# Bone mass in systemic lupus erythematosus

L. Sinigaglia, M. Varenna, L. Binelli, F. Zucchi, D. Ghiringhelli, F. Fantini

*Chair and Department of Rheumatology, Gaetano Pini Institute, University of Milan, Milan, Italy*

*Luigi Sinigaglia, MD, Senior Assistant; Massimo Varenna, MD, PhD, Assistant; Lucia Binelli, MD, Assistant; Francesca Zucchi, MD, Researcher; Daniela Ghiringhelli, Researcher; Flavio Fantini, Associate Professor, Director, Department of Rheumatology.*

*Please address correspondence and reprint requests to: Luigi Sinigaglia, MD, Department of Rheumatology, Gaetano Pini Orthopedic Institute, Piazza Cardinal Ferrari 1, 20123 Milan, Italy. E-mail:Sinigaglia@g-pini.unimi.it*

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## ABSTRACT

*As a consequence of the chronic course of the disease, osteoporosis can be a further clinical challenge in patients with systemic lupus erythematosus (SLE). Most studies have reported that mean bone mineral density is significantly reduced in premenopausal SLE patients as compared to controls and 12 - 25% of premenopausal SLE patients are considered to have osteoporosis. SLE patients have a 5-fold probability of sustaining a fracture as compared to the normal population. Causes of bone loss in SLE include the deleterious effects of long-term glucocorticoids and immunosuppressive drugs on the skeleton, but there is good evidence that the disease per se can lead to reduced bone mass through several mechanisms such as reduced motility, renal impairment, endocrine dysfunctions and the systemic effect of bone-resorbing cytokines. Strategies to counteract bone loss in these patients must be applied soon after the disease onset and include effective treatment of the underlying disease, use of the lowest steroid dosages possible, and the prevention and treatment of glucocorticoid-induced osteoporosis. Available data suggest that postmenopausal women at risk for osteoporosis may benefit from hormone replacement therapy without experiencing further disease flares.*

## Introduction

The outstanding improvement in the survival rates of patients with systemic lupus erythematosus (SLE) achieved over the last few decades (1, 2) has directed attention to the morbidity associated with the disease and its treatment in long-term survivors. Osteoporosis (OP) is acknowledged to be a major health care problem, vertebral and hip osteoporotic fractures being linked to long-term severe morbidity and increased mortality (3, 4), particularly in the elderly. Since a growing number of patients with SLE are expected to reach an older age, many researchers have begun to focus their attention on bone loss in these patients and an increasing number studies are being reported on osteopenia in SLE patients. In general, studies on bone mass in SLE have some limitations and are difficult to compare in that they have different research designs, used different techniques and sites for measuring Bone Mineral Density (BMD), and included small numbers of patients of both sexes, females either in the pre- or postmenopausal state, and patients who had always or never been treated with glucocorticoids. On this basis, studies estimating the prevalence of osteoporosis in SLE have come to conflicting conclusions. Accordingly, strategies for the prevention and treatment of this complication in SLE patients are lacking and therapeutic suggestions are largely based on studies of patients with other conditions, such as rheumatoid arthritis (RA) or glucocorticoid-induced osteoporosis.

The purpose of this paper is to discuss the main pathogenetic mechanisms of bone loss in SLE patients, to review the most important clinical contributions in this field, and to outline their implications for the prevention and treatment of this potentially serious complication in SLE patients.

## Pathophysiology of osteoporosis in SLE

Pathogenetically, SLE could result in bone loss through several mechanisms which in part depend on the disease itself and in part are treatment-related (Table I). Disease-dependent mechanisms include reduced physical activity due to long-standing disabling arthritis or myopathy, renal failure, endocrine dysfunctions and the systemic effects of pro-inflammatory bone-resorbing cytokines. Besides glucocorticoids, which are the mainstay of treatment in SLE, several other medications can contribute to bone loss in these patients, such as azathioprine, cyclophosphamide and cyclosporine, and no definite data exist on the possible detrimental effect of low-dose methotrexate and long-term use of anticoagulants on the skeleton. Finally,

**Table I.** Potential mechanisms of bone loss in systemic lupus erythematosus.

| Disease-dependent | Treatment-dependent |
|---|---|
| Reduced motility | Long-term corticosteroids |
| Renal impairment | Immunosuppressive drugs |
| Endocrine factors | - Azathyoprine |
| - Amenorrhea | - Cyclophosphamide |
| - Premature menopause | - Cyclosporine |
| - Low plasma androgen levels | - Low-dose methotrexate ? |
| - Hyperprolactinemia | Chronic anticoagulation ? |
| Chronic induction of bone-resorbing mechanisms | Sunshine avoiding |

counseling to avoid sunshine exposure can induce vitamin D deficiency, thus contributing to reduced bone mass.

