Osteopenia in young hypogonadal women with systemic lupus erythematosus receiving chronic steroid therapy: a randomized controlled trial comparing calcitriol and hormonal replacement therapy


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Abstract

Objective. To evaluate the efficacy of calcitriol and hormonal replacement therapy (HRT) in the treatment of steroid-induced osteoporosis in hypogonadal women.

Methods. We studied 28 young patients (aged 37 ± 6 yr) with systemic lupus erythematosus (SLE) on chronic steroid therapy for 130 ± 22 months and requiring more than 10 mg/day prednisone. They were amenorrhoeic for more than 2 yr with proven ovarian failure. All had osteopenia with a T score at L2–4 of less than −1. They were randomized to receive HRT (conjugated oestrogen 0.625 mg daily from day 1 to day 21 plus medroxyprogesterone acetate 5 mg daily days 10–21) or calcitriol 0.5 μg daily. All received calcium carbonate 1 g/day.

Results. There were no differences in the baseline demographic, bone mineral density (BMD) and biochemical data between the two groups. Lumbar spine BMD increased by 2.0 ± 0.4% after 2 yr with HRT (P < 0.05), but reduced by 1.74 ± 0.4% (P < 0.05) with calcitriol treatment. No change was seen at the distal one-third radius with HRT treatment but significant bone loss (2.3 ± 1.4%, P < 0.02) was observed with calcitriol therapy. BMD at the hip did not change in both groups. Comparing both treatment groups, significant differences in the BMD at the spine (P < 0.03) and radius (P < 0.05) were seen at the end of 2 yr. The changes in urinary n-telopeptide excretion but not serum osteocalcin at 6 months and 12 months were inversely correlated with the changes in lumbar spine BMD at 24 months. HRT did not cause an adverse effect on SLE disease activity.

Conclusion. HRT but not calcitriol could prevent bone loss in young hypogonadal women on chronic steroid therapy.

Key words: Osteopenia, Young hypogonadal women, Steroid, SLE, Calcitriol, Hormonal replacement therapy.

Glucocorticoids are widely used in the treatment of patients with autoimmune and chronic inflammatory diseases due to their potent immunomodulatory action. However, one of the major side-effects which limits the use of this group of agents is the complication on bone loss and bone fractures, especially vertebral fractures. The pathogenesis of steroid-induced osteoporosis is complex [1]. These include the reduction in intestinal calcium absorption [2], increase in renal calcium excretion [3], secondary hyperparathyroidism [4], suppression of gonadotropin release [5], suppression of bone formation and increase in bone resorption [6]. The mechanism of bone loss is believed to act through inhibition of osteoblastogenesis and promotion of apoptosis of osteoblasts and osteocytes [7]. In recent years, a number of studies have demonstrated that the adverse effect of glucocorticoid on bone loss can be prevented [8]. Active agents include vitamin D and its derivatives, calcitonin and bisphosphonates [8]. Initiation of these agents within 4 weeks of steroid therapy is effective in preventing bone loss which is usually most marked within the first year of therapy [9]. It has been shown that the effect of these agents is similar in both pre- and post-menopausal women. However, in patients who already have bone loss due to chronic steroid therapy, the effect of these agents is less well established. In patients who are hypogonadal,
the general consensus is to give hormonal replacement therapy (HRT) [10, 11]. However, there are only a few studies documenting the effect of HRT in hypogonadal women on chronic steroid therapy [12, 13]. Although the use of HRT may be effective in preventing bone loss, HRT is known to cause flare up of certain autoimmune diseases and may be contraindicated, for example, in diseases such as systemic lupus erythematosus (SLE) [14].

The use of non-hormonal agents such as calcitonin, bisphosphonates and vitamin D derivatives has been reported to give variable benefits in established steroid-induced bone loss [10, 11]. Calcitonin injection has been shown to be effective for primary and secondary prevention of steroid-induced bone loss, but it does not significantly restore bone mass in the presence of steroids [15]. The use of calcitonin is also constrained by its cost, side-effects, resistance to treatment with the development of antibodies and a lack of efficacy to prevent fractures [16, 17]. Bisphosphonates are effective in increasing lumbar spine and femoral neck bone mineral density (BMD) in steroid-treated patients when compared with controls [18, 19]. However, in view of the long half-life of bisphosphonates, the use of these agents in young patients with immature skeletons is still of concern. Calcitriol has been shown to be effective in primary prevention of bone loss with corticosteroids [20], but whether it is effective in chronic steroid therapy is uncertain. The aim of our project was to evaluate the effectiveness of HRT vs calcitriol in treating young hypogonadal women with SLE on chronic steroid therapy.

