Osteoporosis in Patients with Systemic Lupus Erythematosus

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ABSTRACT: In recent years the survival of patients with systemic lupus erythematosus has increased markedly. Consequently, long-term complications, such as osteoporosis, are currently of paramount importance. SLE is known to increase the risk of bone fractures, and numerous studies have found that SLE patients have osteoporosis. Of the various risk factors associated with osteoporosis in SLE, disease duration, the use of corticosteroids and chronic disease-related damage are consistently reported, with differences between studies probably due to the different populations studied. The role of chronic inflammation in osteoporosis is also important. On the other hand, little attention has been paid to osteoporotic fractures, especially of the vertebra, which are associated with reduced quality of life, increased mortality rates and increased risk of new vertebral and non-vertebral fractures in the general population.

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Systemic lupus erythematosus is characterized by chronic inflammation and damage to various organs and systems due to the production of autoreactive cells and antibodies. The clinical course is characterized by periods of flares and remissions. The pathogenic mechanism is probably the result of the interaction of genetic, immunological, endocrine and environmental factors. Survival of patients with SLE has improved in the last 50 years due to novel diagnostic and treatment strategies [1].

Osteoporosis is defined as a systemic skeletal disease characterized by decreased bone density and disruption of the microstructure, with a consequent increase in bone fragility and susceptibility to fractures. Recently, the U.S. Consensus Conference of the National Institutes of Health redefined osteoporosis as a skeletal inconvenience characterized by compromised bone resistance that makes a person more prone to suffer fractures. These changes can be indirectly evaluated by non-invasive measurement of bone mineral density, which quantifies bone mass with high precision and accuracy using dual X-ray absorptiometry. Currently, the diagnostic criteria for osteoporosis are based on measurements of BMD, referring to the number of standard deviations above or below the mean of the predefined BMD value in adults in a specific part of the skeleton [2]. It is known that reduced bone mass increases the risk of fracture. Even though BMD carries 70% of the bone resistance, it is not the only determining factor of fractures; bone quality, bone geometry, the risk of a fall, the force of impact, and the thickness of the soft parts also play an important role [3].

Patients with SLE are at increased risk for osteoporosis for many reasons. First, the glucocorticoid medications often prescribed to treat SLE can trigger significant bone loss. Second, osteoporosis can be secondary to chronic inflammation. Third, pain and fatigue caused by the disease can result in inactivity, further increasing osteoporosis risk. These factors have become more prominent, especially given the improved life expectancy of SLE patients [4]. The aim of this report is to review the most important epidemiological associations and the pathophysiology underlying osteoporosis in patients with SLE.

OSTEOPOROSIS IN SLE: PREVALENCE AND RISK FACTORS

Osteoporosis is a common clinical problem in inflammatory diseases. In SLE, bone loss is more frequent than in the general population. Several cross-sectional studies have evaluated BMD and the prevalence of osteoporosis in patients with

SLE = systemic lupus erythematosus

BMD = bone mineral density

Table 1. Summary of studies of BMD in SLE patients

Authoryear [ref]	Design	No. of patients	BMD lumbar region	BMD hip
Dhillon et al.1990 [24]	Cross-sectional	22	Osteoporosis 4.5%	
Kalla et al. 1993 [29]	Cross-sectional	46	24% osteoporosis in any location	
Formiga et al. 1995 [11]	Cross-sectional	74	12.1% osteoporosis in any location	
Pons et al. 1995 [25]	Cross-sectional and longitudinal	43	18% osteoporosis in patients with corticosteroids	
Kipen et al. 1997 [26]	Cross-sectional	94	44% osteopenia, 13% osteoporosis	42% osteoporosis, 6% osteopenia
Li et al.1998 [33]	Cross-sectional		35% osteopenia and 4% osteoporosis in any location	
Sinigaglia et al.1999 [19]	Cross-sectional	84	23% osteoporosis in any location	
Redlich et al. 2000 [4]	Cross-sectional	30	46% osteopenia, 15% osteoporosis	39% osteopenia, 23% osteoporosis
Gilboe et al. 2000 [20]	Cross-sectional	75	37% osteopenia, 9% osteoporosis	41% osteopenia, 7% osteoporosis
Lakshminarayanan et al. 2001 [13]	Cross-sectional	92	32% osteopenia, 15% osteoporosis	35% osteopenia, 12% osteoporosis
Becker et al. 2001 [5]	Cross-sectional	67	11% osteopenia, 6% osteoporosis	13% osteopenia, 3% osteoporosis
Bhattoa et al. 2002 [8]	Cross-sectional	79	62% osteopenia, 24% osteoporosis	48% osteopenia, 5% osteoporosis
Pineau et al. 2004 [18]	Cross-sectional	205	18% osteoporosis in any location	
Mok et al. 2005 [14]	Cross-sectional	34	33% osteopenia, 42% osteoporosis	74% osteopenia, 3% osteoporosis
Bultink et al. 2005 [9]	Transversal	107	39% osteopenia and 4% osteoporosis in any location	

