Effects of Prasterone on Bone Mineral Density in Women with Systemic Lupus Erythematosus Receiving Chronic Glucocorticoid Therapy

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ABSTRACT. ***Objective.*** To assess the effects of treatment with prasterone (dehydroepiandrosterone) on bone mineral density (BMD) in female patients with mild to moderate systemic lupus erythematosus (SLE) receiving chronic treatment with glucocorticoids.

Methods. Fifty-five female patients with SLE who had received prednisone (or glucocorticoid equivalent) ≤ 10 mg/day for ≥ 6 months were treated for 1 year with either prasterone 200 mg/day (n = 24) or placebo (n = 31) in this randomized, double blind trial. Prasterone or placebo was added to each patient's one or more concomitant standard SLE medications, including glucocorticoids, nonsteroidal antiinflammatory drugs, antimalarials, methotrexate, azathioprine, and other immunosuppressives, which were to be maintained at fixed doses for the duration of the study.

Results. BMD was significantly improved in patients who received prasterone compared to placebo. At the lumbar spine, there was a mean (SEM) gain in BMD of 1.7 ± 0.8% in the prasterone group compared to a mean loss in BMD of –1.1 ± 0.5% in the placebo group (p = 0.003 between groups). For the total hip, mean gain was 2.0 ± 0.9% in the prasterone group vs a mean loss of –0.3 ± 0.4% in the placebo group (p = 0.013 between groups). In the prasterone treatment group, the mean gains from baseline at both lumbar spine and hip were statistically significant.

Conclusion. Prasterone treatment prevented BMD loss and significantly increased BMD at both the lumbar spine and total hip in female patients with SLE receiving exogenous glucocorticoids. (J Rheumatol 2005;32:616–21)

Key Indexing Terms:
DEHYDROEPIANDROSTERONE PRASTERONE SYSTEMIC LUPUS ERYTHEMATOSUS
GL701 BONE MINERAL DENSITY OSTEOPOROSIS

Reduced bone mineral density (BMD) occurs in over 50% of women with systemic lupus erythematosus (SLE) at some time during the course of their disease[1,2]. While most often attributable to treatment with glucocorticoids, inflammation and tissue damage due to the disease process of lupus as well as reduced mobility, avoidance of sun exposure, renal dysfunction, premature ovarian failure, and other factors can lead to bone loss, independent of glucocorticoid use in women with this disease[1-10]. Chronic treatment with prednisone doses as low as 5 mg/day is associated with increased risk of femoral and vertebral fracture, and patients have been reported to be at a 5-fold increased risk of osteoporotic fractures[11,12].

Dehydroepiandrosterone (DHEA) and its sulfated ester DHEA-S are the principal circulating adrenal androgen steroids in humans. Both are abundant in the fetal circulation and remain relatively low from shortly after birth until the onset of adrenarche at about 8 years of age. During puberty, circulating concentrations are high, and peak towards the end of the second decade of life. Circulating DHEA and DHEA-S levels subsequently decline with age so that by age 60, they are only about 25% of peak levels achieved earlier in life[13].

DHEA and DHEA-S undergo conversion to other androgenic and estrogenic steroids on a tissue-specific basis, a concept known as "intracrinology"[14]. Endogenous DHEA and DHEA-S may be important to maintenance of bone mass through localized conversion in bone to active androgens and/or estrogens as well as regulation of multiple pathways, including inflammatory cytokines and tissue growth factors[15,16]. Consistent with this hypothesis, women with low endogenous circulating concentrations of DHEA and/or

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Supported by Genelabs Technologies, Inc., Redwood City, California.

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Accepted for publication November 19, 2004.

DHEA-S have been reported to be at increased risk of osteoporosis[17-19].

