THE DELETERIOUS EFFECTS OF LOW-DOSE CORTICOSTEROIDS ON BONE DENSITY IN PATIENTS WITH POLYMYALGIA RHEUMATICA

G. PEARCE, P. F. J. RYAN,* P. D. DELMAS,† D. A. TABENSKY and E. SEEMAN

Austin and Repatriation Medical Centre, Heidelberg, Victoria, 3084, *Alfred Hospital, Prahran, Victoria, 3181, Australia and INSERM Research Unit 403, E. Herriot Hospital, Lyon, France

SUMMARY

The beneficial effects of corticosteroid therapy in the treatment of rheumatic diseases may be offset by the occurrence of corticosteroid-related osteoporosis. This problem may be overcome by using low-dose corticosteroids; however, the dose of corticosteroids that is both efficacious and skeletal sparing is uncertain. Therefore, the aim of this study was to determine whether low-dose prednisolone treatment results in bone loss and modifies bone turnover. Nineteen patients (12 female, seven male) suffering from polymyalgia rheumatica received 10 mg or less daily, given in reducing dosage, with a range of 2.5–10 mg and an average of 6.0 ± 0.2 mg daily (± s.e.m.). Prior to the commencement of therapy and at regular intervals during treatment, bone mineral density (BMD) using dual X-ray absorptiometry and circulating biochemical and hormonal determinants of bone turnover were measured. The patients were followed for 14.4 ± 1.6 months (range 6–27). They were compared to 19 age-matched controls. Despite a mean exposure dose of 6 mg/day and disease remission, BMD decreased in the patients at the lumbar spine (2.6 ± 0.8%, P < 0.01), femoral neck (2.9 ± 1.5%, P = 0.06), Ward’s triangle (5.5 ± 2.9%, P = 0.06) and the trochanter (4.3 ± 1.9%, P < 0.05). Total body bone mass decreased by 50 ± 19 g in the first 6 months (P < 0.02), and by 39 ± 30 g in the remaining 8 months of follow-up [not significant (NS)]. In the first 6 months, BMD decreased at the lumbar spine (1.7 ± 0.9%, P = 0.06). From 6 months to the end of follow-up, BMD decreased by 8.5 ± 3.5% at Ward’s triangle (P < 0.05) and by 4.8 ± 2.5% at the femoral neck (P = 0.08). The fall in BMD correlated with the cumulative prednisolone dose at trabecular-rich regions (trunk r = −0.72, P < 0.001; ribs r = −0.53, P < 0.05). Bone resorption, assessed by urinary cross-laps, was 54.7% higher than controls before treatment was started (P < 0.05) and decreased by 23.5 ± 7.1% in the first month of treatment when the mean prednisolone dose was 9.1 mg/day, range 5–10 (P < 0.0001). Serum osteocalcin was not suppressed by disease before treatment, decreased by 27.4 ± 5.1% during the first month of treatment (P < 0.001), remained suppressed while the daily dose of prednisolone was >5 mg/day, but returned to baseline below this dose. Serum parathyroid hormone was 19.3% lower in the patients than controls at baseline (NS), and increased by 46.1% (P < 0.05) but was no higher than controls at any time. Muscle strength increased by 20–60% (P < 0.05 to < 0.01). Prophylaxis should be considered in patients receiving ≥5 mg/day prednisolone daily as bone loss is 2- to 3-fold expected rates. Earlier trabecular bone loss may predispose to spine and rib fracture; later cortical bone loss may predispose to hip fractures. Doses of prednisolone of <5 mg daily may be skeletal sparing, but may not be efficacious.

KEY WORDS: Corticosteroid-related bone loss, Bone turnover.

Corticosteroid therapy has an important role in the management of many chronic inflammatory and non-inflammatory illnesses. However, the benefits derived from the use of corticosteroids may be offset by the occurrence of corticosteroid-related osteoporosis. In principle, this problem may be overcome by using low-dose corticosteroids. In practice, the dose of corticosteroids that is both efficacious and skeletal sparing is uncertain.

The lack of credible information concerning the minimum dose of corticosteroids that improves the clinical and biochemical features of disease without causing bone loss is due to the many co-existing and independent factors that influence bone density [1–11]. For example, the illness to be treated may result in bone loss and its severity may influence the dose of corticosteroids chosen [1–8]. The purported safety of lower doses of corticosteroids may be the result of this sampling bias; patients with less severe illness and greater mobility may have higher bone density prior to treatment and are likely to receive lower doses of corticosteroids [7–10].