*Disease-dependent mechanisms of bone loss in SLE*

Physical activity is known to play an essential role in the development and maintenance of bone mass in healthy subjects (5) and reduced physical activity is considered a major determinant of bone loss in several rheumatic disorders (6). Reduced physical activity in SLE patients can be the result of functional impairment secondary to chronic deforming non-erosive arthritis (so-called Jaccoud's arthritis) (7) or fatigue due to muscle pain and weakness. Radiological signs of arthritis may be found in up to 50% of patients (8). Myopathy in SLE can be drug-related, but a true muscle inflammation may be observed, SLE being the second most frequent connective tissue disease to be associated with polymyositis (9).

Studies on physical disability in SLE show a correlation between changes in the disability index and increased prednisone therapy, suggesting that increases in disability reflect the result of disease activity and severity (10). Several recent reports indicate that information on physical function and disability in SLE patients can be inferred from the new SLICC/ACR damage index (11,12) which measures accumulated damage in patients with SLE, defined as irreversible organ dysfunction present for 5 months or longer regardless of aetiology, in all organ systems. Fortin *et al.* (13) found that the initial SLICC/ACR damage index scores correlated with the physical function scores of the SF-36, and others have included the SLICC/ACR damage index in studies of socioeconomic impact and work disability (14, 15). In this perspective the importance of reduced motility as a single determinant of bone loss in SLE is difficult to evaluate owing to the difficulty of controlling for the many factors affecting this variable.

Renal bone disease can contribute to lower bone mineral density in SLE patients with advanced renal failure through several mechanisms. Hyperparathyroidism starts relatively early in these patients, when the glomerular filtration rate is in the range of 60-90 ml/min (16). In around 20-30% of patients with end-stage renal failure, bone histology reveals evidence of osteomalacia that is likely to be related to an impairment of vitamin D 1-hydroxylation by the kidney. Aluminium toxicity and adynamic bone disease are adjunctive mechanisms acting only in patients undergoing chronic dyalisis. Thus, the complexity of renal effects on bone metabolism can be viewed as a separate issue and the relationships among secondary hyperparathyroidism, osteomalacia, SLE and bone mass have not been addressed yet in the literature, since the majority of recent studies on bone mineral density in SLE employed normal renal function as an entry criterion.

Apart from an overt functional renal impairment, occasional reports have indicated the possibility of interstitial nephritis in the absence of glomerular changes in SLE (17-19). The function of the renal tubular system may be impaired in interstitial nephritis, leading to metabolic acidosis which is recognized as secondary type I or distal renal tubular acidosis. Even if chronic interstitial nephritis and renal tubular acidosis are relatively common in primary Sjögren's syndrome, rare patients with SLE and predominant tubulo-interstitial nephritis have been reported in the literature (20). Since distal renal tubular acidosis can contribute to bone loss by a compensatory mobilization of alkali and calcium from the skeleton (21), this complication can be viewed as an adjunctive potential mechanism of bone loss in SLE patients.

SLE is a chronic multi-system condition predominantly affecting young fertile females who often develop the disease in the years preceding the achievement of peak bone mass. Before natural menopause, factors that may interfere with skeletal metabolism include oligomenorrhea or amenorrhea. Both the disease and its treatment can induce ovarian dysfunction leading to premature menopause, thereby reducing overall oestrogen exposure with consequent bone loss. On the other hand, the possibility that SLE patients may be protected from osteoporosis has been claimed in view of data showing increased plasma concentrations of 16 -hydroxyestrone and estrone in both males and females with SLE (22), and elevated estriol levels in female SLE patients (23, 24). To date no studies have focused on the relationship between oestrogen levels and bone mass in SLE.

