

**Ph.D. Thesis**

**Prevalence and Diagnosis of  
Osteoporosis in Patients with  
Systemic Lupus Erythematosus**

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## Introduction

Osteoporosis is a systemic skeletal disorder characterized by low bone mass and microstructural deterioration of bone tissue, with a consequent increase in bone fragility and susceptibility to fracture.<sup>1</sup> Currently the diagnostic criteria for osteoporosis are based on measurements of bone mineral density (BMD), with reference to the number of standard deviations above or below the mean peak adult BMD value at the skeletal site.<sup>2</sup> These values are then expressed in *T*-score (table 1). Using these definitions it has been possible to assess the prevalence of osteoporosis across populations and patient groups, and to examine for disease-associated risk factors. A large number of epidemiological studies have identified risk factors for both idiopathic osteoporosis and secondary osteoporosis. In the latter, use of corticosteroids and the presence of an underlying inflammatory condition have been shown to be important in the development of low BMD and an increased fracture risk. The improved survival of patients with systemic lupus erythematosus (SLE) has focused attention on the morbidity associated both with the disease and its treatment.

**Table 1. World Health Organization diagnostic criteria for osteoporosis.**

Diagnostic Criteria	BMD value
Normal	T-score above -1
Osteopenia	T-score between -1 and -2.5
Osteoporosis	T-score below -2.5
Established osteoporosis	T-score below -2.5 and history of fragility fracture

### *Prevalence of osteoporosis in SLE patients*

Several studies have identified low BMD in SLE patients when compared to age-matched controls.<sup>3-9</sup> There are some discrepancies between these studies as to the sites (hip, spine, forearm) and to the bone type (cortical vs trabecular) that are affected. Overall, however, the results suggest a generalized reduction in BMD that is evident in 'early' disease.<sup>10,11</sup>

In patients with established disease, this deficit in BMD appears to increase with age and may be related in part to both disease duration and prolonged medication use. In patients with disease duration greater than 10 years, the prevalence of osteoporosis as a disease-associated complication has been reported at 15%, with serious osteoporosis noted in 6%.<sup>12</sup>

Despite evidence of reduced BMD, there is only limited data available on the fracture risk in patients with SLE and this probably relates to the relatively young age of SLE patients. Reduced BMD increases the relative fracture risk,<sup>13</sup> although with younger age the absolute risk for individuals will remain low. Only one retrospective study has assessed self-reported fracture history in 702 women (mean age  $45.4 \pm 13.1$  years) with SLE, comparing them with a historical cohort. Despite obvious methodological problems, the results showed an almost 5-fold increase in the occurrence of fractures in the women with SLE compared with women with similar age within the USA.<sup>14</sup> Multivariate analysis suggested that older age at diagnosis of SLE and longer duration of corticosteroid use were independent predictors of this fracture risk.

#### *Etiology for osteoporosis in SLE patients*

Epidemiological risk factor for osteoporosis and fracture in the general population have been identified.<sup>15</sup> These factors can all increase the risk of osteoporosis and/or fracture in the individual SLE patient, independent of their disease status. There are, however, specific factors that need to be considered in SLE-related osteoporosis.

#### *Abnormal vitamin D metabolism*

Vitamin D (cholecalciferol) is important for bone homeostasis and reduced blood levels of its stable metabolite, 25-hydroxyvitamin D<sub>3</sub> have been associated with fracture risk. With low 25-hydroxyvitamin D<sub>3</sub> levels secondary hyperparathyroidism can occur resulting in bone loss. In severe deficiency, osteomalacia can develop. If dietary intake of

vitamin D is low, then sunlight exposure is necessary for the body to synthesize adequate amounts of 25-hydroxyvitamin D<sub>3</sub>. Photosensitivity as a precipitant of rash is a major diagnostic feature of SLE,<sup>16</sup> and many patients avoid the sun or use sunscreens with high UV protection. It is possible, therefore, that this reduced sunlight exposure may result in lower serum 25-hydroxyvitamin D<sub>3</sub> levels with consequent deleterious effects on bone.

Prior to activation, 25-hydroxyvitamin D<sub>3</sub> is hydroxylated in the kidney to the active metabolite 1,25-dihydroxyvitamin D<sub>3</sub>. Reduced 1- $\alpha$ -hydroxylase activity may therefore be noted in SLE patients with impaired renal function.

#### *Ovarian dysfunction*

Amenorrhea and premature menopause have been recognized as risk factors for reduced bone mass in women. Ovarian dysfunction because of disease activity, drug treatment with glucocorticoid and cytotoxic drugs, or associated autoimmune conditions may therefore have detrimental effects on BMD.

#### *Disease activity*

Studies have demonstrated that in patients with SLE the risk of osteoporosis and reduced bone mass is correlated with disease duration.<sup>17</sup> This may be due to direct effects of disease activity on bone metabolism, associated co-morbidity,<sup>18</sup> or drug treatment.<sup>19</sup>

There is evidence that an abnormal response to T-helper cells, either of type 1 (Th1) or type 2 (Th2) is involved in the pathogenesis of autoimmune disease. In SLE the situation is complex, with conflicting findings between *in vitro* and *in vivo* studies on the relationship between the Th1 and Th2 responses.<sup>20</sup> Inflammatory factors appear, however, to be important in the etiology of SLE and are associated with disease flares. Data from postmenopausal osteoporosis and other inflammatory diseases have shown that the release of various cytokines and inflammatory mediators has direct effects on both bone

and fracture.<sup>21,22</sup> It is therefore possible that the inflammatory nature of SLE also results in a direct effect on bone.

In inflammatory disorders such as rheumatoid arthritis and polymyalgia rheumatica, control of disease activity can result in improvement in bone mass, even if treatment with corticosteroids is required.<sup>23</sup> An increased risk of fracture remains associated with inflammatory diseases independent of drug use.<sup>24</sup> This may also reflect reduced physical activity in these patients. In SLE, fatigue, joint and muscle inflammation, and pain may reduce mobility, thereby impairing the amount of weight bearing exercise obtained with a subsequent reduction in bone mass.<sup>25</sup> The relation of disease activity and body composition has been investigated in a population of 28 pre-menopausal women over 3 years.<sup>26</sup> In this study disease activity was predictive of deleterious changes in body composition with increased body mass index (BMI) and fat mass. Exercise levels independently predicted changes in fat-free mass (that is muscle mass). This in turn correlated with the overall total body BMD of patients.

### *Medications*

Corticosteroids are commonly used in the management of SLE. Several studies have reported decreases in BMD during oral corticosteroid treatment irrespective of the disease being treated. Increased fracture risk is also associated with corticosteroid use, although this risk has been shown to reduce on cessation of treatment.<sup>27</sup> The mechanisms by which corticosteroids cause osteoporosis are complex but include the following:

- (a) Altered calcium homeostasis – corticosteroids cause a reduced absorption of calcium from the gastrointestinal tract and an increase in renal calcium excretion. This results in a net deficit of calcium, which if not corrected will result in secondary hyperparathyroidism with a consequent increase in bone resorption.<sup>28</sup>

(b) Reduced bone formation – corticosteroids cause a decrease in bone formation. This arises because of effects on osteoblast activity resulting in decreased matrix synthesis<sup>29</sup> and a decreased active life span of osteoblasts.<sup>30</sup> There is also inhibition of local skeletal growth factors (e.g., insulin-like growth factor and transforming growth factor beta) contributing to the development of osteoporosis.<sup>31</sup>

(c) Hypogonadism – corticosteroids cause a decrease in circulating estrogen<sup>32</sup>, testosterone<sup>28,33</sup>, and adrenal androgens.<sup>34</sup> The relative deficiency of these hormones, particularly in premenopausal women, may have deleterious effects on bone mass.

The relationship between corticosteroids and osteoporosis has been specifically examined in SLE patients in several studies. Risk of fracture is related to length of treatment with corticosteroids<sup>14</sup> and cumulative exposure to corticosteroids.<sup>35</sup> In the latter study, the relative risk of fracture increased almost 2-fold for every 36.5 gm of corticosteroid taken.

Animal studies suggest that methotrexate inhibits osteoblastic activity, and in children receiving high doses for leukemias osteoporosis, bone pain and fractures may occur.<sup>25</sup>

The effects of low doses methotrexate on bone in patients with SLE have not been specifically studied to date. Azathioprine or cyclophosphamide may induce chemical orchidectomy. Other than this effect on hormones they have not been shown to be directly associated with osteoporosis.

Patients with SLE may need to be treated with anticoagulants if they have had a thrombotic episode, perhaps secondary the anti-phospholipid syndrome. Although warfarin impairs the carboxylation of osteocalcin,<sup>36</sup> the effect of this treatment in osteoporotic fracture remains unclear.<sup>37</sup>

Anticonvulsants may also be required in the management of patients with cerebral lupus.

Long-term anticonvulsant therapy has been associated with reduced bone mass, with

direct evidence *in vitro* of effects on osteoblast-like cells.<sup>38</sup> Epidemiological studies also have demonstrated increased hip fracture risk in women using anticonvulsants.<sup>15</sup>



### **Aims of the thesis**

The aim of the thesis is to characterize the BMD of women and men suffering from SLE. The prevalence of low BMD in SLE patients is determined and the literature available on the subject reviewed. The relationship of bone mass to disease related variables and the hormonal background is elucidated.

## Materials and Patients

A group of Caucasian SLE women (n = 79) attending the 3<sup>rd</sup> Department of Internal Medicine, a Regional Clinical Immunology Center, who had a Dual Energy X-ray Absorptiometry (DXA) examination were studied. In addition, 23 ambulatory Caucasian SLE men and a group of 40 healthy age and sex matched controls were also studied. They all fulfilled the updated American College of Rheumatology classification<sup>16</sup> criteria for SLE.