Exposure to corticosteroids before the onset of a clinical study is common and may result in an under-estimate of the effects of corticosteroids, particularly if an accelerated phase of bone loss had occurred during the initial months of therapy [2, 5, 10, 12]. In addition, the retrospective estimation of exposure dosage in cross-sectional studies is likely to be unreliable as dosage schedules are rarely recorded meticulously and compliance cannot be verified [1, 3, 7, 10, 13, 14]. Moreover, study participants differ by age [1, 2, 5, 8, 11], gender [1, 2, 4, 5, 7, 8, 11, 13], years since menopause [1–3, 5, 6, 8, 9, 12, 13] and the type of illness being treated [1, 2, 4, 5, 8, 11]; all important independent determinants of bone density. These factors may either account for the failure to detect an association between dose and bone density, or may be responsible for any reported association. Many patients receive treatment (other than corticosteroids) that may influence bone density directly or through the drug’s effect on the underlying illness [1, 6, 12, 13, 15, 16].

Methodological problems compound these difficulties in study design. The precision error of the

Submitted 14 January 1997; revised version accepted 2 July 1997.

Correspondence to: E. Seeman, Department of Endocrinology, Austin and Repatriation Medical Centre, Heidelberg, 3084, Australia.
methods used to measure bone density is 2–3%, similar to the expected change with treatment [1, 4, 5, 8–11, 14]. Cortical bone has a lower turnover than trabecular bone [17]. Thus, measurements confined to predominantly cortical regions may be less sensitive to corticosteroids than those in trabecular-rich regions [3]. In addition, small numbers of participants and brief follow-up may result in null observations [1, 4, 7, 12].

These problems in study design, execution and interpretation are also partly responsible for there being several unanswered questions concerning the pathogenesis of corticosteroid-related bone loss. Reduced bone formation has been consistently shown to contribute to bone loss [18–23]. Whether increased bone resorption occurs is less clear. The hormonal changes held to be responsible for reduced bone formation or increased bone resorption may be the result of disease activity before and during treatment, not the corticosteroids [16]. Although secondary hyperparathyroidism is often cited as a cause of bone loss, reduced, normal or elevated circulating parathyroid hormone (PTH) levels have been reported [24–30]. Rather than causing bone loss, PTH may be suppressed as a consequence of bone loss secondary to illness and immobility. Changes in gonadal and adrenal steroids, growth hormone and insulin-like growth factor 1 (IGF-1) have been implicated in the pathogenesis of reduced bone formation [31–34].

To overcome some of these difficulties, and to address several of these questions, we conducted a controlled prospective study in patients with newly diagnosed polymyalgia rheumatica who received 10 mg or less of prednisolone daily and had no prior exposure to corticosteroids. The patients received no other drugs and had no other illnesses known to affect bone. We asked the following questions. (i) Does corticosteroid therapy of 10 mg per day or less result in bone loss? (ii) Is there a dose–response relationship? (iii) Is bone loss accelerated in the early stages of treatment? Does it diminish with time? (iv) What is the pathogenesis of bone loss?

PATIENTS AND METHODS

All consecutive patients with polymyalgia rheumatica at the Alfred Hospital, Melbourne, between 1992 and 1995, were considered for participation in the study. We studied 19 patients (12 post-menopausal women, seven men) aged 71.8 ± 1.6 yr with polymyalgia rheumatica. Diagnostic criteria included: (1) symmetrical upper and lower limb girdle myalgia for 6 weeks or more; (2) erythrocyte sedimentation rate (ESR) > 50 mm/h; (3) absence of obvious polyarthritis, polytendonitis or polymyositis; (4) no clinical evidence of giant cell arteritis; (5) negative rheumatoid factor, antinuclear antibody and normal creatinine phosphokinase levels.

The patients were treated with 10 mg/day of prednisolone or less, which averaged 6.0 ± 0.2 mg/day during the observation period. The dose was tapered as clinical and biochemical improvement occurred. Treatment regimens were [daily dose (number of patients treated)]: 10 mg (13 for 1 and one for 2 months); 8.5 mg (one for 1 month); 8 mg (one for 2 months); 7.5 mg (four for 1, eight for 2, two for 3 and one for 4 months); 5 mg (six for 1, three for 2, one for 3, three for 4 and one for 6 months); 4 mg (one for 2 months); 3.5 mg (one for 2 months); 3 mg (two for 1 month); 2.5 mg (seven for 1, two for 2 and one for 6 months). The patients were followed for a mean of 14.4 months, ranging from 6 to 27 months (four for 6, one for 9, seven for 12, one for 15, three for 21 and three for 27 months).

