Original Article

Urolithiasis in ankylosing spondylitis: Correlation with Bath ankylosing spondylitis disease activity index (BASDAI), Bath ankylosing spondylitis functional index (BASFI) and Bath ankylosing spondylitis metrology index (BASMI)

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Abstract

Background: Increased incidence of renal stone has been reported in ankylosing spondylitis (AS), but unlike some well-known renal involvements, they have not been fully studied. The aim of this study was to investigate the association of AS with urolithiasis and also the relation between urinary stone and severity markers.

Methods: One hundred-sixty three AS patients were included in a cross-sectional study from Iranian AS association, Iran Rheumatology Center and Rheumatology Clinic of Shariati Hospital in Tehran. Prevalence of urolithiasis in AS patients was compared with results of a nationwide survey in Iran. Bath ankylosing spondylitis disease activity index (BASDAI), bath ankylosing spondylitis functional index (BASFI) and bath ankylosing spondylitis metrology index (BASMI) were determined for assessment of disease severity.

Results: Urolithiasis was observed in 11.7% of AS patients versus 5.7% of normal population (p=0.001). After the elimination of corticosteroid effect, the prevalence of urolithiasis was still higher in AS patients than normal population but without maintaining significant difference. Significant higher values of BASFI, BASMI, BASDAI scores were observed in AS with urolithiasis than AS without urolithiasis.

Conclusion: The results confirmed the association of AS with urolithiasis. However, this may be partly due to the effect of other factors such as corticosteroid. Moreover, urolithiais is accompanied with more severe diseases.

Keywords: Ankylosing spondylitis, Urolithiasis, BASDAI, BASFI

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Ankylosing Spondylitis (AS) is the prototype of the widely interrelated group of Spondyloarthropathies with common genetic predisposing factors in particular HLA-B27. This chronic inflammatory disease primarily affects sacroiliac joints and at later stages imperils axial skeleton. Among Caucasians, the prevalence of AS has been reported from 68 per 100000 in the Netherlands to 210 per 100000 in the Norway (1-5). WHO-ILAR Community Oriented Program for Control of Rheumatic Diseases (COPCORD) study in Iran revealed the prevalence of AS from urban to rural areas are 0.12% and 1.1%, respectively (6, 7). Extra-articular disease can often be an associated feature in AS. Renal involvement which is one of the extra skeletal manifestations including IgA nephropathy, secondary amyloidosis and analgesic nephropathy (8). Urolithiasis is also a probable renal complication in AS but unlike some well-known renal involvements, this has not been fully studied. In some recent studies, an increased incidence of renal stone was reported in AS and AS has been proposed as an independent risk factor for nephrolithiasis (9, 10). The main aim of this study was to clarify the relationship between AS and symptomatic urolithiasis in Iranian patients with AS. We also intended to investigate the impact of urolithiasis on severity markers in AS patients.

Methods

This study was conducted from May 2010 to March 2011. One hundred-sixty three patients with AS were recruited from three sources via convenience sampling method: Iranian AS Association, Iran Rheumatology Center (a center dedicated to rheumatologic patients) and rheumatology clinic of Shariati hospital (Tehran, Iran). AS was defined according to the 1984 modified New York criteria (11). The patients with recurrent urinary tract infections and hyperparathyroidism were not included in study. All patients gave informed consent in accordance with principles of the 1964 declaration of Helsinki prior to the inclusion in the study. A structural questionnaire was used to assess the presence of urolithiasis (ultrasound was performed only for the patients who had symptoms suspicious to urinary stone and the stones with any size were considered as positive result), peripheral arthritis, inflammatory bowel disease (diagnosed by colonoscopy only when the patients had symptoms suspicious to this co-morbidity) and to define the age, sex, disease duration, body mass index (BMI) (weight/height^2), disease severity indices scores including Bath ankylosing spondylitis disease activity index (BASDAI) (12), Bath ankylosing spondylitis functional index (BASFI) (13), Bath ankylosing spondylitis metrology index (BASMI) (14, 15), physical activity, calcium supplementation, drug treatments such as corticosteroid (regular systemic corticosteroid equivalent to at least 5 mg prednisolone). Validity and reliability of the Persian version of BASDAI and BASFI questionnaires were assessed prior to the present study with adequate values (16). The prevalence of urolithiasis in AS patients was compared with the result of a population-based survey which had been performed on 7649 individuals in 2007 at all regions of Iran (17). This population was considered as control group. The data analysis was performed using SPSS version18.

