x-ray absorptiometry and circulating biochemical and hormonal determinants of bone turnover in 9 men before and during prednisolone treatment and in 10 age-matched controls. The results were expressed as the mean ± SEM.

There were no differences in BMD between the two groups at baseline. The patients received 50 mg prednisolone daily for 3.7 months (range, 1–6). BMD decreased by 4.6 ± 0.8% at the lumbar spine (P = 0.0007), by 2.6 ± 0.6% at the trochanter (P = 0.004), and by 4.8 ± 1.9% at the Ward’s triangle (P < 0.04). The decrease in lumbar spine BMD correlated with the cumulative dose of corticosteroids (r = −0.49; P = 0.03). Serum osteocalcin and skeletal alkaline phosphatase decreased by 28.5 ± 15.5% (P = 0.08) and 24.2 ± 8.6% (P < 0.03), respectively. The decrease in lumbar spine BMD correlated with the decrease in osteocalcin (r = −0.48; P < 0.02). Serum testosterone and sex hormone-binding globulin decreased by 28.6 ± 4.4% (P < 0.003) and 28.5 ± 8.3% (P < 0.007), respectively. The testosterone/sex hormone-binding globulin ratio did not change. The decrease in total testosterone correlated with the decrease in osteocalcin (r = −0.40; P = 0.05). There were no detectable changes in urinary C-telopeptide, serum PTH, or serum calcium. Estradiol decreased by 23.5 ± 11.4% (P < 0.003).

Corticosteroid therapy results in rapid bone loss, probably due to reduced bone formation. Neither increased bone resorption nor secondary hyperparathyroidism appears to contribute to the rapid bone loss. Whether the reduction in bone formation may be partly mediated by changes in sex steroids remains unclear.

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the two groups because it is unethical to give corticosteroids to healthy subjects or withhold treatment from the patients. Informed consent was obtained from all patient and control subjects before enrollment in the study.

Bone density, and biochemical and hormonal measurements

Total body and regional BMD were measured by dual x-ray absorptiometry (grams per cm²; DPX-L, Lunar Corp., Madison, WI) (16). The coefficient of variation ranged from 1.5–2.4%. Morning blood and urine samples were collected in all subjects. Bone formation was assessed by measuring serum osteocalcin, bone-specific alkaline phosphatase, and serum collagen propeptide of type I collagen. Serum osteocalcin was measured with a human-specific immunoradiometric assay (nanograms per mL; ELISA-OSTEO, Cis Biointernational, France) (17). Serum bone-specific alkaline phosphatase was measured with an immunoradiometric assay (Cross Laps, Osteometer A/S, Rodovre, Denmark) (20). Bone resorption was assessed by measuring urinary type I C-telopeptide breakdown products (CTX) with an enzyme-linked immunosorbent assay (Cross Laps, Osteometer A/S, Rodovre, Denmark) (20).

A RIA was used to measure GH (nanograms per mL; Orion Diagnostics, Espoo, Finland), IGF-I (nanograms per mL; using anti-human IGF-I polyclonal rabbit antibodies), serum dehydroepiandrosterone sulfate (DHEA-S; nanograms per mL; Biotecx, Houston, TX), and androstenedione (nanograms per mL; Diagnostics Biochem Canada, Ontario, Canada). Competitive chemiluminescent immunoassays (Ciba Corning ASC:180 machine, Australian Diagnostics) were used to measure serum testosterone (nanomoles per L), LH (milliinternational units per mL), and FSH (milliinternational units per mL). Immunoassay metrics were used to measure sex hormone-binding globulin (SHBG; nanomoles per L; Orion Diagnostica) and serum intact PTH (picograms per mL; ELISA-OSTEO, Cis Biointernational, France) (17). Serum bone mineral density, and biochemical and hormonal measurements at baseline and the mean of the paired changes (baseline minus final) in patients and controls

TABLE 1. Age, height, weight, bone mineral density, and hormone measurements at baseline and the mean of the paired changes (baseline minus final) in patients and controls