The patients were compared with controls (15 females, four males) recruited from a normal age-matched population who were followed for 13.1 ± 1.3 yr. It was not possible to randomize the two groups because corticosteroids cannot be given to healthy subjects or withheld from patients. Eight patients were excluded because of prior corticosteroid therapy and three preferred not to participate. No patients received > 10 mg/day during the study, so no patients were excluded on this basis. One male control was excluded when found to be hypogonadal. Measurements were made before treatment, monthly for 3 months and then 3 monthly.

Total body and regional bone density were measured by dual X-ray absorptiometry (g/cm²; Lunar Corp., Madison, WI, USA) [35]. The coefficients of variation were determined in our own department, on our own machines, and ranged from 1.5 to 2.4%. Isokinetic muscle strength, generated during flexion and extension of the knee and hip at 60°/s, and during shoulder internal and external rotation at 30°/s, was measured in the patients using dynamometry (Merac, Universal, Cedar Rapids, IA, USA). The coefficient of variation for the movements ranged from 2.6 to 5.6% (lower limb) and from 10.9 to 13.7% (upper limb).

Morning blood and urine samples were collected in all subjects, frozen and stored at −20°C until the end of the study. Serum osteocalcin was measured with a human specific immunoradiometric assay (ng/ml; ELISA-OSTEO®, Cis BioInternational®, France) which recognizes a large N-terminal mid-fragment and the intact molecule [36]. Serum bone alkaline phosphatase was measured with an immunoradiometric assay using two monoclonal antibodies directed against the human bone isoenzyme (Ostase®, Hybritech Inc®, USA) [37]. Serum collagen propeptide of type 1 collagen (P1CP) was measured with a two-site enzyme-linked immunoassay (ELISA) which uses a polyclonal and a monoclonal antibody raised against human procollagen 1 carboxypeptide purified from skin fibroblast culture (Procollagen-C®, Metra Biosystems®, USA) [38]. Bone resorption was assessed by measuring urinary type 1 C-telopeptide breakdown products with an ELISA (CTX, cross laps®, Osteometer A/S®, Denmark) based on an immobilized synthetic peptide with an amino acid sequence specific for a part of the C-telopeptide of the alpha 1 chain of type 1 collagen [39].
TABLE I
Age, height, weight, bone density, biochemical measures of bone turnover and hormonal measures at baseline and the mean of the paired changes (baseline minus final)

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>Changes</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Patients</td>
<td>Controls</td>
</tr>
<tr>
<td>Age (yr)</td>
<td>71.8 ± 1.6**</td>
<td>66.9 ± 1.3</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>164 ± 1.8</td>
<td>164 ± 1.7</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>68.9 ± 2.8</td>
<td>67.6 ± 2.4</td>
</tr>
<tr>
<td>Bone mineral density (g/cm²)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Lumbar spine</td>
<td>1.18 ± 0.05</td>
</tr>
<tr>
<td></td>
<td>Femoral neck</td>
<td>0.83 ± 0.03</td>
</tr>
<tr>
<td></td>
<td>Ward’s triangle</td>
<td>0.66 ± 0.03</td>
</tr>
<tr>
<td></td>
<td>Trochanter</td>
<td>0.76 ± 0.03</td>
</tr>
<tr>
<td>Biochemical and hormonal measurements</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CTX (µmol/mmol creatinine)</td>
<td>224 ± 28**</td>
<td>145 ± 22</td>
</tr>
<tr>
<td>Osteocalcin (ng/ml)</td>
<td>25.5 ± 3.1</td>
<td>26.4 ± 2.2</td>
</tr>
<tr>
<td>Alkaline phosphatase (ng/ml)</td>
<td>9.9 ± 1.0</td>
<td>11.1 ± 1.2</td>
</tr>
<tr>
<td>P1CP (ng/ml)</td>
<td>95.0 ± 6.2</td>
<td>88.6 ± 6.1</td>
</tr>
<tr>
<td>Androstenedione (ng/ml)</td>
<td>3.5 ± 0.4</td>
<td>2.8 ± 0.4</td>
</tr>
<tr>
<td>DHEA-S (ng/ml)</td>
<td>950 ± 227</td>
<td>1043 ± 155</td>
</tr>
<tr>
<td>IGF-1 (ng/ml)</td>
<td>72.6 ± 7.0</td>
<td>85.1 ± 6.4</td>
</tr>
<tr>
<td>Growth hormone (ng/ml)</td>
<td>3.2 ± 0.5</td>
<td>3.3 ± 0.9</td>
</tr>
</tbody>
</table>

Data expressed as mean ± s.e.m.

