Assessment of fracture risk in a cohort of Egyptian female Systemic Lupus erythematosus patients

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Aim of the work: To assess the fracture risk in a cohort of Egyptian systemic lupus erythematosus (SLE) females in correlation to some disease variables.

Patients and methods: Seventy female SLE patients ≥40 years old were enrolled with detailed history taking, assessment of disease activity and damage index. Measurement of serum calcium, phosphorus and alkaline phosphatase, bone mineral density (BMD) by dual emission X-ray absorptiometry (DEXA) at lumbar spine (LS) and femoral neck (FN), serum osteocalcin level and World Health Organization (WHO) fracture risk assessment tool (FRAX®).

Results: 20% of the patients had LS osteoporosis, 35.7% LS osteopenia, 8.6% FN osteoporosis, and 42.9% FN osteopenia. Ten-year risk of major and hip fractures was high in SLE patients evidenced by FRAX-Major ≥20% in 10% of patients, and FRAX-Hip ≥3% in 27.1% of patients. Serum osteocalcin level was significantly decreased in SLE patients with lower BMD than those with normal BMD, and significantly decreased in patients with osteoporosis than those with osteopenia. A significant negative correlation was found between osteocalcin level and age of patients, disease duration, disease activity and damage index scores, current intravenous pulse and cumulative steroids, immunosuppressants, anticoagulants, but there was a positive correlation with antimalarials and calcium supplements.

Conclusion: Ten-year risk of major and hip fractures was high in SLE patients. Increasing age, disease duration, high anti-DNA titres, higher disease activity and damage index were associated with a higher fracture risk. FRAX predicted fractures among SLE patients with normal and low bone mass not just those with frank osteoporosis. Physicians should be alerted to the higher risk of future fractures in SLE patients for periodic monitoring.

1. Introduction

Systemic lupus erythematosus (SLE) is a multisystem autoimmune disease affecting mainly women in childbearing age [1]. However, patients have shown increased survival due to the greater knowledge and advances in treatment. Owing to this fact, physicians are encountering long term complications including osteoporosis which of course increases risk of fracture because of low bone mass and damaged structural integrity. Although occurring mainly in the child-bearing age, the disease often persists into the postmenopausal period [2].

The causes of osteoporosis in SLE are multifactorial, involving both non-disease-related and disease-related factors, including traditional osteoporosis risk factors, inflammation, metabolic, hormonal, serologic factors, vitamin D deficiency due to avoidance of sun exposure, early menopause because of cytotoxic drugs, and glucocorticoids use [3].

Patients chronically receiving glucocorticoids have decreased serum osteocalcin level, which is a bone formation biomarker. This observation is in accordance with the predominant inhibitory effect of glucocorticoids on bone formation by suppression of osteoblastogenesis and increased apoptosis of osteoblasts and osteocytes [4].

While few recent studies demonstrated that subnormal bone mineral density (BMD) and patient-reported vertebral fractures were more prevalent in patients with SLE than healthy individuals, prospective comparative studies on the incidence and associated
risk factors of fragility fracture are extremely scarce [5]. Some of the largest studies indicate that the burden of osteoporosis may be more than 20% [6].

Assessment of fracture risk in SLE patients deserves special attention because fractures may occur while their BMD is above the osteoporotic threshold, or even at the normal range [7]. Prevalent vertebral fractures are present in 20–26.1% of the SLE patients, and 1 in 3 of these patients has normal BMD at the lumbar spine (LS) and hip [8]. BMD alone furnishes little information on bone quality and there are several other independent clinical and demographic factors related to fractures which cannot be totally reflected by low BMD [5].

2. Patients and methods

2.1. Study design

This is a cross sectional-observational study.

2.2. Clinical evaluation

Seventy female patients aged more than 40 years, with SLE satisfying at least four of Systemic Lupus International Collaborative Clinics (SLICC) classification criteria [9] were recruited randomly by simple sampling method from Rheumatology and Internal Medicine outpatient clinics and inpatient departments at Ain Shams University hospitals.

Patients with renal or hepatic osteodystrophy, or receiving anti-osteoporotic drugs (except for calcium and vitamin D) were excluded from the study.

All participants gave written informed consent to participate in the study, which was approved by our local Ethics Committee.

