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Nephrolithiasis in ankylosing spondylitis and its relation with disease assessment scales

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ABSTRACT

OBJECTIVE: To investigate the frequency of renal stone in patients with ankylosing spondylitis and to determine its relation with disease assessment variables.

METHODS: The study was designed retrospectively in a cohort of 320 patients with AS diagnosed by Modified NewYork Criteria. 119 patients having renal ultrasonography (USG), erythrocyte sedimentation rate, C-reactive protein, blood calcium, phosphorus, Vitamin-D, parathormone and urinary calcium excretion and also having lateral cervical and lumbar radiography in the same time period were extracted from the cohort. All patients' demographic characteristics, level of blood and urine tests were recorded. Ankylosing spondylitis disease activity Index (BASDAI), Ankylosing Spondylitis Functional Index (BASFI), Ankylosing Spondylitis Mobility Index (BASMI) and Modified Stoke Ankylosing Spondylitis Spinal Score (mSASSS) were evaluated in all patients.

RESULTS: Thirteen (13) of the one hundred-nineteen (119) patients had renal calculi confirmed by USG data. The frequency of nephrolithiasis detected by USG was 10.9% in AS patients. Disease duration was significantly higher in patients with renal stone [(nephrolithiasis (+): 18.39±8.72 years, nephrolithiasis (-): 12.02±8.43 years, p=0.01]. BASMI total score was significantly higher in the group of renal stone patients. There was not any significant difference in terms of blood samples, HLA-B27, BASDAI, BASFI and mSASSS between groups.

CONCLUSION: The frequency of renal stones is increased in AS patients compared with healthy population. Especially AS patients with long disease duration and higher BASMI values are more susceptible to renal stones. It is important to point out that the results of this type of studies would be more reliable if the study takes part in large patient groups and population-based prevalence.

Keywords: Ankylosing spondylitis; BASDAI; BASFI; BASMI; mSASSS; nephroilitasiz; urolithiasis.

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Ankylosing Spondylitis (AS) is a chronic inflammatory disease having predilection for the spine and sacroiliac joints causing back pain and post inactivity stiffness [1]. In addition, AS is characterised by different manifestations such as; peripheral arthritis, enthesitis and extra-articular involvement such as eye, lung, kidney, and heart [1]. The prevalence of AS is generally believed to be between 0.1% and 1.4% and the gender disparity is reported ratios of around 2:1 (male/female) [2].

IgA nephropathy, secondary amyloidosis and analgesic nephropathy are the most common renal involvement seen in AS [3]. However, the incidence of renal stone has been shown to be higher in these patients than in normal populations [4]. The prevalence of urolithiasis ranges from 2%-20% throughout the world based on different characteristics of populations [5]. With a prevalence of 11.1%, urinary stone disease is considered endemic in Turkey and showed a specific geographical distribution, in which south-eastern Anatolia and Aegean regions had the highest prevalence [6].

Several studies showing the increased incidence of renal stones in patients with AS are published [7-13]. Jacobson et al. found the risk of nephrolithiasis in AS patients to be more than two-fold compared to the general population. They described nephrolithiasis as an extra-articular manifestation in AS and factors such as; male gender, history of inflammatory bowel disease, and previous history of kidney stones being significant and clinical important predictors of nephrolithiasis in AS patients [12]. Consistently a recent published study from Taiwan with a large patient number assessed the risk of nephrolithiasis among AS patients compared to matched general population. The percentages of newly diagnosed nephrolithiasis was 5.76% in AS and 4.58% in the non-AS patients. The results showed that patients with AS were more likely to be associated with nephrolithiasis than non-AS patients [14].

Although unknown etiology, the formation of stones requires the complex integration of numerous factors, for example, high blood calcium and phosphate saturation, high levels of urinary calcium, the formation, retention, and accumulation of crystals, urinary pH, and abnormalities in crystallization inhibitors [15] . In addition of increase in cytokines, bone resorption and increased bone turnover, prolonged use of anti-inflammatory drugs and accompanied intestinal problems also play a role in stone formation in AS [16].

