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ORIGINAL ARTICLE

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Bone and stone in ankylosing spondylitis: osteoporosis and urolithiasis

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Abstract Ankylosing spondylitis (AS) has well-defined renal complications, but urolithiasis has not been studied in detail. We aimed to evaluate the relation between AS and urolithiasis presence and the effect of this coexistence on the bone mineral status of patients. By dual-energy x-ray absorptiometry measurements at the femoral neck and lumbar vertebrae, we assessed the influence of urolithiasis, disease activity, and duration on bone mineral density (BMD) at different sites. Fifty-three AS patients and 25 control subjects were enrolled in the study. Mean age was 39.49±13.01 years for the AS group and 43.80±10.69 years for the control group, with no statistically significant difference. Patients were accepted as having active disease if two of the following were present: (1) symptomatic peripheral arthritis, (2) erythrocyte sedimentation rate greater than 30 mm/h, (3) C-reactive protein greater than 5 mg/L, and (4) dorsal–lumbar morning stiffness more than 60 min. The ratios of urinary stone presence were 11.32 and 12% for AS and control groups, respectively. We observed that a statistically significant difference in femur neck BMD between AS patients with or without urolithiasis was apparent. The lumbar BMD values were also lower in the urolithiasis subgroup but could not reach the statistical significance. There were no significant BMD alterations in the control group due to stone presence. Comparison of active–inactive disease groups revealed significantly low *T* scores in either the femur neck or L2–4 regions of patients with higher activity indices, but this difference was more prominent in the femur neck. In the early AS group (23 patients), 18 patients (78.26%) had L2–4 *T* scores lower than −1 SD, and in the advanced AS population, 19 of 30 patients (63.33%) had either osteopenia or osteoporosis (OP). We conclude that severe disease and concomitant urolithiasis might increase bone loss and fracture risk especially at the femur neck.

Keywords Ankylosing spondylitis · Bone mineral density · Urolithiasis

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Introduction

Inflammatory arthritis syndromes are often complicated by extra-articular manifestations. Ankylosing spondylitis (AS) has well-defined renal complications, but presence of urolithiasis has not been studied in detail [1]. Spinal immobility, inflammatory cytokines, prolonged use of nonsteroidal anti-inflammatory drugs (NSAID) as well as new bone formation (ankylosis–syndesmophytes) are all contributing factors for calcium metabolism changes in AS [2]. Osteopenia, a well-documented and frequent feature of AS, is also affected from the similar risk factors [3]. Most urinary stones are calcium-based and can be a feature of altered calcium metabolism. It has been suggested that pathological processes of resorption and formation can occur in close proximity. Thus, we hypothesized that the alterations in Ca metabolism of AS patients may result in urinary stone formation. Ito et al. demonstrated an increase in urolithiasis incidence in rheumatoid arthritis (RA) patients, another inflammatory arthritis syndrome sharing some features like inflammatory cytokines, immobility, and prolonged drug usage. In this study, we aimed to evaluate the relation between AS and urolithiasis presence and the effect of this coexistence on the bone mineral status of patients. Bone loss in AS is an independent

predictor of fracture risk; thus, it is important to determine the degree of osteopenia with appropriate methods. By dual-energy x-ray absorptiometry (DEXA) measurements at the femoral neck and lumbar vertebrae, we assessed the influence of urolithiasis, disease activity, and duration on bone mineral density (BMD) at different sites.

Subjects and methods

The study was designed to be a cross-sectional study, and all subjects were recruited from the outpatient clinics of Ankara Education and Research Hospital. Fifty-three AS patients (46 males, 7 females), consecutively selected among the patients attending physical medicine and rehabilitation outpatient clinics, were classified according to modified New York criteria participated in the study [4]. Twenty-five control subjects (5 females and 20 males) selected from the same clinics were also invited to participate in the study. They had minor musculoskeletal complaints of noninflammatory origin and were otherwise healthy. Exclusion criteria for both groups were malnutrition, any intestinal disease, metabolic disease, or drug intake known to effect bone metabolism, except antirheumatic drugs, glucocorticoids, calcium, and vitamin D supplementation as well as bisphosphonates and calcitonin for more than 6 months.

Informed consents and detailed histories of AS and renal diseases were obtained by self-report. Medication history was examined from patient records and self-report. None of our AS patients was immobile or seriously disabled. Disease activity of AS patients was assessed by clinical and laboratory parameters, and patients were accepted as having active disease if at least two of the following variables were present: (1) presence of symptomatic peripheral arthritis, (2) erythrocyte sedimentation rate (ESR) greater than 30 mm/h, (3) CRP greater than 5 mg/L, and (4) dorsal–lumbar morning stiffness lasting more than 60 min [5, 6].