SLE [3-34]. Differences in the prevalence have been found in these studies, but the results suggest a generalized reduction in BMD [Table 1].

Abnormalities in bone metabolism were described by Redlich et al. [3]. They found that osteocalcin was significantly decreased in patients with SLE. They also analyzed other parameters of bone formation and found that the specific alkaline phosphatase for bone and the propeptide of procollagen type 1 with a carboxy terminal were also decreased. However, Becker and colleagues [5] found no correlation between reduced BMD and markers of bone formation, and reported a negative correlation between vitamin D and BMD in the hip. They [5] also investigated the impact of chronic SLE damage on BMD and found an inverse correlation with chronic damage measured by the SLICC-ACR damage index instrument (Systemic Lupus International Collaborating Clinics/American College of Rheumatology) [10].

Photosensitivity of patients with SLE has led to recommendations to avoid exposure to the sun, thus inducing vitamin D deficiency

On the other hand, the photosensitivity of patients with SLE has led to recommendations to avoid sun exposure and this may induce vitamin D deficiency. Some studies have associated vitamin D deficiency with low BMD in patients with SLE [6-9].

Renal involvement may occur in up to 40% of SLE patients; when it progresses to renal failure it may impair bone metabolism by inducing secondary hyperparathyroidism [9]. There are no studies that directly analyze the association between nephropathy and low BMD in SLE.

According to some studies, estrogens are involved in the pathogenesis of SLE because an increase in 16-α-hydroxylation of estradiol was noted, in addition to an increase in testosterone oxidation with a decrease in dehydroepiandrosterone, which correlates with low BMD [11,12]. Additionally, ovarian dysfunction is a risk factor for reduction of bone mass in young women. Low testosterone and high follicle-stimulating hormone levels have been reported in a large percentage of premenopausal SLE women with osteopenia and osteoporosis. Some studies found that menopause is an independent risk factor for osteoporosis in patients with SLE [13,14]. Mok and co-researchers [14] studied 34 postmenopausal women with an average age of 52.9 years and found osteopenia in 33% and osteoporosis in 42% at the lumbar spine level; osteopenia of the hip was found in 74% and osteoporosis in 3% of the patients.

Osteoporosis in men has received much less attention than in women. Formiga et al. [11] studied BMD in 20 patients with SLE and its relationship with prolactin and testosterone. They found no relationship between BMD and the cumulative dose and baseline dose of corticosteroids and no correlation between BMD, prolactin and androgens.

Several inflammation markers, such as interleukin-1, interleukin-6 and tumor necrosis factor-alpha, can induce osteoclastogenesis, which promotes the proliferation of precursor osteoclastic cells or the activation of differentiated osteoclasts. These cytokines are found in patients with chronic inflammatory diseases such as SLE. Different studies have provided insight into the pathogenesis of inflammatory bone loss [6,8].

Houssiau and team [15] compared 47 premenopausal women suffering from SLE and renal damage with healthy controls and found that patients taking corticosteroids had a greater reduction in BMD than other patients and that patients not taking corticosteroids had a greater reduction in BMD than healthy controls.