DXA examination was performed using the LUNAR DPX-L densitometer at the Regional Osteoporosis Center. Data collected included date of birth, body weight, height, history of fracture due to minor trauma, menopausal status, age at menopause, duration of menopause, history of medication with effect on skeleton, age at date of DXA examination. BMD was measured at L<sub>2</sub>-L<sub>4</sub> lumbar spine (LS), left proximal femur neck (FN), left forearm radius at ultradistal (RUD) and 33% shaft (R33%) regions. The ultradistal region consists of a region of interest (ROI) of 15 mm axial length centered at a region that is 4% of the ulna length from the end of the ulna. The 33% shaft region consists of a ROI of 20 mm axial length centered at a site 33% of the ulna length at the end of the ulna. The coefficient of variation of the technique at our institute was 0.8%, using a phantom measured thrice a week during the two month period of this cross-sectional study. BMD was expressed as T score, number of standard deviations from the mean of young women/men attaining peak bone mass, using the normative reference values provided by the manufacturer. Normalcy, osteopenia and osteoporosis were defined according to the WHO classification.<sup>2</sup>

Disease variables collected from patient files included duration of disease calculated from time of diagnosis, history of use of any kind of cytostatics (e.g., methotrexate, cyclophosphamide and azathioprine), daily corticosteroid dose in mg/day prednisolone

equivalent, total cumulative steroid dose in grams, functional classification using the criteria of Steinbrocker,<sup>39</sup> the SLE Disease Activity Index (SLEDAI) to assess disease activity<sup>40</sup> and the SLE Collaboration Clinics / American College of Rheumatology (SLICC/ARC) damage index to assess accumulated damage.<sup>41</sup> The cumulative history database included information from routine visits scheduled every 2-3 months and additional visits occurred as dictated by disease activity or complications.

On the basis of their daily steroid dose the patients were categorized as those receiving no steroid therapy,  $\leq 7.5$  mg/day or  $> 7.5$  mg/day prednisolone equivalent dose,<sup>42</sup> patients were categorized as such only if they were on the same daily steroid dose for at least 6 months before the DXA examination.

Experience was gained regarding DXA measurements and collecting patient data in conjunction with two other studies carried out by us.<sup>43,44</sup>

The history of fractures at the vertebra, femur, humerus, pelvis, forearm, rib and ankle due to minor trauma were also categorized together with the history of use or no use of cytostatics. Patients with premature menopause (menopause  $< 40$  years of age) were identified.

Blood and urine samples were collected from the male patients on the morning of the DXA examination. Standard methods were used to measure serum calcium, phosphate, glutamic oxaloacetic and pyruvic transaminases, creatinine, total alkaline phosphatase, urine calcium, and creatinine. The following parameters were measured by commercial radioimmunoassay (RIA), enzyme linked immunoassay (ELISA) or immunoradiometric assay (IRMA): bone specific alkaline phosphatase (BSAP) (ELISA, ALKPHASE-B™, Metra Biosystems, CA, USA), osteocalcin (OC) (RIA, OSCAtest® BRAHMS Diagnostica, GmbH, Henningsdorf, Germany), serum degradation products of C-terminal

telopeptides of Type-I collagen (serum crosslaps) (ELISA, Serum CrossLaps™, Osteometer BioTech A/S, Herlev, Denmark), parathyoid hormone (PTH) (IRMA, CoTube™, BIO-RAD Diagnostic Group. CA, USA), dehydroepiandrosterone-sulphate (DHEAS) (RIA, Ortho-Clinical Diagnostics GmbH, Neckargemünd, Germany), testosterone (T) (RIA, Institute of Isotopes, Budapest, Hungary), and 25-hydroxyvitamin D (25-OH-D) (RIA, Incstar Co, MN, USA). Morning urine was also used to measure Type-I collagen specific sequence (urinary crosslaps) using CrossLaps™ kit (ELISA) purchased from Osteometer BioTech A/S, Herlev, Denmark.

Descriptive statistics are presented as means, median, range and standard deviation (SD). The *t* test for independent samples was used to compare the means of two groups. One way analysis of variance (ANOVA) was used for group comparison. Pearson's correlation coefficients and *t* tests examined bivariate relations. A value of  $p < 0.05$  was considered statistically significant. All analyses were performed with the Statistical Package for Social Sciences (SPSS) statistical software for Windows, version 9.0 (SPSS Inc., IL, USA).

## Results

### *SLE women*

A total of 79 SLE women were studied (age (mean, range) = 49 (22-73) years). The demographic and clinical characteristics of female patients are summarized in Table 2. The mean LS and FN BMD was  $1.032 \pm 0.178$  and  $0.867 \pm 0.133$  gm/cm<sup>2</sup>, respectively (Table 2). Osteopenia was found in 61.9% at the LS and 46.5% at the FN and 18 (23.7%) patients qualified as having osteoporosis (T-score  $\leq -2.5$ ) at LS as compared to only 3 (5.4%) patients at FN. For LS and FN BMD, the observed proportion of patients with Z-score  $< -1.0$  was significantly greater than the expected 15.9%, calculated from the theoretical population distribution of BMD curves.

On sub grouping the patients according to menopausal status, 46.7% of the premenopausal women had T scores  $< -1.0$  at LS and 36.3% at FN, as compared to 71.7% at LS and 55.9% at FN among the postmenopausal patients. A T score of  $\leq -2.5$  was found at LS in 10% and 32.6% of pre and postmenopausal women, respectively and at FN in 4.5% and 5.9% of pre and postmenopausal women, respectively. Using the Independent Samples T test no statistically significant difference ( $p = 0.147$ ) was seen comparing the FN BMD of the pre and postmenopausal patients. While a statistically significant difference ( $p = 0.014$ ) was found comparing the LS BMD of the pre and postmenopausal patients.

Of the 13 (16.5%) who had a history of fractures due to minor trauma, 6 (7.6%) had a vertebral, 3 (3.8%) had a forearm, 2 (2.5%) had a pelvic, 1 (1.3%) had a proximal femur and another 1 (1.3%) had a fracture of the humerus.

**Table 2. Demographic and clinical characteristics of the SLE women.**

Patient Characteristics	All (n = 79)	Premenopausal (n = 30)	Postmenopausal (n = 49)
Age, yrs <sup>a</sup>	49 ± 11	39 ± 7	55 ± 8
Age, yrs <sup>b</sup>	49 (22-73)	42 (22-47)	54 (36-73)
BMI, kg/m <sup>2a</sup>	26 ± 4.7	25 ± 4.5	27 ± 4.7
Duration of SLE, yrs <sup>a</sup>	9 ± 8.6	7 ± 7	10 ± 9
Duration of SLE, yrs <sup>b</sup>	6 (1 – 37)	4 (1 – 24)	7 (1 – 37)
Steroids ever used	70 (89.7%)	28 (93.3%)	42 (87.5%)
Daily steroid dose, mg/day <sup>b</sup>	7.5 (0 – 40)	8 (0 – 20)	8 (0 – 40)
Steroids dose			
0 mg/day	16 (20.3%)	6 (20%)	10 (20.4%)
≤ 7.5 mg/day	26 (32.9%)	10 (33.3%)	16 (32.6%)
> 7.5 mg/day	37 (46.8%)	14 (46.7%)	23 (47%)
Cumulative steroid dose, grams <sup>b</sup>	13.895 (0 – 94.717)	14.589 (0 – 60.505)	13.883 (0 – 94.717)
Fractures	13 (16.5%)	4 (13.3%)	9 (18.4%)
SLEDAI <sup>b</sup>	4 (0-16)	4 (0-16)	4 (0-12)
Steinbrocker functional			
class I	26 (32.9%)	17 (56.7%)	9 (18.4%)
class II	39 (49.4%)	10 (33.3%)	29 (59.2%)
class III	13 (16.5%)	3 (10%)	10 (20.4%)
class IV	1 (1.3%)	0	1 (2%)
Menopause	49 (62%)	-	-
Years since menopause <sup>b</sup>	-	-	8 (1 – 24)
Premature menopause	-	-	9 (18.4%)
Use of cytostatics	11 (13.9%)	4 (13.3%)	7 (14.3%)
BMD lumbar spine, gm/cm <sup>2a</sup>	1.032 ± 0.178	1.099 ± 0.156 <sup>c</sup>	0.983 ± 0.177 <sup>c</sup>
BMD femur neck, gm/cm <sup>2a</sup>	0.867 ± 0.133	0.901 ± 0.123	0.844 ± 0.137
Based on L <sub>2</sub> -L <sub>4</sub> T score			
Normal	38.2%	53.3%	28.2%
Osteopenia	38.2%	36.7%	39.1%
Osteoporosis	23.7%	10%	32.6%
Based on femur neck T score			
Normal	51.8%	63.6%	44.1%
Osteopenia	42.9%	31.8%	50%
Osteoporosis	5.4%	4.5%	5.9%
L <sub>2</sub> -L <sub>4</sub> Z score < -1.0	44.7%	43.4%	42.9%
Femur neck Z score < -1.0	17.9%	20%	8.2%

<sup>a</sup>mean ± SD; <sup>b</sup>median (range); <sup>c</sup>p = 0.014 using the Independent Samples T test

Statistically significant Pearson's correlation coefficient ( $r$ ) was found between LS BMD and FN BMD ( $r = 0.688$ ;  $p < 0.001$ ), age ( $r = -0.421$ ;  $p < 0.001$ ), duration of menopause ( $r = -0.362$ ;  $p = 0.013$ ) and BMI ( $r = 0.241$ ;  $p = 0.039$ ), respectively. And also between FN BMD and duration of menopause ( $r = -0.518$ ;  $p = 0.002$ ), age ( $r = -0.405$ ;  $p = 0.002$ ) and BMI ( $r = 0.278$ ;  $p = 0.042$ ), respectively. Log transformation was performed for cumulative steroid dose, daily steroid dose and SLEDAI, since their distribution was not normal. Among the variables that did not show a normal distribution the LS BMD had a statistically significant coefficient with the daily steroid dose (Spearman's rho =  $-0.275$ ,  $p = 0.016$ ) and cumulative steroid dose (Spearman's rho =  $-0.248$ ,  $p = 0.031$ ).