Complete blood count (CBC), ESR, rheumatoid factor (RF) with latex agglutination method, and C-reactive protein (CRP) tests as well as urinalysis were performed for both groups. Twenty-four hours of urinalysis was performed, and all participants were on normal home diet during urine collection. Hypercalciuria was defined as a 24-h calcium excretion of more than 300 mg/day. For detecting urinary stones, plain x-ray and ultrasound imaging were performed by a blinded radiologist. BMD measurements of the patients were carried out at the lumbar spine (L2–4) and femur neck regions with DEXA (Lunar). BMD was also expressed as a *T* score, which represents the number of standard deviations with respect to the mean BMD of a control population. *T* scores more than 1 SD below the mean value were accepted as low BMD according to WHO recommendations, whereas *T* scores less than −1 SD are accepted as osteopenia and those less than −2.5 SD are accepted as osteoporosis (OP) [7]. The number of AS patients with or without urolithiasis has been calculated, and the effect of AS–urinary stone concomitance on BMD has been analyzed by these measurements.

Statistical analyses were performed using the Statistical Package for Social Sciences (SPSS) 8.0 for Windows. Analytical methods include descriptive statistics and Students' *t* test or Mann–Whitney *U* test for comparison of differences between groups. Correlations are presented as the Spearman's or Pearson's correlation coefficient. Values are presented as means and standard errors of means, and differences of $p<0.05$ were taken as significant.

Results

Fifty-three AS patients and 25 control subjects were enrolled in the study. Mean age was 39.49±13.01 years (19–70 years) for the AS group and 43.80±10.69 years (24–60 years) for the control group, with no statistically significant difference. Mean disease duration was 10.56±7.83 years for the AS patients. All women in both groups were premenopausal. All patients were seronegative for RF. None of these patients was known to have a renal disease or persistent symptom, except for urolithiasis by self-report.

Thirty-two patients with AS were taking NSAID and sulfasalazine 2 g/day, whereas 21 patients were only using a variety of NSAID. Three patients were taking methotrexate 15 mg/day. None of our patients was on or had received anti-TNF therapy.

Mean CRP and ESR and BMD data of patient subgroups and controls are given in Table 1.

In the AS group, six patients had urinary stones while three in the control group did, as shown by x-ray and ultrasound imaging. The ratios of urinary stone presence were 11.32 and 12% for AS and control groups, respectively. Mean serum calcium, phosphorus, alkaline phosphatase, 24-h urinary calcium excretion, and parathormone levels were within normal limits, and no significant difference between groups was present. There was no statistically significant difference in dietary Ca intake between study groups and stone-forming and nonstone-forming subgroups. Inflammatory parameters were significantly higher for AS patients than controls as

Table 1 Data about disease activity and mean *T* score values of patient subgroups

Group	Number	ESR (mm/h)	CRP (mg/L)	L2–4 (mean±SD)	Femur neck (mean±SD)
Control	25	21.11±13.12	0.39±1.18	−1.00±1.17	−0.64±0.95
Stone(+) AS	6	43.66±12.20	4.26±1.96	−2.03±0.61	−2.23±0.57
Stone(−) AS	47	32.21±22.55	3.67±6.56	−1.04±1.50	−0.92±1.19
Active AS	19	55.15±13.65	6.36±9.58	−1.75±1.45	−1.69±0.82
Mild AS	34	21.41±15.18	2.28±2.12	−0.83±1.37	−0.72±1.26

ESR Erythrocyte sedimentation rate, *AS* ankylosing spondylitis, *CRP* C-reactive protein

expected, but there was no significant difference between stone patients and others in the AS group. We aimed to see the BMD changes in stone-forming and nonstone-forming AS patients, and after DEXA measurements, we observed that a statistically significant difference in femur neck BMD values between AS patients with or without urolithiasis with a decline in stone patients was apparent (p=0.009). The lumbar BMD values were also lower in the urolithiasis subgroup but could not reach the statistical significance (p=0.106). There were no significant BMD alterations in the control group due to stone presence (p>0.05).

Nineteen patients were accepted to have high disease activity in the patient group according to the criteria given above. Comparison of active–inactive disease groups revealed significantly low scores in either the femur neck or L2–4 regions of patients with higher activity indices, but this difference was more prominent in the femur neck (p=0.002 and 0.036, respectively).

For further evaluation, we subgrouped our patients as early or advanced AS, 10 years being the limit. In the early AS group (23 patients) 18 patients (78.26%) had L2–4 T scores lower than −1 SD, and in the advanced AS population, 19 of 30 patients (63.33%) had either osteopenia or OP.