Menopause is an independent risk factor for osteoporosis in patients with SLE

In addition to corticosteroids, other factors associated with SLE can influence bone metabolism, such as lack of sun exposure, chronic arthritis, chronic induction of pro-inflammatory bone-reabsorbing cytokines, renal failure, transient amenorrhoea and premature menopause. Tests measuring disease activity were used as instruments for its evaluation, such as SLEDAI (Systemic Lupus Erythematosus Disease Activity Index) [16] and ECLAM (European Consensus Lupus Activity Measure) [17]. However, most failed to find a correlation between disease activity and BMD. The reason is probably that indexes used to evaluate disease activity are only measured at one point in time.

On the other hand, Pineau et al. [18] evaluated the clinical characteristics in 516 women with SLE sent for a DEXA study and analyzed the factors associated with low BMD. They found that the two significant predictors of low BMD were higher age at the time of DEXA ($P = 0.0003$) and a higher SLICC/ACR damage index score ($P = 0.0019$). They concluded that osteoporosis is a significant comorbidity in SLE but observed that in their study disease activity and corticosteroid use were not associated with osteoporosis, which may suggest other potential causes such as decreased physical activity associated with damage. Furthermore, severity of SLE has been associated with reduced BMD. Becker and collaborators [5] assessed the effects of disease severity and organ damage as risk factors for the development of osteoporosis in 64 SLE patients (mean disease duration 7.7 ± 5.7 years) and found that BMD was inversely correlated with disease duration, damage score and cumulative glucocorticoid intake, but no correlation was found with current glucocorticoid use or with markers of bone metabolism. In the multivariate analysis, body weight, disease duration and damage index fitted best for the prediction of BMD at both lumbar spine ($r = 0.68$, $P < 0.0001$) and femoral neck ($r = 0.76$, $P < 0.0001$). They concluded therefore that a reduced BMD at both lumbar spine and femoral neck rarely occurs during the first 7.5 years.

Sinigaglia et al. [19] found that in 84 premenopausal patients with SLE (age 30.5 ± 7.5 years), vertebral and femoral BMD were significantly lower in SLE patients than in age-matched controls, and no significant differences in BMD were detected between patients according to the clinical pattern or activity index, whereas patients with high damage index had a significantly lower BMD at both the lumbar ($P = 0.008$) and the femoral ($P = 0.05$) level. This analysis showed that disease duration is independently associated with osteoporosis (odds ratio 1.2 for each year of disease, 95% confidence interval 1.07–1.33). Prednisone was associated with an increased risk for osteoporosis (OR 1.16 for each year of treatment, 95% CI 1.05–1.29).

Other studies also observed this association. Lakshminarayanan et al. [13] studied risk factors for low BMD in patients with SLE and showed that there was a significant correlation between longer disease duration and lower BMD of the hip ($P = 0.006$) but not of the spine ($P = 0.21$). They also found a correlation between higher SLE damage index and lower BMD for both the hip ($P = 0.002$) and the spine ($P = 0.02$). In addition, they found a significant correlation between age at the time of BMD and lower BMD of both the hip ($P < 0.001$) and the spine ($P = 0.05$). Therefore, disease damage can be seen as a marker of the severity of the disease, while on the other hand chronic damage can also increase with age and this could be associated with osteoporosis [20].

It is well established that corticosteroids, frequently prescribed to patients with SLE in high doses and for long periods, improve survival and the quality of life. However, corticosteroids induce osteoporosis, affecting mainly trabecular bone in the vertebral spine. The side effects of corticosteroids on the skeleton occur rapidly after initiation of therapy. The main mechanisms by which corticosteroids affect bone formation are suppression of osteoblastogenesis and increased apoptosis of osteoblasts and osteocytes. Corticosteroids down-regulate osteoprotegerin mRNA expression in primary human osteoblast-like cells and stimulate the receptor activator of nuclear kappa B ligand (RANKL), being an inhibiting factor of osteo-

The 16-α-hydroxylation of estradiol, in addition to an increase in testosterone oxidation with a diminishing of dehydroepiandrosterone, is correlated with low BMD in patients with SLE

DEXA = dual X-ray absorptiometry
SLICC/ACR = Systemic Lupus International Collaborating Clinics/American College of Rheumatology

OR = odds ratio
CI = confidence interval

clastogenesis and a stimulating factor for the differentiation of the respective osteoclasts. Osteoprotegerin is a member of the tumor necrosis factor receptor family that antagonizes the interaction of RANKL with its receptor, RANK [21,22].