CTX, cross-laps; P1CP, procollagen 1 carboxypeptide; IGF-1, insulin-like growth factor 1; DHEA-S, dehydroepiandrosterone sulphate.

*P < 0.06; **P < 0.05 compared to controls.
†P < 0.09; ††P < 0.05; †P < 0.01; ††P < 0.001 compared to zero.

Serum intact PTH was measured by an immunoradiometric assay (pg/ml; Nichols Institute Diagnostics, San Luan Capistrano, CA, USA). Serum calcium and creatinine (mmol/l) were measured photometrically using the Hitachi autoanalyser. A radioimmunoassay was used to measure growth hormone (GH; ng/ml; Growth Hormone Spectra Kit, Orion Diagnostica, Finland), IGF-1 (ng/ml; using anti-human IGF-1 polyclonal antibodies raised in rabbits), serum dehydroepiandrosterone sulphate (DHEA-S; ng/ml; Direct RIA Kit, Biotech, Houston, TX, USA) and androstenedione (ng/ml; Direct Androstenedione Kit, Diagnostics Biochem Canada Inc., Ontario, Canada). Testosterone, sex steroid binding globulin (SHBG), luteinizing hormone (LH) and follicle-stimulating hormone (FSH) were measured in the men. Testosterone was measured using a competitive chemiluminescent immunoassay (Ciba Corning ASC:180 machine, Australian Diagnostics). SHBG was measured using an immunoradiometric assay (nmol/l; SHBG Spectra Kit, Orion Diagnostica, Finland). FSH and LH were measured using a two-site chemiluminometric immunoassay (mIU/l; Ciba Corning ACS:180 machine, Australian Diagnostics). Coefficients of variation for the assays were 5–10%.

Analyses were performed using Statview II (Abacus Concepts Inc., Berkeley, CA, USA). Paired t-tests were used to compare the pre- and post-treatment results in the patients and controls. Differences between the two groups were analysed using ANOVA. Adjustments for age were made using ANCOVA. The relationship between bone density and the cumulative dose of prednisolone was examined using simple regression. The data were expressed as mean ± s.e.m.

RESULTS

The patients received a mean prednisolone dose of 6.0 ± 0.23 mg/day (range 2.5–10) and a cumulative dose of 2356 ± 244 mg (range 1065–4765). Remission was characterized by resolution of muscle pain and weakness, and a fall in ESR from 58.9 ± 4.5 mm/h to baseline to 15.3 ± 3.8, 14.5 ± 3.1 and 11.6 ± 2.2 mm/h at 3, 6 and 12 months, respectively (all P < 0.0001 compared to baseline).

As shown in Table I, the patients were ~5 yr older than the controls due to exclusion of the hypogonadal male control. There was no significant age difference between the female patients and controls (70.0 ± 1.9 and 66.0 ± 1.4 yr, respectively). There were no differences in baseline bone density in the patients and controls, before or after adjusting for age. The columns ‘Changes’ show the mean of the paired difference (baseline minus final) in bone density in each subject. Bone density decreased at the each site in the patients, not controls. The decrease in the patients was 2.6 ± 0.8% at the lumbar spine (P < 0.01), 2.9 ± 1.5% at the femoral neck (P = 0.06), 5.5 ± 2.9% at Ward’s triangle (P = 0.06) and 4.3 ± 1.9% at the trochanter (P < 0.05). The change was greater in the patients than the controls at the lumbar spine (2.6 ± 0.8% vs -0.2 ± 0.9%, P < 0.06) and trochanter (4.3 ± 1.9% vs 0.8 ± 1.4%, P < 0.05).

Total body bone mineral content decreased by 30 ± 19 g (2.1 ± 0.7%; P < 0.02) in the first 6 months and by 39 ± 30 g [1.9 ± 1.4%; not significant (NS)] from 6 to 14 months. The change in bone density was site specific and varied according to the duration of therapy. Table II shows the changes expressed in absolute terms. Figure 1 shows the changes expressed in
TABLE II  Absolute (g/cm²) changes in bone density in the patients during the first 6 months of corticosteroid treatment and from 6 months to the end of observation (mean ± S.E.M.)