In the light of information provided, the aim of this study was to investigate the frequency of detected renal stones by ultrasonography and its relation with disease assessment scales in our AS patients.

MATERIALS AND METHODS

The study was designed retrospectively. A total of 320 AS patients being followed by 'Activity Platform' were included in the study. 'Activity platform' is comprised of eleven physiatrists from 9 different centers in Turkey showing a especial interest in spondyloarthritis and rheumatoid arthritis who have received a standardized training that included examination, assessment of the questionnaire forms and radiological grading performance of AS patients. A total of 119 patients who had renal USG, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), blood level of calcium, phosphorus, Vitamin-D, parathormone and urinary calcium levels and also lateral cervical and lumbar conventional radiography in the same time period were extracted from the cohort.

All of AS were diagnosed according to the modified New York criteria [17]. The sociodemographic characteristics (age, gender and disease duration), clinical features and comorbidities of patients were recorded. Patients had data for the history of hypertension, diabetes, and cardiovascular disease were excluded. Patients were identified as "renal stone positive" with stone-compatible images and "renal stone negative" if stone incompatible. A written informed consent was obtained from each patient.

The patients were assessed using the Assessment of SpondyloArthritis International Society (ASAS) recommendations for core outcome domains for the assessment in AS [18]. Turkish versions of Bath AS Disease Activity Index (BASDAI) [18], Turkish version of Bath AS Functional Index (BASFI) [20], Bath AS Metrology Index (BASMI) [21] were evaluated for disease activity, functional status and mobility respectively. BASMI subscale was calculated by chest expansion, cervical rotation, lumbar flexion, lumbar lateral flexion and intermalleolar distance evaluations. Modified Stoke Ankylosing Spondylitis Spinal Score (mSASSS) [22] was used for radiologic assessment of structural damage. For this reason, lateral views of the lumbar and cervical spine of 119 patients also having renal ultrasonographic evaluation in the same time period were scored by same researcher (R.Ç) with experience in grading the mSASSS [22]. The frequency of nephrolithiasis of our patients was assessed

Table 1. Demographic characteristics of AS patients with and without nephrolithiasis

Characteristics	Nephrolithiasis (-)	Nephrolithiasis (+)	p
Age (years)	40.42±10.59	45.69±10.10	0.91
Male gender	%61	%84.6	0.13
Disease duration (years)	12.02±8.43	18.39±8.72	**0.01***
HLA B27 (+)	93/106	13/13	0.33

*p<0.05.

Table 2. Laboratory results of patients in the same time period of ultrasonographic evaluation

Characteristics	Nephrolithiasis (-)	Nephrolithiasis (+)	p
Calcium (mg/dl)	10.11±8.24	9.42±0.36	0.45
Phosphorus (mg/dl)	3.30± 0.58	3.19±0.53	0.59
Vitamin D (ng/ml)	29.36±33.92	23.87±10.06	0.89
Parathormon (pg/ml)	55.79±31.01	57.03±41.59	0.55
Urine calcium (24 h)	145.04±84.97	238.91±403.70	0.76

by being compared to Turkish population nephrolithiasis data.

Statistics

We used chi square and/or Fisher's exact test for comparing the categorical variables such as; nephrolithiasis between the AS patients and normal population. Independent two-samples t-test was used to compare continuous variables such as; mSASSS, BASFI, BASMI, BASDAI scores between the AS patients with nephrolithiasis and without nephrolithiasis. In each case, $p<0.05$ was considered significant. The data analysis was performed using SPSS version 18.