A decrease in calcium absorption and an increase in calcium excretion have also been demonstrated in glucocorticoid users [23,24]. Other factors that may contribute to the pathogenesis of glucocorticoid-induced osteoporosis include a vitamin D-independent reduction in calcium absorption from the gastrointestinal tract and an increase in renal calcium excretion. There is little evidence of abnormal vitamin D metabolism as prospective studies have failed to demonstrate any change in 25 (OH) D_3 or vitamin D binding protein. In addition, levels of parathyroid hormone are not consistently elevated, although glucocorticoids may result in an abnormal renal and osteoblast sensitivity to PTH [6,7,22-24].

Several additional large-scale epidemiological studies have examined the association between corticosteroid exposure and osteoporosis [Tables 2 and 3] [25-34]. Other drugs used for SLE that play a role in bone loss are cyclosporine, methotrexate, anticonvulsants, oral anticoagulants and heparin. In contrast, hydroxycloroquine is known to be a protecting factor for osteoporosis [23,35].

Table 2. Studies with and without an association of corticosteroids with reduced BMD in patients with SLE

No association	Association
Dhillon et al., 1990 [24]	Pons et al., 1995 [5]
Kalla et al., 1993 [29]	Houssiau et al., 1996 [1]
Formiga et al., 1997 [11]	Kipen et al., 1997 [26]
Li et al., 1998 [33]	Sinigaglia et al., 1999 [19]
Becker et al., 2001 [5]	Gilboe et al., 2000 [20]
Pineau et al., 2004 [18]	Lakshminarayanan et al., 2001 [13]
Bultink et al., 2005 [9]	Bhattoa et al., 2002 [8]
	Boyanov et al., 2003 [35]
	Mok et al., 2005 [14]

Table 3. Risk factors for bone mineral density in the lumbar column and hip

	Independent factors associated with reduced BMD	
Reference	In the lumbar region	In the hip
Kipen et al. [26]	Use and dosage of corticosteroids	Use and dosage of corticosteroids
Li et al. [33]	Low body mass index	Low body mass index
Sinigaglia et al. [19]	Duration of the illness	Duration of the illness
Gilboe et al. [20]	Age, low body mass index, dosage of corticosteroids	Age, low body mass index
Lakshminarayanan et al. [13]	Menopause	Parity, chronic damage, Caucasian race, accumulated dosage of corticosteroids
Becker et al. [5]	Body weight, duration of SLE, chronic damage	Body weight, duration of SLE, chronic damage
Mok et al. [14]	Use of hydroxicloroquin at high values of BMP	Anti-Ro and Anti-Sm
Bultink et al. [9]	Menopause, low body mass index, deficiency of vitamin D	Low body mass index, menopause

FRACTURES IN SLE PATIENTS: PREVALENCE AND RISK FACTORS

Although there are numerous reports on osteoporosis and SLE, there is little information on fractures in patients with SLE, even though fractures are the main complication of osteoporosis and are measured in the SLICC index used to evaluate chronic SLE damage.

Ramsey-Goldman and co-workers [36] described the frequency of factors in a cohort of women with SLE and compared this frequency with that in the general age-matched population. They found that of 702 women, 12.3% had at least one fracture after being diagnosed with SLE. The most common sites were the leg, foot, arm, vertebrae and hip. Variables associated with these fractures were old age, diagnosis of SLE and long-term corticosteroid use.

Vertebral fractures predict new fractures and are a cause of morbidity and mortality and reduced quality of life

Vertebral fractures are the most frequent complication of osteoporosis and a cause of high mortality. Recently, Hasserius et al. [37] analyzed the morbidity and mortality of patients with clinically diagnosed vertebral fractures; 70 men and 187 women were studied over 12 and 22 years respectively. There were more female patients with lumbar pain and a worsened health status at 12 years of follow-up compared with controls. Women with a new vertebral fracture had a higher mortality rate in the subsequent 10 years (relative risk 2.8). The mortality rate among male patients over 22 years follow-up was 111.7 per 1000 person-year, compared to 73.4 per 1000 person-year for the male population at risk. The mortality rate of female patients was 95.1 per 1000 person-year compared with 62.0 per 1000 person-year within the female population at risk [37].