Considering only the premenopausal women, statistically significant Pearson's correlation coefficient was found between LS BMD and FN BMD ( $r = 0.700$ ,  $p < 0.001$ ), BMI ( $r = 0.553$ ,  $p = 0.002$ ), daily steroid dose ( $r = -0.395$ ,  $p = 0.031$ ) and cumulative steroid dose ( $r = -0.382$ ,  $p = 0.037$ ), respectively. And also between FN BMD and daily steroid dose ( $r = -0.489$ ,  $p = 0.021$ ) and cumulative steroid dose ( $r = -0.428$ ,  $p = 0.047$ ), respectively.

Similarly when considering only the postmenopausal women, statistically significant Pearson's correlation coefficient was found between LS BMD and FN BMD ( $r = 0.667$ ,  $p < 0.001$ ), age ( $r = -0.438$ ,  $p = 0.002$ ) and duration of menopause ( $r = -0.362$ ,  $p = 0.013$ ), respectively. And also between FN BMD and age ( $r = -0.596$ ,  $p < 0.001$ ) and duration of menopause ( $r = -0.518$ ,  $p = 0.002$ ), respectively.

Grouped on the basis of daily steroid dose in mg/day, 13.3%, 15.4% and 34.3% of the 0,  $\leq 7.5$  and  $> 7.5$  mg/day subgroups, respectively had T scores  $\leq -2.5$ , at the LS. The same trend was not seen at the FN BMD, i.e., 8.3%, 0% and 7.7% of the 0,  $\leq 7.5$  and  $> 7.5$  mg/day subgroups, respectively had T scores  $\leq -2.5$ . Using One-Way ANOVA LSD test

there was a significant difference in BMD at LS between groups  $\leq 7.5$  and  $>7.5$  ( $p = 0.008$ ) and also in BMD at FN comparing groups 0 and  $\leq 7.5$  ( $p = 0.027$ ) as well as groups 0 and  $> 7.5$  ( $p = 0.022$ ).

Grouped on the basis of the Steinbrocker Functional Classification, 15.4%, 27.1% and 25% of the patients belonging to class I, II and III, respectively had T scores  $\leq -2.5$  at LS. The only patient in class IV had a T score  $\leq -2.5$  at both LS and FN. Using the One-Way ANOVA LSD test there was significant difference in LS BMD between Class I and II ( $p = 0.027$ ) as well as Class I and III ( $p = 0.016$ ) and in FN BMD on comparing Class I and III ( $p = 0.005$ ) and Class II and III ( $p = 0.042$ ).

No statistically significant difference in LS or FN BMD was found between those diagnosed with SLE at age  $>35$  years and later; among never and ever users of cytostatics and with or without history of fracture on minor trauma on analysis of all the SLE women and individually the pre and the postmenopausal subgroups (data not presented).

The prevalence of premature menopause in the studied population was independent from the use of cytostatics in the history ( $p = 0.161$ ; using the Chi Square test).

#### *SLE men*

The demographic and basic clinical characteristics of 23 men with SLE and control group ( $n=40$ ) are shown in table 3. On comparing the SLE and control group there were no statistically significant differences in age, BMI, daily dietary calcium intake, and BMD at LS, FN, RUD, and R33% (Table 3). The disease related variables of the SLE men are shown in Table 4. Two patients had never taken corticosteroids. Eighteen patients were currently receiving corticosteroids. None of the patients were on current therapy with drugs affecting bone metabolism. With regards to history of fracture on minor trauma one patient had an ankle fracture and another a rib fracture.



**Table 3. Demographic and basic clinical characteristics of the SLE and control group.**

Patient characteristics	SLE (n = 23)	Control (n = 40)	*p value
Age, yrs	45.6 ± 12.6	48 ± 10	0.543
Age, yrs <sup>a</sup>	45 (24-69)	51.5 (22-55)	-
Weight, kg <sup>b</sup>	78.9 (43.6-102)	77.2 (42-96)	0.437
Height, cm <sup>b</sup>	171.8 (156-187)	171.6 (155-183)	0.869
BMI, kg/m <sup>2</sup>	25.3 ± 4.5	26.1 ± 3.2	0.588
Daily dietary calcium intake, grams	509.6 ± 191.2	502.4 ± 193.3	0.912
Daily dietary calcium intake, grams <sup>a</sup>	500.4 (191.2-877)	448 (296.8-827.6)	-
BMD lumbar spine, gm/cm <sup>2</sup>	1.058 ± 0.166	1.117 ± 0.189	0.329
BMD femur neck, gm/cm <sup>2</sup>	0.947 ± 0.141	0.988 ± 0.154	0.421
BMD forearm-radius ultradistal, gm/cm <sup>2</sup>	0.397 ± 0.065	0.416 ± 0.070	0.400
BMD forearm-radius 33%, gm/cm <sup>2</sup>	0.773 ± 0.070	0.769 ± 0.071	0.854

\*using the *t* test for independent samples<sup>a</sup>median (range); <sup>b</sup>mean (range); all other values are mean ± SD**Table 4. Disease related variables in SLE males.**

Disease related variables	n = 23
Duration of SLE, yrs <sup>a</sup>	11.9 ± 6.9
Duration of SLE, yrs <sup>b</sup>	10 (1-29)
Steroids ever used	21 (91%)
Daily steroid dose, mg/day <sup>a</sup>	7.5 ± 6.5
Daily steroid dose, mg/day <sup>b</sup>	5 (0-20)
Steroids dose	
0 mg/day	5 (21.7%)
≤ 7.5 mg/day	10 (43.5%)
> 7.5 mg/day	8 (34.8%)
Cumulative steroid dose, grams <sup>c</sup>	33.410 (0-144.135)
History of fractures on minor trauma	2 (8.6%)
SLEDAI <sup>c</sup>	2.1 (0-15)
SLICC/ARC <sup>a</sup>	3.9 ± 2.1
SLICC/ARC <sup>b</sup>	3 (2-9)
Steinbrocker functional	
Class I	21 (91.3%)
Class II	2 (8.7%)
History of use of cytostatics	7 (30.4%)

<sup>a</sup>mean ± SD; <sup>b</sup>median (range); <sup>c</sup>mean (range)

According to the WHO criteria at LS 43.5% and 17.4%, at FN 56.5% and 4.3%, at RUD 26.1% and 13% and at R33% 21.7% and 4.3%, of the SLE patients had osteopenia and osteoporosis, respectively. On sub-grouping the SLE patients according to their daily corticosteroid dose, no statistically significant difference was found with regards to their age, BMI, SLEDAI, SLICC/ARC, daily dietary calcium intake, cumulative steroid dose

and BMD at any of the sites measured. The demographic and clinical characteristics of the SLE patients, sub-grouped according to daily steroid dose in mg/day (0,  $\leq 7.5$ ,  $>7.5$ ) are presented in table 5.

**Table 5. The demographic and clinical characteristics of the SLE patients, grouped according to daily steroid dose in mg/day (0,  $\leq 7.5$ ,  $>7.5$ )**

Patient Characteristics	Daily Steroid Dose (mg/day)		
	0 (n = 5)	$\leq 7.5$ (n = 10)	$> 7.5$ (n = 8)
Age, yrs	47.8 $\pm$ 16.9	44.3 $\pm$ 14.4	45.7 $\pm$ 7.8
Age, yrs <sup>a</sup>	56 (24-62)	40 (27-69)	45.5 (32-59)
BMI, kg/m <sup>2</sup>	16.2 $\pm$ 8.4	10.7 $\pm$ 5.1	10.7 $\pm$ 7.5
Daily dietary calcium intake, grams <sup>a</sup>	578.8 (377.7-775)	474.6 (191.2-705.4)	510.3 (242-877)
Duration of SLE, yrs <sup>a</sup>	13 (8-29)	10 (2-21)	8.5 (1-23)
Duration of SLE, yrs <sup>a</sup>	0	5 (5-7.5)	15 (10-20)
Daily steroid dose, mg/day <sup>a</sup>	0	5 (5-7.5)	15 (10-20)
Cumulative steroid dose, grams <sup>a</sup>	5.850 (0-10.050)	34.220 (4.270-68.400)	34.650 (5.680-137.400)
SLEDAI <sup>a</sup>	0 (0-4)	1.5 (0-6)	0 (0-15)
SLICC/ARC <sup>a</sup>	3 (2-7)	3.5 (2-9)	3.5 (2-8)
BMD lumbar spine, gm/cm <sup>2</sup>	1.071 $\pm$ 0.159	1.050 $\pm$ 0.118	1.060 $\pm$ 0.234
BMD femur neck, gm/cm <sup>2</sup>	0.941 $\pm$ 0.169	0.962 $\pm$ 0.129	0.932 $\pm$ 0.157
BMD forearm-radius ultradistal, gm/cm <sup>2</sup>	0.398 $\pm$ 0.062	0.382 $\pm$ 0.066	0.415 $\pm$ 0.070
BMD forearm-radius 33%, gm/cm <sup>2</sup>	0.742 $\pm$ 0.039	0.754 $\pm$ 0.086	0.817 $\pm$ 0.041

<sup>a</sup>median (range); all other values are mean  $\pm$  SD

Basic laboratory indices were within the normal range. Mean BSAP, OC, serum crosslaps, urinary crosslaps, PTH, and 25-OH-D levels were within normal reference range, and mean DHEAS and T levels were lower than normal reference range (Table 6). Twelve (52.2%) of the patients had vitamin D insufficiency (25-OH-D  $\geq 12.5$  and  $\leq 45$  nmol/l) and 3 (13%) had vitamin D deficiency (25-OH-D  $< 12.5$  nmol/l). PTH was high in 3 (13%) patients.

In the SLE patients there was no significant correlation between BMD at any of the sites measured and age, body mass index (BMI), duration of disease, daily and cumulative corticosteroid dose, daily dietary calcium intake, SLEDAI, SLICC/ARC damage index,

and biochemical markers of bone turnover. BMD at any of the sites measured did not correlate with the hormones studied.

