Ph.D. Thesis

Prevalence and Diagnosis of Osteoporosis in Patients with Systemic Lupus Erythematosus

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Introduction

There are many disease related variables that could play a role in determining the bone mineral density in individuals with SLE. Cytokines including interleukin (IL)-6, IL-1, and tumor necrosis factor (TNF)-α are elevated in the serum of patients with SLE and have direct action on bone including the stimulation of bone resorption and suppression of bone formation. Other mechanisms resulting in increased susceptibility to bone loss include female sex, reduced physical activity associated with arthritis or constitutional symptoms, the deliberate avoidance of sunlight exposure, renal involvement resulting in abnormalities of vitamin D hydroxylation, and menstrual irregularity, amenorrhea, or premature ovarian failure due to the disease itself or secondary to corticosteroid and cytotoxic therapy. In addition, individuals with early onset SLE may not attain optimal peak bone mass at skeletal maturity. Continued progress in the management of SLE has resulted in increased survival of women to a postmenopausal age. There may also be geographical and ethnic differences in the BMD values and also in the characteristics of SLE itself.

Recent research on osteoporosis in SLE patients shows conflicting results about its prevalence and the relationship to corticosteroid use or to the disease process itself.

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 3rd 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 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_2-L_4 lumbar spine (LS), left proximal femur neck (FN), left forearm radius at ultradistal (RUD) and 33% shaft (R33%) regions. 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.

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, the SLE Disease Activity Index (SLEDAI) to assess disease activity and the SLE Collaboration Clinics / American College of Rheumatology (SLICC/ARC) damage index to assess accumulated damage. 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, ≤ 7.5 mg/day or > 7.5 mg/day prednisolone equivalent dose, 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.

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.

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), osteocalcin (OC), serum degradation products of C-terminal telopeptides of Type-I collagen (serum crosslaps), parathyoid hormone (PTH), dehydroepiandrosterone-sulphate (DHEAS), testosterone (T), and 25-hydroxyvitamin D (25-OH-D). Morning urine was also used to measure Type-I collagen specific sequence (urinary crosslaps).

Descriptive statistics are presented as mean, 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 1. The mean LS and FN BMD was 1.032 ± 0.178 and 0.867 ± 0.133 gm/cm^2, respectively (Table 1). 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 ≤ -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 ≤ -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.

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 = -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).

Table 1. Demographic and clinical characteristics of the SLE women.

Patient Characteristics		n = 79
Age, yrs[a]		49 ± 11
Age, yrs[b]		49 (22-73)
BMI, kg/m^{2}[a]		26 ± 4.7
Duration of SLE, yrs[a]		9 ± 8.6
Duration of SLE, yrs[b]		6 (1 – 37)
Steroids ever used		70 (89.7%)
Daily steroid dose, mg/day[b]		7.5 (0 – 40)
Steroids dose	0 mg/day	16 (20.3%)
	≤ 7.5 mg/day	26 (32.9%)
	> 7.5 mg/day	37 (46.8%)
Cumulative steroid dose, grams[b]		13.895 (0 – 94.717)
Fractures		13 (16.5%)
SLEDAI[b]		4 (0-16)
Steinbrocker functional	class I	26 (32.9%)
	class II	39 (49.4%)
	class III	13 (16.5%)
	class IV	1 (1.3%)
Menopause		49 (62%)
Use of cytostatics		11 (13.9%)

[a]mean ± SD; [b]median (range)

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, ≤ 7.5 and > 7.5 mg/day subgroups, respectively had T scores ≤ -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, ≤ 7.5 and > 7.5 mg/day subgroups, respectively had T scores ≤ -2.5. Using One-Way ANOVA LSD test there was a significant difference in BMD at LS between groups ≤ 7.5 and >7.5 ($p = 0.008$) and also in BMD at FN comparing groups 0 and ≤ 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 ≤ -2.5 at LS. The only patient in class IV had a T score ≤ -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 earlier; 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.

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 2. 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 2). The disease related variables of the SLE men are shown in Table 3. 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.

Table 2. Demographic and basic clinical characteristics of the SLE and control group.

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

[a]median (range); [b]mean (range); all other values are mean ± SD

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.

Table 3. Disease related variables in SLE males.

