Clinical Correlates of Urolithiasis in Ankylosing Spondylitis

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ABSTRACT. ***Objective.*** To determine the association between urolithiasis and syndesmophyte formation and the effect of urolithiasis on ankylosing spondylitis (AS) disease activity.

Methods. In a longitudinal cohort of 504 patients with AS, we conducted an analysis of all patients with AS who have a history of urolithiasis. All patients met the modified New York criteria for AS. Demographics, clinical characteristics, extraarticular features, and comorbidities are systematically recorded in the database. We compared disease activity, functional indices, medical therapy and radiographic damage between AS patients with (Uro+) and without urolithiasis (Uro–) using the modified Stoke Ankylosing Spondylitis Spinal Score (mSASSS).

Results. Thirty-eight patients with AS (7.5%) had a history of urolithiasis in our cohort. Seventy-six patients with AS who did not have urolithiasis, matched for age, sex, and ethnicity, were selected as controls. Patients who were Uro+ were more likely to have more functional disability, based on the Bath AS Functional Index (BASFI; mean 5.3 vs 3.6 in control group, p = 0.003). Trends were noted in the Uro+ group toward higher Bath AS Disease Activity Index (BASDAI; mean 4.9 vs 4.0, p = 0.09), more peripheral joint involvement (p = 0.075), and higher frequency of biologic therapy (p = 0.09). No significant difference was detected in mSASSS or the Bath AS Metrology Index (BASMI). Significant association with diabetes mellitus (DM; p = 0.016) and Crohn's disease (p = 0.006) was noted in the Uro+ group.

Conclusion. Although there is no acceleration of syndesmophyte formation or spinal mobility restriction, more functional disability was detected in the urolithiasis group. The higher risk with concomitant DM or Crohn's disease should alert clinicians to these comorbidities in Uro+ patients with AS.
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Despite the tendency in ankylosing spondylitis (AS) for progressive new bone formation in the spine, trabecular bone loss leading to osteoporosis is a frequent and well-recognized problem in patients with this disease[1,2], and the presence of syndesmophytes seemed to be associated with a higher rate of bone loss[3]. Interestingly, urolithiasis in patients with AS has also been found to significantly increase bone loss and fracture risk, especially at the femoral neck[4]. This relationship has also been reported in patients without AS, and may be related to increased bone turnover[5].

Because both syndesmophytes formation and urolithiasis are related to increased risk of osteoporosis, there is a need to examine the relationship between the 2 entities to determine whether there is any association, and the prognostic significance. Urolithiasis represents an inherent propensity for calcium precipitation and there is a possibility that this may influence or be influenced by the osteoproliferation process in AS. While it remained unclear whether there is an association between urolithiasis and AS, 2 studies have reported a higher incidence of urolithiasis in patients with AS[6,7].

We performed this retrospective study to examine the association between urolithiasis and syndesmophyte formation and the effect of urolithiasis on AS disease activity in general.

MATERIALS AND METHODS

Using an AS database in a large prospective observational cohort, we conducted a study to analyze patients with AS who have a history of urolithiasis (Uro+). This cohort consists of 504 patients with AS who fulfilled the modified New York classification criteria for AS. History of renal stones was identified by the respective self-reported questions included as part of a regular protocol visit to the clinic.

Each case was matched with 2 patients with AS who did not have urolithiasis (Uro–) from the same AS cohort for age, sex, and ethnicity. We compared the following variables between Uro+ and Uro– patients: basic demographics, clinical features, extraarticular features, comorbidities, disease activity and functional indices, medical therapy, and the modified Stoke Ankylosing Spondylitis Spinal Score (mSASSS).

In evaluating the AS disease activity, we used the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI; range 0-10), while the Bath

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Ankylosing Spondylitis Functional Index (BASFI; range 0-10) and the Bath Ankylosing Spondylitis Metrology Index (BASMI; range 0–10) were used to determine functional impairment and spinal mobility, respectively. Radiographic damage of the spine was assessed using mSASSS, which reflects syndesmophyte formation and ankylosis.

Statistical analyses were performed using R version 2.11.0. In comparing the differences between the groups, continuous and categorical variables were analyzed using the Student's t-test and Fisher's exact tests, respectively. Logistic regression was used to determine the predictors for renal stone formation.

