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Increased frequency of ultrasonographic findings suggestive of renal stones in patients with ankylosing spondylitis

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ABSTRACT

Objective. *To determine the frequency of hypercalciuria and renal stones in ankylosing spondylitis (AS) sufferers.*

Methods. *This study involved 83 consecutive AS patients (21 female, 62 male; mean age 36.7 yr), 72 consecutive Behçet's disease (BD) patients (29 female, 43 male; mean age 37.7 yr) as disease control and 92 healthy control (HC) (26 female, 66 male; mean age 32.9 yr.) Twenty-four hour urine analyses for urinary calcium and uric acid levels were performed in each patient. Likewise, blood samples for erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), parathyroid hormone (PTH), calcium and uric acid evaluation were taken. Renal ultrasonography to evaluate the presence of renal stone was performed in patients with AS, as well as in the BD patients and HC individuals after a fasting period of 12 hours.*

Results. *20 of the 80 (25%) patients with AS were diagnosed with renal stones. Only 4/72 (5.5%) BD patients, and 3/98 (3.3%) HC individuals had renal stones by ultrasonography. AS patients had a significantly higher frequency of renal stones compared with BD ($p < 0.001$) and HC ($p < 0.0001$). AS patients with renal stones were much older and their disease duration was much longer in comparison with AS patients without renal stones. Ultrasonographic and laboratory findings did not correlate. The number of AS patients with hypercalciuria who had renal stones was higher than that of AS patients who did not have renal stones ($p < 0.01$). There was a negative correlation between acute phase response and spinal mobility.*

Conclusion. *Renal stone prevalence was found to increase in AS patients. The likelihood of renal stone formation was also found to increase with the extension of the disease duration of AS sufferers.*

Introduction

Ankylosing spondylitis (AS) is an inflammatory disease with a main involvement of the spine and sacroiliac joints. Sacroiliac joint pain and backache are typical features of AS, and spine ankylosis is progressively induced by specific ossifications. Osteoporosis (OP) is a complicating feature of this disease (1,2), and there is some evidence of a certain degree of osteopenia in AS; patients with established AS had a higher incidence of vertebral fractures (3,4) and a decreased bone mineral density of the spine and the femoral neck (5). Osteoporosis was also observed in early AS patients without syndesmophyte formation (6).

The aetiology of OPremains controversial; a reduced range of spinal movement in ankylosing patients, but the treatment given or the inflammatory cytokines could contribute to this bone loss (1). It has been reported that inflammatory cytokines such as IL-6, IL-1, TNF-alpha not only play a role in the inflammatory process of AS, but are involved in the osteoporosis of AS as well (6, 7). It is well known that TNF-alpha and IL-1 are among the most powerful stimulators of bone resorption and are well-recognised inhibitors of bone formation (8). They may also result in hypercalciuria (8). Taken together, theoretically, hypercalciuria may be expected in AS patients due to both immobilization and inflammatory cytokines. There are conflicting studies as to whether or not hypercalciuria exist in patients with AS (1, 9). These conflicting results may be explained by differences in stages of disease activity, in disease duration and in clinical features. In this study, we aimed to determine the presence of hypercalciuria in AS patients and to study the frequency of renal stone, which is highly associated with hypercalciuria, by ultrasonography.

Patients and methods

Eighty-three consecutive AS patients (21 female, 62 male; mean age 36.7 yr, range 16-70), 72 consecutive Behçet's disease (BD) patients (29 female, 43 male, mean age 37.7 yr, range 17-60), and 92 healthy individuals (doctors and hospital staff) (26 female, 66 male; mean age 32.9 yr, range 24-57) were included in the study. These were accepted as healthy individuals if they did not have any systemic metabolic diseases, or did not take drugs likely to affect their calcium metabolism, or did

not have a familial or an individual history of renal stone discharge. Since the usage of steroids and some agents used for osteoporosis are less common in BD compared with some other diseases as rheumatoid arthritis, we chose BD patients as the disease control, which helped form a much easier age and sex matching between BD and AS.

AS and BD patients were diagnosed according to relevant classification criteria (10, 11). Patients with renal failure, diabetes mellitus, psoriasis and metabolic diseases were not considered for the study. The patients who were on steroid or anti-osteoporosis drugs were not included in the study.