BSAP correlated significantly with daily corticosteroid dose ( $r = -0.500$ ,  $p = 0.018$ ), cumulative corticosteroid dose ( $r = -0.441$ ;  $p = 0.040$ ), OC ( $r = 0.565$ ;  $p = 0.006$ ), serum crosslaps ( $r = 0.512$ ,  $p = 0.015$ ) and urinary crosslaps ( $r = 0.672$ ,  $p = 0.002$ ). OC correlated with serum crosslaps ( $r = 0.543$ ;  $p = 0.007$ ) and urinary crosslaps ( $r = 0.628$ ;  $p = 0.004$ ). Serum crosslaps correlated significantly with urinary crosslaps ( $r = 0.622$ ,  $p = 0.004$ ). Daily corticosteroid dose correlated significantly with cumulative corticosteroid

**Table 6. Biochemical markers of bone turnover and hormonal status in SLE males.**

Biochemical markers of bone turnover and hormone levels	SLE (n=23) (mean, range)	Reference range
Bone specific alkaline phosphatase, U/L	16.38 (7.89-33.09)	15.0-41.3
Serum degradation products of C-terminal telopeptides of Type-I collagen, pM	3497.64 (197.45-10900)	302-7208
Urine Type-I collagen specific sequence, $\mu\text{gm}/\text{mmol}$ creatinine	299.18 (60.81-1659.37)	79-335
Osteocalcin, nmol/ L	1.9 (0.6-4)	0.67-3.35 (21-30 yrs) 0.67-2.01 (> 30 yrs)
Parathyroid hormone, pmol/L	4.5 (1.1-12.2)	1.2-6.8
25-hydroxyvitamin D, nmol/L	39.8 (6-97.5)	23-125
Dehydroepiandrosterone-sulphate, mmol/L	1.9 (0.3-4.9)	5.4-9.1
Testosterone, nmol/L	8.9 (3.3-17)	9-38

dose ( $r = 0.608$ ;  $p = 0.002$ ) and DHEAS ( $r = -0.511$ ,  $p = 0.013$ ). Cumulative corticosteroid dose correlated significantly with DHEAS ( $r = -0.486$ ,  $p = 0.019$ ). 25-OH-D correlated significantly with PTH ( $r = -0.431$ ,  $p = 0.040$ ).

## Discussion

### *SLE women*

In our study, we found a higher prevalence of osteoporosis and osteopenia, at both LS and FN, in the studied Hungarian female SLE population as compared to an Australian<sup>7</sup> and a Norwegian<sup>18</sup> study. On analyzing the premenopausal group separately to eliminate the confounding effect of menopause on bone loss, the prevalence of osteopenia and osteoporosis is higher as compared to similar studies.<sup>3,5,6,9,45,46</sup> This discrepancy may be due to the small number of premenopausal women in the studied population, apart from that the majority of them were chronic steroid users and were of diverse disease severity and the difference in site of BMD measurements<sup>47</sup> and study population.<sup>46</sup> Li et al<sup>46</sup> explained the low rate of osteoporosis in the Chinese population by a difference in their calcium homeostasis.<sup>48-52</sup> Although Sinigaglia et al<sup>17</sup> showed a higher prevalence of osteoporosis, this may be due to the higher number of patients studied and all were on corticosteroids. In a recent study,<sup>11</sup> the prevalence of osteopenia and osteoporosis was higher than that studied by us, even though the women studied were ambulatory out-patients, their average daily steroid dose was lower than in our patients and had mild disease activity.

Significant correlation was found between age and LS and FN BMD. Cumulative steroid dose and daily dose correlated well with LS BMD. One explanation for this could be the greater negative effect of corticosteroids on trabecular bone. This is in agreement with the other two studies<sup>7,18</sup> that analyzed the pre and postmenopausal SLE women as a whole.

On considering only the premenopausal group, significant correlation was found between cumulative steroid dose and FN BMD a finding in agreement with that of Pons et al,<sup>9</sup> whereas Houssiau et al<sup>45</sup> and Sinigaglia et al<sup>17</sup> found such correlation with both LS and FN BMD. We also found significant correlation between daily steroid dose and FN and

LS BMD, which is in agreement with the findings of Petri,<sup>53</sup> but in contrast to those of others.<sup>3,5,46</sup>

In the postmenopausal subgroup, the duration of menopause significantly correlated with FN as well as LS BMD. A finding that is normally expected with postmenopausal women, but no compounding effect of any disease related variable could be elucidated.

Although our patients represent a wide range of disease duration (1 – 37 years), no significant correlation was found in either subgroup between the BMD and the duration of SLE, severity of disease, history of cytostatic use, Steinbrocker classification and the history of fracture on minor trauma. Like us, quite a few other authors found no correlation between BMD and the studied disease variable. Dhillon et al<sup>3</sup> found no correlation between BMD and the variables studied, Kalla et al<sup>6</sup> reported that bone loss was not related to duration of disease, Li et al<sup>46</sup> found no correlation between BMD of the studied Chinese SLE women and their disease duration, disease activity, daily corticosteroid dose, cumulative corticosteroid dose, and corticosteroid treatment duration, Hansen et al<sup>47</sup> found no correlation between BMD at the 3<sup>rd</sup> metacarpal and disease duration and SLEDAI, Sinigaglia et al<sup>17</sup> found no correlation between disease activity and osteoporosis, Gilboe et al<sup>18</sup> reported that duration of corticosteroid therapy correlated less to BMD and disease duration and SLE DAI showed no correlation to BMD. Although Sinigaglia et al<sup>17</sup> showed an association of disease duration with osteoporosis.

On comparing the different Steinbrocker functional classifications the higher classes had a significantly reduced LS and FN BMD. Dhillon et al<sup>3</sup> observed general mobility in their patients but found no difference in their BMD. Pons et al<sup>9</sup> compared classes I and II and found no difference in BMD. Kalla et al<sup>6</sup> and Formiga et al<sup>5</sup> included class I and II patients but did not compare their BMD. Kalla et al<sup>4</sup>, Houssiau et al<sup>45</sup>, Li et al<sup>46</sup>, Teichmann et al<sup>10</sup> and Gilboe et al<sup>18</sup> analyzed patients belonging to class I only, Petri<sup>53</sup>,

Kipen et al<sup>7</sup>, Hansen et al<sup>47</sup> and Kipen et al<sup>26</sup> calculated the SLICC index and the patients with a higher score had reduced LS and FN BMD. Although the harmful effect of SLE on bone mass was independent of clinical activity, SLE does not show a considerable functional impairment,<sup>54</sup> which is one of the most important determinants of bone mass in RA.<sup>23,55-58</sup>

No significant difference in BMD was found, neither at LS nor at FN, between patients who were diagnosed with SLE at age >35 years and those diagnosed at age ≤ 35 years, as such the age of disease manifestation does not seem to have any particular effect on BMD. History of cytostatic use had no effect on the BMD either, in accordance with the findings of Sinigaglia et al.<sup>17</sup>

The above findings may be due to the fact that although the total number of our female SLE patients is high, in certain subgroups the numbers fell below the limit of safe statistical handling. Kalla et al<sup>6</sup> did not match the groups for disease duration whereas Houssiau et al<sup>45</sup> matched disease duration when comparing no corticosteroid to ever corticosteroid, here too only LS BMD was low in the corticosteroid group. Some<sup>59-61</sup> suggest that corticosteroid has a more pronounced inhibitory effect on LS, whereas the low BMD at LS may also be due to the effects of the pro-inflammatory cytokines involved in the pathogenesis of SLE itself.<sup>62</sup> Osteoporosis can occur with doses as low as 7.5 – 10 mg/day,<sup>63</sup> the greatest bone loss occurs in the first 6-12 months of use.<sup>40,64</sup> Alternate day prednisone does not reduce the incidence of osteoporosis or fractures.<sup>65</sup> Dhillon et al<sup>3</sup>, Kalla et al<sup>6</sup>, Formiga et al<sup>5</sup> and Hansen et al<sup>47</sup> showed no BMD loss due to corticosteroid whereas Pons et al<sup>9</sup>, Houssiau et al<sup>45</sup> and Kipen et al<sup>66</sup> showed BMD loss due to corticosteroid use. This discrepancy may be related to the lack of uniformity of samples under study. Several studies included premenopausal and postmenopausal subjects,<sup>47,53,66</sup> steroid treated patients, and subjects who had never taken steroids,<sup>6,9,45,47,66</sup>

males and females together.<sup>47,53</sup> In general, all findings of relationship between steroid intake and osteoporosis in SLE are based mainly on the comparison between subgroups of ever and never glucocorticoid treated patients and on the correlations found between BMD and cumulated oral prednisone intake. The comparison between steroid treated patients with SLE and subjects who had never taken steroids should be interpreted with caution since it reflects differences between 2 separate populations with a substantially different degree of severity. Further, the correlations found between cumulative steroid intake and BMD are generally poor, with r values not exceeding 0.55.

The question of the dependence or independence of SLE osteoporosis on glucocorticoid intake has been addressed by Sel et al,<sup>8</sup> who examined separately in non-steroid treated patients with SLE reported in the literature the percentage difference in BMD from age and sex matched controls. Even if the overall sample size is small, a modest loss of BMD is seen at the LS, hip, and the radius, suggesting that osteopenia might be disease related. Tanaka et al<sup>67</sup> observed spontaneous production of bone resorbing lymphokines in SLE patients in the absence of corticosteroid therapy. A view supported by a recent study,<sup>10</sup> where recently manifested premenopausal SLE women were studied and showed the disease per se can result in significant reduction in the BMD. Houssiau et al<sup>45</sup> also reported that patients who were never treated with corticosteroid had a lower hip BMD compared to controls, concluding that the disease per se might induce bone loss.

On the other hand, some suggest<sup>3,68</sup> that the steroids could protect bone mass by reducing inflammation and improving physical activity. In view of their own results and the observations of Lahita et al<sup>68</sup> of increased rates of 16 $\alpha$ hydroxylation of E<sub>2</sub> metabolites such as 15  $\alpha$ hydroxyestrone and estriol, Dhillon et al<sup>3</sup> suggested the possibility that lupus patients may be protected from osteoporosis. This is in contrast to the general opinion that glucocorticoids are responsible for bone loss.<sup>69,70</sup> It could well be

suggested here that the measured bone mass is a result of both positive and negative effects of corticosteroids on bone mass.