RESULTS

Thirty-eight patients with AS who had a history of urolithiasis were studied, accounting for 7.5% of our AS cohort. Seventy-six Uro– patients with AS were selected as controls. Mean age of patients was 48.1 ± 11.9 years for the Uro+ AS group and 47.5 ± 11.5 years for the Uro– AS group. The mean age of onset of Uro+ patients with AS was 27.5 ± 11.0 years and for the Uro– AS group, 25.8 ± 11.8 years. The mean duration of AS in the Uro+ group was 15.1 years, and in the Uro– group, 14.9 years. Overall, male AS patients accounted for 92.1% of the urolithiasis cases, with the majority of them (92.1%) being Caucasian (Table 1).

Of the 38 Uro+ patients with AS, 9 patients had a history of iritis and/or inflammatory bowel diseases, which did not demonstrate a difference in frequency from controls. However, there were 7 patients (18.9%) with concomitant Crohn's disease in the Uro+ AS group compared to 2 (2.7%) in the Uro– AS group (p = 0.006). Psoriasis did not appear to be associated with increased frequency of urolithiasis, although patients with family history of psoriasis did show significantly higher prevalence of urolithiasis (p = 0.004). Diabetes mellitus (DM), known to be a risk factor in urolithiasis formation, was present in 5 patients (13.2%) in the Uro+ AS group compared to only 1 (1.3%) in the Uro– AS group (p = 0.016).

There was no difference in the incidence of urolithiasis in terms of sex, ethnic groups, HLA-B27 status, smoking history, or alcohol consumption. Uro+ patients with AS were more likely to have enhanced functional disability, as measured by the Bath AS Functional Index (BASFI; mean 5.3 vs 3.6 in control group, p = 0.003). In the Uro+ group there were trends toward higher Bath AS Disease Activity Index (BASDAI; mean 4.9 vs 4.0, p = 0.09), more peripheral joint involvement (p = 0.075), and higher frequency of biologic therapy (p = 0.09; Table 2). However, no significant difference was detected in mSASSS (p = 0.65) or the Bath AS Metrology Index (BASMI, p = 0.98).

Table 1. Baseline demographics and associated conditions for patients with ankylosing spondylitis (AS).

Characteristics	Urolithiasis+, n = 38	Urolithiasis–, n = 76	p
Age of AS onset, yrs, mean	27.5	25.8	0.53
Sex, male	35 (92.1%)	70 (92.1%)	1
Disease duration of AS, mean	15.1	14.9	0.92
Race, Caucasian	35 (92.1%)	70 (92.1%)	1
Advanced education —Yes	25 (65.8%)	58 (79.5%)	0.166
Alcohol consumption			
Yes (social drinker)	15 (39.5%)	20 (26.3%)	0.194
Yes (daily drinker)	0 (0.0)	3 (3.9)	
None	23 (60.5%)	53 (69.7%)	
HLA-B27+	27 (81.8%)	60 (85.7%)	0.771
Associated conditions, n (%)			
Iritis	9 (23.7)	28 (36.8)	0.204
Without iritis	29 (76.3)	48 (63.2)	
Crohn's disease	7 (18.9)	2 (2.7)	0.006
Without Crohn's disease	30 (81.1)	72 (97.3)	
Ulcerative colitis	1 (2.7)	8 (10.7)	0.267
Without ulcerative colitis	36 (97.3)	67 (89.3)	
Psoriasis	3 (8.1)	9 (11.8)	0.748
Without psoriasis	34 (91.9)	67 (88.2)	
DM	5 (13.2)	1 (1.3)	0.016
Without DM	33 (86.8)	74 (98.7)	
Hypertension	11 (28.9)	18 (23.7)	0.649
Without hypertension	27 (71.1)	58 (76.3)	
Peripheral joint arthritis	25 (65.8)	36 (47.4)	0.075
Without peripheral arthritis	13 (34.2)	40 (52.6)	

DM: diabetes mellitus.

DISCUSSION

While both syndesmophytes and urolithiasis have been reported to be associated with increased risk of osteoporosis in patients with AS, there does not appear to be any link between the 2 entities from our study. No association between Uro+ and Uro– patients with AS and syndesmophytes formation (as measured by mSASSS) was detected, and as expected, no worsening of BASMI in the Uro+ AS group. However, BASFI, which has been found to correlate moderately well with mSASSS[8], was unexpectedly higher in Uro+ patients with AS, suggesting more functional impairment in those patients.