Women with active SLE have low circulating levels of DHEA-S, which are suppressed further by treatment with exogenous glucocorticoids[20,21]. Given that DHEA is a precursor for conversion in bone cells and osteoclast precursors to active androgenic and estrogenic steroids and may be an immunomodulator of bone cytokine production[15,16,22-25], we hypothesized that treatment with oral prasterone (the United States Adopted Names Council designation for the synthetic form of DHEA) would have a positive effect on BMD in women with SLE who were receiving chronic treatment with glucocorticoids.

We describe results of a double blind, placebo controlled study assessing BMD changes in female lupus patients treated with glucocorticoids during 1 year of treatment with prasterone or placebo. The investigation was conducted prospectively at the selected investigator centers as a nested study within a larger 381-patient phase III study that was designed to assess effects of prasterone on overall lupus disease[26].

MATERIALS AND METHODS

The study was conducted at 8 investigator centers, which were selected for BMD assessments as they had access to dual x-ray absorptiometry (DXA) equipment (all used either densitometers from Hologic Inc., Bedford, MA, or GE Lunar, Madison, WI, USA) and met specified quality control criteria. Women with SLE at these 8 centers who had been treated with glucocortioid medications chronically (see below) and met all other inclusion criteria for the overall 381-patient study[26] underwent assessments of BMD by DXA scanning of the lumbar vertebrae (either L1 or L2–L4 depending upon DXA equipment software) and the nondominant total hip at baseline and at the end of up to 12 months of treatment with either prasterone 200 mg/day or placebo. Patient menopausal status and baseline T-scores were not used as entry criteria. Patients were scanned on the same DXA instrument at baseline and last visit, with the same software utilized for each scan. As percentage change in BMD was the primary analysis and there were no changes in equipment of software for DXA instrumentation used for each patient, correction equations were not used to normalize DXA values between the different manufacturers. Each investigator site was prequalified and required to provide prestudy and continuing phantom data for quality control for review; a common phantom, however, was not circulated for cross-calibration during the study. All DXA scans were reread for quality control by a central monitoring center (P. Schmeer, Northwest Bone Densitometry Consultants, Renton, WA, USA).

Baseline assessments of lupus disease activity and health related quality of life included the SLE Disease Activity Index (SLEDAI), Systemic Lupus Activity Measure (SLAM), Krupp Fatigue Severity Score (KFSS), the Systemic Lupus International Collaborating Clinics (SLICC) Damage Index, and patient and physician visual analog scales (VAS) of global disease assessment[27-30].

Patients undergoing BMD assessments were to have been treated with glucocorticoids continuously for at least the immediate 6 months prior to study entry and to have stable SLE disease activity at baseline, with no changes in exogenous glucocorticoid or immunomodulatory medications for at least 6 weeks prior to study entry. Physicians and patients were instructed to make all efforts to keep doses of prednisone and other SLE medications constant during the study. The protocol did not require modifications of calcium or vitamin intake.

Total testosterone and estradiol were measured at Covance Inc. (Indianapolis, IN, USA) using commercial radioimmunoassay test kits (Diagnostic Products Corp., Los Angeles, CA, USA). Sensitivity of the testosterone assay was 8 ng/dl with intra- and inter-assay coefficients of variation (CV) ranging from 6% to 11%. Sensitivity of the estradiol assay was 1.2 pg/ml with intra- and inter-assay CV ranging from 7% to 9%.

Statistical analyses were conducted using SAS software (SAS Institute, Cary, NC, USA). A 2 tailed, paired t test was used for testing the percentage change in BMD from baseline within each treatment group. Analysis of variance method was used to test between-treatment mean differences in percentage changes in BMD from baseline using treatment group as a factor. Between-treatment comparisons for laboratory values were also performed by ANOVA method.

The protocol was conducted in accord with the Declaration of Helsinki and was approved by the institutional review board at each center. All patients gave written informed consent.