Discussion

AS is a chronic inflammatory spondyloarthropathy characterized by inflammation of the vertebral joints, enthesis, and adjacent soft tissue, occasionally associated with peripheral arthropathy. Extra-articular manifestations such as upper lobe pulmonary fibrosis, cardiovascular diseases (aortitis), and ocular lesions (uveitis, conjunctivitis) have been widely described [1]. Renal alterations reported include amyloidosis, IgA nephropathy, NSAID-associated nephropathies, and glomerulonephritis with subendothelial deposits of immunoglobulin and complement [1, 8]. To our knowledge, relationship between AS and urolithiasis has not been clearly defined or studied in detail. Various factors are related to stone formation like urinary tract infections, urinary pH changes, urostasis, metabolic diseases, congenital abnormalities, as well as heredity, climate, profession, etc. [9]. However, to date, there is no certain data concerning relation of chronic inflammatory diseases and urinary stone disease. Eighty to ninety percent of urinary stones are calcium-based and can be an indicator of altered calcium metabolism. AS itself is a contributing factor for calcium metabolism changes with spinal immobility, inflammatory cytokines, prolonged use of NSAID, etc. [2, 10, 11]. In our study, 6 of our 53 AS patients had urinary stones, and the number of urolithiasis patients were similar to non-AS population [12]. Our hypothesis that the stone presence could be higher than the normal population has not been proved to be true with our findings. However, we would like to remind that the limited sample of patients, a handicap of our study, might be insufficient to make definite conclusions, and further studies with larger sample sizes would be appropriate for prevalence-incidence calculations.

BMD measurements of our AS patients revealed a decrease in the urinary stone presence. Some authors have reported altered BMD in renal stone formers with reduction of bone mass which seemed particularly evident in hypercalciurics [13]. In a previous study, we reported a decrease in BMD of patients with concomitant RA and urolithiasis without hypercalciuria [14]. Similarly, Jaeger et al. [15] found that BMD in most patients with urolithiasis, including normocalciurics, were lower than controls. However, in our control group, bone mineral status did not seem to be effected from the stone presence. In different studies, bone density correlated with urinary sodium, pH, and uric acid, indicating that osteopenia was associated with factors of renal function as well as calcium metabolism. In AS patients, it must be taken into consideration that factors like inflammation, medication, and immobility may also interfere with calcium metabolism and can be suspected for calcium-based stone formation as well as bone density changes. From our point of view, renal stone formation and bone loss can be accepted as the consequences of the same metabolic status. Bone loss in AS is an independent predictor of fracture risk; thus, it is important to determine the degree of osteopenia with appropriate methods.

It is well known that inflammatory activity in rheumatic diseases itself play a possible role in the pathophysiology of bone loss [6]. High disease activity in AS is associated with an alteration in vitamin D metabolism and increased bone resorption. Marhoffer et al. [16] revealed evidence of impaired cartilage/bone turnover in active AS patients. On the contrary, Meirelles et al. [5] found no significant difference between BMD in AS patients with active disease. Also, Sivri et al. [17] reported in 1996 that neither the duration of the disease and the degree of sacroiliitis nor the disease activity assessed by laboratory and clinical parameters was found to significantly affect the results. In our study population, comparison of active–inactive groups revealed significantly low scores particularly at the femur neck of patients with higher activity indices. Longer disease duration also was associated with bone loss but seemed less effective in our analysis.

The bone mineral loss in concomitant stone and AS patients was significant at femoral neck measurements. Despite apparently low T scores in the femur neck region, the differences in the lumbar vertebrae were less significant. Hence, BMD measurement in AS has controversies. In different studies, various frequencies of OP at different sites have been reported. Comparison of Brazilian AS patients and controls revealed a significant difference between patients and controls for BMD in all the investigated regions, except for the femoral neck [5]. However, Will et al. [18] and Donnelly et al. [19] found significant decreases in the mean BMD of the femoral neck in their study populations. Several investigators found a significant increase in mean BMD values in their patients with long-standing AS [20]. Possible positive correlation between disease duration and lumbar spine BMD can be explained by the presence of

paravertebral bone and ligamentous calcification and ossification (syndesmophytes) in patients with chronic disease. These artifacts falsely increase the lumbar spine BMD, decreasing the sensitivity of bone densitometry in patients with long-standing disease [5]. As a result, they claim that in the same way that lumbar spine bone densitometry is less sensitive for patients with chronic osteoarthritis, it is also less sensitive for patients with advanced AS; therefore, the proximal femur should be used to evaluate bone mass in these patients. Our results are also in concordance with these reports with the BMD alterations in femur *T* scores of stone patients. Additionally, in our active AS group, femoral and lumbar BMD *T* scores were poorly correlated, a finding independent from stone presence or disease duration (r=0.211), indicating the importance of femoral measurements in patients with high disease activity, too.

Bone density measurement should not be performed routinely considering the high cost of this investigation; thus, it might be appropriate to determine certain risk factors. AS itself is a risk factor for low BMD, and the presence of severe disease and concomitant urolithiasis in these patients might increase bone loss. Thus, BMD measurements should be taken into consideration while assessing these patients with an increased OP incidence and resultant fracture risk.

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