Whether this functional impairment is related to urolithiasis or AS is unresolved and may be misconstrued by both patients and physicians. In non-AS patients with urolithiasis, 2 surveys using the Medical Outcomes Study Short Form-36 questionnaire found these patients to have a lower quality of life compared to healthy adults[9,10]. In particular, these patients had poorer physical function, easy fatiguability, and poor gen-

Table 2. Differences in BASDAI, BASFI, BASMI, and mSASSS between Uro+ and Uro– patients with ankylosing spondylitis (AS). Data are mean (SD).

	Uro+ AS	Uro – AS	p
BASDAI	4.88 (2.44)	4.01 (2.62)	0.09
BASFI	5.25 (2.50)	3.64 (2.77)	0.003
BASMI	3.42 (2.75)	3.41 (2.62)	0.98
mSASSS	25.7 (26.3)	30.0 (25.4)	0.65

BASDAI: Bath AS Disease Activity Index; BASFI: Bath AS Functional Index; BASMI: Bath AS Metrology Index; mSASSS: modified Stoke AS Spinal Score.

eral health perceptions, which are also factors incorporated into the BASFI and BASDAI scales. While it is difficult to differentiate the contributions of these factors, it is still crucial that these symptoms are not misinterpreted as AS disease activity. Biologic therapy, which showed a high trend of usage in our study, could be erroneously administered to patients who are Uro+ and have AS as a result of this misinterpretation because their higher BASFI and BASDAI scores might be thought to reflect active AS disease. However, this remains speculative because the higher BASFI in the patients with AS who are Uro+ is unexplained.

Studies have found increased prevalence of urolithiasis in patients with DM[11,12,13] and Crohn's disease[14,15] compared to the general population. These correlations were confirmed in our study, with more DM and Crohn's disease in the Uro+ AS group. The cause of this is uncertain given the numerous causes of renal stones, which range from environmental and lifestyle factors to urinary tract infection, and metabolic causes such as hypercalciuria and hyperparathyroidism[16]. Similarly, the link between AS and urolithiasis is also unclear. Most urinary stones are calcium-based and neither AS nor its treatment is known to alter calcium metabolism. However, AS may indirectly affect bone metabolism because of the effect of chronic nonsteroidal antiinflammatory drugs (NSAID) ingestion to treat the condition[17,18]. Interestingly, urolithiasis was found with increased incidence in patients with AS who had hypercalciuria[7]. Further studies are required to determine the circumstances in which hypercalciuria occurs in patients with AS and if this is related to AS disease activity.

Though controversial, NSAID and cyclooxygenase-2 inhibitors have been suggested to affect bone metabolism through the inhibition of prostaglandins, in particular, prostaglandin E2, resulting in reduced osteoclastic resorption and osteoblastic activity[17,19]. Prostaglandin and other biochemical mediators such as interleukin 6 and tumor necrosis factor (TNF)-α affect bone metabolism, and following a fracture these cytokines are produced in huge quantities in the bone and surrounding soft tissues. Prostaglandin, in particular, promotes bone healing with its effect on both osteoclastic and osteoblastic activities. However, in the absence of a fracture, it remains uncertain whether longterm NSAID consumption can affect the normal bone turnover homeostasis[20,21]. Whether serum calcium level can be affected in the process is also unknown, and it would remain a speculation that this may provide the link to explain the increased frequency of urolithiasis in patients with AS.

One of the limitations of our study was the diagnosis of urolithiasis, which was based on patient's self-report, and the possibility that the diagnosis may be presumptive in a few cases with no confirmatory tests done. This could have led to an overestimate of the number of patients with urolithiasis. However, based on 2 small studies that showed prevalence of 25–29.1% of urolithiasis in their AS cohort[6,7], we believe that the 38 (7.5%) cases of urolithiasis in our cohort is an underestimate, especially without systematic evaluation of the patients with radiographic imaging. Future studies could address bone densitometry and biomarkers of bone formation/resorption to evaluate possible links between urinary stones and syndesmophyte formation.

Patients with AS who have urolithiasis have unexpectedly more functional disability than patients with AS overall, and physicians should be wary of this before escalating treatment for these patients from NSAID to an anti-TNF. Prospective studies of this topic with detailed serum and urinary calcium tests, radiographic imaging to confirm renal stones, and followup mSASSS may further explain the relationship between bone loss, urolithiasis, and syndesmophyte formation in AS.

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