Study populations and dispositions. Sixty-six patients underwent baseline DXA assessments, of which 55 patients had both baseline and post-baseline DXA assessments. Eight of the 66 patients (7 placebo and one prasterone patient) had no post-baseline BMD measurements because of early discontinuation of treatment. Reasons for discontinuation among the 7 placebo treated patients were death (one patient), coronary artery disease, rash, lack of efficacy, use of a prohibited medication (adrenocorticotropic hormone), scheduling conflict, and loss to followup, respectively. One prasterone treated patient was withdrawn from treatment by the investigator in order that she start high dose glucocorticoid treatment for renal deterioration and hypertension. Additionally, 3 patients (one placebo and 2 prasterone) completed the study, but because they were not taking glucocorticoids at baseline (a protocol violation for the DXA portion of the study), the investigators chose not to conduct a last-visit DXA assessment. Among the remaining 55 patients with pre- and post-baseline BMD assessments, 4 patients (2 placebo and 2 prasterone patients) were not taking glucocorticoids at baseline (a protocol violation for the DXA portion of the study). However, an intention-to-treat approach was used to include these 4 patients for study reporting purposes.

Demographics for the 55 patients with baseline and post-baseline DXA assessments are presented in Tables 1 and 2. Clinical imbalances were present in some of the baseline variables, including estrogen use, antimalarials, supplemental calcium use, and hip and lumbar spine T-scores, but with the exception of calcium supplementation, all others favored the placebo treatment group. None of the differences in baseline variables was statistically significant between treatment groups (Table 2).

Table 1. Baseline characteristics. There were no statistically significant differences between treatment groups in baseline characteristics.

	Placebo, n = 31	Prasterone 200 mg, n = 24
Age, mean (SD) yrs	42.5 (9.7)	45.2 (11.9)
Postmenopausal, n (%)	13 (42)	11 (46)
Prednisone use, n (%)	29 (94)	22 (92)
Prednisone mg/day, mean (SD)	6.3 (3.4)	5.8 (2.9)
Estrogen use, n (%)	11 (36)	5 (21)
(HRT or oral contraceptives)	(8 HRT; 3 OC)	(4 HRT; 1 OC)
Immunosuppressive use, n (%)	8 (26)	8 (33)
Antimalarials, n (%)	16 (52)	10 (42)
Calcitonin, n (%)	0 (0)	0 (0)
Bisphosphonate, n (%)	2 (6)	2 (8)
Calcium supplements, n (%)	6 (19)	8 (33)
Hip T-score, mean (SD)	–0.884 (1.10)	–1.027 (1.07)
Lumbar spine T-score, mean (SD)	–0.658 (1.36)	–0.971 (1.10)

HRT: hormone replacement therapy. OC: oral contraceptive.

Table 2. Mean (SD) baseline disease scores by treatment group. Higher scores reflect worse activity for each of the scoring instruments. There were no statistically significant differences between treatment groups for any of the baseline characteristics.

Measure	Placebo, n = 31	Prasterone 200 mg, n = 24	p
Patient visual analog scale	51.0 (21.0)	60.1 (17.6)	0.096
Physician visual analog scale	37.7 (15.9)	35.3 (16.5)	0.591
SLE Disease Activity Index	8.2 (5.7)	7.0 (3.9)	0.379
Systemic Lupus International Collaborating Clinics/ American College of Rheumatology Damage Index	1.1 (1.3)	1.8 (1.8)	0.122
Systemic Lupus Activity Measure	12.4 (2.7)	13.1 (2.1)	0.309
Krupp Fatigue Severity Scale	5.1 (1.3)	5.4 (1.4)	0.546

RESULTS

Primary BMD analysis. The primary analysis was conducted on the group of patients with paired baseline and post-baseline BMD assessments (n = 55).

Significant differences between treatment groups for percentage change in BMD for both the lumbar spine and total hip were present (Figure 1). Additionally, the mean percentage increases from baseline were statistically significant in the prasterone treatment group at both the lumbar spine and total hip, while there was a near-significant decline in BMD at the lumbar spine and a significant reduction at the total hip for the placebo treated group.