Our results show reduced trabecular bone mass, as a higher percentage of our patients were osteopenic at LS as compared to that at FN. Further, LS BMD correlated well with both cumulative and daily steroid doses. Prevalence of reduced bone mass at LS is pronounced among postmenopausal SLE women, in those with high Steinbrocker functional classification and those on high daily steroid dose. Therefore, these patients should be considered as a high-risk group deserving regular spine BMD scans and therapy in due time to prevent vertebral fractures.

### *SLE men*

Osteoporosis in patients with SLE has been widely studied in the last 2 decades, but most of the series have focused on women.<sup>3-7,9-11,17,18,26,45-47,53,59,66</sup> Some of these studies have included a limited number of men with SLE.<sup>47,53,18,71</sup>

We found no difference in BMD at LS, FN, RUD and R33% between SLE men and control group, a finding similar to that of Hansen et al<sup>47</sup> and Formiga et al.<sup>71</sup> Formiga et al<sup>71</sup> found no difference in LS and hip BMD and Hansen et al<sup>47</sup> found no significant difference in BMD at LS, FN, distal forearm and distal 1.5 cm of the 3<sup>rd</sup> metacarpal bone of the non-dominant forearm between the patients and the healthy controls. Whereas, in another study<sup>18</sup> LS, FN and total hip BMD was significantly reduced as compared to healthy controls. Among all the sites measured in our study, LS showed the highest percentage of osteoporosis.

Although no fractures were reported by Formiga et al<sup>71</sup> we found 2 patients with one fracture each. Like other studies<sup>18,47,71</sup> we too failed to show correlation between disease activity, disease duration and BMD. We did not find a correlation between BMD and



daily and cumulative corticosteroid dose, a finding similar to that of Hansen et al<sup>47</sup> and Formiga et al<sup>71</sup>, although Gilboe et al<sup>18</sup> found a significant correlation.

Our laboratory results showed that the mean BSAP, OC, serum and urinary crosslaps were in the normal reference range. We found no correlation between the biochemical markers of bone turnover and BMD. In a study by Hansen et al,<sup>47</sup> serum OC, alkaline phosphatase, carboxyterminal cross-linked telopeptide of type I procollagen, urinary deoxypyridinoline, and pyridinoline were within the normal range. We found negative correlation between BSAP and daily and cumulative corticosteroid dose. Hansen et al<sup>47</sup> showed no correlation between the markers and BMD and corticosteroid therapy. In our study none of the markers correlated with the disease activity, a finding similar to that of Hansen et al.<sup>47</sup>

Prolonged exposure to extraphysiologic corticosteroid concentrations inhibits synthetic processes in the osteoblast<sup>72</sup> a finding supported by our negative correlation between corticosteroid therapy and BSAP.

We found a high prevalence of hypovitaminosis D (65.2%), hypotestosteronism (62.5%) and hypodehydroepiandrosterone-sulphate (100%). Others<sup>73-79</sup> have also reported abnormalities in DHEAS and T levels among SLE patients. The role of 25-OH-D and T in bone metabolism is well documented. Glucocorticoid therapy inhibits testicular secretion of T and adrenal secretion of DHEAS, this fact is supported by our finding of negative correlation between corticosteroid therapy and DHEAS but we failed to find a correlation between corticosteroid therapy and T. The low 25-OH-D levels may be explained by the deliberate avoidance of exposure to the sun and a poor diet.

The lack of correlation between low hormone levels of DHEAS, T and BMD may be explained by the fact that for both DHEAS and T levels we found a wide range and high

standard deviation and apart from this the number of patients studied may have fallen below the limit of safe statistical handling.

We also calculated the daily dietary calcium intake in the SLE men. There was no difference as compared to the controls, but both groups had an intake below the Hungarian average<sup>80</sup> and the mean intake of patients studied by Formiga et al.<sup>71</sup>

Low T, DHEAS, 25-OH-D, dietary calcium intake, and corticosteroid therapy all theoretically point to low bone mass. But despite the fact that our study includes the highest number of SLE men with a higher mean age, SLEDAI, cumulative steroid dose and longer mean disease duration than earlier studies,<sup>47,71</sup> we did not observe a lower bone mass in our patients as compared to the controls. Due to the limitation in the numbers of male patients with SLE, future studies shall require multicenter participation.

Knowledge regarding etiology of osteoporosis in SLE patients allows for preventive and treatment options to be considered. In all patients, general lifestyle measures should be considered. These include: smoking cessation, moderate consumption of alcohol, adequate intake of dietary calcium and vitamin D, regular weight bearing exercise, and in the elderly, measures to prevent falls.

The importance of corticosteroids in the etiology of osteoporosis has already been highlighted. An attempt should be made to ensure the lowest dose is used to adequately control symptoms, with utilization of other immunosuppressive agents if necessary.

There are currently published guidelines for the management of glucocorticoid-induced osteoporosis,<sup>81,82</sup> and the evidence for the licensed therapies has been recently reviewed.<sup>83</sup>

It is possible to utilize these agents in the management of osteoporosis associated with SLE (Table 7).

As noted, corticosteroids have detrimental effects on calcium homeostasis. Calcium and vitamin D supplement has therefore been used as prophylaxis against bone loss in

patients both initiating and on maintenance corticosteroids. A recent meta-analysis has demonstrated that calcium and vitamin D were superior to both calcium alone or no treatment in patients on corticosteroids.<sup>84</sup> This treatment should therefore be considered as a minimum measure in SLE patients being managed with corticosteroids.

**Table 7. Treatments available for the management of osteoporosis in SLE patients.**

Current treatments	Future
Calcium and vitamin D	Parathyroid hormone
Calcitriol	DHEA
Hormone replacement therapy	Growth Factor
Calcitonin	
Thiazides	
Biphosphonates	
Etidronate	
Alendronate	
Risedronate	

Hypovitaminosis and/or altered vitamin D metabolism may be noted in SLE patients. In subjects with appreciable renal impairment, treatment with  $1\alpha$ -hydroxyvitamin D<sub>3</sub> or 1, 25-dihydroxyvitamin D<sub>3</sub> should be considered. The use of calcitriol (1, 25-dihydroxyvitamin D<sub>3</sub>) has been studied in both premenopausal<sup>85</sup> and hypogonadal<sup>86</sup> SLE patients on corticosteroids. Over a 2 year period, calcitriol appeared to moderately reduce bone loss at certain skeletal sites, although both studies were limited due to small subject numbers (81 and 28, respectively).

The American College of Rheumatology guidelines for the prevention and treatment of glucocorticoid-induced osteoporosis recommends the use of a thiazide diuretic if the urinary calcium excretion is elevated.<sup>82</sup> To date, no studies have examined the effect of this treatment in patients with SLE.

Hypogonadism in SLE can result from disease activity, corticosteroid treatment, and as a result of chemotherapy and medical oophorectomy. Replacement of these hormones would therefore seem a logical approach to reduce any associated bone loss. Despite

case-reports that estrogen replacement may induce lupus, it remains unproven that this hormone does indeed precipitate SLE.<sup>87</sup> Estrogen replacement should therefore be considered in postmenopausal women with SLE.<sup>86</sup>

Selective estrogen receptor modulators (SERMs) have been shown to be effective at preventing bone loss and reducing fracture in postmenopausal women.<sup>88,89</sup> Only limited data is available regarding their use in glucocorticoid – induced osteoporosis and there have been no specific studies examining use of SERMs in SLE patients.

There has been recent interest in the use of dehydroepiandrosterone (DHEA) in SLE patients.<sup>90</sup> Levels of DHEA and DHEA-sulphate are low in SLE patients and are also affected by corticosteroid use. DHEA supplementation may reduce SLE disease activity, reduce the requirement and dose of corticosteroids needed, and may have direct positive effects on bone. Further trials are on-going in these areas.

Calcitonin has been studied in patients starting corticosteroids and receiving chronic treatment with varying results. The data overall suggests a beneficial effect on spine bone density, although no effect has been noted at the hip.<sup>91-93</sup> In addition, treatment with calcitonin has not been shown to result in a significant reduction in fractures in patients receiving corticosteroids.<sup>94</sup>

There have been several recent randomised-controlled studies examining the efficacy of biphosphonates on glucocorticoid-induced bone loss and vertebral fractures.<sup>95-98</sup> These studies included heterogeneous patients populations, including men and postmenopausal women. The percentage of patients with SLE ranged from 5 to 15% across the studies. Positive effects on the bone density, particularly at the spine, were seen and this response was consistent across the diseases. In addition, reduction of vertebral fractures was seen within 12 months of initiating treatment in postmenopausal women. The numbers needed to treat (NNT) for a 12 month period to prevent one vertebral fracture in postmenopausal

women are as follows: cyclical etidronate, 5; alendronate, 26; residronate, 8. There are methodological differences in the definition of vertebral fracture between these studies that account some of these differences in NNTs. The figures, however, compare favourably to those obtained for bisphosphonate treatment in idiopathic postmenopausal osteoporosis. It should be noted that in the trials no fractures occurred in premenopausal women on corticosteroids, so the effectiveness of bisphosphonates on fracture in this group could not be determined, although positive effects on BMD were noted.

Parathyroid hormone (PTH), given by subcutaneous daily injection, has been shown to increase BMD in postmenopausal women on corticosteroids. These women were already receiving hormone replacement and there appeared to be additional benefit associated with PTH with uncoupling of bone remodelling in favour of formation.<sup>99</sup> Preliminary data also suggests a positive benefit of PTH on spine and appendicular fractures in idiopathic postmenopausal osteoporosis.

There is also interest in other agents such as growth hormone and insulin-like growth factor type 1, although research is still ongoing in these areas.