All patients were subjected to the following: Full history taking including: SLE duration in years, drugs in use, smoking, alcohol intake, regular exercise, history of previous fractures, menstrual history, history of hypertension, diabetes mellitus (DM). Thorough clinical examination including: Blood pressure, body mass index (BMI) and rheumatological examination. In addition to assessment of SLE disease activity using the Systemic Lupus Erythematosus Disease Activity Index (SLEDAI) [10], and accumulated damage using the Systemic Lupus International Collaborative Clinics/American College of Rheumatology Damage Index (SLICC/ACR DI) [11].

2.3. Laboratory assessment

Routine biochemistry blood tests were done. Complete blood count using Coulter JS and ESR by the Westergren method. Urine analysis, protein/creatinine ratio, serum calcium (Ca++), phosphorus (PO4−−) and alkaline phosphatase (AlkP). Anti-nuclear antibody (ANA) by ELISA, anti-dsDNA antibody by immunofluorescence and serum complement fixation test (C3 and C4) levels by radial immunodiffusion assay.

2.4. Assessment of BMD and bone turnover

2.4.1. Bone mineral density measurement

BMD was measured by dual energy X-ray absorpiometry (DEXA) scans using (densitometers from GE Lunar, Madison, WI 53717-1915, USA). Measurements were made at lumbar spine (LS) (L2-L4) and femoral neck (FN).

All measurements were performed in accordance with standard instrument procedures and matched to gender, race and weight. All BMD measurements were expressed in grams per square centimeter and as the number of standard deviations (SD) above or below mean results of young female adults (T-score). Osteoporosis was determined using World Health Organization (WHO) definitions for participants [12]. As patients recruited in our study were aged 40 years or older (i.e. perimenopausal), applying diagnostic categories of osteopenia and osteoporosis based on T-score and T-score cut-offs is appropriate [13].

2.4.2. Serum osteocalcin

Serum osteocalcin level as a bone forming marker by enzyme-linked immunosorbent assay kit (Quantikine ELISA, R&D systems, Inc., USA) according to the manufacturer’s instructions.

2.4.3 World Health Organization fracture risk assessment tool (FRAX®).

The study being done in Egypt, where no FRAX calculator is available, we used Jordan FRAX calculator as it has been suggested that using the FRAX calculator of a surrogate country is a possible alternative [14].

2.5. Statistical analysis

The collected data were coded, tabulated, and statistically analyzed using Statistical program for Social Science (SPSS 20). Mean ± SD were used to describe quantitative variables. Number and percent were used to describe qualitative variables and Chi-square test used to compare qualitative variables. Fisher exact test was used when when the expected count is less than 5 in more than 20% of cells. Independent t-test was used to compare two independent groups as regards quantitative variables. Spearman correlation coefficients were used to assess the significant relation between two quantitative parameters. Linear regression was used to test and estimate the dependence of a quantitative variable based on its relationship with a set of independent variables. The receiver operating characteristic (ROC) curve was used to evaluate the sensitivity and specificity for quantitative diagnostic measures that categorize cases into one of two groups. The confidence interval was set to 95% and values were considered significant at p < 0.05 and highly significant at p < 0.01.

3. Results

In this exploratory cross sectional study, 70 female SLE patients aged 40 years or older satisfying at least four of SLICC classification criteria were enrolled. The mean age was 50.03 ± 5.49 years with disease duration 14.29 ± 4.91 years. As regards menstrual history, 44.2% were premenopausal, 55.8% were post-menopausal and 27.1% had premature menopause. The mean SLEDAI was 7.03 ± 3.33, while the mean SLICC/ACR was 4.94 ± 2.39. None of the patients gave history of smoking, alcohol intake and they were not on regular exercise.

DEXA was done to all patients where the mean T-score lumbar spine was −1.37 ± 1.34 gm/cm2 and mean T-score femoral neck was −0.96 ± 1.1 gm/cm2. It was found that 20% of patients had osteoporosis at LS, 35.7% osteopenia at LS, 8.6% osteoporosis at FN, 42.9% osteopenia at FN and 18.6% had history of previous fracture.

Using FRAX tool, we found that the 10-year probability of a major osteoporotic fracture (FRAX-Major >20%) was observed in 10% of patients while the 10-year probability of hip fracture (FRAX-Hip >3%) was observed in 27.1% of patients.

In our study, we found that the FRAX-Hip and FRAX-Major among SLE patients were higher in patients with low bone mineral density (LBMD) compared to those with normal bone mineral density (NBMD) at LS and FN (p < 0.01). Also FRAX-Hip and FRAX-Major were higher in those with osteoporosis compared to patients with osteopenia (p < 0.01).
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