Besides ovarian dysfunction, other endocrine factors may interfere with bone metabolism in SLE patients. Increased testosterone oxidation (25) and low plasma androgens have been reported in active and inactive lupus (26, 27). The relationship beween circulating levels of androgens and bone mass has recently been addressed in a study on 37 premenopausal SLE women which reported a significant positive relationship between serum dehydroepiandrosterone (DHEAS) and BMD at the lumbar and femoral levels (28). The concomitant negative correlation between DHEAS levels and the daily prednisone dose may underscore the role of glucocorticoids in the induction of a hypoandrogenic state in these women, whose bone mass can be affected either directly by the protective effect of these hormones on the skeleton or indirectly via aromatase-derived oestrogens. Data on sex hormone abnormalities consistent with a functional state of hypoandrogenism have been reported in SLE men, as well (29). Low testosterone levels and high follicle stimulating

hormone concentrations have recently been reported in 30 premenopausal women with SLE and a high frequency of osteopenia and osteoporosis (30).

Several reports exist on hyperprolactinemia in lupus patients and it appears that up to 22% of adults with SLE may be hyperprolactinemic (31). Prolactin levels appear to be immunostimulatory in SLE patients, but the existence of an association between prolactin levels and disease activity is not yet clear. Some researchers have reported an association (32, 33) while others have not (34, 35). The inverse relationship beween prolactin levels and gonadal hormones is well suppported by experimental studies in animals, as well as in human patients with tumoral hyperprolactinemia and in patients with SLE (36). The relevance of this finding in lupus patients and its correlation with bone homeostasis has not been addressed yet but a further prolactin-mediated reduction of oestrogen and androgen levels may represent a supplemental mechanism of bone loss in SLE patients.

There is now good evidence that several mediators produced by cells of the immune system affect osteoclast formation and function *in vitro*. The most widely studied factors are three cytokines: interleukin-1 (IL-1), interleukin-6 (IL-6) and tumor necrosis factor- (TNF ). These three cytokines induce osteoclastogenesis either by causing the proliferation of osteoclast precursor cells or by promoting the activation of the differentiated osteoclast (37). The role of these mediators has been widely documented in the mechanism of localized and generalized bone loss in systemic inflammatory conditions such as RA (reviewed in 37).

In SLE patients the spontaneous production of bone-resorbing lymphokines by B-cells has been reported (38), suggesting that systemic inflammation can contribute to the development of osteoporosis in this disease as well. Recent studies in experimental models reported increased levels of IL-1 in murine lupus together with a worsening of nephritis after recombinant IL-1 administration (reviewed in 39). In lupus strains, either unaltered or increased levels of IL-6 have been reported and the administration of recombinant IL-6 to susceptible mice

caused accelerated glomerulonephritis (39). Finally, variances in TNF- levels have been reported in murine lupus, and TNF- replacement therapy has unpredictable effects on autoimmunity, since both beneficial (40,41) and detrimental (42,43) effects in murine lupus have been reported. The relevance of these observations to human disease is difficult to infer, but the process of bone loss is certainly orchestrated by a vast cocktail of cytokines secreted by the T and B cells, fibroblastic and osteoblastic cells and mononuclear cells. The systemic effect of these mediators can explain the relationship beween disease activity and osteopenic bone disease in chronic inflammatory conditions such as RA and SLE.

*Treatment-dependent mechanisms of bone loss in SLE*

SLE patients are commonly treated with high-dose corticosteroids for prolonged periods of time and it is generally accepted that the prolonged use of these hormones is associated with osteoporosis and an increased fracture rate. Glucocorticoids affect skeletal homeostasis by different pathways. These hormones exert an anti-osteoblastic effect by inhibiting growth factors or their binding proteins (44) and osteoblast differentiation (45). Recent animal studies have demonstrated that high-dose glucocorticoids can induce osteoblast and osteocyte apoptosis in mice (45). Besides their effect on bone formation, these hormones have been shown to down-regulate osteoprotegerin mRNA expression in primary human osteoblast-like cells, and to stimulate osteoprotegerin ligand (46), thus promoting an effect on bone resorption via a paracrine mechanism (47). Besides these cellular effects, glucocorticoids reduce calcium absorption by the duodeno-jejunal mucosa and reduce calcium reabsorption in the distal renal tubule, thus inducing a negative calcium balance after few days of treatment. All of these mechanisms, together with multi-endocrine interactions, contribute to bone loss in all conditions requiring chronic steroid administration. Glucocorticoid-induced bone loss is dose and time related and fractures are common, especially in the trabecular bones, and

have been reported in 30-50% of patients. Recent studies reported that glucocorticoids may exert a detrimental effect on the skeleton in chronic rheumatic conditions even at low dosages (48, 49). In addition to corticosteroids, other drugs commonly used in SLE may predispose to osteoporosis. Immunosuppressive drugs such as azathioprine or cyclophosphamide can induce ovarian failure and premature menopause. Bone loss is often seen in patients treated with cyclosporin A (CsA), which is able to induce high bone turnover (50). Interestingly, recent studies reported that the effect of CsA on bone turnover is mediated by T cells since the drug has no effect on the skeleton in T-lymphocyte deficient rats (51).