Supplementary BMD analyses. Among postmenopausal patients, the mean (± SEM) bone density of the lumbar spine increased by 3.1 ± 1.3% in the prasterone group (n = 11) compared to a decrease of 1.7 ± 1.2% in the placebo group (n = 13) (p = 0.012 between groups). Bone density at the total hip increased by 2.3 ± 1.7% in the prasterone group compared to a decrease of 0.59 ± 0.6% in the placebo group (p = 0.107 between groups).

Gains in mean percentage change in BMD were evident in the prasterone treatment group regardless of whether patients were receiving calcium supplements at baseline (Figure 2) or exogenous estrogens (Figure 3).

Four of the patients with paired baseline and post-baseline BMD assessments were not receiving treatment with glucocorticoids at baseline, but were inadvertently enrolled by investigators in the DXA portion of the study. Exclusion of these patients from the analysis did not substantially change the results, as statistically significant differences between treatment groups remained at the lumbar spine and total hip in favor of prasterone (data not shown).

The 11 patients who did not have a post-baseline DXA were included with baseline values carried forward as last observation carried forward. Thus, for each of these patients, there would have been no change in BMD from

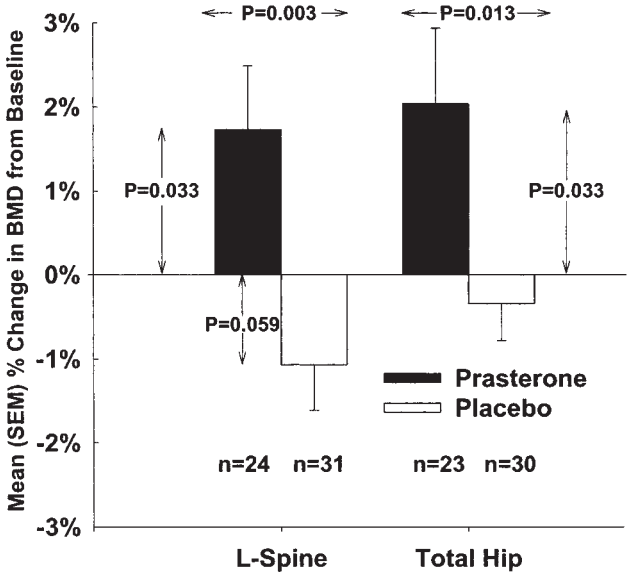

Figure 1. Mean percentage (± SEM) changes in BMD by treatment group for lumbar spine (L-spine) and total hip.

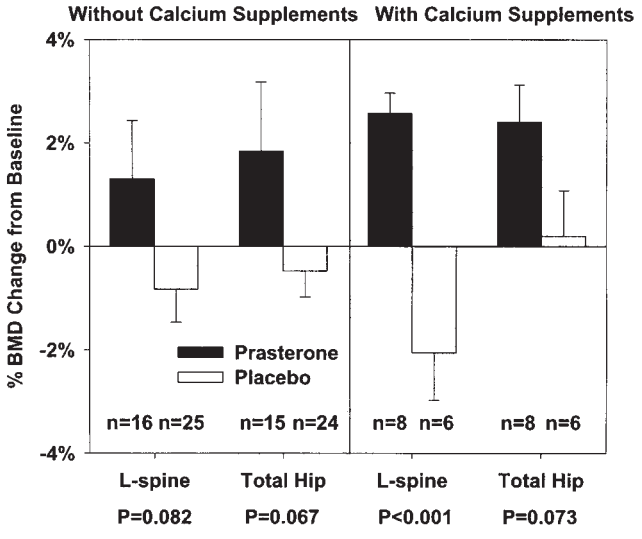

Figure 2. Mean percentage (± SEM) changes in BMD by treatment group for lumbar spine (L-spine) and total hip by baseline calcium supplement use.