RESULTS

Thirteen (13) of the one hundred-nineteen (119) patients included in the study had renal calculi confirmed by USG data. The prevalence of nephrolithiasis detected by USG was 10.9% in our AS patients. One hundred-six (106) patients had no history of renal stones and no compatible renal stones in USG. There was no difference in age, gender, HLA-B27 positivity between AS patients with and without renal stone ($p>0.05$). Disease duration was significantly higher in patients with renal stone (nephrolithiasis (+): 18.39±8.72 years, nephrolithiasis (-): 12.02±8.43 years, $p=0.01$). Demographic characteristics of the patients are presented in Table 1.

There was no significant difference in the serum calcium, phosphorus, Vitamin-D, parathormone and urinary calcium excretion results obtained in the same date of USG evaluation of patients in both groups (>0.05) (Table 2).

There was no significant difference in terms of BASFI between two groups (Table 3). The BASMI total score was significantly higher in the group of renal stone positive patients. Although no significant difference was observed between two groups in terms of chest expansion, lateral spinal flexion, modified Schober test, intermalleolar distance in BASMI subscale, tragus-wall distance was significantly increased and cervical rotation values were significantly decreased in patients with renal stone.

mSASS values were 39.08±22.72 in patients with renal stone and 32.09±16.76 in the other group. There was no singificant difference in terms of mSASS between two groups ($p=0.244$) (Table 4).

Table 3. The relationship between nephrolithiasis and BASMI subscale

	Chest expantion (cm)	Cervical rotation (degree)	Tragus to wall distance (cm)	Lateral spinal flexion (cm)	Modified schober test (cm)	Intermalleolar distance (cm)
Nephrolithiasis (-)	3.79± 1.71	61.09±22.41	16.23±5.58	11.24±6.26	4.13±2.06	93.47±19.13
Nephrolithiasis (+)	3.04±1.68	42.04±27.30	19.68±5.94	7.83±5.05	3.29±1.80	90.88±25.12
p	0.156	**0.01***	**0.02***	0.07	0.20	0.86

BASMI: Ankylosing Spondylitis Mobility Index; *p<0.05.

Table 4. The relation of nephrolithiasis with BASMI, BASFI, BASDAI and mSASS

	BASMI	BASFI	BASDAI	mSASS
Nephrolithiasis (-)	3.50±2.45	3.11±2.30	3.69±2.34	32.08±16.76
Nephrolithiasis (+)	5.17±2.44	3.28±2.77	3.17±2.75	39.08±22.72
p	0.02*	0.93	0.40	0.24

BASMI: Ankylosing Spondylitis Mobility Index; BASFI: Ankylosing Spondylitis Functional Index; BASDAI: Ankylosing spondylitis disease activity Index; mSASS: Modified Stoke Ankylosing Spondylitis Spinal Score; *p<0.05.

DISCUSSION

Considering the results of our study in general, the frequency of renal stones was found to be 10.9% in our AS patients. Presence Renal stones were correlated with mobility indices (BASMI) and were more common in AS patients with longer disease duration.

Extra-articular involvement is common in inflammatory diseases. Although renal involvement has been shown in many studies in AS, the number of studies investigating the coexistence of renal stone in AS is very limited [7-13].

The frequency of renal stones in our AS patients was 10.9%. Our results were compatible with other studies. A significantly higher prevalence of urolithiasis in AS patients (11.7%) versus normal population (5.7%) was reported by Fallahi et al [13]. Korkmaz et al reported that renal stones were more common in patients with AS (20%) than Behçet's disease (5.5%) and healthy controls (3.3%) [4]. They found renal stone more common in their AS patients with longer disease duration. Canales et al. reported the increased frequency of renal stones in patients with spondyloarthropathies (29%) versus rheumatoid arthritis (12%) [23].

On the contrary, Incel et al. reported no difference in frequency of renal stone between AS patients and normal population. It maybe related with the low number of patients in their study [24].