The effects of low-dose methotrexate (MTX) have been studied both *in vitro* and *in vivo*. Methotrexate causes osteopenia and inhibits osteoblast cell function in rats in a dose-dependent manner, even when administered at dosages that reach serum levels similar to those in human receiving low dose weekly vials for rheumatoid arthritis (52). The role of MTX *in vivo* is difficult to evaluate since all of the patients studied had other risk factors for osteoporosis, but no differences in the BMD of MTX-treated women with RA compared to non-MTX-treated patients have been reported (53). More recently, no association between baseline lumbar and femoral BMD and MTX use was observed in 133 patients with RA, and low dose MTX was not associated with increased bone loss over 3 years of follow-up (54).

In addition, chronic anticoagulation treatment with heparin or vitamin K inhibitors has been reported to induce bone loss (55) and long-term exposure to oral anticoagulation was associated with an increased risk of vertebral and rib fractures in one retrospective study (56). However, in a prospective observational study other authors came to opposite results, concluding that warfarin does not decrease BMD or increase fracture rates in chronic users as compared with non-users (57). Furthermore, a recent meta-analysis reviewing 9 original cross-sectional studies confirmed a negative association of oral anticoagulants with bone density only at the ultradistal radius with

a modest increase in the osteoporotic fracture risk (58). Given these conflicting data, patients on chronic anticoagulation therapy with vitamin K inhibitors, especially if other risk factors are present, are likely to need close BMD surveillance. Exposure to sunlight has long been associated with cutaneous and systemic exacerbation of SLE and avoidance of sunshine is commonly counseled by physicians to patients with SLE. UV irradiation triggers the release of TNF- , IL-1 and IL-6 (59), induces thymine dimers as products of DNA damage and accelerates autoimmunity (60). Although present in food, the major source of vitamin D is skin synthesis after sunlight exposure. Conscious avoidance of sunshine in patients with SLE may interfere with the photoconversion of pre-vitamin D into liposoluble vitamin D3, thereby inducing a deficiency of vitamin D. An alteration in vitamin D status and/or the reduced synthesis of 1,25-dihydroxyvitamin D predispose to secondary hyperparathyroidism which enhances bone remodeling and causes cortical bone loss (61). In 21 patients with SLE the levels of endogenous 25-hydroxy vitamin D3 were significantly lower than those in healthy subjects or controls with osteoarthritis, independent of the steroid dose, suggesting that a higher dietary intake of vitamin D analogues should perhaps be considered in patients with SLE in order to maintain the mineral homeostasis (62).

**Overview of studies on osteoporosis in SLE**

In recent years several studies focusing on osteopenia in SLE patients have been published. Most of these studies are cross-sectional and share some of the same limitations, since these observational models do not allow the evaluation of risk factors for low bone mass, such as disease activity, which may change over time. On the other hand, the few longitudinal studies performed on patients with long-standing disease may miss the effects of chronicity and treatment on the individual's bone density. The main controversies among the abovementioned cross-sectional studies are related to the prevalence of osteoporosis in SLE patients and the dependence or

independence of this complication on glucocorticoid use are under debate as well. The discrepancies in the prevalence of osteoporosis in SLE are the result of several factors, including differences in age-related bone loss in different skeletal sites, differences in the young adult reference populations used by the various bone densitometry devices, and technology-related differences (63).

