








Nephrolithiasis in ankylosing spondylitis and its relationship with disease assessment scales

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ABSTRACT

OBJECTIVE: The aim of this study was to investigate the frequency of renal calculi in patients with ankylosing spondylitis (AS) and to determine its relationship with disease assessment variables.

METHODS: The study was designed retrospectively, and it included a cohort of 320 patients with AS diagnosed using the Modified New York Criteria. A total of 119 patients who underwent renal ultrasonography (USG), in who the erythrocyte sedimentation rate, C-reactive protein, blood calcium, phosphorus, Vitamin D, parathormone, and urinary calcium excretion were measured, and who also had lateral cervical and lumbar radiography in the same time period were extracted from the cohort. All patients' demographic characteristics and the results of blood and urine tests were recorded. The 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 of the 119 patients had renal calculi confirmed by USG data. The frequency of nephrolithiasis detected by USG was 10.9% in patients with AS. The disease lasted significantly longer in patients with renal calculi ([nephrolithiasis (+): 18.39±8.72 years; nephrolithiasis (-): 12.02±8.43 years, p=0.01]). The BASMI total score was significantly higher in the group of patients with renal calculi. 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 patients with AS compared to healthy population. Especially patients who had AS for a long time and higher BASMI values are more susceptible to renal calculi. It is important to point out that the results of this type of studies would be more reliable if the study is conducted on large patient groups and population-based prevalence.

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

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Ankylosing spondylitis (AS) is a chronic inflammatory disease with the predilection for the spine and sacroiliac joints, thus causing back pain and post-inactivity stiffness [1]. In addition, AS can manifest itself as peripheral arthritis and enthesitis, and it can also have extra-articular involvement such as the eye, lung, kidney, and heart [1]. The prevalence of AS is generally believed to be 0.1%–1.4%, and the gender disparity is reported as the male-to-female ratio of around 2:1 [2].

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

Several studies showing an increased incidence of renal calculi in patients with AS have been published [7–13]. Jacobsen et al. found the risk of nephrolithiasis in patients with AS to be more than twofold compared to the general population. The authors described nephrolithiasis as an extra-articular manifestation in AS and factors such as the male gender, history of inflammatory bowel disease, and previous history of kidney stones were significant and clinically important predictors of nephrolithiasis in patients with AS [12]. Furthermore, a recently published study from Taiwan with a large patient number assessed the risk of nephrolithiasis among patients with AS compared to matched general population. The percentages of newly diagnosed nephrolithiasis were 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 its etiology is unknown, the formation of calculi requires a complex integration of numerous factors, such as 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 to an increased level of cytokines, bone resorption, and increased bone turnover, a prolonged use of anti-inflammatory drugs and accompanied intestinal problems also play a role in calculi formation in AS [16].

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

MATERIALS AND METHODS

The study was designed retrospectively. A total of 320 patients with AS being followed by the “Activity Platform” were included in the study. The Activity Platform is comprised of 11 physiatrists from nine different centers in Turkey, showing a special interest in spondyloarthritis and rheumatoid arthritis, who have received a standardized training that included examination, an assessment of the questionnaire forms, and radiological grading performance of patients with AS. A total of 119 patients who had renal USG, erythrocyte sedimentation rate, C-reactive protein, 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 the AS cases were diagnosed according to the Modified New York Criteria [17]. The sociodemographic characteristics (age, gender, and disease duration), clinical features, and comorbidities were recorded. Patients who had a history of hypertension, diabetes, and cardiovascular disease were excluded. Patients were identified as “renal calculi positive” with calculi-compatible images and “renal calculi negative” if they were calculi incompatible. A written informed consent was obtained from each patient.

The patients were assessed using the Assessment of SpondyloArthritis International Society recommendations for core outcome domains in the AS assessment [18]. Turkish versions of Bath AS Disease Activity Index (BASDAI) [19], Turkish version of Bath AS Functional Index (BASFI) [20], and Bath AS Metrology Index (BASMI) [21] were evaluated for disease activity, functional status, and mobility, respectively. The BASMI subscale was calculated using the chest expansion, cervical rotation, lumbar flexion, lumbar lateral flexion, and intermalleolar distance evaluations. A Modified Stoke Ankylosing Spondylitis Spinal Score (mSASSS) [22] was used for the radiological 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 the same researcher (R.Ç.) experienced in grading the mSASSS

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

[22]. The frequency of nephrolithiasis in our patients was assessed by comparing it to Turkish population nephrolithiasis data.