**Patients and methods**

**Patients**

Twenty-eight women aged 37 ± 6 yr with SLE [21] on chronic steroid therapy were studied. These patients were put on steroid therapy at the diagnosis of the disease. All of them were taking at least 10 mg of prednisone daily and were on steroid treatment for a mean period of 130 ± 22 (range 30–240) months. They were amenorrhoic for at least 2 yr and proven to have ovarian failure with elevated luteinizing hormone/follicular stimulating hormone. All had osteopenia with the T score at L2–4 of less than −1 according to local southern Chinese peak young mean values. All of them had stable disease and were considered suitable for HRT treatment.

**Methods**

The patients were randomly assigned to receive either HRT (conjugated oestrogen premarin 0.625 mg daily from day 1 to day 21 plus medroxyprogesterone acetate 5 mg daily from day 10 to day 21 of the 28 day cycle (Wyeth, USA) or calcitriol (Rocaltrol, Roche Laboratories, USA) 0.5 µg daily. All patients received calcium carbonate 1 g daily. Biochemical bone markers and BMDs were determined at baseline and every 6 months for 2 yr.

**Bone densitometry**

BMD, expressed as an areal density, was measured at the lumbar spine (L2–4), femoral neck, trochanter, Ward’s triangle, and distal radius using dual-energy X-ray absorptiometry (DEXA; Hologic QDR 2000 plus, Hologic, Waltham, MA, USA). The in vivo precision of the machine obtained from five post-menopausal women measured four times over 2 weeks for the lumbar spine, femoral neck, Ward’s triangle, and distal one-third radius was 1.2, 1.5, 2.2 and 1.4%, respectively. The bone scans were performed by an independent person who was unaware of the treatment the patients were receiving. Results are presented as mean ± s.d.

**Laboratory tests**

Fasting blood was obtained for laboratory tests. Serum calcium, phosphorus, albumin, creatinine, total alkaline phosphatase were measured using a Hitachi 747 random access analyser (Boehringer, Mannheim, Germany). Serum intact osteocalcin, a marker of bone formation, was measured by enzyme-linked immunosorbent assay (ELISA) method using commercial kits (Novocalkin, Metra Biosystems, Inc., CA, USA). The laboratory intra- and interassay coefficients of variation were 8.8 and 10.1%. Subjects were asked to bring a 24-h urine collection for calcium and creatinine measurement. A 2-h fasting morning urine sample was also collected for n-telopeptide (NTx) measurement. Urine NTx, a marker for bone resorption, was determined by ELISA (Osteomark, Ostex, Seattle, WA, USA). The intra- and interassay coefficients of variation were 8.7 and 10.9%, respectively. All samples for individual subjects were measured in a single assay.

**Statistical analysis**

Baseline values were compared using two-sample Student’s t-test. Results are reported as mean ± s.d. The longitudinal data were analysed as the percentage change of steroid-induced bone loss, but it does not significantly restore bone mass in the presence of steroids [15]. The use of calcitonin is also constrained by its cost, side-effects, resistance to treatment with the development of antibodies and a lack of efficacy to prevent fractures [16, 17]. Bisphosphonates are effective in increasing lumbar spine and femoral neck bone mineral density (BMD) in steroid-treated patients when compared with controls [18, 19]. However, in view of the long half-life of bisphosphonates, the use of these agents in young patients with immature skeletons is still of concern. Calcitriol has been shown to be effective in primary prevention of bone loss with corticosteroids [20], but whether it is effective in chronic steroid therapy is uncertain. The aim of our project was to evaluate the effectiveness of HRT vs calcitriol in treating young hypogonadal women with SLE on chronic steroid therapy.

Table 1 shows the baseline characteristics of the two groups of patients. No differences were observed in their demographic, biochemical as well as BMD data. There was no correlation between the BMD values and the total steroid dose used and the duration of steroid therapy in these patients.