The patient with SLE is at risk of osteoporosis because of the inflammatory disease itself, disease-related co-morbidity, and its treatment. Bone loss is apparent early in the disease and this may be confounded by treatment with corticosteroids. Patients should be assessed for additional risk factors for osteoporosis and general lifestyle measures adopted. BMD measurement should be considered in SLE patients at high risk of osteoporosis, particularly those starting corticosteroids and in postmenopausal women. Effective treatments can be targeted to those at high fracture risk, to prevent deterioration in bone mass and reduce the risk of fracture. Hopefully awareness of this problem and the potential for treatment will reduce the burden of osteoporosis and fracture in the patients with Lupus.

## **General Summary**

Osteoporosis in patients with SLE has been widely studied in the last 2 decades, but most of the series have focused on women. Some of these studies have included a limited number of men with SLE.

### *Bone Mineral Density in Women with Systemic Lupus Erythematosus*

Our results show reduced trabecular bone mass, as a higher percentage of our patients were osteopenic at the lumbar spine (LS) as compared to that at the femur neck (FN). Further, LS BMD correlated well with both cumulative and daily steroid doses. Prevalence of reduced bone mass at LS is pronounced among postmenopausal SLE women, in those with high Steinbrocker functional classification and those on high daily steroid dose. Therefore, these patients should be considered as a high-risk group deserving regular spine BMD scans and therapy in due time to prevent vertebral fractures.

### *Bone Mineral Density and Hormonal Status in Men with Systemic Lupus Erythematosus*

We found no difference in BMD at LS, FN, ultra-distal radius (RUD) and mid-33% radius (R33%) between SLE men and control group. Our laboratory results showed that the mean bone specific alkaline phosphatase, osteocalcin, serum and urinary crosslaps were in the normal reference range. We found no correlation between the biochemical markers of bone turnover and BMD. We found a high prevalence of hypovitaminosis D (65.2%), hypotestosteronism (62.5%) and hypodehydroepiandrosterone-sulphate (100%). But despite the fact that our study includes the highest number of SLE men with a higher mean age, SLEDAI, cumulative steroid dose and longer mean disease duration than earlier studies, we did not observe a lower bone mass in our patients as compared to the controls.

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## References

1. Bouillon R, Burkhardt P, Christiansen C, et al. Consensus development conference: prophylaxis and treatment of osteoporosis. *Osteoporosis Int* 1991;1:114-117.
2. World Health Organization. Assessment of fracture risk and its application to screening for postmenopausal osteoporosis. Technical Report Series 843. WHO: Geneva, 1994.
3. Dhillon BV, Davies MC, Hall ML, et al. Assessment of the effect of oral corticosteroids on bone mineral density in systemic lupus erythematosus. *Ann Rheum Dis* 1990;49:624-626
4. Kalla AA, van-Wyk-Kotze TJ, Meyers OL. Metacarpal bone mass in systemic lupus erythematosus. *Clin Rheumatol* 1992;11(4):475-482
5. Formiga F, Moga I, Nolla JM, et al. Loss of bone mineral density in premenopausal women with systemic lupus erythematosus. *Ann Rheum Dis* 1995;54(4):274-276
6. Kalla AA, Fataar AB, Jessop SJ, Bewerunge L. Loss of trabecular bone mineral density in systemic lupus erythematosus. *Arthritis Rheum* 1993;36(12):1726-1734
7. Kipen Y, Buchbinder R, Forbes A, et al. Prevalence of reduced bone mineral density in systemic lupus erythematosus and the role of steroids. *J Rheumatol* 1997;24(10):1922-1929
8. Sels F, Dequeker J, Verwilghen J, Mbuyi-Muamba JM. SLE and osteoporosis: dependence and/or independence on glucocorticoids. *Lupus* 1996;5(2):89-92
9. 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(8):742-746



10. Teichmann J, Lange U, Stracke H, et al. Bone metabolism and bone mineral density of systemic lupus erythematosus at the time of diagnosis. *Rheumatol Int* 1999;18(4):137-140
11. Redlich K, Zeigler S, Kiener P, et al. Bone mineral density and biochemical parameters of bone metabolism in female patients with systemic lupus erythematosus. *Ann Rheum Dis* 2000;59:308-310
12. Swaak AJ, van-den-Brink HG, Smeenk RJ, et-al. Systemic lupus erythematosus: clinical features in patients with a disease duration of over 10 years, first evaluation. *Rheumatology (Oxford)* 1999;38(10):953-958
13. Cummings SR, Black DM, Nevitt MC, et al. Bone density at various sites for prediction of hip fractures. The Study of Osteoporotic Fractures Research Group. *Lancet* 1993;341(8837):72-75
14. Ramsey-Goldman R, Dunn JE, Cheng-Fang H, et al. Frequency of fractures in women with systemic lupus erythematosus. *Arthritis Rheum* 1999;42:882-890
15. Cummings SR, Nevitt MC, Browner WS, et al. Risk factors for hip fracture in white women. Study of Osteoporotic Fractures Research Group. *N Engl J Med* 1995;332(12):767-773
16. Hochberg M. Updating the American college of rheumatology revised criteria for the classification of systemic lupus erythematosus. *Arthritis Rheum* 1997;40:1725-1734
17. Sinigaglia L, Varena M, Binelli L, et al. Determinants of bone mass in systemic lupus erythematosus: a cross sectional study on premenopausal women. *J Rheumatol* 1999;26(6):1280-1284
18. 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(2):110-115

19. Jardinet D, Lefebvre C, Depresseux G, et al. Longitudinal analysis of bone mineral density in pre-menopausal female systemic lupus erythematosus patients: deleterious role of glucocorticoid therapy at the lumbar spine. *Rheumatology (Oxford)* 2000;39(4):389-392
20. Wong CK, Li EK, Ho CY, Lam CWK. Elevation of plasma interleukin-18 concentration is correlated with disease activity in systemic lupus erythematosus. *Rheumatology* 2000;39:1078-1081
21. Ralston SH. Analysis of gene expression in human bone biopsies by polymerase chain reaction: evidence for enhanced cytokine expression in postmenopausal osteoporosis. *J Bone Miner Res* 1994;9(6):883-890
22. Pacifici R. Postmenopausal osteoporosis: how the hormonal changes of menopause cause bone loss. In: Marcus R, Feldman D, Delsey J (eds.). *Osteoporosis*. Academic Press: San Diego, CA, 1996, pp 727-743
23. Gough AK, Lilley J, Eyre S, et al. Generalised bone loss in patients with early rheumatoid arthritis. *Lancet* 1994;344(8914):23-27
24. Cooper C, Coupland C, Mitchell M. Rheumatoid arthritis, corticosteroid therapy and hip fracture. *Ann Rheum Dis* 1995;54(1):49-52
25. Star VL, Hochberg MC. Osteoporosis in patients with rheumatic diseases. *Rheum Dis Clin North Am* 1994;20(3):561-576
26. Kipen Y, Briganti E, Strauss B, et al. Three year followup of bone mineral density change in premenopausal women with systemic lupus erythematosus. *J Rheumatol* 1999;26(2):310-317
27. Van Staa TP, Leufkens HG, Abenhaim L, et al. Use of oral corticosteroids and risk of fractures. *J Bone Miner Res* 2000;15(6):993-1000
28. Reid IR. Steroid osteoporosis. *Calcif Tissue Int* 1989;45:63-67

29. LoCasio V, Bonucci E, Imbimbo B, et al. Bone loss in response to long-term glucocorticoid therapy. *Bone Miner* 1990;8(1):39-51
30. Dempster DW, Arlot MA, Meunier PJ. Mean wall thickness and formation periods of trabecular bone packets in corticosteroid-induced osteoporosis. *Calcif Tissue Int* 1983;35:410-417
31. Canalis E. Mechanisms of glucocorticoid action in bone: implications to glucocorticoid-induced osteoporosis. *J Clin Endocrinol Metab* 1996;81(10):3441-3447
32. Hseuh AJ, Erickson GF. Glucocorticoid inhibition of FSH-induced estrogen production in cultured rat granulosa cells. *Steroids* 1978;32:639-648
33. Reid IR, Ibbertson HK, France JT, Pybus J. Plasma testosterone concentrations in asthmatic men treated with glucocorticoids. *Br Med J* 1985;291(6495):574
34. Crilly IG, Cawood M, Marshall DH, et al. Hormonal status in normal, osteoporotic and corticosteroid-treated postmenopausal women. *J R Soc Med* 1978;71:733-736
35. Zonana-Nacach A, Barr SG, Magder LS, Petri M. Damage in systemic lupus erythematosus and its association with corticosteroids. *Arthritis Rheum* 200;43(8):1801-1808
36. Menon RK, Gill DS, Thomas M, et al. Impaired carboxylation of osteocalcin in warfarin-treated patients. *J Clin Endocrinol Metab* 1987;64(1):59-61
37. Booth SL, Mayer J. Warfarin use and fracture risk. *Nutr Rev* 2000;58(1):20-22
38. Feldkamp J, Becker A, Witte OW, et al. Long-term anticonvulsant therapy leads to low bone mineral density--evidence for direct drug effects of phenytoin and carbamazepine on human osteoblast-like cells. *Exp Clin Endocrinol Diabetes* 2000;108(1):37-43

