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Original Article

Sulfasalazine-associated Nephrolithiasis in Patients with Rheumatoid Arthritis and Ankylosing Spondylitis

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ABSTRACT

Background Sulfasalazine (SSZ) is an anti-inflammatory and immunomodulatory drug used to treat many inflammatory diseases. Bacteria in the gut metabolize SSZ to active 5-aminosalicylic acid and inactive sulfapyridine. Sulfapyridine can crystallize in the kidney. We aimed to investigate the frequency of nephrolithiasis in patients who were diagnosed with rheumatoid arthritis (RA), ankylosing spondylitis (AS) and who received SSZ treatment retrospectively.

Material and Methods We retrospectively analyzed the files of AS and RA patients in the rheumatology outpatient clinic between 2009 and 2018. We identified patients who underwent kidney ultrasonography at least six months after initiation of SSZ. One hundred six patients and 50 healthy adults were included in the study.

Results Only eight patients (6 AS, 2 RA) had nephrolithiasis on ultrasonography, but none in the control group (p=0.046). In logistic regression analysis, no correlation was found between gender, age, vitamin D, parathyroid hormone, and urinary calcium excretion with SSZ use (p>0.05).

Conclusion Although, it is noteworthy that these patients are prone to stone formation for various reasons. Therefore, paying attention to the patient's hydration while using these drugs may prevent such side effects.

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Introduction

Sulfasalazine (SSZ) is an anti-inflammatory and immunomodulatory drug used in the treatment of rheumatoid arthritis (RA), ankylosing spondylitis (AS) and inflammatory bowel diseases (IBD). The anti-inflammatory effects of SSZ are mediated by 5- aminosalicylic acid (5-ASA).[1] The anti-inflammatory effect of 5- ASA in IBD is enhanced by its concentration in the intestinal lumen. Therefore, 5-ASA is combined with substances such as sulfapyridine to reduce intestinal absorption to inhibit metabolism. Bacteria metabolize SSZ in the gut to active 5-ASA and inactive sulfapyridine. Following degradation, sulfapyridine passes into the bloodstream while a large amount of 5-ASA remains in the intestine. Approximately 90% of sulfapyridine and its metabolites are excreted in the kidneys and can crystallize. The best-known side effects of SSZ are nausea-vomiting, skin rashes and fever.[2-4] SSZ's renal adverse effects are less than mesalazine, another drug commonly used in IBD.[5,6] In this study, we aimed to investigate the frequency of nephrolithiasis in patients with the diagnosis of RA and AS and who received SSZ treatment retrospectively.

Material and Methods

The files of patients with AS and RA who were followed in the rheumatology outpatient clinic between 2009-2018 were reviewed. Those who had renal ultrasonography (USG) for reasons other than the suspicion of nephrolithiasis (such as hepatosteatosis and choledocholithiasis) at least six months after SSZ was initiated were planned to be included in the study.

Demographic characteristics of the patients, such as age, gender, comorbidity, and medications, were recorded from the files. Laboratory values such as calcium, phosphorus, uric acid, vitamin D, parathyroid hormone (PTH) and urinary calcium excretion (routinely requested when evaluating osteoporosis in our clinic) were recorded from the electronic database. Those with a history of nephrolithiasis, a family history of kidney stones, kidney disease, metabolic disease, chronic diarrhoea, vitamin C, vitamin D, diuretic users, and sickle cell anaemia were excluded from the study. It was given to SSZ at a dose adjusted for body surface area. The control group consisted of healthy individuals who underwent abdominal USG except for the suspicion of nephrolithiasis and who did not use any medication. Permission was obtained from the local ethics committee for the study. Consent of the patients was obtained.

Statistical Analysis

Data were evaluated with SPSS (version 25.0, SPSS Inc, Chicago, IL). The control and study groups were compared in terms of factors that may pose a risk for nephrolithiasis. Chi-square for categorical data and t-test or Mann-Witney U test for continuous data were chosen related to the data distribution. Spearman correlation analysis was performed to detect factors associated with nephrolithiasis. Regression analysis was performed to determine the factors affecting the occurrence of nephrolithiasis. If the p-value was less than 0.05, it was considered significant.

Results

One hundred and six patients and 50 healthy adults were included in the study. The characteristics of the patients and the control group were shown in Table 1. Nephrolithiasis was seen in 8 patients (6 AS, 2 RA), although it was not detected in any patient in the control group (p=0.046).

In correlation analysis, no relationship was found between the presence of nephrolithiasis and gender, age, calcium, phosphorus, uric acid, vitamin D, PTH, urinary calcium excretion and time of SSZ use (p>0.005). The time between SSZ usage and USG was 50.85±76.54 months. There was no correlation between the duration of SSZ usage and the detection of nephrolithiasis (p=0.213). There was no correlation between nephrolithiasis and related factors in the logistic regression analysis performed with the model created with gender, age, vitamin D, PTH, urinary calcium excretion, and SSZ usage (p>0.05) (*Table 2*).