<table>
<thead>
<tr>
<th>Base line</th>
<th>Patients</th>
<th>Controls</th>
<th>Patients</th>
<th>Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>33.1 ± 1.7</td>
<td>33.5 ± 1.4</td>
<td>-0.04 ± 0.01a,b</td>
<td>0.00 ± 0.01</td>
</tr>
<tr>
<td>Ht (cm)</td>
<td>184 ± 2.2</td>
<td>179 ± 1.5</td>
<td>-0.04 ± 0.02c</td>
<td>-0.01 ± 0.01</td>
</tr>
<tr>
<td>Wt (kg)</td>
<td>86.3 ± 4.2</td>
<td>79.1 ± 2.9</td>
<td>-0.03 ± 0.01c</td>
<td>-0.00 ± 0.02</td>
</tr>
<tr>
<td>Bone mineral density (g/cm²)</td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Lumbar spine</td>
<td>1.23 ± 0.06</td>
<td>1.25 ± 0.08</td>
<td>-0.01 ± 0.01</td>
<td>0.00 ± 0.01</td>
</tr>
<tr>
<td>Femoral neck</td>
<td>1.09 ± 0.03</td>
<td>1.08 ± 0.05</td>
<td>-0.04 ± 0.02c</td>
<td>-0.01 ± 0.01</td>
</tr>
<tr>
<td>Ward’s triangle</td>
<td>0.99 ± 0.04</td>
<td>0.98 ± 0.06</td>
<td>-0.03 ± 0.01c</td>
<td>-0.00 ± 0.02</td>
</tr>
<tr>
<td>Trochanter</td>
<td>0.96 ± 0.03</td>
<td>0.97 ± 0.04</td>
<td>-0.01 ± 0.01</td>
<td>0.00 ± 0.01</td>
</tr>
<tr>
<td>Total body</td>
<td>1.23 ± 0.03</td>
<td>1.24 ± 0.03</td>
<td>-0.01 ± 0.01</td>
<td>0.00 ± 0.01</td>
</tr>
<tr>
<td>Hormone measurements</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>PTH (pmol/L)</td>
<td>3.4 ± 0.5</td>
<td>3.8 ± 0.8</td>
<td>-0.5 ± 0.5</td>
<td>-0.6 ± 0.8</td>
</tr>
<tr>
<td>Serum calcium (mmol/L)</td>
<td>2.3 ± 0.1</td>
<td>2.4 ± 0.1</td>
<td>0.1 ± 0.1</td>
<td>0.0 ± 0.1</td>
</tr>
<tr>
<td>Testosterone (nmol/L)</td>
<td>18.1 ± 2.0</td>
<td>16.1 ± 1.5</td>
<td>-2.7 ± 1.5</td>
<td>0.3 ± 1.5</td>
</tr>
<tr>
<td>SHBG (nmol/L)</td>
<td>33.9 ± 5.2</td>
<td>37.5 ± 5.9</td>
<td>-5.9 ± 4.0</td>
<td>-0.2 ± 2.4</td>
</tr>
<tr>
<td>TSHBG ratio</td>
<td>0.6 ± 0.1</td>
<td>0.5 ± 0.1</td>
<td>0.0 ± 0.1</td>
<td>0.0 ± 0.1</td>
</tr>
<tr>
<td>Estradiol (pmol/L)</td>
<td>273 ± 39</td>
<td>297 ± 25</td>
<td>-44.7 ± 37.8</td>
<td>-16.4 ± 36.9</td>
</tr>
<tr>
<td>LH (mIU/mL)</td>
<td>3.4 ± 0.4</td>
<td>3.8 ± 0.6</td>
<td>-0.6 ± 0.2b,c</td>
<td>0.6 ± 0.6</td>
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<tr>
<td>FSH (mIU/mL)</td>
<td>4.1 ± 1.0</td>
<td>3.6 ± 0.6</td>
<td>0.3 ± 0.3</td>
<td>0.0 ± 0.2</td>
</tr>
<tr>
<td>Androstenedione (ng/mL)</td>
<td>2.6 ± 0.6</td>
<td>1.9 ± 0.2</td>
<td>-1.7 ± 0.5b,c</td>
<td>-0.1 ± 0.3</td>
</tr>
<tr>
<td>DHEA-S (ng/mL)</td>
<td>3075 ± 585</td>
<td>5066 ± 847</td>
<td>-1725 ± 542b,c</td>
<td>-836 ± 1060</td>
</tr>
<tr>
<td>GH (ng/mL)</td>
<td>1.4 ± 0.1</td>
<td>0.8 ± 0.1</td>
<td>0.5 ± 0.6</td>
<td>0.1 ± 0.1</td>
</tr>
<tr>
<td>IGF-I (ng/mL)</td>
<td>169 ± 16</td>
<td>103 ± 7</td>
<td>29.8 ± 19.0</td>
<td>-11.6 ± 15.3</td>
</tr>
</tbody>
</table>

SHBG, Sex hormone-binding globulin; TSHBG, testosterone/sex hormone-binding globulin ratio; DHEA-S, dehydroepiandrosterone sulfate; IGF-I, insulin-like growth factor I.

a P < 0.05 compared to zero.
b P < 0.05 compared to controls.
c P < 0.001 compared to zero.
d P < 0.07 compared to zero.