The serial changes of the various BMD results are shown in Fig. 1. Treatment with HRT resulted in a 2.0 ± 0.4% increase in the lumbar spine BMD (P < 0.05). There was no significant change in the BMD at both the hip and the forearm. Women treated with calcitriol continued to demonstrate bone loss. At the lumbar spine, there was a 1.6 ± 0.4% reduction at 18 months (P < 0.05 vs baseline) and a 1.74 ± 0.4% reduction at 24 months (P < 0.05 vs baseline). Similarly,
bone loss was present at the forearm. At the distal one-third radius, bone loss could be detected as early as 6 months of the study, and by the end of 2 yr there was a 2.3 ± 1.4% reduction (P < 0.02). The same change was seen at the mid-radius (−1.94 ± 0.26%, P < 0.01 at 2 yr) and the total radius (−1.79 ± 0.23%, P < 0.01 at 2 yr). However, there was no change at the ultradistal radius. Similarly, no change was seen at the hip.

Comparing the two treatment groups, a significant difference was observed at the end of 2 yr at the lumbar spine (P < 0.03) and at the total radius (P < 0.05). The difference at the distal one-third radius failed to reach statistical significance (P = 0.07).

Biochemical data
Baseline values for the biochemical bone markers are shown in Table 1. Urine NTx showed a 30 ± 57% reduction after 6 months of HRT therapy and the values remained suppressed during the 2 yr of treatment. Contrarily those receiving calcitriol had an 8% increase in NTx excretion at 6 months, and a 53.5% increase by 24 months. However, the differences observed with both treatment groups were statistically insignificant. Grouping all patients together, the changes in NTx at 6 months and 12 months correlated negatively with the changes in the lumbar spine at 12 (r = −0.633, P < 0.005) and 24 months (r = −0.629, P < 0.005) (Table 2, Fig. 2). However, in individual patients, the lack of NTx response did not necessarily equate to a lack of BMD increase with treatment. There was a mild correlation between the change in NTx at 6 months with the total radius BMD at 6 months, but the correlation disappeared during longer follow-up. Interestingly, despite the lack of statistical changes in the trochanteric and total hip BMD, their percentage changes at 12 and 24 months were actually correlated with the changes in NTx at 6 and 12 months (Table 2).

Serum osteocalcin levels were markedly suppressed at baseline (local normal reference value for premenopausal women is 3–10 ng/ml) (Table 1). Treatment with both HRT and calcitriol resulted in a significant increase in serum osteocalcin level by 2 yr (HRT 9.2 ± 10.4 mg/ml, calcitriol 9.7 ± 6.2 mg/ml, both P < 0.05 vs baseline), and there was no difference in the serum osteocalcin level between the two groups throughout the study. The changes in serum osteocalcin level correlated significantly with the changes in urine NTx excretion at all time points of the study (r values at 6, 12, 18 and 24 months were 0.36, 0.44, 0.48, 0.40, respectively, P all <0.05). However, the changes in

<table>
<thead>
<tr>
<th>Table 1. Baseline characteristics of the patients (mean ± s.d.)</th>
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<tr>
<td>Hormonal replacement therapy</td>
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<tr>
<td>n</td>
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<tr>
<td>Age (yr)</td>
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<tr>
<td>Weight (kg)</td>
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<td>Height (cm)</td>
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<tr>
<td>Years of amenorrhoea</td>
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<tr>
<td>Total hip BMD (g/cm²)</td>
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<td>Trochanteric BMD (g/cm²)</td>
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<td>Total radius BMD (g/cm²)</td>
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<td>BMD, bone mineral density.</td>
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TABLE 2. Correlations of percentage changes in α-telopeptide (NTx) and bone mineral density (BMD) with treatment

<table>
<thead>
<tr>
<th>Changes at 1 yr</th>
<th>Changes at 2 yr</th>
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<tbody>
<tr>
<td>Changes in NTx at 6 months</td>
<td></td>
</tr>
<tr>
<td>L2–4 BMD</td>
<td>−0.633**</td>
</tr>
<tr>
<td>Trochanteric BMD</td>
<td>−0.578**</td>
</tr>
<tr>
<td>Hip neck BMD</td>
<td>−0.263</td>
</tr>
<tr>
<td>Total hip BMD</td>
<td>−0.470*</td>
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<tr>
<td>Distal one-third radius BMD</td>
<td>−0.249</td>
</tr>
<tr>
<td>Total radius BMD</td>
<td>−0.312</td>
</tr>
<tr>
<td>Changes in NTx at 12 months</td>
<td></td>
</tr>
<tr>
<td>L2–4 BMD</td>
<td>−0.628**</td>
</tr>
<tr>
<td>Trochanteric BMD</td>
<td>−0.451*</td>
</tr>
<tr>
<td>Hip neck BMD</td>
<td>−0.131</td>
</tr>
<tr>
<td>Total hip BMD</td>
<td>−0.423*</td>
</tr>
<tr>
<td>Distal one-third radius BMD</td>
<td>−0.210</td>
</tr>
<tr>
<td>Total radius BMD</td>
<td>−0.030</td>
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*P < 0.05, **P < 0.01.
osteocalcin did not correlate with any regional BMD measured.