Table 2. Comparison of demographic and laboratory data of patient and control groups.

Variables	Patients (n: 106)	Control (n:50)	P-value
Age (year)	55.2±12.2	52.4±6.8	0.073
Gender (Male/Female)	30/76	16/34	0.636
Diabetes mellitus	14 (13.2%)	6 (12%)	0.833
Hypertension	30 (28.3%)	9 (18%)	0.430
Urea (mg/dL)	28.7±10.2	27.2±7.9	0.699
Creatinine (mg/dL)	0.79±0.22	0.68±0.07	0.000
Calcium (mg/dL)	9.6±0.4	9.5±0.3	0.063
Phosphorus (mg/dL)	3.7±2.3	4.8±6.4	0.438
Uric acid (mg/dL)	4.0±1.0	4.3±1.2	0.588
Parathyroid hormone (mg/dL)	56.5±20.8	62.1±30.6	0.431
25-OH-D (ng/mL)	19.7±9.5	21.5±8.6	0.053
Spot urine calcium/creatinine ratio	0.10±0.06	0.08±0.05	0.270
Nephrolithiasis	8 (7.5%)	0 (0%)	0.046

Data were given as mean±SD (standard deviation) or n (%).

Table 2. Multivariate regression analysis to identify the relationship between nephrolithiasis and SSZ usage after adjusted for gender, age, vitamin D, parathyroid hormone and urinary calcium excretion.

	Presence of nephrolithiasis		
	Beta	P-value	95% Confidence interval
SSZ-usage	–0.928	0.360	–0.002 to 0.001

Discussion

SSZ is an agent frequently used in patients with AS and RA. SSZ-related nephrolithiasis is reported as case reports. Our study included 106 patients, and we found increased kidney stone formation. However, in the regression analysis, we could not show the relationship between nephrolithiasis and SSZ. This may be due to the limited number of patients and the limited follow-up period.

Of all kidney stones, 1-2% are medication-related. SSZ is one of the drugs that can rarely cause kidney stones. Compared to mesalazine, SSZ rarely causes kidney adverse effects. Sulfa drugs possess low water solubility and can precipitate in renal tubules.[7] Dehydration and low urinary pH pose a risk for sulfonamide stones.[8] It has been reported that kidney stones consisting of sulfadiazine are detected in low density on computed tomography and cannot be visualized in USG.[9] USG is insufficient to exclude this disease because of failure to demonstrate sulfa-drug-related renal stones radiologically in patients treated with SSZ. However, USG was used in our study since there were no other signs and symptoms related to stones, such as flank pain,

hematuria, and impaired renal function.

Studies have found that the frequency of urolithiasis increases in patients with AS compared to the normal population. In the study by Fallahi et al.[10] in 2012, the frequency of urolithiasis among patients with AS was 11.7%, while this rate was 5.7% in the normal population. In Sweden, Jakobsen et al.[11] studied a large patient cohort, which included 8,572 AS patients and 39,639 healthy individuals. They found the unadjusted hazard ratio of urolithiasis for AS compared to the healthy population of 2.4 (95% CI 2.1-2.9).[11] In Turkey in 2015, Resorlu et al.[12] detected urolithiasis in 18.4% of AS patients and 10.4% of controls. Eliah et al.[13] claimed that limited spinal mobility and pyelo-pelvic position in AS patients might be an underlying predisposing factor for urolithiasis. Korkmaz et al.[14] suggested that one of the mechanisms responsible for the development of urolithiasis in AS may be intestinal inflammation as a result of enteric hyperoxaluria. Bone turnover and bone resorption activated by inflammatory cytokines can also cause hypercalciuria.[15,16] Korkmaz et al.[17] found that urinary calcium levels increased in AS patients with urolithiasis, but the difference was not statistically significant.

In our patient group, 6 of 8 patients with stones had AS, and 2 had RA. None of our patients had signs of IBD. In addition, we could not find a relationship between the duration of SSZ use and the detection of nephrolithiasis (p=0.213).

Conclusions

No information was found in the literature regarding the relationship between SSZ and the occurrence of nephrolithiasis. The advantage of our study was that we had vitamin D, PTH, and urinary calcium excretion values, as they were routinely requested in our clinic when evaluating osteoporosis. However, our study had some limitations. The follow-up period of the patients was short, and the stones were not assessed with computed tomography. Since kidney stone analyzes were not performed in our study, the content of the stones could not be determined. However, it is noteworthy that these patients are prone to stone formation for various reasons. Therefore, paying attention to the patient's hydration while using these drugs can prevent such side effects. More extensive, controlled studies, including stone analysis, are needed on this subject.

Conflict of interest

The authors declare that they have no conflict of interest.

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There are no funding sources to declare.

Ethical Approval

For this study, approval was obtained local ethics committee with the decision number 2018/017.

Authors' Contribution

Study Conception, Literature Review, Critical Review, Data Collection and/or Processing, Statistical Analysis and/or Data Interpretation, Manuscript preparing held by all authors.

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