With the exception of the first study, which was performed using dual energy X-ray absorptiometry (DXA) on a small sample of SLE patients and found lumbar BMD values to be comparable to controls (64), all studies subsequently performed using the DXA technique found the mean BMD values in premenopausal SLE patients to be significantly lower than in controls both at the lumbar spine and at the proximal femur. Three studies failed to find any dependency of low bone mass in SLE patients on corticosteroids (65-67). This conclusion was reached either by comparing BMD values between patients who had or who had never been treated with corticosteroids, or by searching for correlations between the cumulative or actual doses of prednisone and BMD. The comparison between steroid and non-steroid treated patients must be regarded with caution, however, since SLE patients not requiring steroids are likely to belong to a subset with milder disease. Furthermore, the cumulated oral corticosteroid intake was not calculated in the study by Kalla (65) and the majority of patients included in the study by Formiga *et al.* (66) were on an alternate day regimen of corticosteroids. The study performed on an Asian population (67) came to the same conclusions, but reported a prevalence of osteoporosis which is the lowest (4%) in the literature. This result was ascribed by the authors to inter-ethnic differences, probably linked to genetic polymorphism in the vitamin D receptor gene (68).

Two studies underscore that the disease *per se* may induce bone loss. The study by Houssieau *et al.* (69) performed on 47 premenopausal SLE patients strongly supports a negative impact of glucocorticoids on bone mass, but the most important finding was that patients never treated with glucocorticoids had a lower

hip BMD as compared to controls. These data are consistent with a separate analysis of non-steroid SLE patients reported in the literature in 1996 in which a modest loss of BMD was seen at the spine, hip and forearm, suggesting that osteopenia in SLE patients may be disease-related (70).

With the inclusion of Houssieau's findings (69), most subsequent cross-sectional studies have found that corticosteroids are the major determinants of low bone mass in SLE patients. Pons *et al.* (71) found that lumbar and femoral BMD were significantly lower in SLE patients treated with prednisone doses 7.5 mg/day, with an overall prevalence of osteoporosis as high as 18% in steroid users. Kipen and co-workers demonstrated the role of corticosteroid exposure in predicting lumbar spine and femoral neck BMD (72). In this study the cumulative steroid dose, the duration of steroid treatment, and the peak and current steroid dosage were all significantly associated with low lumbar or femoral BMD, even after controlling for disease-related variables. The same authors reported a prevalence of osteoporosis as high as 13.4% at the lumbar spine and 6.3% at the hip in 97 lupus patients. A subsequent interesting study on body composition in 82 pre- and postmenopausal female SLE patients by the same authors underscored that disease severity and corticosteroid exposure were independently associated, with a negative effect both on total body BMD and on fat-free mass (73).

Our own study performed on 84 premenopausal SLE patients found an overall prevalence of osteoporosis as high as 22.6% and demonstrated that SLE patients with osteoporosis had a longer disease duration, higher cumulative steroid intake, longer steroid exposure and higher disease severity as assessed by the SLICC/ACR score. In the stepwise logistic regression analysis, one year of prednisone therapy increased by 16% the risk for osteoporosis (74) (Fig. 1). These data are consistent with a recently published paper on bone mineral density in 75 SLE patients (75) The most extensive report on osteoporosis in SLE patients was published by Petri in 1995 (76) as part of an update analysis on muscu-

loskeletal complications in the Hopkins Lupus Cohort. The sample included 407 patients, but no data are reported on the sex distribution and menopausal status. This study found a strong association of BMD at the lumbar spine with both the cumulative and the highest prednisone dose. In the multiple regression model, SLE patients who were older, female (versus male), Caucasian, weighed less, had lower serum C4 levels, and who had taken prednisone in higher doses, had lower BMD in the lumbar spine and prednisone use remained an independent predictor of lumbar BMD even after adjusting for all of the significant covariates.

Only a few studies on bone mass in SLE reported longitudinal results. Formiga *et al.* repeated the measurement of bone mass in 25 consecutive patients all of whom had continued on corticosteroid treatment. After 18 months there was no significant decrease in BMD at the lumbar spine or the femoral neck (77). Similar results were reported by Hansen *et al.* in 21 SLE patients after a 2-year follow up (78). In another follow-up study on 32 SLE women, a daily dose of prednisolone 7.5 mg was associated with a year loss of lumbar spine BMD not exceeding 0.5% (79). Furthermore, baseline collagen crosslink urinary levels were not predictive of BMD change in this group and this is in contrast with data reported in early RA (80) and in several

studies performed in healthy postmenopausal women (81, 82). A small but significant loss at the lumbar spine was detected after one year of observation in 20 younger patients affected with juvenile SLE and treated with steroids (83). Taken together, the results of these studies performed on small groups of patients in different stages of the disease indicate that the sequential loss of lumbar spine and femoral neck BMD in premenopausal SLE patients is minimal. However, as has been reported in RA (84), rapid bone loss may occur at the onset of the disease and therefore can only be detected in an inception cohort. A study performed on a small sample of premenopausal women with a very short disease duration showed a significant reduction of BMD at the lumbar spine and at Ward's triangle in SLE patients compared to age-matched healthy controls (85).