Vertebral fractures also predict new fractures, both vertebral and non-vertebral [37], and reduce the quality of life in women with osteoporosis [38]. Despite the studies on fractures in patients with SLE, vertebral fractures have only been evaluated incidentally due to symptoms in the vertebral column, but we should remember that only a third of vertebral fractures exhibit symptoms. There are several methods of evaluating vertebral fractures, including quantitative, semi-

PTH = parathyroid hormone

quantitative, and by algorithm. A simple thoracic vertebral column and lateral lumbar radiograph continue to be the most accepted method for the evaluation of vertebral fractures. Recently, Bultink [9] evaluated the prevalence of and factors associated with vertebral fractures in patients with SLE (93% women and 7% men) using Genant's standardized method [39]. They defined a vertebral fracture as a reduction of ≥ 20% at the height of the vertebral body. They found that osteopenia was present in 39% of patients and osteoporosis in 4%; the factors associated with reduced BMD in the lumbar column were a low body mass index, postmenopausal state, and vitamin D deficiency. Reduced hip BMD was associated with a low body mass index and postmenopausal state; moreover, the prevalence of vertebral fractures was found in 20% of patients with SLE who had at least one vertebral fracture. The factors associated with these fractures were the use of methylprednisolone pulse and male gender. What was interesting about this study was the lack of correlation between osteoporosis and fractures. Consequently, vertebral fractures do not occur exclusively in patients with osteoporosis.

Current guidelines recommend radiographs of the vertebral spine in a patient with a suspicion of vertebral fracture or loss of height [40]. Nevertheless, it is important to remember that only a third of patients with vertebral fractures exhibit clinical signs. Spine radiographs should be performed (using a standardized method of vertebral deformities), as should BMD measurements of the vertebral spine and hips.

CONCLUSIONS

The prevalence of osteoporosis has been widely studied. The majority of studies found that osteoporosis is frequent in SLE. This is mainly due to disease duration, chronic damage, and the effects of corticosteroids – irrespective of whether the lumbar spine or hip is involved in the bone loss, though mainly at the lumbar column. Fractures are a complication of osteoporosis but they have received little attention, especially at the vertebral level. Vertebral fractures also predict new fractures and are a cause of morbidity and mortality and reduced quality of life. There is a paucity of studies analyzing the prevalence of vertebral fractures and their causes. Since the prevalence is greater in SLE patients than in the general population, diagnosis of bone loss and its complications should include density determination as well as vertebral fracture evaluation using a standardized method for SLE patients.