Urinary calcium excretion increased significantly after treatment with both HRT and calcitriol (both \( P < 0.05 \)), but those receiving calcitriol had significantly higher calcium excretion (calcitriol 0.31 ± 0.32 mmol/mm; calcium 0.19 ± 0.10 mmol/mm at 24 months, \( P < 0.05 \)). There were five episodes of hypercalcaemia (serum calcium >2.6 mmol/l) in those receiving calcitriol over the 2 yr of the study, but the serum calcium level returned to normal upon transient withdrawal of the drug.

There was no significant change in SLE disease activity during the study period. None of the studied subjects had reactivation of the disease. No fractures were recorded during the study period.

Discussion

Our results show that HRT but not calcitriol could prevent bone loss in young hypogonadal women on long-term glucocorticoid treatment. The response seen in our women taking HRT was similar to the previous observation of Lukert et al. [12], who reported an increase in spine BMD of 0.03 g/cm\(^2\) after 1 yr in the eight women given oestrogen during prednisone treatment for asthma. Similarly, in another study of postmenopausal women with rheumatoid arthritis, Hall et al. [22] reported, in the 18 HRT-treated patients taking steroids, that lumbar spine BMD increased significantly by 3.75% after 24 months, whereas there was no significant change in the femoral neck BMD in both the HRT and placebo groups. Lane et al. [23] studied 12 subjects on chronic low-dose steroid therapy for chronic inflammatory disease and measured BMD every 6 months. No change was observed in the lumbar spine, hip or distal radius after 1 yr, although the reduction at

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**Fig. 1.** Serial changes of bone mineral density (BMD) in lumbar spine (L2–4), hip neck, distal one-third radius and total radius. ○ HRT, ● calcitriol. (a) \( P < 0.05 \), (b) \( P < 0.02 \), (c) \( P < 0.01 \) vs 0 month; * \( P < 0.05 \), ** \( P < 0.03 \) HRT vs calcitriol.

**Fig. 2.** The change of urinary \( n \)-telopeptide (NTx) excretion at 6 months and the change of lumbar spine L2–4 BMD at 24 months. ○ HRT, ● calcitriol \( (r = -0.629, P < 0.01) \).
the distal one-third radius was 1.2%. As it is difficult to recruit a homogenous group of patients, the majority of these studies, including the present one, were performed with a small number of subjects. It is important to have a homogenous group of patients, as the underlying disorder may also affect the BMD results, e.g. patients with rheumatoid arthritis and gastrointestinal disease had a greater degree of bone loss compared with other conditions due to associated immobilization and malabsorption. Our results also confirm a lack of correlation between BMD values and cumulative steroid dose, and that the efficacy of HRT is similar in women with or without coexisting steroid therapy [8].

The role of vitamin D in treating steroid-induced osteoporosis is more controversial. Adachi et al. [24], using 50,000 units of vitamin D3 per week for primary prevention, found no significant change in the lumbar spine after 3 yr when compared with calcium treatment alone. However, Buckley et al. [25] observed that vitamin D3 could prevent secondary bone loss in both the lumbar spine and the trochanter in patients with rheumatoid arthritis who were already receiving low-dose steroids. With 1,25-dihydroxyvitamin D, Dyskman et al. [26] demonstrated evidence of suppression of osteoclast and osteoblast activity through measurements of biochemical bone markers, although there was no increase in forearm BMD as well as no reduction in fracture rate. Sambrook et al. [20] evaluated a heterogeneous group of subjects who were put on steroids within 4 weeks of therapy. The subjects included pre- and postmenopausal females as well as male patients with various medical conditions. The subjects were given calcitriol (0.5–1.0 μg/day), calcitonin, and varying doses of calcium. The results showed that calcitriol, with or without calcitonin, prevented more bone loss at the spine in the first year than calcium alone. Neither calcitriol nor calcitonin prevented bone loss at the femoral neck and distal radius. Withdrawal of calcitriol in the second year was associated with bone loss at the lumbar spine, although the author ascribed this to the effect of a higher steroid dosage in these patients. However, the dose of calcitriol used was relatively high and 25% of the subjects taking calcitriol developed hypercalcaemia and hypercalciuria.