Many factors such as; spinal immobilization, presence of inflammatory cytokines, new bone formation and prolonged use of NSAIDs have been associated with alteration in calcium metabolism [15]. On the other hand there are many factors that contribute to stone formation process in AS. The duration of disease, the effect of disease such as; immobility and treatment process, urinary tract infection, changes in urinary pH, urostasis, metabolic diseases, congenital abnormalities, heredity, dietary, climate and occupation [25].

Although unknown etiology, the formation of stones requires the complex integration of numerous factors. Resorlu et al. reported that 80-90% of the renal stones in patients with AS were calcium-based stones supporting the possibility of problem primarily due to calcium metabolism [10].

It is stated that osteopenia associated with impairment of calcium metabolism in AS, increase the frequency of calcium-induced renal stones. Here, with the pathological process of resorption, the predominancy of

formation phase in the bone cycle could also affect the formation of renal stones [24].

In a recent prospective study, Gönüllü et al. found significantly higher level of blood calcium at the baseline in AS patients with renal stone compared with AS patients without renal stone [11]. Although this study didn't reach statistical significance, they also found high urinary calcium levels compared with patients who don't have stones. They concluded that a subgroup of AS patients tend to have high blood and urinary calcium and that these biochemical abnormalities and other factors might be responsible for the development of urolithiasis [11]. Our study was not in line with their trial as we couldn't find any significant difference in blood level of calcium, phosphorus, Vitamin-D, parathormone and urinary calcium excretion.

Lui et al. found functional disability (BASFI) and disease activity (BASDAI) higher in AS patients with renal stones but not any significant difference was detected in mobility index (BASMI) [8]. They found a significant association with Crohn's disease in AS patients with urolithiasis [8]. Similarly Fallahi et al found a significantly higher BASFI, BASMI and BASDAI in their AS patients with urolithiasis [13]. There was not any significant difference in terms of BASFI and BASDAI in our study but in contrary, BASMI showed significantly worse value in AS patients with renal stone. It is stated that, the renal stone does occur in AS patients with long disease duration. Our results confirm this information as in our study the frequency of renal stone was found significantly higher in both AS patients with long disease duration and with low BASMI values which do occur in established patients.

The absence of difference in intermalleolar distance here may be related to the fact that osteoproliferation is more intense in spine than in the hips. Although there are apparent differences, the statistically insignificancy in chest expansion and Schober test, may be related to the late involvement of costocondral and costovertebral joints.

In contrast to general expectation in believing that renal stone accompanies AS cases with more severe radiographic damages and presumably poor prognosis, Lui et al. found no significant difference in terms of mSASSS in their AS patients with history of renal stone [8]. Although higher radiological score, Cansu et al. also didn't report any significant difference in AS patients with urolithiasis [9].

Our study was compatible with these two mentioned studies. Interestingly at the molecular level, an increased amount of bone-related proteins such as osteonectin (OSN), osteoprotegerin (OPN), bone sialoprotein (BSP), and transcription factors evolving in bone ossification have been found in epithelial kidney cell which can differentiate into an osteoblastic phenotype in pathogenesis of renal stone formation [26]. Although common features involving in pathogenesis of bone ossification and renal stone formation, the inconsistency of results suggests the other unknown factors and pathways should be researched in the future.

There were some limitations in our study. One of them was the retrospective design of the study. Nevertheless, despite the retrospective study, we found increased frequency of renal stone in AS patients parallel with the literature showing the reality of presence of urolithiasis in these patients which should be taken in consideration. The second one was the evaluation of mSASSS, which could be more valid if it had been done by two of our investigators instead of one. Finally, the third limitation was the patients' treatment data, which was not included in our study.

Conclusion

Evaluating all these data, we can easily conclude that the frequency of renal stones is increased in AS patients. Especially AS patients with longer disease duration and higher BASMI scores are more susceptible to renal stones and the evaluation of nephrolithiasis should not be forgotten in such patients. It is important to point out that the results of this type of studies would be more reliable if the study takes part in large patient groups and population-based prevalence.

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