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References

1. Gripenberg M, Helve T. Outcome of systemic lupus erythematosus. A study of 66 patients over 7 years with special reference to the predictive value of anti-DNA antibody determinations. *Scand J Rheumatol* 1991; 20: 104-9.
2. WHO Study Group. Assessment of fracture risk and its application to screening of postmenopausal osteoporosis. WHO Technical Report Series 843. Geneva, 1994.
3. Redlich K, Ziegler S, Kiener HP, et al. Bone mineral density and biochemical parameters of bone metabolism in female patients with systemic lupus erythematosus. *Ann Rheum Dis* 2000; 59: 308-10.
4. Gordon C. Long-term complications of systemic lupus erythematosus. *Rheumatology (Oxford)* 2002; 41(10): 1095-100.
5. Becker A, Fischer R, Scherbaum WA, Schneider M. Osteoporosis screening in systemic lupus erythematosus. *Lupus* 2001; 10: 809-14.
6. Manalagas SC, Jilka R. Bone marrow, cytokines, and bone remodeling. Emerging insights into the pathophysiology of osteoporosis. *N Engl J Med* 1995; 332: 305-11.
7. Muller K, Kriegbaum NJ, Baslund B, Sorensen OH, Ihymann M, Benztzan K. Vitamin D3 metabolism in patients with rheumatic diseases: low serum levels of 25-hydroxyvitamin D3 in patients with systemic lupus erythematosus. *Clin Rheumatol* 1995; 14: 397-400.
8. Bhattoa HP, Bettembuk P, Balogh A, Szegedi G, Kiss E. Bone mineral density in women with systemic lupus erythematosus. *Clin Rheumatol* 2002; 21: 135-41.
9. Bultink I, Lems WF, Kostense PJ, Dijkmans BAC, Voskuyl AE. Prevalence of and risk factors for low bone density and vertebral fractures in patients with systemic lupus erythematosus. *Arthritis Rheum* 2005; 54: 2044-50.
10. Gladman D, Ginzler E, Goldsmith C, Fortin P, Liang M, Urowitz M. The development and initial validation of the Systemic Lupus International Collaborating Clinics/American College of Rheumatology damage index for systemic lupus erythematosus. *Arthritis Rheum* 1996; 39: 363-9.
11. Formiga F, Moga I, Nolla JM, Navarro MA, Bonnin R. Roig-Escofet D. The association of dehydroepiandrosterone sulphate levels with bone mineral density in systemic lupus erythematosus. *Clin Exp Rheumatol* 1997; 15: 387-92.
12. Mendoza-Pinto C, García-Carrasco M, Sandoval-Cruz H, et al. Risk factors for low bone mineral density in pre-menopausal Mexican women with systemic lupus erythematosus. *Clin Rheumatol* 2009; 28: 65-70.
13. Lakshminarayanan S, Walsh S, Mohanraj M, Rothfield N. Factors associated with low bone mineral density in female patients with systemic lupus erythematosus. *J Rheumatol* 2001; 28: 102-8.
14. Mok CC, Mak A, Ma KM. Bone mineral density in postmenopausal Chinese patients with systemic lupus erythematosus. *Lupus* 2005; 14: 106-12.
15. Houssiau FA, Lefebvre C, Depresseux G, Lambert M, Devogelaer JP, Deuxchaisnes N. Trabecular and cortical bone loss in systemic lupus erythematosus. *Br J Rheumatol* 1996; 35: 244-7.
16. Bombardier C, Gladman DD, Urowitz MB, Caron D, Chang CH, and the Committee on Prognosis on Studies in SLE. Derivation of the SLEDAI: a disease activity index for lupus patients. *Arthritis Rheum* 1992; 35: 630-40.
17. Vitali D, Becivelli W, Isenberg DA, et al., and the European Consensus Study Group for Disease Activity in SLE. Disease activity in SLE. Disease activity in systemic lupus erythematosus: report of the Consensus Study Group of the European Workshop for Rheumatology Research. II. Identification of the variables indicative of disease activity and their use in the development of an activity score. *Clin Exp Rheumatol* 1992; 10: 541-7.
18. Pineau CA, Urowitz MB, Fortin PJ, Ibanez D, Gladman DD. Osteoporosis in systemic lupus erythematosus: factors associated with referral for bone mineral density studies, prevalence of osteoporosis and factors associated with reduced bone density. *Lupus* 2004; 13: 436-41.
19. Sinigaglia L, Varenna M, Binelli L, et al. Determinants of bone mass in systemic lupus erythematosus: a cross sectional study on premenopausal women. *J Rheumatol* 1999; 26: 1280-4.
20. Gilboe IM, Kvien TK, Haugeberg G, Husby G. Bone mineral density in systemic lupus erythematosus: comparison with rheumatoid arthritis and healthy controls. *Ann Rheum Dis* 2000; 59: 110-15.
21. Vidal NAO, Brandstrom H, Jonson KB, Ohlsson C. Osteoprotegerin mRNA is expressed in primary human osteoblast-like cells: down regulation by glucocorticoids. *J Endocrinol* 1998; 102: 274-82.

22. Manolagas SC, Weinstein RS. New developments in the pathogenesis and treatment of steroid-induced osteoporosis. *J Bone Miner Re*s 1999, 14: 1061-6.

23. Steinbuch M, Youket TE, Cohen S. Oral glucocorticoid use is associated with an increased risk of fracture. *Osteoporos Int* 2004; 15: 323-8.