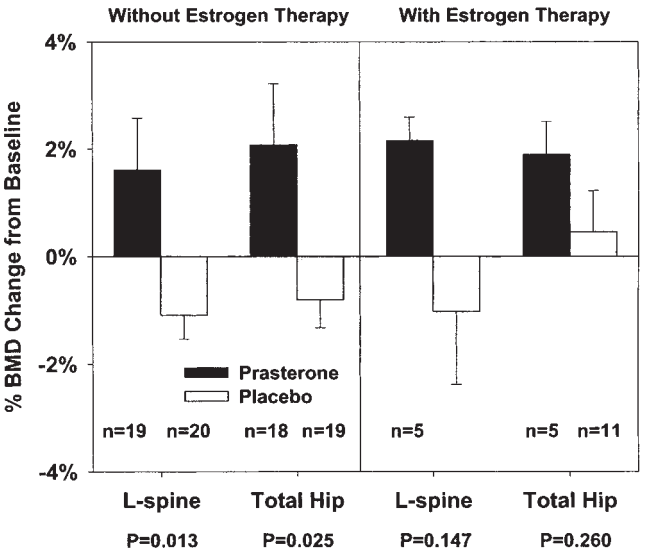

Figure 3. Mean percentage (± SEM) changes in BMD by treatment group for lumbar spine (L-spine) and total hip by baseline use of exogenous estrogens.

baseline. With the inclusion of these patients, statistically significant between-treatment differences were again present in favor of prasterone at both the lumbar spine and total hip (data not shown).

The p values for between-treatment comparisons for percentage change in spine BMD and percentage change in total hip BMD remained statistically significant in favor of prasterone when adjusted for baseline T-scores, menopausal status, baseline use of hormone replacement therapy, prednisone dose (< 5 mg/day; ≥ 5 mg/day), and treatment group.

Serum hormone changes. As expected, testosterone and, to a lesser extent, estradiol increased in patients treated with prasterone (Table 3). There were no significant correlations, however, between percentage changes in BMD and changes in either testosterone or estradiol (data not shown).

DISCUSSION

We hypothesized that treatment with oral prasterone would have positive effects on BMD in women with lupus treated with glucocorticoids, as women with active SLE have low circulating levels of DHEA[20,21], which is a precursor for conversion in bone and other tissues to active androgenic and estrogenic steroids[14,15,22-25] and may modulate bone cytokine and insulin growth factor-1 (IGF-1) production[15,16].

The study confirmed that oral prasterone prevented loss of BMD and resulted in significant gains in BMD in patients treated for up to 1 year, compared to patients who received placebo.

BMD loss is a frequent occurrence in both pre- and postmenopausal patients with SLE, particularly those taking glucocorticoids[1-10]. Kipen, *et al* reported in their series that about 40% of SLE patients were osteopenic by t score defined criteria, while 10–15% were overtly osteoporotic[1]. Bone loss in SLE is likely to be multifactorial, including disease activity, reduced physical activity, ovarian dysfunction, avoidance of sun exposure, renal dysfunction, treatment with glucocorticoids, other immunosuppressive agents or other drugs, and miscellaneous other causes[2,10,12]. Furthermore, circulating concentrations of adrenal androgens, including DHEA and DHEA-S, are reduced in women with active SLE, including those not taking glucocorticoids[20,21].

The adverse effects of glucocorticoids on bone metabolism are well known. Unlike osteoporosis due to aging, however, which is primarily related to increased bone resorption, the bone loss associated with glucocorticoids is primarily due to decreased bone formation, as glucocorticoids have direct effects on osteoblasts, including induction of apoptosis and reduced osteoblastic function[10,31-33]. Further, glucocorticoids promote bone loss via effects on multiple pathways, such as inhibition of gastrointestinal absorption of calcium, suppression of gonadotropin secretion, suppression of adrenal androgen secretion, increases in collagenase activity, increased bone resorption, and enhanced osteoclastogenesis through increases in the expression of RANK ligand (RANK-L) and decreases in the expression of its decoy receptor, osteoprotegerin and others[31,32].

Table 3. Mean/median (SD) serum testosterone and estradiol at baseline and changes from baseline to last visit.