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

[a]mean ± SD; [b]median (range); [c]mean (range)

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 4). Twelve (52.2%) of the patients had vitamin D insufficiency (25-OH-D >/= 12.5 and </= 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.

Table 4. Biochemical markers of bone turnover and hormonal status in SLE males.

Biochemical markers of bone turnover and hormone levels	n = 23 (mean, range)	Reference range
BSAP, U/L	16.38 (7.89-33.09)	15.0-41.3
Serum crosslaps, pM	3497.64 (197.45-10900)	302-7208
Urine crosslaps, µgm/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
Dehydroepiendrosterone-sulphate, mmol/L	1.9 (0.3-4.9)	5.4-9.1
Testosterone, nmol/L	8.9 (3.3-17)	9-38

BSAP = bone specific alkaline phosphatase; Serum crosslaps = serum degradation products of C-terminal telopeptides of Type-I collagen; Urine crosslaps = urine type-I collagen specific sequence.

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 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 and a Norwegian 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. 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 and study population. Li et al explained the low rate of osteoporosis in the Chinese population by a difference in their calcium homeostasis. Although Sinigaglia et al 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, 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.

Cumulative steroid dose and daily dose correlated negatively 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 that analyzed the pre and postmenopausal SLE women as a whole.

On considering only the premenopausal group, significantly negative correlation was found between cumulative steroid dose and FN BMD a finding in agreement with that of Pons et al, whereas Houssiau et al and Sinigaglia et al 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, but in contrast to those of others.

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 found no correlation between BMD and the variables studied, Kalla et al reported that bone loss was not related to duration of disease, Li et al 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 found no correlation between BMD at the 3rd metacarpal and disease duration and SLEDAI, Sinigaglia et al found no correlation between disease activity and osteoporosis, Gilboe et al 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 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 observed general mobility in their patients but found no difference in their BMD. Pons et al compared classes I and II and found no difference in BMD. Kalla et al and Formiga et al included class I and II patients but did not compare their BMD. Kalla et al, Houssiau et al, Li et al, Teichmann et al and Gilboe et al analyzed patients belonging to class I only, Petri, Kipen et al, Hansen et al and Kipen et al 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, which is one of the most important determinants of bone mass in RA.

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.

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 did not match the groups for disease duration whereas Houssiau et al matched disease duration when comparing no corticosteroid to ever corticosteroid, here too only LS BMD was low in the corticosteroid group. Some 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. Osteoporosis can occur with doses as low as 7.5 – 10 mg/day, the greatest bone loss occurs in the first 6-12 months of use. Alternate day prednisone does not reduce the incidence of osteoporosis or fractures. Dhillon et al, Kalla et al, Formiga et al and Hansen et al showed no BMD loss due to corticosteroid whereas Pons et al, Houssiau et al and Kipen et al 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, steroid treated patients, and subjects who had never taken steroids, males and females together. 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, 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 observed spontaneous production of bone resorbing lymphokines in SLE patients in the absence of corticosteroid therapy. A view supported by a recent study, 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 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 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 of increased rates of 16-α-hydroxylation of E_2 metabolites such as 15-α-hydroxyestrone and estriol, Dhillon et al 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. 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. Some of these studies have included a limited number of men with SLE.

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 and Formiga et al. Formiga et al found no difference in LS and hip BMD and Hansen et al found no significant difference in BMD at LS, FN, distal forearm and distal 1.5 cm of the 3rd metacarpal bone of the non-dominant forearm between the patients and the healthy controls. Whereas, in another study 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 we found 2 patients with one fracture each. Like other studies 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 and Formiga et al, although Gilboe et al 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, 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 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.

Prolonged exposure to extraphysiologic corticosteroid concentrations inhibits synthetic processes in the osteoblast 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 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 and the mean intake of patients studied by Formiga et al.

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, we did not observe a lower bone mass in our patients as compared to the controls. Due to the limitation in the number of male patients with SLE, future studies shall require multicenter participation.

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 (in press) (Impact Factor = 0.615)

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;21(3):97-102 (Impact Factor = 1.108)

3. More C, Bettembuk P, **Bhattoa HP**, Balogh A. The effects of pregnancy and lactation on bone mineral density. *Osteoporosis Int* 2001;12(9):732-737 (Impact Factor = 2.677)

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 (in press) (Impact Factor = 0.776)

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
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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
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