24. Dhillon VB, Davies MC, Hall ML, et al. Assessment of the effect of oral corticosteroids on bone mineral density in systemic lupus erythematosus: a preliminary study with dual energy x ray absorptiometry. *Ann Rheum Dis* 1990; 49: 624-6.

25. Pons F, Peris P, Guanabens N, et al. The effect of systemic lupus erythematosus and long term steroid therapy on bone mass in pre-menopausal women. *Br J Rheumatol* 1995; 34: 742-6.

26. Kipen Y, Buchbinder R, Forbes A, Strauss B, Littlejohn G, Morand D. Prevalence of reduced bone mineral density in systemic lupus erythematosus and the role of steroids. *J Rheuma*tol 1997; 24: 1922-9.

27. Kipen Y, Briganti E, Strauss B, Littlejohn G, Morand E. Three year follow-up of bone mineral density change in premenopausal women with systemic lupus erythematosus. *J Rheumatol* 1999; 26: 310-17.

28. Jardinet D, Lefebre C, Depresseux G, Lambert M, Devogalaer JP, Houssiau FA. Longitudinal analysis of bone mineral density in premenopausal female systemic lupus erythematosus patients: deleterious role of glucocorticoid therapy at the lumbar spine. *Rheumatology (Oxford)* 2000; 39: 389-92.

29. Kalla AA, Kataar AB, Jessop SJ, Bewerunge L. Loss of trabecular bone mineral density in systemic lupus erythematosus. *Arthritis Rheum* 1993; 36: 1726-34.

30. Franchimont N, Canalis E Management of glucocorticoid induced osteoporosis in premenopausal women with autoimmune disease. *Autoimmun Rev* 2003; 2(4): 224-8.

31. Van Staa TP, Leufkens HG, Abenhaim L, Zhang B, Cooper C. Use of oral corticosteroids and risk of fractures. *J Bone Miner Res* 2000; 15: 993-1000.

32. Natsui K, Tanaka K, Suda M, et al. High-dose glucocorticoid treatment induces rapid loss of trabecular bone mineral density and lean body mass. *Osteoporos Int* 2006; 17(1): 105-8.

33. Li EK, Tam LS, Young RP, Ko GT, Li M, Lau EM. Loss of bone mineral density in Chinese pre-menopausal women with systemic lupus erythematosus treated with corticosteroids. *Br J Rheumatol* 1998; 37: 405-10.

34. Almagor O, Dunlop DD, Manzi S, Spies S, Chadha AB, Ramsey-Goldman R. Disease damage and low bone mineral density: an analysis of women with systemic lupus erythematosus ever and never receiving corticosteroids. *Rheumatology* 2006; 45(1): 53-60.

35. Boyanov M, Roveba R, Popivanov P. Bone mineral density changes in women with systemic lupus erythematosus. *Clin Rheumatol* 2003; 22: 318-23.

36. Ramsey-Goldman R, Dunn JE, Huang CHF, et al. Frequency of fractures in women with systemic lupus erythematosus. Comparison with United States population Data. *Arthritis Rheum* 1999; 42(5): 882-90.

37. Hasserius R, Karlsson B, Jonsson B, Redlund-Johnell I, Johnell O. Long-term morbidity and mortality after a clinically diagnosed vertebral fracture in the elderly – a 12 and 22 year follow-up of 257 patients. *Calcif Tissue Int* 2005; 76: 235-42.

38. Oleksik A, Lips P, Dawson A, et al. Health-related quality of life in postmenopausal women with low BMD with or without prevalent vertebral fractures. *J Bone Miner Res* 2000; 15: 1384-92.

39. Genant HK, Wu CH, Van Kuijk C, Nevitt MC. Vertebral fractures assessment using a semiquantitative technique. *J Bone Miner Res* 1993; 8: 1137-48.

40. American Association of Clinical Endocrinologists Medical Guidelines of Clinical Practice for the Prevention and Treatment of postmenopausal Osteoporosis: 2001 http:www.aace.com/clin/guidelines/osteoporosis2001Revised.pdf.