Osteoporosis in men with SLE has received much less attention than in women. This issue was specifically addressed in a study performed on 20 patients and controls in which no significant decrease in BMD was detected either at the lumbar spine or the femoral neck. The authors did not find any correlation between prolactin and androgen levels and BMD in this series and concluded that on the basis of this preliminary study there is no evidence of bone loss in male SLE patients on corticosteroid therapy (86).

**Systemic lupus erythematosus and fractures**

Data on fractures in SLE are scanty. In the report published by Petri, the total number of fractures was 32 in 364 patients and 24 of these fractures were defined as atraumatic. Predictors of fractures in this cohort included age at the time of the study, the cumulative and highest dose of prednisone, avascular necrosis of bone, postmenopausal status, and the prior identification of osteopenia on any x-ray (76). Previous anecdotal reports regarded a case of transverse myelitis mimicked by multiple vertebral compression fractures in a 47-year-old woman with SLE (87) and a case of stress fractures of the legs mimicking lupus synovitis in a 51-year-old woman (88). Recently, an extensive retrospective population-based study on self-reported fractures in 702 women with lupus followed for 5,951 person-years stated that the fracture risk was increased in the lupus cohort as compared to control women of similar age, with a standardized morbidity ratio of 4.7 and a 95% confidence interval of 3.8, 5.8. Variables significantly associated with fracture were older age at diagnosis, longer disease duration, longer corticosteroid exposure, less use or oral contraceptives, and menopause. In the multi-variate model only older age at lupus diagnosis and a longer duration of corticosteroid use were independent determinants of fractures in this population. Furthermore, in this study almost 50% of the fractures occurred in women with lupus who were under the age of 50 or before menopause (89). In summary these data confirm that steroid exposure is an independent determinant of the time from lupus diagnosis to fracture and is in agreement with studies suggesting that the prednisone dosage is an important predictor of low BMD (69, 71, 72, 74, 76).

**Therapeutic implications**

Available data on osteoporosis in SLE suggest that a similar strategy for the prevention and treatment of bone loss can be used in lupus patients as that commonly applied to other rheumatic diseases. Even if data on this matter are lacking, the importance of calcium and vitamin D supplements, which may be es-
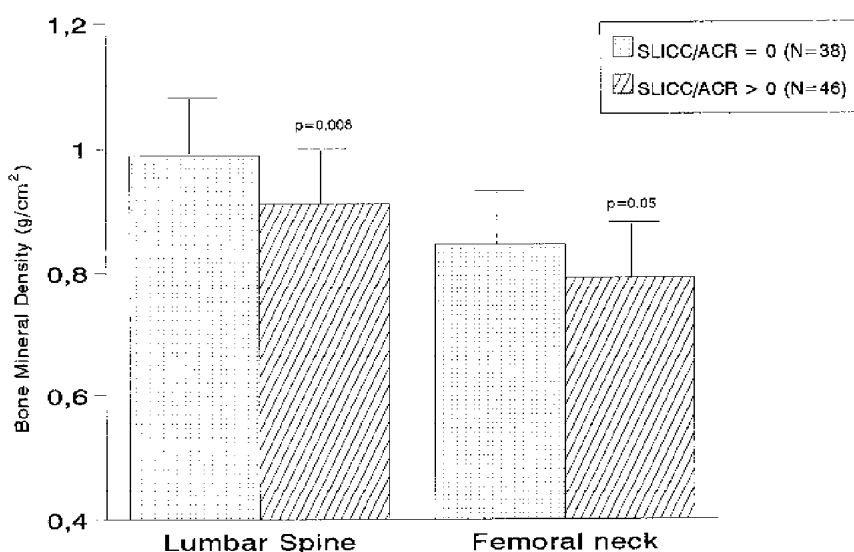


**Fig. 1.** Lumbar and femoral bone mineral density according to the SLICC/ACR score in 84 premenopausal women with systemic lupus erythematosus.

pecially important in SLE patients who avoid sunshine exposure, is worth emphasizing. Particular attention must be reserved for the detrimental effects of corticosteroids on the skeleton, and strategies for the prevention and treatment of glucocorticoid-induced osteoporosis are well delineated in the literature (90). Recently, the efficacy of two aminobisphosphonates in the prevention and treatment of steroid-induced osteoporosis has been claimed in 2 large studies (91,92) which included, among others, patients with systemic lupus.