Statistics

We used a chi-squared and/or Fisher's exact test to compare categorical variables such as nephrolithiasis between the patients with AS and normal population. An independent two-samples t-test was used to compare continuous variables such as mSASSS, BASFI, BASMI, and BASDAI scores between the patients with AS with and without nephrolithiasis. In each case, a p-value <0.05 was considered to be statistically significant. A data analysis was performed using the SPSS version 18.

RESULTS

Thirteen of 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 patients with AS. One hundred and six patients had no history of renal calculi and no compatible renal calculi in USG. There was no difference in age, gender, and the HLA-B27 positivity between AS patients with

and without renal calculi ($p>0.05$). Disease duration was significantly higher in patients with renal calculi (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 on the same date of USG evaluation in patients from both groups (>0.05) (Table 2).

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

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

TABLE 3. The relationship between nephrolithiasis and BASMI subscale

	Chest expansion (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 calculi was found to be 10.9% in our patients with AS. The presence of renal calculi was correlated with mobility indices (BASMI) and were more common in AS patients with a longer disease duration.

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

The frequency of renal calculi in our patients with AS was 10.9%. Our results were compatible with other studies. A significantly higher prevalence of urolithiasis in patients with AS (11.7%) versus normal population (5.7%) was reported by Fallahi et al. [13]. Korkmaz et al. reported that renal calculi were more common in patients with AS (20%) than with Behçet's disease (5.5%) and healthy controls (3.3%) [4]. They found renal calculi to be more common in their patients who had AS for a longer time. 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 the frequency of renal calculi in patients with AS and normal population. It may be related with the low number of patients in their study [24].

Many factors such as spinal immobilization, the presence of inflammatory cytokines, new bone formation, and a prolonged use of nonsteroidal anti-inflammatory agents has been associated with alterations in calcium metabolism [15]. On the other hand, there are many factors that contribute to the process of calculi formation in as duration of the disease, the effect of conditions such as the immobility and treatment process, urinary tract infection, changes in urinary pH, urostatics, metabolic diseases, congenital abnormalities, heredity, dietary, climate, and occupation [25].

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

It is stated that osteopenia associated with calcium metabolism impairment in AS increases the frequency of calcium-induced renal calculi. Here with the pathologi-

cal process of resorption, the predominance of formation phase in the bone cycle could also affect the formation of renal calculi [24].

In a recent prospective study, Gonullu et al. found a significantly higher level of blood calcium at the baseline in AS patients with compared to AS patients without renal calculi [11]. Although this study did not reach statistical significance, the authors also found high urinary calcium levels compared to patients who did not have calculi. 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 could not find any significant difference in the blood level of calcium, phosphorus, Vitamin D, parathormone, and urinary calcium excretion.

Lui et al. found a functional disability (BASFI) and disease activity (BASDAI) to be greater in AS patients with renal calculi, but no significant differences were detected in the 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 on contrary, BASMI showed to be significantly worse in patients with AS who had renal calculi. It has been stated that renal calculi do not occur in AS patients with long disease duration. Our results confirm this piece of information, as in our study, the frequency of renal calculi was found to be 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 the intermalleolar distance may be related to the fact that osteoproliferation is more intense in the spine than in the hips. Although there are apparent differences, the statistical insignificance in the chest expansion and the Schober test may be related to the late involvement of costochondral and costovertebral joints.

In contrast to general expectation in believing that renal calculi accompanies AS cases with more severe radiographic damages and a presumably poor prognosis, Lui et al. found no significant difference in terms of mSASSS in their AS patients with a history of renal calculi [8]. Although there was a higher radiological score, Cansu et al. also did not report any significant differences

in AS patients with urolithiasis [9].

Our study was compatible with these two studies. Interestingly, at the molecular level, an increased amount of bone-related proteins such as osteonectin, osteoprotegerin, bone sialoprotein, and transcription factors evolving in bone ossification have been found in the epithelial kidney cell, which can differentiate into an osteoblastic phenotype in the pathogenesis of renal calculi formation [26]. Although common features are involved in the 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 to our study. One of them was its retrospective design. Nevertheless, despite the retrospective study, we found an increased frequency of renal calculi in patients with AS parallel with the literature, showing the presence of urolithiasis in these patients, which should be taken into consideration. The second one was the evaluation of mSASSS, which could have been more valid if it had been done by two of our investigators instead of one. Finally, the third limitation were the patients' treatment data, which were not included in our study.

Conclusion

Evaluating all these data, we can easily conclude that the frequency of renal calculi is increased in patients with AS. Especially, patients who had AS for a long time and higher BASMI scores are more susceptible to renal calculi, 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 are more reliable if the study includes large patient groups and population-based prevalence.

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