39. Steinbrocker O, Traeger CH, Batterman RC. Therapeutic criteria in rheumatoid arthritis. *J Am Med Assoc* 1949;140:659-662
40. Bombardier C, Gladman DD, Urowitz MB, et al. Derivation of the SLEDAI. A disease activity index for lupus patients. The Committee on Prognosis Studies in SLE. *Arthritis Rheum* 1992;35(6):630-640
41. Gladman D, Ginzler E, Goldsmith C, et al. 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(3):363-369
42. Lukert BP, Raisz LG. Glucocorticoid-induced osteoporosis: pathogenesis and management. *Ann Intern Med* 1990;112(5):352-364
43. More C, Bettembuk P, Bhattoa HP, Balogh A. The effects of pregnancy and lactation on bone mineral density. *Osteoporosis Int* 2001 (accepted for publication)
44. Kiss E, Bhattoa HP, Bettembuk P, Balogh A, Szegedi G. Pregnancy in Women with Systemic Lupus Erythematosus. *Eur J Obstet Gynecol Reprod Biol* 2001 (accepted for publication)
45. Houssiau FA, Lefebvre C, Depresseux G, et al. Trabecular and cortical bone loss in systemic lupus erythematosus. *Br J Rheumatol* 1996;35:224-227
46. Li EK, Tam LS, Young RP, et al. Loss of bone mineral density in Chinese premenopausal women with systemic lupus erythematosus treated with corticosteroids. *Br J Rheumatol* 1998;37(4):405-410
47. Hansen M, Halberg P, Kollerup G, et al. Bone metabolism in patients with systemic lupus erythematosus. Effect of disease activity and glucocorticoid treatment. *Scand J Rheumatol* 1998;27(3):197-206

48. Lee WTK, Leung SSF, Fairweather SJ, et-al. The fractional calcium absorption in Chinese children measured with stable isotopes ( $^{42}\text{Ca}$  and  $^{44}\text{Ca}$ ). *Br J Nutr* 1994;72:883-897
49. Leung SSF, Lee WTK, Cheng JCY, Fairweather-Tait S. The calcium absorption in Chinese children in relation to their intake. *Hong Kong Med J* 1995;1:58-62
50. Sugimoto T, Tsutsumi M, Fujii Y, et al. Comparison of bone mineral content among Japanese, Koreans, and Taiwanese assessed by dual-photon absorptiometry. *J Bone Miner Res* 1992;7(2):153-159
51. Hegsted DM. Calcium and osteoporosis. *J Nutr* 1986;116:2316-2319
52. Luz Villa M, Nelson L. Race, ethnicity and osteoporosis. In: Marcus R, Feldman P, Kelsy J, eds. *Osteoporosis*. Academic Press, USA, 1996
53. Petri M. Musculoskeletal complications of systemic lupus erythematosus in the Hopkins Lupus Cohort: an update. *Arthritis Care Res* 1995;8(3):137-145
54. Jonsson H, Nived O, Sturfelt G. Outcome in systemic lupus erythematosus: a prospective study of patients from a defined population. *Medicine-Baltimore* 1989;68(3):141-150
55. Hall GM, Spector TD, Griffin AJ, et al. The effect of rheumatoid arthritis and steroid therapy on bone density in postmenopausal women. *Arthritis Rheum* 1993;36(11):1510-1516
56. Laan RFJM, van-Riel PLCM, van-de-Putte LBA. Bone mass in patients with rheumatoid arthritis. *Ann Rheum Dis* 1992;51:115-123
57. Sambrook PN, Eisman JA, Champion GD, et al. Determinants of axial bone loss in rheumatoid arthritis. *Arthritis Rheum* 1987;30(7):721-728

58. Als OS, Gotfredsen A, Riis BJ, Christiansen C. Are disease duration and degree of functional impairment determinants of bone loss in rheumatoid arthritis? *Ann Rheum Dis* 1985;44(6):406-411
59. Petri M. Osteoporosis in SLE: prednisone affects lumbar spine more than other areas. *Arthritis Rheum* 1996;39(suppl):S667
60. Seeman E, Wahner HW, Offord KP, et al. Differential effects of endocrine dysfunction on the axial and the appendicular skeleton. *J Clin Invest* 1982;69:1302-1309
61. Sambrooks PN, Birmingham J, Kempler S, et al. Corticosteroid effects on proximal femur bone loss. *J Bone Miner Res* 1990;5:1211-1216
62. Linker-Israeli M, Deans RJ, Wallace DJ, et al. Elevated levels of endogenous IL-6 in systemic lupus erythematosus. A putative role in pathogenesis. *J Immunol* 1991;147(1):117-123
63. Hahn TJ. Drug-induced disorders of vitamin D and mineral metabolism. *Clin Endocrinol Metab* 1980;9:107-129
64. Laan RFJM, van-Riel PLCM, van-de-Putte LBA, et al. Low-dose prednisone induces rapid reversible axial bone loss in patients with rheumatoid arthritis: a randomised, controlled study. *Ann Intern Med* 1993;119:963-968
65. Gluck OS, Murphy WA, Hahn TJ, Hahn B. Bone loss in adults receiving alternate day glucocorticoid therapy: a comparison with daily therapy. *Arthritis Rheum* 1981;24:892-898
66. Kipen Y, Strauss BJG, Morand EF. Body composition in systemic lupus erythematosus. *Br J Rheumatol* 1998;37:514-519

67. Tanaka Y, Watanabe K, Suzuki M, et al. Spontaneous production of bone-resorbing lymphokines by B cells in patients with systemic lupus erythematosus. *J Clin Immunol* 1989;9(5):415-420
68. Lahita RG, Bradlow HL, Fishman J, Kunkel HG. Abnormal oestrogen and androgen metabolism in the human with systemic lupus erythematosus. *Am J Kidney Dis* 1982;2(Suppl 1):206-211
69. Gennari C, Imbimbo B, Montagnani M, et al. Effects of prednisone and deflazacort on mineral metabolism and parathyroid hormone activity in humans. *Calcif Tissue Int* 1984;36:245-252
70. Adinoff AD, Hollister JR. Steroid-induced fractures and bone loss in patients with asthma. *N Eng J Med* 1983;309:265-268
71. Formiga F, Nolla JM, Mitjavila F, et al. Bone mineral density in men with systemic lupus erythematosus. *Lupus* 1996;5:623-626
72. Wong GL. Basal activities and hormone responsiveness of osteoblastic activity. *J Biol Chem* 1979;254:6337-6340
73. Inman RD, Jovanovic L, Markenson JA, Longcope C, Dawood MY, Lockshin MD (1982) Systemic lupus erythematosus in men. Genetic and endocrine features. *Arch Intern Med* 142(10):1813-1815
74. Carrabba M, Giovine C, Chevillard M, et al. Abnormalities in sex hormones in men with systemic lupus erythematosus. *Clin Rheumatol* 1985;4(4):420-425
75. Folomeev M, Dougados M, Beaune J, et al. Plasma sex hormone and aromatase activity in tissues of patients with systemic lupus erythematosus. *Lupus* 1992;1:191-195
76. Jungers P, Nahoul K, Pelessier C, et al. Low plasma androgens in women with active or quiescent systemic lupus erythematosus. *Arthritis Rheum* 1982;25:454-457

77. Lahita RG, Bradlow HL, Ginzler E, et al. Low plasma androgens in women systemic lupus erythematosus. *Arthritis Rheum* 1987;30:241-247
78. Vilarinho ST, Costallat LTL. Evaluation of the hypothalamic-pituitary-gonadal axis in males with systemic lupus erythematosus. *J Rheumatol* 1998;25:1097-1103
79. Sequeira FJ, Keser G, Greenstein B, et al. Systemic lupus erythematosus: sex hormones in male patients. *Lupus* 1993;2:315-317
80. Biro G, Antal M, Zajkas G. Nutritional survey of the Hungarian population in a randomized trial between 1992-1994. *Eur J Clin Nutr* 1996;50:201-208
81. Eastell R, Reid DM, Compston J, et al. A UK Consensus Group on management of glucocorticoid-induced osteoporosis: an update. *J Intern Med* 1998;244(4):271-292
82. Recommendations for the prevention and treatment of glucocorticoid-induced osteoporosis. American College of Rheumatology Task Force on Osteoporosis Guidelines. *Arthritis Rheum* 1996;39(11):1791-1801
83. Sambrook PN. Corticosteroid osteoporosis: practical implications of recent trials. *J Bone Miner Res* 2000;15(9):1645-1649
84. Amin S, LaValley MP, Simms RW, Felson DT. The role of vitamin D in corticosteroid-induced osteoporosis: a meta-analytic approach. *Arthritis Rheum* 1999;42(8):1740-1751
85. Lambrinoudaki I, Chan DT, Lau CS, et al. Effect of calcitriol on bone mineral density in premenopausal Chinese women taking chronic steroid therapy. A randomized, double blind, placebo controlled study. *J Rheumatol* 2000 Jul;27(7):1759-1765
86. Kung AW, Chan TM, Lau CS, et al. Osteopenia in young hypogonadal women with systemic lupus erythematosus receiving chronic steroid therapy: a randomized controlled trial comparing calcitriol and hormonal replacement therapy. *Rheumatology (Oxford)* 1999;38(12):1239-1244



87. Arden NK, Lloyd ME, Spector TD, Hughes GR. Safety of hormone replacement therapy (HRT) in systemic lupus erythematosus (SLE). *Lupus* 1994;3(1):11-13
88. Delmas PD, Bjarnason NH, Mitlak BH, et al. Effects of raloxifene on bone mineral density, serum cholesterol concentrations, and uterine endometrium in postmenopausal women. *N Engl J Med* 1997;337(23):1641-1647
89. Ettinger B, Black DM, Mitlak BH, et al. Reduction of vertebral fracture risk in postmenopausal women with osteoporosis treated with raloxifene: results from a 3-year randomized clinical trial. Multiple Outcomes of Raloxifene Evaluation (MORE) Investigators. *JAMA* 1999;282(7):637-645
90. van-Vollenhaven RF. Dehydroepiandrosterone in systemic lupus erythematosus. *Rheum Dis Clin North Am* 2000;26:349-362
91. Sambrook P, Birmingham J, Kelly P, et al. Prevention of corticosteroid osteoporosis. A comparison of calcium, calcitriol, and calcitonin. *N Engl J Med* 1993;328(24):1747-1752
92. Montemurro L, Schiraldi G, Fraioli P, et al. Prevention of corticosteroid-induced osteoporosis with salmon calcitonin in sarcoid patients. *Calcif Tissue Int* 1991;49(2):71-76
93. Healey JH, Paget SA, Williams-Russo P, et al. A randomized controlled trial of salmon calcitonin to prevent bone loss in corticosteroid-treated temporal arteritis and polymyalgia rheumatica. *Calcif Tissue Int* 1996;58(2):73-80
94. Luengo M, Pons F, Martinez-de-Osaba MJ, Picado C. Prevention of further bone mass loss by nasal calcitonin in patients on long term glucocorticoid therapy for asthma: a two year follow up study. *Thorax* 1994;49(11):1099-1102
95. Adachi JD, Bensen WG, Brown J, et al. Intermittent etidronate therapy to prevent corticosteroid-induced osteoporosis. *N Engl J Med* 1997;337(6):382-387