A genuine question arises regarding the safety of hormone replacement therapy (HRT) in postmenopausal women with SLE, since many observations in both animal models and human subjects suggest that estrogens play a role in the beginning or perpetuation of the disease. On the other hand, HRT is widely accepted as the treatment of choice for the prevention and treatment of postmenopausal osteoporosis and it has proven efficacy in the management of steroid-induced osteoporosis (93). To date few studies have addressed the effect of HRT on SLE development and activity. In 1995 a study focusing on HRT and the risk for developing SLE indicated that postmenopausal HRT was associated with an increased risk for developing SLE (94). This study has been questioned, as the disease may have been over-ascertained in women receiving estrogens due to closer clinical monitoring or to the possibility that the diagnosis of postmenopausal syndrome which required HRT could have masked a mild late-onset SLE (95). Notwithstanding this, a subsequent study confirmed that the long-term use of postmenopausal estrogens plays a role in the etiology of both SLE and discoid lupus (96).

Apart from the possibility that estrogens could be viewed as an inciting event for postmenopausal SLE, Arden and co-workers in 1994 published a retrospective study on 60 postmenopausal women with relatively stable SLE, including 30 HRT users and 30 who had never taken HRT. Results indicated that HRT users experienced significant improvements in general well being, libido and depression without significant differences between the two groups in the number of flares

of disease activity, changes in the erythrocyte sedimentation rate, or the number of hospital admissions (97). Two subsequent prospective studies specifically addressing the same issue came to similar conclusions (98, 99), i.e. that HRT appeared to be well tolerated and safe in postmenopausal SLE patients.

Finally, a recent controlled randomized study comparing calcitriol and HRT in 28 young hypogonadal SLE women on chronic steroid treatment showed that HRT but not calcitriol prevented bone loss and that HRT did not cause an adverse effect on SLE disease activity over 2 years (100). In summary, on the basis of the available data, the evidence that estrogens are detrimental in stable, postmenopausal SLE is unproven (101). In addition, in women with SLE HRT may have further advantages relating to the reduced risk of coronary heart disease, which represents a major cause of late morbidity in this population (102). From this point of view, estrogen should not be witheld from patients with relatively stable SLE and without severe renal disease.

Finally, a reduction in the vertebral fracture risk in postmenopausal women with osteoporosis has been recently reported with Raloxifene, a non-steroidal benzothiophene that binds to estrogen receptors and inhibits bone resorption without stimulating the uterine endometrium (103). Since beneficial effects of treatment with the raloxifene analogue tamoxifen have been reported on experimental SLE with cytokine modulation (104), a basis to study the effects of this new agent both for treating human SLE and for preventing bone loss in these patients could exist.

## Conclusions

Among the protean manifestations of the disease, osteoporosis represents a further clinical challenge relating to morbidity in long-term survivors with SLE. Bone mineral density is reduced in SLE patients as compared to healthy, age-matched controls and 15-25% of premenopausal SLE women can be classified as having osteoporosis. SLE patients have a 5-fold greater probability of sustaining a fracture compared to the normal population. Bone loss in SLE is largely rela-

ted to the chronic administration of drugs such as corticosteroids, which exert a detrimental effect on the skeleton, but many reports indicate that the disease *per se* may contribute to changes in bone turnover resulting in the loss of bone mass. Cross-sectional data indicate that the main determinants of osteoporosis in SLE patients are steroid treatment and the severity of disease. In this respect, the presence of osteoporosis can be probably viewed as an index of poor health status in SLE patients.

Strategies to counteract bone loss must be applied soon after the disease onset and include effective treatment of the underlying disease, modification of any known risk factor for osteoporosis, use of corticosteroids at the lowest useful dosage and the pharmacological treatment of osteoporosis in all patients with evidence of rapid bone loss. Drug treatment includes agents commonly used to counteract steroid-induced osteoporosis. Available data suggest that postmenopausal women with relatively stable SLE who are at risk for osteoporosis can benefit from hormonal replacement therapy without experiencing further disease flares.

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