Renal ultrasonography (USG) to evaluate the presence of renal stone were performed in patients with AS and the control patients after fasting for 12 hours. All the sonographic examinations were performed with the same equipment (SDS-340 Eccocee, Toshiba, Japan) and the same frequency probe (3.5 MHz) by an experienced radiologist (NA) who was uninformed about the patients'clinical status. Renal stones were defined as hyperechoic spots with acoustic shadows. All the subjects were queried for any history of renal stone discharge or renal stone removal. If those experiencing a stone discharge had seen the stone being discharged, they were defined as spontaneous stone discharge (SSD). Renal colic is defined as an excruciating and intermittent pain originating in the flank and radiating across the abdomen along the course of the ureter. For the patients undergoing renal stone removal, the type of removal process was ascertained from either the patients themselves or from the hospital records only.

Twenty-four hour urine studies for urinary calcium and uric acid levels were made in each patient. Blood samples for erythrocyte sedimentation rate, C-reactive protein, parathyroid hormone (PTH), calcium and uric acid evaluation were also taken. If urinary calcium excretion was more than 250 mg/24h for women and 300 mg/24h for men, it was accepted as hypercalciuria. Schober's test and chest expansion test were done as described before (12). Hematuria was defined as 3 or more erythrocytes per high power field on at least 2 separate occasions. Stone analysis was made by X-ray powder diffraction method.

Statistically significant differences were determined by ANOVA followed by a post-hoc multiple comparison test. Pairs of groups were compared using Student's t-test for normally distributed continuous variables. The correlation between variables was investigated by the Spearman rank order correlation procedure. The chi-squared test or Fisher's exact test was used for categorical variables as needed. A p values < 0.05 was considered statistically significant.

Table I. Some clinical and laboratory features of ankylosing spondylitis patients and control.

	AS (n = 83)	BD (n = 72)	HC (n = 92)
Age (mean ± SD)	36.7 ± 10	37.7 ± 8.9	32.9 ± 7.4[a]
Sex (F/M)	21/62	29/43	26/66
Renal stone by USG	20 /80 (25%)[b]	4/72 (5.5%)	3/92 (3.3%)
Hematuria	34 (42%)[c]	9 (12.5%)	8 (8.7%)
Serum calcium (n = 9-11 mg/dl)	9.7 ± 0.4	9.8 ± 0.5	9.9 ± 0.3
Serum uric acid (n < 7 mg/dl)	4.9 ± 1.3	5.1 ± 1.54	5.2 ± 1.5
Urinary calcium (mg/24h)	167 ± 137	153 ± 113	189 ± 122
Urinary uric acid (mg/24h)	562 ± 212	509 ± 207	590 ± 246
Serum PTH (n = 15-65 pg/ml)	34 ± 24	32.5 ± 21	34.9 ± 16
ESR (n < 20 mm/h)	32 ± 3[d]	13 ± 1.9	6.9 ± 0.7
CRP(n < 0.8 mg/dl)	1.9 ± 0.4[e]	0.6 ± 0.1	0.26 ± 0.5

[a] $p < 0.001$ HC v AS and BD; [b] $p < 0.001$ AS v BD; $p < 0.0001$ AS v HC; [c] $p < 0.0001$ AS v BD and HC; [d] $p < 0.001$ AS v BD and HC; [e] $p < 0.01$ AS v BD, $p < 0.001$ AS v HC.
ESR: Erythrocyte sedimentation rate; CRP: C-reactive protein; PTH: Parathyroid hormone; N: Normal level.

Table II. Comparison of some clinical and laboratory results of AS patients with/without renal stones.

	AS pts with renal stones (n = 30) (Group I)	AS pts without renal stones (n = 53) (Group II)
Age (mean ± SD)	40 ± 8[a]	34 ± 11
F/M	9/21	12/41
Disease duration (year)	16.8 ± 1.7[b]	8 ± 1
ESR (mm/h)	30 ± 4.5	33 ± 4
CRP(mg/dl)	1.32 ± 0.3	2.3 ± 0.6
Serum PTH (pg/ml)	40 ± 31 (4; 13%)	31 ± 19 (2; 3.75%)
Serum calcium (mg/dl)	9.7 ± 0.4 (1; 3%)	9.8 ± 0.5 (1; 2%))
Serum uric acid (mg/dl)	4.9 ± 1.3 (3; 10%)	5.1 ± 1.5 (3; 5.6%)
Urinary calcium (mg/dl)	182 ± 135 (8; 27%)[c]	159 ± 139 (3; 6%)
Urinary uric acid (mg/dl)	569 ± 240 (4; 13%)	558 ± 201 (4; 7.5%)
Hematuria	19; 63%[d]	15; 28%
Schober test (n >10-15 cm)	10-11.7 ± 1.8	10-12.3 ± 1.8
Chest expansion (n >5 cm)	2.5 ± 0.8[e]	3.1 ± 0.2