	Placebo, n = 21	Prasterone 200 mg, n = 19	p
Testosterone, ng/dl			
Mean (SD) at baseline	14.0 (9.1)	24.0 (24.3)	0.086
Median at baseline	16.0	19.0	
Mean (SD) change from baseline to last visit	–0.43 (13.2)	40.6 (32.98)	< 0.001
Median change from baseline to last visit	–2.0	38.0	
Estradiol, pg/ml			
Mean (SD) at baseline	104.8 (114.7)	59.11 (75.4)	0.149
Median at baseline	75.3	22.4	
Mean (SD) change from baseline to last visit	–12.3 (138.3)	5.4 (80.4)	0.629
Median change from baseline to last visit	0.3	15.2	

Androgens and estrogens decrease bone resorption but may have different effects on bone formation. Estrogen replacement therapy is usually associated with a decrease in bone formation, while androgens may stimulate bone formation[15,34]. Raisz, *et al*[34] compared bone metabolic turnover parameters of postmenopausal women treated with conjugated equine estrogens alone versus postmenopausal women treated with combination therapy of conjugated equine estrogens plus oral methyltestosterone. Both bone formation and resorption markers declined in the estrogen-only group. In the estrogen plus androgen group, however, bone resorption markers also declined, but bone formation markers (osteocalcin, bone-specific alkaline phosphatase, and C-terminal procollagen peptide) increased. Gordon, *et al* have also reported reductions in bone resorption markers and increases in bone formation markers during treatment of women with anorexia nervosa with oral prasterone[35,36]. We did not assess bone markers, however, and it is not known what changes in bone markers would occur in the setting of women with SLE who are cotreated with prasterone and glucocorticoids.

Only a few studies have addressed effects of prasterone treatment on BMD or bone markers in humans[35-40], and with one exception[39], none has studied 200 mg/day DHEA administered orally for a full year of therapy or in steroid treated patients.

The increases in estradiol observed in postmenopausal women in our study were similar to those reported for postmenopausal women taking low-dose esterified estrogen therapy[41]. The effects of prasterone on bone may be direct or mediated via its metabolism to androgenic or estrogenic steroids by bone cells[23]. DHEA and/or its downstream metabolites may have other diverse effects in bone cells, including suppression of resorptive cytokines such as interleukin 6 (IL-6)[16,42], which is often elevated in patients with lupus[43,44] and is an important mediator of RANK-L expression to stimulate osteoclastic bone resorption[33,45].

Bone is both a target and source of insulin growth factor, its binding proteins, and proteases[15]. Prasterone administration increases circulating IGF-1 levels in humans[46-49]. The physiologic decline with age in circulating DHEA-S levels in humans is associated with a decline in circulating IGF-I levels and an increase in serum IL-6 levels, and it has been speculated that DHEA deficiency may contribute to age related bone loss through both anabolic (IGF-1) and antiosteolytic (IL-6) mechanisms[31,49,50].

Thus, we believe many of the positive effects of prasterone on BMD in women with lupus who are receiving treatment with glucocorticoids can be explained on the basis of some of the known physiologic effects of prasterone.

Significant and clinically meaningful effects of prasterone 200 mg/day on increasing bone mineral density in women with SLE receiving chronic treatment with glucocorticoids were observed in this study. These effects were notable at both the lumbar spine and total hip, although concurrent calcium and vitamin D supplements were not administered to most of the patients. Studies are under way to investigate prasterone as a potential therapy for prevention of steroid induced bone loss in women with SLE.

Note added in proof. Since completion of this 12-month study, an additional double blind study compared BMD changes among 155 SLE patients after 6 months of treatment with prasterone 200 mg/day or placebo. No statistically significant differences were noted between the prasterone and placebo groups at 6 months with regard to BMD changes at the lumbar spine or total hip (Genelabs Technologies, Inc., unpublished observations). Additional 12-month BMD data are being collected but are not available at this time.

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