<table>
<thead>
<tr>
<th>Bone mineral density site</th>
<th>0–6 months</th>
<th>6 months–final</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lumbar spine</td>
<td>−0.020 ± 0.010*</td>
<td>−0.011 ± 0.007</td>
</tr>
<tr>
<td>Femoral neck</td>
<td>−0.001 ± 0.019</td>
<td>−0.009 ± 0.020*</td>
</tr>
<tr>
<td>Trochanter</td>
<td>−0.012 ± 0.022</td>
<td>−0.052 ± 0.024**</td>
</tr>
<tr>
<td>Trunk</td>
<td>−0.033 ± 0.020*</td>
<td>−0.008 ± 0.028</td>
</tr>
<tr>
<td>Ribs</td>
<td>−0.015 ± 0.006**</td>
<td>−0.010 ± 0.008</td>
</tr>
</tbody>
</table>

Data expressed as mean ± S.E.M.  *P < 0.05; **P < 0.02 compared to zero.

Fig. 1.—Percentage changes in bone density at the axial skeleton (left panel) and the proximal femur (right panel) in patients during the first 6 months and from 6 months to the end of prednisolone treatment (mean ± S.E.M.).  *P < 0.05; **P < 0.02 compared to previous measurement.

percentage terms. Bone density at the spine decreased by 1.7 ± 0.9% (P = 0.06) in the first 6 months (expressed as a percentage of the baseline value) and by 1.0 ± 0.6% from 6 to 14 months (expressed as a percentage of the 6 month value) (NS). Bone density decreased at the trochanter by 2.5 ± 1.9% in the first 6 months (P = 0.1) and by 1.7 ± 6.5% from 6 months to the final observation (NS). There was no significant change in the first 6 months at the femoral neck and Ward’s triangle (0.9 ± 2.4 and 0.1 ± 3.4%, respectively). From 6 to 14 months of follow-up, bone density decreased by 8.5 ± 3.5% (P < 0.05) at Ward’s triangle and by 4.8 ± 2.5% at the femoral neck (P = 0.08). The total decrease in bone density correlated negatively with the cumulative prednisolone dose at the trunk (r = −0.72, P < 0.001), the ribs (r = −0.53, P < 0.05) and the lumbar spine (r = −0.3, P = 0.16) (Fig. 2).

As shown in Table I, at baseline, before prednisolone was started, bone resorption, as assessed by urinary CTX, was 54.7% higher in the patients (P < 0.01). (Urinary CTX was also higher in the female patients than female controls: 263 ± 40 and 146 ± 30 µmol/mmol, respectively, P < 0.05.) As shown in Fig. 3, urinary CTX decreased and had a trend towards higher values in the latter months of treatment among the small number of patients followed at time points beyond 15 months. At the end of the 6–27 month observation period (mean of 14 months), the mean urinary CTX was 167 ± 20 µmol/mmol, below the baseline value of 224 ± 28 µmol/mmol (P < 0.05), and no longer greater than in controls (205 ± 42 µmol/mmol). There were no changes in the controls.
As shown in Table I, at baseline, before prednisolone was started, bone formation, as assessed by serum osteocalcin, was not suppressed. As shown in Fig. 3, at the end of the first month of therapy, serum osteocalcin decreased by 27.4 ± 5.1% (P < 0.0001). Osteocalcin tended to increase during the later stages of treatment. At the end of the follow-up period of 14 months (ranging from 6 to 27), when the mean dose of prednisolone was 3.6 mg/day (range 2.5–7.5), the mean serum osteocalcin was 23.0 ± 2.6 ng/ml, no different to controls (29.0 ± 3.5 ng/ml) or to the pretreatment value (25.5 ± 3.1 ng/ml). The osteocalcin levels did not change in the controls.

Skeletal alkaline phosphatase increased by 11.8 ± 1.6% (P < 0.05) in the first month (Fig. 3). There were no changes in the controls. The PINP levels did not change in the patients or the controls (data not shown). Figure 5 shows that serum PTH was 19.3% lower in the patients than controls at baseline (3.9 ± 0.6 vs 4.8 ± 0.9 pg/ml, respectively) and increased by 46.1 ± 12.8% in the patients (P < 0.05), but did not change in the controls (5.3 ± 18.4% NS). At no stage was serum PTH higher than in controls. Serum calcium *P = 0.09; **P < 0.05; †P < 0.01; ‡P < 0.001; ††P < 0.0001 compared to baseline.