[a] $p < 0.009$ group I v group II; [b] $p < 0.001$ group I v group II [c] $p < 0.01$ group I v group II; [d] $p < 0.006$ group I v group II; [e] $p < 0.02$ group I v group II;.
Parenthesis refer to number and percentage of patients with levels above normal.

Results

A matching for age distribution between AS and BD groups could be achieved but it could not be provided for HC. No significant difference was found between groups according to their sex distribution (Table I).

Eighty of the 83 AS patients underwent renal USG. 20 of these 80 patients were diagnosed as having renal stone (25%). Only 4 of 72 BD patients (5.5%), 3 of 98 HC patients had renal stones (3.3%). Patients with AS had a significantly higher incidence of renal stones compared with BD ($p < 0.001$) and HC ($p < 0.0001$) (Table I).

Among the 20 patients with AS with current renal stones, 14 patients had one or more renal colic histories; 12 patients had a history of SSD; 9 patients were both renal colic and SSD. Another 10 patients with AS without present renal stone suffered from either SSD (4 pts) or renal colic (4 pts) or from both (2 pts). Consequently, 30 patients with AS (36%) were renal stone sufferers. While 4 BD patients with renal stone also had a history of SSD, 2 BD patients without renal stone had a history of renal colic. Each 3 HC individual with current renal stone had a history of a renal colic. There was no history of SSD or of renal colic in HC individuals without renal stone.

No close relationship was found between the presence of renal stone and biochemical parameters in both AS and control groups. Although urinary calcium excretion was higher in AS patients with renal stones than in those without, it did not reach a statistical significance (Table II). The number of patients with hypercalciuria was higher in AS patients with renal stone than those without ($p < 0.01$) (Table II).

Schober's test and chest expansion of the renal stone formers (30 pts) were far more limited than those without renal stone formers. However, only chest expansion was of some statistical significance ($p < 0.02$) (Table II). As far as the age and the disease duration of the renal stone formers are concerned, they were both far older and had a much longer disease duration (Table II) ($p < 0.009$, $p < 0.001$, respectively).

There was a negative correlation between chest expansion and CRP levels ($r = -0.35$, $p < 0.02$) and between ESR and Schober's test ($r = -0.23$, $p < 0.04$) in AS patients. We did not observe any correlation between acute phase response and renal stone frequency in AS patients. No difference was found in terms of acute phase response between group I (AS patients with renal stone) and group II (AS patients without renal stone) (Table II).

34 patients with AS had hematuria (42%). Hematuria was significantly more frequent than those in BD and HC ($p < 0.0001$) (Table I). 30 patients altogether were determined to be renal stone sufferers when allowing for all the AS sufferers, 19 of whom had hematuria (63%). Also, 16 of the 20 patients with present renal stone had hematuria (84%). On the other hand, 15 of the AS patients without renal stone had hematuria (28%). As was presumed, hematuria was significantly higher in the stone formers than those without stone formers ($p < 0.006$) (Table II).

No significance relationship was determined to exist between using sulfasalazine or nonsteroid anti-inflammatory drugs and renal stone formation ($p = 0.7$, $p = 0.5$, respectively). Renal stones of two patients with AS were analysed, as a result of which they were diagnosed as having calcium oxalate.