We used chi square and/or Fisher's exact test for comparing the categorical variables such as urolthiasis between the AS patients and normal population. Independent two-samples t-test was used to compare continuous variables such as BASFI, BASMI, BASDAI scores between the AS patients with urolithiasis and without urolithiasis. In each case, $p<0.05$ was considered significant.

Results

The mean age for AS and normal population groups were 37.7±9.87 and 40±4.7 years, respectively. The distribution of baseline characteristics, including age, sex, obesity (BMI ≥ 30) in AS patients and normal population are summarized in table1.

Table 1. Comparison of age, sex and body mass index in AS patients versus normal population

Variable		Ankylosing Spondylitis NO (%)	Normal Population NO (%)
Age Group	**15-29**	**36 (22.1)**	**1332 (17.4)**
	30-39	64 (39.3)	1282 (16.8)
	40-49	44 (27)	1330 (17.4)
	≥50	19 (11.7)	2705 (48.4)
Sex	male	129 (79.1)	3748 (49)
	female	34 (20.9)	3901 (51)
BMI [a]	<30	129 (79.1)	6223 (81.36)
	≥30	33 (20.24)	1426 (18.64)

a. One missing value among patients' data

Comparison of AS patients with normal population: Symptomatic urolithiasis was reported by 19 (11.7%) of AS patients compared with 436 (5.7%) of normal population (p=0.001, OR=2.18, 95% CI, 1.34-3.56). The ethnic distribution of patients and control group was approximately the same. With the exclusion of patients that received calcium supplementation, the difference between AS patients and normal population was maintained significantly: 13 out of 122 (10.7%) vs. 5.7%, respectively (p=0.02, OR=1.97, 95% CI, 1. 1-3.53).

Similarly, after excluding the patients with corticosteroid treatment, the results still revealed higher prevalence of urolithiasis in AS patients versus normal population but significant difference was not maintained: 9 out of 100 patients (9%) versus. 5.7% in normal population (P = 0.16). Moreover, the prevalence of urinary stone was separately evaluated among males and females. In men, renal stone was reported in 16 out of 129 AS patients (12.4%) as compared with the 229 out of 3748 normal population (6.11%) with significant difference between groups (p=0.04, OR=2.18, 95% CI, 1.27-3.74). In women, the renal stone was reported in 3 out of 34 AS patients (8.82%) compared with 207 out of 3901 normal population (5.31%) without significant difference between them (p=0.425, OR=1.73, 95% CI, 0.52-5.70). After adjustment for age, the more frequent history of

urolithiasis was seen in AS patients compared with normal population in all age groups; but this difference was significant only in age group 30-39, 40-49 years (p< 0.0001, p=0.038, respectively) (table2).

Table 2. Prevalence of urolithiasis in AS patients and normal population in different age groups

Age Group	AS NO (%)	Normal Population NO (%)	Pvalue
15-29	1 (2.8)	12 (0.9)	0.294
30-39	10 (15.6)	44 (3.4)	<0.001
40-49	6 (13.6)	74 (5.6)	0.024
≥50	2 (10.5)	306 (8.3)	0.667
Total	19 (11.7)	436 (5.7)	0.001