Statistical analysis

Analyses were performed using StatView II (Abacus Concepts, Berkeley, CA). Paired t tests were used to compare the pre- and post-treatment results in the patients. Differences between the two groups were analyzed using ANOVA. The data were expressed as the mean ± SEM. The relationship among dose, changes in BMD, and biochemical measures was analyzed using regression analysis. For the regression analyses, each time point was expressed as a percent change from the initial (pre treatment) value.

Results

The patients were treated with 50 mg prednisolone for 3.7 ± 0.6 months (range, 1–6 months). All of the patients were taking 50 mg/day prednisolone during the first 2 months. At 3 months, five patients received 50 mg, and two received the tapering regimen (see Subjects and Methods). At 6 months, one patient received 50 mg, and two received the tapering regimen.

BMD did not differ between the two groups at baseline (Table 1). In the patients, BMD decreased by 4.6 ± 0.8% at the lumbar spine (P < 0.0007), by 2.6 ± 0.6% at the trochanter (P = 0.004), and by 4.8 ± 1.9% at the Ward’s triangle (P < 0.04; Fig. 1). BMD did not change in the controls. The decrease in lumbar spine BMD correlated with the cumulative dose of prednisolone (r = -0.49; P = 0.03; Fig. 2).

Serum osteocalcin decreased by 28.5 ± 15.5% (P = 0.08), and skeletal alkaline phosphatase decreased by 24.2 ± 8.6% (P < 0.03; Fig. 3). There was no detectable change in collagen propeptide of type I collagen. Bone resorption, as assessed by urinary CTX, did not increase. PTH did not increase during corticosteroid treatment (Fig. 3). There was no de-
tectable change in serum calcium. The fall in lumbar spine BMD correlated with the fall in serum osteocalcin ($r = -0.48$; $P < 0.02$; Fig. 4).

The sex steroid concentrations did not differ between the patients and controls at baseline (Table 1). In the patients, total testosterone decreased by $28.6 \pm 4.4\%$ ($P < 0.003$) and then increased as the dose of corticosteroids was tapered (Fig. 5). There was a correlation between the decrease in testosterone and the change in osteocalcin ($r = -0.4; P = 0.05$; Fig. 6). SHBG decreased by $28.5 \pm 8.3\%$ ($P < 0.007$); the testosterone/SHBG ratio did not change (Fig. 5). Estradiol decreased by $23.5 \pm 11.4\%$ ($P < 0.003$), and FSH increased by $67.2 \pm 35.1\%$ ($P = 0.08$; Fig. 5). There were no changes in the controls. At the final measurement, LH was lower in the patients ($2.8 \pm 0.3$) than in the controls ($4.8 \pm 0.6$ IU/mL; $P < 0.006$).

Androstenedione and DHEA-S did not differ between patients and controls at baseline (Table 1). After treatment, androstenedione decreased by $58.2 \pm 14.6\%$ ($P < 0.008$), and DHEA-S decreased by $50.3 \pm 9.8\%$ ($P < 0.002$; Fig. 5). There were no changes in the controls. At the end of treatment, androstenedione and DHEA-S were lower in the patients than the controls [0.8 ± 0.2 vs. 2.1 ± 0.2 ng/mL ($P = 0.0006$) and 1349 ± 234 vs. 4596 ± 982 ng/mL ($P < 0.003$), respectively]. At baseline, serum IGF-I and GH were higher in the patients than in the controls (Table 1). In the patients, IGF-I increased by $52.0 \pm 19.2\%$ ($P < 0.05$; Fig. 5). There were no
detectable changes in GH. IGF-I and GH did not change in the controls. At the final measurement, IGF-I was higher in the patients (199.2 ± 19.2) than in the controls (104.4 ± 2.9 ng/mL; P < 0.0007).