In our present study, we observed significant bone loss at the lumbar spine by 18 months of calcitriol therapy. Significant bone loss was also found in the trabecular bone regions of the distal forearm. No change was observed in the hip and in the cortical bone region at the distal forearm. Despite stimulation of bone turnover with a significant increase in osteocalcin level, calcitriol actually failed to increase bone mass, similar to the previous report by Dyskman et al. [26]. However, since our study did not have a placebo group, we cannot be certain whether the effect of calcitriol is superior to treatment with calcium alone. There are a number of possibilities to explain the findings in the present study. First, in order to avoid the side-effects of hypercalcaemia and hypercalciuria of calcitriol, we used a dose of 0.5 μg/day as recommended [11]. Despite this lower dose, there were five episodes of hypercalcaemia that required short-term withdrawal of the drug. Greater effects on BMD improvement had been observed with a higher dose of calcitriol. In patients with post-menopausal osteoporosis, a significant increase in bone mass was found in patients given higher doses of calcitriol (>0.6 μg/day) when compared with those given lower doses (<0.5 μg/day) [27]. Second, the effect of calcitriol was reported to be associated with the fractional absorption of calcium, so that a lower intestinal absorption of calcium was associated with a better response of calcitriol and greater improvement in BMD [28]. However, since we have demonstrated that the fractional intestinal absorption of calcium in our population is approximately 61% [28], which is much higher than that for Caucasian subjects, the use of calcitriol in our Chinese population may be less effective compared with other published reports. Third, although all patients were more than 2 yr post-menopause, some of these women might still be having an accelerated phase of bone loss associated with early menopause which could only be treated adequately by HRT replacement. Finally, in chronically ill patients and in those who had underlying disorders that were associated with limited physical mobility such as rheumatoid arthritis, vitamin D deficiency is common as a result of limited sunlight exposure and this may partially explain the effectiveness of calcitriol in some of these studies. However, as Hong Kong is a subtropical area and our studied subjects were all ambulatory, it is very unlikely that they had a significant degree of vitamin D deficiency. Our previous study also did not demonstrate vitamin D deficiency in ambulatory post-menopausal osteoporotic women [29].

In this study, we also evaluated the use of biochemical bone markers in the prediction of BMD response with treatment. Unlike in post-menopausal osteoporosis, NTx, a marker of bone resorption, was not elevated in these subjects with steroid-induced bone loss. Although the change of NTx at 6 and 12 months of treatment correlated with the BMD response at the lumbar spine at 12 and 24 months, the actual magnitude of change in NTx level was small. Besides, the individual response in NTx varied so that a lack of change in NTx did not necessarily reflect a lack of response to antiresorptive therapy. The change in osteocalcin, a marker for bone turnover and bone formation, showed no relation to BMD changes. The overall impression agreed with previous observations that NTx is more sensitive than osteocalcin as a group in predicting BMD response to antiresorptive therapy [30]. The mean percentage reduction in NTx with HRT in our present study was less than that observed in non-steroid users, which is approximately 50% reduction by 1 yr [30], but the increase in the lumbar spine BMD in our patients was similar to that observed with non-steroid users.

In conclusion, HRT but not calcitriol could prevent bone loss in young hypogonadal women on corticosteroid therapy. HRT is a safe treatment for stable SLE patients and there was no evidence of an adverse effect of HRT on disease activity. Urinary NTx excretion is...
better than serum osteocalcin in reflecting the BMD response to antiresorptive treatment.

Acknowledgements
The authors wish to thank Mr Stanley Yeung for statistical advice, Miss Karman Yu for typing the manuscript. This project was supported by the Endocrine & Osteoporosis Research Fund #394.041.1510, the University of Hong Kong and partly by Roche Pharmaceuticals, Hong Kong Limited.

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