96. Saag KG, Emkey R, Schnitzer TJ, et al. Alendronate for the prevention and treatment of glucocorticoid-induced osteoporosis. Glucocorticoid-Induced Osteoporosis Intervention Study Group. *N Engl J Med* 1998;339(5):292-299
97. Cohen S, Levy RM, Keller M, et al. Risedronate therapy prevents corticosteroid-induced bone loss: a twelve-month, multicenter, randomized, double-blind, placebo-controlled, parallel-group study. *Arthritis Rheum* 1999;42(11):2309-2318
98. Reid DM, Hughes RA, Laan RF, et al. Efficacy and safety of daily risedronate in the treatment of corticosteroid-induced osteoporosis in men and women: a randomized trial. European Corticosteroid-Induced Osteoporosis Treatment Study. *J Bone Miner Res* 2000;15(6):1006-1013
99. Lane NE, Sanchez S, Modin GW, et al. Parathyroid hormone treatment can reverse corticosteroid-induced osteoporosis. Results of a randomized controlled clinical trial. *J Clin Invest* 1998;102(8):1627-1633

## List of Publications related to the thesis

### Full-Length

1. **Bhattoa HP**, Bettembuk P, Balogh A, Szegedi G, Kiss E. Bone mineral density in women with systemic lupus erythematosus. *Clin Rheumatol* 2001 (accepted for publication)
2. **Bhattoa HP**, Kiss E, Bettembuk P, Szegedi G, Balogh A. Bone Mineral Density, Biochemical Markers of Bone Turnover and Hormonal Status in Men with Systemic Lupus Erythematosus. *Rheumatol Int* 2001 (accepted for publication)
3. More C, Bettembuk P, **Bhattoa HP**, Balogh A. The effects of pregnancy and lactation on bone mineral density. *Osteoporosis Int* 2001;12:732-737
4. Kiss E, **Bhattoa HP**, Bettembuk P, Balogh A, Szegedi G. Pregnancy in Women with Systemic Lupus Erythematosus. *Eur J Obstet Gynecol Reprod Biol* 2001 (accepted for publication)
5. Bettembuk P, **Bhattoa HP**, More C, Balogh A. A Debreceni Regionális Osteoporosis Centrum denzitometriai vizsgálatainak tapasztalatai [Experience with bone densitometry at the Regional Osteoporosis Center of Debrecen]. *Ca és Csont* 2001;4(2):61-65

### Abstracts

1. **Bhattoa HP**, Bettembuk Peter. Bone mineral density in men with systemic lupus erythematosus. *PhD és TDK tudományos diáktalálkozója* [PhD and Scientific Student Circle Conference] 1998:47
2. Kiss E and **Bhattoa HP**. The bone mineral density of pre- and post-menopausal women with systemic lupus erythematosus. *Rheumatology in Europe* 1998;27 (suppl 2):160
3. **Bhattoa HP**, Bettembuk P, Kiss E, Balogh A. Bone mineral density in men with systemic lupus erythematosus on different current steroid doses. *The Immunologist* 1998;suppl 1:79
4. **Bhattoa HP**, Bettembuk P, Kiss E, Balogh A. Bone mineral density and hormone status in men with systemic lupus erythematosus. *Bone* 1998;23 (suppl 2):S585
5. Bettembuk P, **Bhattoa HP**, Balogh A. One year randomized, placebo controlled, double-blind study on the effects of alendronate on bone mineral density and bone

- turnover in postmenopausal osteoporotic women. *Bone* 1998, Vol 22, No.3 (suppl) S53
6. Bettembuk P, **Bhattoa HP**, Balogh A. Differences in the hip axis length and the femoral axis length between osteoporotic and healthy postmenopausal women. *Bone* 1998, Vol 23, No. (suppl) S597
  7. Balogh A, Bettembuk P, **Bhattoa HP**, Szathmari M, Toth M, Horvath M. Hypovitaminosis D in postmenopausal osteoporotic patients in Hungary. *Bone* 1998, Vol 23, No. 5 (suppl) S492
  8. **Bhattoa HP**, Bettembuk P, Balogh A, Kiss E. Csontásványianyag-sűrűség mérése systemas lupus erythematosusban szenvedő férfibetegekben. [Bone Mineral Density measurement in male systemic lupus erythematosus patients]. *Ca és csont* 1998;1(2):11
  9. More C. Bettembuk P, **Bhattoa HP**, Balogh A. A csont ásványianyag-tartalmának változása a terhesség és szoptatás során. [Changes in bone mineral density during pregnancy and lactation]. *Ca és csont* 1998;1(2):13
  10. Balogh A, Bettembuk P, **Bhattoa HP**, Szathmari M, Toth M, Horvath M. D-hypovitaminosis posztmenopauzában lévő osteoporotikus betegekben. [Hypovitaminosis D in postmenopausal osteoporotic women]. *Ca és csont* 1998;1(2):14
  11. Bettembuk P, **Bhattoa HP**, Balogh A. A calcaneuson végzett képalkotó ultrahangos csontvizsgálat és a DXA-mérés közötti korreláció. [Correlation between bone examination of the calcaneus using ultrasound and bone mass measurement of the spine using DXA]. *Ca és csont* 1998;1(2):18
  12. **Bhattoa HP**. Bone mineral density and hormone status in men with systemic lupus erythematosus. *PhD és TDK tudományos diáktalálkozója* [PhD and Scientific Student Circle Conference] 1999:41
  13. Bettembuk P, **Bhattoa HP**, Balogh A. Nők csontásványianyag-sűrűségének mérése a lumbalis gerincen: több mint 10 000 felvétel analízisének tapasztalatai. [Analysis of bone mineral density of over 10,000 female lumbar spines.]. *Ca és csont* 1999;2(2):7
  14. **Bhattoa HP**, Bettembuk P, Balogh A. A Csontásványianyag-sűrűség mérése systemas lupus erythematosusban szenvedő férfi betegekben: egyéves követés eredményei. [Examination of bone mineral density in men with systemic lupus

- erythematosus: Results of a one-year prospective controlled study]. *Ca és csont* 1999;2(2):14
15. Bettembuk P, Bodogan Z, **Bhattoa HP**, Balogh A. A csontásványianyag sűrűség és az osteoblast-aktivitás mérése korai rheumatoid arthritises betegen. [Measurement of bone mineral density and osteoblast activity in patient with juvenile rheumatoid arthritis]. *Ca és csont* 1999;2(2):25
  16. **Bhattoa HP**, Bettembuk P, Kiss E, Balogh A. Bone mineral density in women with systemic lupus erythematosus. *J Bone Mineral Res* 1999;14 (suppl 1):S388
  17. Bettembuk P, Bodogan Zs, **Bhattoa HP**, Balogh A. Examination of bone mineral density and bone formation in patients with early rheumatoid arthritis. *J Bone Mineral Res* 1999, 14 (suppl 1), S389
  18. Balogh A, **Bhattoa HP**, Bettembuk P. Osteoporosis risk profile and bone mineral density among postmenopausal women in a Hungarian region. *J Bone Mineral Res* 1999, 14 (suppl 1), S508
  19. Balogh A, **Bhattoa HP**, Bettembuk P. Bone mineral density and major risk factors of osteoporosis among postmenopausal women in Hungary. *Climacterium* 1999;2 (suppl 1):225
  20. Balogh A, **Bhattoa HP**, Bettembuk P. Bone mineral density in lumbar spine in males over 50 years of age. *The Aging Male* 2000;3 (suppl 1):25
  21. **Bhattoa HP**. Examination of bone mineral density in men with systemic lupus erythematosus: Results of a one-year prospective controlled study. *PhD és TDK tudományos diáktalálkozója* [PhD and Scientific Student Circle Conference] 2000:82
  22. **Bhattoa HP**, Bettembuk P, Kiss E, Balogh A. A Csontásványianyag-sűrűség mérése systemas lupus erythematosusban szenvedő nőkn. [Bone mineral density measurement in women with systemic lupus erythematosus]. *Ca és csont* 2000;3(1):9
  23. **Bhattoa HP**, Bettembuk P, Kiss E, Balogh A. Examination of bone mineral density in men with systemic lupus erythematosus: Results of a one-year prospective controlled study. *J Bone Mineral Res* 2000; 15 (suppl 1):S420
  24. Bettembuk P, **Bhattoa HP**, Balogh A. Analysis of bone mineral density of over 10,000 female lumbar spines using dual energy x-ray absorptiometry. *J Bone Mineral Res* 2000;15 (suppl 1):S290

25. **Bhattoa HP**, Kiss E, Bettembuk P, Balogh A. Csontásványianyag-sűrűség és markerek vizsgálata postmenopausalis systemás lupus erythematosusos betegekben - kettős vak placebo kontrollált hormonpótló kezelés kiindulási adatai. [Hormone replacement therapy in osteopenic postmenopausal women with systemic lupus erythematosus - bone mineral density and biochemical markers of bone turnover at baseline data]. *Ca és Csont* 2001;4(1):13
26. Bettembuk P, **Bhattoa HP**, Balogh A. Minőségbiztosítás a denzitometriai munkában – Debreceni regionális osteoporosis centrumban. [Quality assurance of densitometers – at the Debrecen regional osteoporosis center]. *Ca és Csont* 2001;4(1):20
27. **Bhattoa HP**, Kiss E, Bettembuk P, Balogh A. Hormone replacement therapy in osteopenic postmenopausal women with systemic lupus erythematosus - bone mineral density and biochemical markers of bone turnover at baseline. *J Bone Mineral Res* 2001;16 (suppl 1):S415