**Discussion**

This study was undertaken to evaluate the magnitude and pathophysiology of corticosteroid-related bone loss in the absence of disease, which itself may influence BMD and biochemical measurements. Patients were disease free, and the dose and duration of treatment were documented prospectively. Treatment with 50 mg/day resulted in rapid bone loss; BMD decreased by 2–4.5% during the 6 months. These rates of loss are 8–16 times higher than those encountered in healthy men aged between 20–40 yr (21). If these rates of bone loss persist, then the risk of fracture will double within about 1 yr (22).

Bone loss is likely to be due to reduced bone formation, as serum osteocalcin and skeletal alkaline phosphatase decreased after corticosteroid treatment, and the change in lumbar spine BMD correlated with the change in osteocalcin. Serum osteocalcin and alkaline phosphatase decrease after short courses of corticosteroids in normal volunteers (23, 24), confirming that it is the drug, not the disease, that is likely to reduce bone formation.

We found no biochemical evidence of increased bone resorption, as urinary CTX was unchanged during the study of healthy subjects. In a study of patients with polymyalgia rheumatica, we found that urinary CTX was elevated before treatment and decreased after treatment with 10 mg prednisolone daily, suggesting that the illness was responsible for the increased bone resorption (12). Patients with rheumatoid arthritis have elevated urinary CTX and deoxypyridinoline, with higher values in those receiving corticosteroids. The researchers suggested that the higher values may have been the result of the corticosteroid therapy. However, the patients with rheumatoid arthritis treated with corticosteroids may have had more severe disease (4).

There was no evidence of secondary hyperparathyroidism, suggesting that it is unlikely to be involved in the pathogenesis of the bone loss occurring in the first 3–6 months of corticosteroid therapy. Secondary hyperparathyroidism has been reported in some studies, but most have shown no difference in PTH (9, 13, 23, 25). PTH levels were suppressed before corticosteroid treatment in patients with polymyalgia rheumatica, suggesting that the disease may result in increased bone resorption with suppression of PTH (12).

Serum total testosterone has been shown to be reduced in men receiving corticosteroids in some (26–30), but not in all studies (31, 32). Most of these studies were cross-sectional
When attempts were made to control for disease, it was unclear whether the disease was of comparable severity and contributed to the reduction in serum testosterone (26–29, 31, 32). In addition, few studies have measured free testosterone directly. When reported, a calculated free testosterone index was reported to be reduced (26–28, 32). Serum total testosterone and SHBG decreased in this study. As there was an association between the reduction in total testosterone, but not the testosterone/SHBG ratio, and the reduction in serum osteocalcin, we are reluctant to infer that there may be a causal relationship between the decline in testosterone and bone formation. Increased, decreased, and unaltered FSH and LH have been reported, but the episodic secretion of these gonadotropins makes interpretation of single values difficult (26). Corticosteroids may have direct effects on the testis and indirect effects on sex steroid production due to suppression of ACTH production (6).

Circulating GH and IGF-I levels increased in healthy subjects after corticosteroid treatment, which is similar to the increased GH and IGF-I observed in the present study (33). In normal subjects acute administration of dexamethasone has been shown to increase plasma GH levels compared to saline administration (34). However, GH was lower in patients receiving long term corticosteroid treatment compared to normal values (8). The pattern of serum IGF-I changes in the present study was similar to observations in patients with polymyalgia rheumatica treated with low dose prednisolone (12). IGF-I bioactivity may be reduced in normal men treated with corticosteroids, patients with Cushings disease, and patients receiving corticosteroid therapy despite an increase in plasma IGF-I concentrations (7, 33). The mechanisms responsible for the increase in IGF-I are uncertain (33).

In conclusion, corticosteroid therapy induced rapid bone loss. The loss of bone is most likely due to a reduction in bone formation; increased bone resorption does not appear to contribute. There was no evidence for secondary hyperparathyroidism. Prospective studies in men free of illness with direct measurements of free testosterone will be required to determine whether the reduction in bone formation may be partly mediated by changes in sex steroids.

Acknowledgment

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References

1. Dempster DW, Arlot MA, Meunier PJ. 1983 Mean wall thickness and formation periods of trabecular bone packets in corticosteroid-induced osteoporosis. Calcif Tissue Int. 35:410–417.

WANTED

Castrate men wanted for frequent blood sampling studies to examine GnRH pulse frequency in the absence of either sex steroid or nonsteroidal feedback regulation. Suitable cases include post-bilateral orchidectomy, vanishing testes syndrome, or congenital anorchia. Participants must be agreeable to discontinue androgen replacement therapy for 4 weeks prior to the study. Stipend available. Please correspond directly with:

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