Discussion

During the application of renal USG, we may have missed out on small stones and stones present in the lower urinary tract. With this possibility in mind, we found that the frequency of renal stone in AS patients was higher than in BD and HC. In a nationwide surveyed conducted in 14 provinces on 1500 individuals in Turkey, an overall prevalence was found to be 14.8% for urinary stone diseases (13). The individuals in this study were only interviewed for their spontaneous stone discharge rather than being investigated thoroughly. In this study, low socioeconomic and educational statuses were determined to be associated with a higher renal stone prevalence rate. The prevalence of urolithiasis among illiterates and/or primary school graduates was found to be 19%, but that was only 8.5% in university graduates. Our HC individuals consisted of doctors and hospital staff, for whom the stone frequency was found to be 3.3%. The cause of this difference may have resulted from the selective selection of a restricted number of HC individuals who were obtained from a limited area. The first study into the frequency of renal stones in AS was made by Mladenoviç 30 years ago in Croatia and renal stone prevalence was found to be 8.5% among 400 AS patients (14). The renal stone prevalence in the general population was 1.9% at that time. More than 80% of the patients who had renal stones had also spinal ankylosis and osteoporosis. Mladenoviç *et al.* suggested spinal ankylosis and hip joint ankylosis to be risk factors for renal stone formation.

Elian *et al*. studied the urological manifestations of 22 AS patients (15). The renal stone frequency was found to be 13.6% in this study. They suggested that the changes in spinal mobility and pyelo-pelvicial position may result in renal stone formation in AS.

Two risk factors could contribute to renal stone formation in AS patients, which are immobilization and inflammatory cytokines. Immobilization and inflammatory cytokines may lead to both osteoporosis and hypercalciuria (7,8,16). It has been reported that inflammatory cytokines such as IL-6, IL-1, TNF-alpha play a role in the inflammatory process of AS, and there is a close relationship between their high levels and severity of the AS (6). We did not evaluate cytokines levels of our cases. We only determined their acute phase responses reflecting cytokines stimulation. A negative correlation was found between spinal mobility, especially for chest expansion, and acute phase response. As is well known, as the age of AS patients progresses, spinal immobility also increases (17,18). Our results seem to support this observation because chest expansion and Schober's test were more restricted in long-time AS sufferers of AS. Moreover, the frequency of renal stone and hypercalciuria was higher in these patients.

In our series, 3 AS patients with current renal stone who had severe spinal deformity in addition to hip joints involvement had undergone a total hip joint replacement operation. These patients also had a history of 10 times SSD.

Hematuria can be seen in the course of AS ranging from 17% to 22.5% (19, 20). It has been shown that circulating Ig A containing immune complexes and Ig A nephropathy are the main reasons for the hematuria in AS. These studies have not reported the presence of renal stone to contribute to hematuria (19,20). Therefore, the reason for increased frequency of hematuria (42%) in our study, compared with those in the literature, might be a combination of increased frequency of renal stone and possible IgAnephropathy.

There are conflicting studies as to whether or not hypercalciuria exists in patients with AS (1,21,22). Most of these studies were cross-sectional. On the other hand, Lee *et al*. showed that urinary calcium excretion increased in AS patients over 15 months of follow-up period (23). Unfortunately, we also did not make series analysis in our cases and thus could not find any difference between groups in terms of hypercalciuria. Although urinary calcium excretion was higher in AS patients with renal stones than in those without, it did not reach a statistical significance. On the other hand, the number of the patients with hypercalciuria was much higher in AS patients with renal stones than those without. It is tempting to speculate that hypercalciuria can be seen in at least some patients with AS and its presence may yield renal stone formation.

The weak aspect of this study is that we could not investigate some important biochemical parameters for the evaluation of renal stone formation, such as urinary oxalate, citrate and magnesium excretion. Because urinary calcium excretion may change depending on the intake of oral calcium and sodium (24), the cut off we took may not be an optimal enough one. Another limitation to this study would be that a serial evaluation for biochemical parameters could not be made. We, therefore, believe that if further studies focus on the pathogenesis of the renal stone formation in AS patients, they could provide us with more valid results. Then, we may be able to give our patients some instructions for prevention of stone formation as far as their diet ingredient is concerned. We were able to work with only one sonographer in evaluating the presence of renal stone, though we know that working with a second one at the same time could have provided more valid results.

In conclusion, renal stone prevalence increased in our AS patients and the likelihood of renal stone formation increases with the extension of the disease period of AS patients. We suggest that determination and treatment of the precise predisposing factors could be an interesting subject for future studies. Serial biochemical analyses may yield more valid results for a better understanding of the true mechanism of renal stone formation in AS patients.

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