AS patients: In AS patients, urolithiasis was more frequent among the males than the females but the difference was not statistically significant (12.4% vs. 8.8%, p=0.77). BMI in AS patients with urolithiasis was higher than AS patients without urolithiasis (p= 0.01). The tendency to be sedentary was higher in patients with urolithisis (31.6%) versus those without urolithiasis (28.1%), although statistically the significant difference was not observed (p=0.75, OR=1.183, 95% CI, 0.42-3.33). About 15.8% of AS patients with urolithiasis had IBD versus 5.6% of patients without urolithiasis (p=0.121, OR=3.19, 95% CI, 0.8-13.3) (table 3). Nearly, 25.2% of total AS patients received Calcium supplements. Among AS cases with urolithiasis, 31.6% had history of calcium consumption versus 24.3% in patients without urolithiasis (p=0.33, OR=0.70, 95% CI, 0.25-1.97). But, in the age category (30-39 years old), calcium consumption was less frequent in patients with urolithiasis in comparison with patients without urolithiasis (10.0% vs. 27.8%, p=0.429). Ten out of 19 (52.6%) AS patients with urolithiasis had received corticosteroid treatment in comparison with 53 out of 144 (36.8%) patients without urolithiasis (p=0.18) (table 2).

Urolithiasis and AS: severity markers: The higher values of BASFI, BASMI, BASDAI scores were observed in AS patients with urolithiasis than patients without urolithiasis (p=0.003, p=0.037, p=0.055). Peripheral arthritis was seen in 12 patients with urolithiasis (63%) and 71 patients without urolithiasis (49.3%); although this association was not statistically significant (p=0.256, OR=1.76, 95% CI, 0.66-4.73). The disease duration difference between AS patients with urolithiasis and without urolithiasis was not statistically significant (p=0.12) (table 3).

Table 3. Comparison of severity markers and other characteristics in AS with and without urolithiasis

	Urolithiasis + (N=19)	Urolithiasis - (N=144)	P-value
BASFI	57.737±26.049	38.44±26.829	0.004
BASDAI	32.526±15.079	26.06±13.63	0.06
BASMI	4.826±1.949	3.83±1.85	0.03
Arthritis NO (%)	12 (63.2)	71 (49.3)	0.26
IBD NO (%)	3 (15.8)	8 (5.6)	0.12
Corticosteroid NO (%)	10 (52.6)	53 (36.8)	0.2
Calcium supplement NO (%)	6 (31.6)	35 (24.3)	0.33
Disease duration	17.53±9.008	14.09±8.346	0.09
Sedentary NO (%)	6 (31.6)	39 (28.1) [a]	0.79
BMI [b]	29.522±5.595	26.25±5.15	0.01

Values are mean ± SD, unless otherwise stated

a. Five missing data were considered in the analysis b. One missing data was considered in the analysis

Discussion

Our results revealed significantly the higher prevalence of urolithiasis in AS patients versus normal population. The exact etiology of urolithiasis in AS is unknown but some hypotheses for hypercalciuria and resulting nephrolithiasis

have been proposed including the elevated circulating cytokines such as TNF-α, IL-6 and IL-17, disruption of vitamin D and Calcium metabolism due to sub-clinical bowel disease (IBD) which is common in AS, coexistent gout, prolonged immobilization caused by arthralgia, anti-inflammatory drugs such as corticosteroid, nonsteroidal anti inflammatory drugs (NSAIDs), calcium supplementation and genetic polymorphisms such as ANKH mutation (18-30).

Urolithiasis unlike some well-known renal involvements has not been fully studied in AS. Among the few reported studies, a group of studies detected higher prevalence of urinary stone in AS but some others did not present similar reports (9, 10, 22). Our results were compatible with the two following studies:

Korkmaz et al. compared 80 AS patients with 72 Behcet's patients and 98 healthy individuals as controls. Renal stone prevalence was found to increase in AS patients (25%) versus Behcet's disease (5.5%) and healthy controls (3.3%). Also, they found disease duration was longer in AS patients with renal stone compared with patients without urolithiasis (9).

Canales et al. reported kidney stones in 29% of the 79 spondyloarthropathies (SpA) patients compared with 12.5% of the 64 rheumatoid arthritis (RA) patients as controls. Populations were similar in all features except that RA patients were more likely to have used corticosteroid, bisphosphonate, and calcium supplementation. Despite adjusting for medication use and matching two similar populations, the patients with SpA had a higher incidence of kidney stones than those with RA and finally they suggest that SpA may be an independent risk factor for urinary stone formation (22). The results of these two above studies are similar to the findings of our study.