**DISCUSSION**

This study was designed to address the efficacy and safety of ‘low’-dose corticosteroids in the absence of several independent factors that may influence bone density. Patients were excluded if they had had exposure to corticosteroids before the study or exposure to >10 mg/day at any time. The patients were ambulant, they received no other bone-modulating treatment or had no other illnesses known to affect bone. The dose and duration of treatment were documented prospectively.

We report the following. (i) Treatment with an average of 6 mg/day produced remission with improved mobility and muscle strength. Bone loss occurred at this ‘low’ mean daily dose. (ii) The pattern of bone loss was site specific; occurring at the spine, a region containing substantial amounts of trabecular bone, in the first 6 months, and becoming measurable at the proximal femur, a predominantly cortical site, in the latter months of the study. (iii) Bone loss is likely to be due to reduced bone formation. Serum osteocalcin was reduced when prednisolone doses were...
Increased bone resorption was a consequence of the illness, not its treatment, as urinary CTX was elevated before treatment and decreased during treatment. (iv) There was no evidence for secondary hyperparathyroidism.

Skeletal sparing has been reported using 5–10 mg prednisolone daily. These null observations may have been due to: (i) the imprecision of dual photon absorptiometry and neutron activation compared with dual X-ray absorptiometry [1, 4, 5, 8–11, 14]; (ii) the measurements being confined to less sensitive cortical sites [7]; (iii) the effects of illness and steroid exposure before commencement of the study which may underestimate the effect of corticosteroids [1–8, 10, 12, 16]; and (iv) selection bias; normal bone density in persons receiving < 10 mg daily may reflect bone loss from a high peak value (due to less severe illness and less immobilization) [1, 3, 5, 9, 14].

In most studies, participants have ongoing disease; bone loss due to the disease or the corticosteroids cannot be distinguished [2, 5, 7–10, 12, 29]. The data in the present study support the findings of a randomized control trial in which lumbar spine bone density decreased in prednisone-treated rheumatoid arthritis patients and did not change in the placebo group [15]. Although in the present study there is no means of entirely distinguishing the effect of corticosteroids from those of the disease, it is likely that the bone loss can be attributed to the corticosteroids, not the polymyalgia rheumatica, for the following reasons: (i) bone loss occurred despite improvement in muscle strength, a reduction in pain, joint stiffness and in the ESR; (ii) serum osteocalcin was not suppressed before treatment, decreased during the first month of therapy when the doses of prednisolone were around 9 mg daily, and then remained reduced throughout the treatment period; (iii) there was an association between the fall in bone density and the cumulative dose of corticosteroids.

The data presented here suggest that bone loss differed from region to region. Bone loss occurred at sites containing substantial amounts of trabecular bone, such as the spine and trochanter, during the first 6 months. Bone loss at the femoral neck was detectable in the later months of follow-up. Several investigators have reported that bone loss is detected earlier at sites containing trabecular bone, with cortical bone loss emerging later so that, after long-term corticosteroids, deficits occur throughout the skeleton [8, 11, 40–42]. The bone loss was ~2–5% during the 14 months with no evidence of bone loss in controls. These rates of loss are 2–4 times higher than those encountered in healthy subjects of the same age and gender [43]. If these rates of bone loss persist, then the risk of fracture will double within ~2–3 yr [44].

LoCascio et al. [2] reported that most of the decrease in iliac crest trabecular bone volume occurred in the first 5–7 months of treatment with no reduction in the following 6 months. This conclusion was based on three sequential bone biopsies in four of 19 subjects without prior exposure to treatment. Only trabecular bone was measured. Cortical bone loss may have occurred during the later stages of therapy. Similarly, Sambrook et al. [5] concluded that bone loss with corticosteroids is most rapid soon after starting treatment. This conclusion was not based on comparing earlier and later rates of bone loss in the same patients. More rapid bone loss was reported in 17 patients (mean age 54.7 yr) treated for the first time with corticosteroids, compared with rates of bone loss in 12 different subjects (mean age 38.3 yr) treated with long-term corticosteroids. More advanced age and perimenopausal status may have contributed to the differing rates of bone loss.

Studies of the pathogenesis of corticosteroid-related osteoporosis using histomorphometry, biochemical measurements of bone turnover, in vitro models and animal models support the view that reduced bone formation is primarily responsible for corticosteroid-related bone loss [18–23]. Although disease itself may suppress osteocalcin [23], baseline osteocalcin was normal in this study and decreased in the first month of treatment. At the final measurement, osteocalcin was 26% lower in the patients than the controls; however, the patients were receiving very low doses of corticosteroids at this time and osteocalcin had been recovering to normal levels after being suppressed by the higher doses at the beginning of the study. An increase in bone-specific alkaline phosphatase was observed in this and in several other studies. The significance of this observation is uncertain [28, 45–48]. The fall in androstenedione and DHEA-S may have contributed, in part, to the reduced bone formation [33, 49]. A decline in serum testosterone was not detected in this study, perhaps because the effects of corticosteroids are dose related [50]. The significance of the increase in serum IGF-1 reported here and elsewhere is uncertain [51, 52].

The pathogenesis of corticosteroid-related bone loss is also commonly attributed to increased bone resorption, despite there being little evidence to support this view. We found no biochemical evidence of increased bone resorption. The higher pre-treatment biochemical measure of bone resorption (urinary CTX excretion) and suppressed PTH are consistent with increased bone resorption being due to the underlying disease before treatment was started. The fall in the urinary CTX may be due to disease remission. Resorption may ‘increase’ by increased depth and increased numbers of resorption sites. Neither have been demonstrated to result from exposure to corticosteroids. On the contrary, in vitro, there is a dose-dependent reduction in the number and area of excavations, a reduction in osteoclast numbers and survival rate [54, 55]. Interstitial wall thickness is not reduced [19]. (This distance between two cement lines of adjacent resorption should be reduced if the depth of a resorption cavity is increased [19].) Failure to fill resorption sites may be partly responsible for the increased extent of resorption surfaces in iliac crest bone biopsy samples from patients receiving corticosteroids [19].
There was no evidence of a higher PTH in this study; PTH was modestly reduced and rose into the normal range with treatment of the illness. Suppressed or normal PTH with corticosteroid treatment has been reported [20, 24, 25, 29]. Thus, these data fail to support the view that secondary hyperparathyroidism contributed to the pathogenesis of bone loss in this disease.

Thus, bone loss associated with corticosteroid therapy in an inflammatory rheumatic disease, polymyalgia rheumatica, is generalized, involving trabecular and cortical bone [8, 11, 40–42]. The bone loss is likely to proceed more rapidly and become detectable sooner in the trabecular compartment of a region because trabecular bone has more surface available upon which the cycle of resorption and formation occurs. Reduced bone formation has two effects; at the tissue level, resorption sites created in the cycle preceding initiation of treatment remain unfilled and contribute to early bone loss. At the level of the basic multicellular unit (BMU), a long-term bone loss results from continued (but not increased) bone resorption and reduced bone formation.

Doses of 5 mg daily are associated with bone loss due to reduced bone formation. Doses of <5 mg daily may be skeletal sparing as serum osteocalcin was not reduced. Whether doses of <5 mg are efficacious is unpredictable. In rheumatoid arthritis, doses >7.5 mg daily are needed for efficacy [53]. Thus, prophylaxis against bone loss is needed with doses >5 mg daily. Under this dose, additional therapy may be needed to treat the underlying disease.

In conclusion, it is likely that treatment above 5 mg prednisolone daily reduces bone formation and results in earlier bone loss at regions containing trabecular bone, which may predispose to spine and rib fractures, and later bone loss at cortical sites may predispose to hip fracture. Thus, prophylaxis should be considered at the onset of treatment and for its duration, particularly in patients already at risk of fracture with reduced bone density prior to treatment due to advanced age and underlying disease. Doses below 5 mg daily may be skeletal sparing, but may lack efficacy.

ACKNOWLEDGEMENTS
We thank Associate Professor Stephen Hall, rheumatologist, Cabrini Medical Centre, and Dr Russell Buchanan, Director of Rheumatology, Austin and Repatriation Medical Centre, for assistance in recruiting patients, and Ms Evelyne Gineyts, Herriot Hospital, Lyon, France, for excellent technical assistance. We also thank Professor Phillip Sambrook, Garvan Institute of Medical Research, St Vincents Hospital, Sydney, for his most incisive and helpful criticisms.

REFERENCES