In the current study after adjusting sex and age groups, more frequent history of urolithiasis persisted in AS patients compared with normal population, but this difference was maintained significantly only in age group 30-39, 40-49 years and male gender (table 1). Therefore, the association of AS with urolithiasis seems to be more significant in males.

One of the influential parameters in renal stone formation is the history of calcium supplementation which has a controversial role. Some recent studies have challenged the notion that calcium supplementation inhibits urinary stone formations (31). With the exclusion of patients that received calcium supplementation in present study, the difference between the prevalence of urolithiasis in AS patients and normal population decreased but was maintained significantly. Consequently, the calcium supplementation is unlikely to play role as inhibitory stone former in our AS patients. The other predisposing factor for nephroilithiasis in AS is receiving prednisone treatment which is expected to be more frequent in AS patients (24, 25). Although after excluding the patients with corticosteroid treatment, the results still revealed higher prevalence of urolithiasis in AS patients as compared with normal population but the difference was not significant. Hence, the association of AS with urolithiasis may be somewhat due to the effect of corticosteroid treatment. Obesity seems to be a notable nephrolithiasis risk factor considering the significant association between higher BMI and urolithiasis in our AS patients which is similar to the results observed in Iranian normal population (17).

Interestingly, urolithiasis accompanied some different clinical and therapeutic patterns in AS. Overall, a line of evidence linked coexistent renal stone with more intense progression of AS (32). Lui et al. showed in their cohort (performed on 38 AS patients with urolithiasis and 76 patients without urolithiasis matched for age, sex, and ethnicity) that patients with urolithiasis had more functional disability, based on BASFI. Trends were noted in the urolithiasis group toward higher BASDAI and more peripheral joint involvement. No significant difference was detected in BASMI (32). Also, Cansu et al. reported renal stone history in 27.5% of Turkish patients with AS, introducing a correlation between nephrolithiasis and higher radiological scores in AS. It is believed that renal stone accompanies AS cases with more severe radiographic damages and presumably poor prognosis (33). In accordance with these studies, we found a significantly higher BASFI, BASMI and also borderline significantly higher BASDAI in AS patients with urolithiasis.

Furthermore, Lui et al. revealed a significant association of AS with Crohn's disease in AS patients with urolithiasis (32). A higher prevalence of IBD was also detected in our AS patients with urolithiasis than AS without urolithiasis; but the difference was not statistically significant. A causative correlation between Crohn's disease and urolithiasis has been explained and different pathologic pathways may cause stone formation in Crohn's patients (34, 35). Thus, higher prevalence of urolithiasis in AS patients to some extent may be due to more frequent IBD in these patients. One of the limitations of our study was the

inaccessibility of complete drug history in our control group, most importantly calcium supplementation and corticosteroid treatment. Moreover, some other risk factors including IBD, hyperparathyroidism or prolonged immobilization was not recorded in healthy controls. Despite the consideration of age, sex, corticosteroid and calcium supplementation in analysis, adjustment for some other urinary stone risk factors between normal population and AS patients was not completely possible. For example, the majority of AS patients received NSAIDs as treatment and we were not able to adjust it with control population.

Only the symptomatic urolithiasis was considered in current study. Therefore, the exact prevalence of urolithiasis could have been underestimated among the AS patients and consequently the prevalence of urolithiasis (symptomatic and asymptomatic totally) in our AS patients is probably higher than the values reported in this survey.

One of the advantages of the current study was that the control group included individuals from a population-based survey and not from patients with other diseases such as Behcetś disease or rheumatoid arthritis. In addition, the higher number of AS patients studied in current survey compared with other studies is another advantage of our study. Although, based on earlier studies in the control group, the sample size of patients is still small and a larger sample size may be required. Our results showed the association of AS with urolithiasis. However, this association may be in part due to other factors like corticosteroids consumption or associated IBD. Furthermore, urolithiais is accompanied with more severe diseases. Therefore, concerning the urolithiasis in AS patients seems to be useful and we suggest the evaluation of nephrolithiasis in follow up and management of AS patients especially those that receive corticosteroid for any reason. Further studies about genetic polymorphisms such as ANKH mutation that probably involve urolithiasis of AS is also suggested.

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Conflict of interest: None.

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