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Risk factors of calcium stone formation in patients with primary Sjögren's syndrome

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Abstract Distal renal tubular acidosis (dRTA), which occurs in patients with primary Sjögren's syndrome (SS), is a risk factor for the development of urolithiasis. Twenty-seven patients with SS were evaluated with respect to biochemical risk factors of calcium stone formation. Sixteen had no history of urolithiasis (group 1) whereas 11 had such a history (group 2). The stone composition was known for seven of the patients, and calcium phosphate was the major stone constituent in all of them. dRTA was present in all patients in group 2, and in 7 of the 16 patients in group 1. Hypocitraturia was common in both groups, and the urinary excretion of citrate did not differ between the two groups. There was a higher urinary excretion of calcium and urate in group 2 and this group also had a higher urine volume. The risk of forming a urine supersaturated with calcium oxalate (CaOx) expressed in terms of AP(CaOx)index(s), which is an approximate estimate of the ion-activity product of CaOx calculated for a 24-h urine volume of 1500 ml, was higher in stone formers. A similarly derived estimate of the ion-activity product of calcium phosphate, AP(CaP)index(s), was calculated for a urine pH of 7. Although AP(CaP)index(s) was not significantly higher in group 2, there was a good correlation between AP(CaP)index(s) and AP(CaOx)index(s). We conclude that the urine composition in patients with SS, dRTA and urolithiasis is similar to that of other stone-forming patients with dRTA, and recurrence preventive therapy can be designed as for these patients.

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Introduction

Distal renal tubular acidosis (dRTA), which is a risk factor for the development of urolithiasis [6], occurs in 15–33% of patients with primary Sjögren's syndrome (SS) [6, 28, 36]. In addition to the xerostomia and keratokonjunctivitis sicca that characterize this autoimmune disease the kidneys can also be involved. Renal histopathology in SS patients with renal disease has mostly shown a chronic tubulointerstitial nephritis (TIN) [27, 35]. Recently we found a decreased rate of glomerular filtration in 9 of 27 patients with SS [10]. During our studies of the renal function in patients with SS the question was raised why some patients with dRTA had a history of urolithiasis whereas others had no such history, and whether the course of stone disease can be predicted. The purpose of this investigation was to study different risk factors of calcium stone formation [1, 6, 7, 13, 14, 15, 22, 29, 30, 32] in these patients.

Material and methods

Twenty-seven women with SS from the Departments of Rheumatology and Nephrology, Linköping, were included in the study after informed consent. Sixteen patients were without a history of urolithiasis (group 1), whereas 11 patients had formed at least one stone (group 2). Patients were referred to the latter group if stones were radiographically demonstrated, or if there was a history of stone passage. The mean age of the patients in group 1 was 66 years (range 44–81 years), and in group 2 56 years (range 42–79 years). The criteria used for diagnosis of SS were those described by Daniels and Talal [9], but three of the patients had only one of the ocular components of these criteria. A history of previous acute upper urinary tract infection (UTI) was present in one of the patients in group 1 and in four of the patients in group 2 (no significant

difference). Only one patient had recurrent infections and bacteriuria.

Urinary calculi were analysed with a quantitative wet chemical method [18]. Urine samples were collected during 24 h in bottles containing 15 ml of 6 mol/l hydrochloric acid. The samples were analysed with respect to their content of calcium (Ca), oxalate (Ox), citrate (Cit), magnesium (Mg), phosphate (P) and urate with methods described elsewhere [3, 16, 19, 31, 33, 34]. Reference values for women were: Ca less than 6.0, Ox less than 0.40, Cit more than 2.5, Mg more than 3.0 and urate 1.7–5.3 mmol/24 h. Fresh urine samples were checked for the presence of cystine by means of a cyanide nitroprusside reaction (Brand's test) [4]. Ionized calcium in serum was determined with an ion-selective electrode (Radiometer) [17] (reference range 1.18–1.34 mmol/l).

The ion activity product of calcium oxalate was expressed in terms of AP(CaOx)index [30]:

$$1.9 \times Ca^{0.84} \times Ox \times Mg^{-0.12} \times Cit^{-0.22} \times volume^{-1.03}$$

and the ion activity product of calcium phosphate was calculated in terms of AP(CaP)index [29] for a urine pH of 7.0:

$$2.7 \times 10^{-3} \times Ca^{1.07} \times P^{0.70} \times (pH - 4.5)^{6.8} \times Cit^{-0.20} \times V^{-1.31}$$

Standardized estimates of the ion-activity products were calculated as above for AP(CaOx)index(s) and AP(CaP)index(s), but for a 24-h urine volume of 1.5 l. We also calculated the Ca/Cit ratio.

Patients were considered to have a complete dRTA if the pH in fresh urine samples was above 5.5 despite a metabolic acidosis. An oral ammonium chloride loading test [2] was carried out in all patients without complete dRTA except in one patient who had renal insufficiency and a low urine pH without loading. Patients were referred to the group of incomplete dRTA if the urine pH never fell below 5.5 [2]. Urine pH was measured with a PHM 62 pH-meter (Radiometer).

Statistical analysis

Groups 1 and 2 were compared using the unpaired Student's *t*-test for all data except for frequencies of dRTA, earlier upper UTI and family history of urolithiasis. For the latter Fisher's exact test was used. The linear correlations between AP(CaOx)index(s) and AP(CaP)index(s) were estimated using the product moment correlation coefficient (*r*) (Stat View 4.0 computer program).

Results

The stone composition was known for seven of the patients in group 2. Calcium phosphate was the major constituent in all patients, two of whom also had an admixture of struvite. The calcium oxalate content did not exceed 6% in any of the analysed stones. Brand's test was negative in all patients.

A diagnosis of dRTA was established in seven of the patients in group 1 (44%) and in all patients in group 2. One patient in group 1 and two patients in group 2 had complete dRTA. The mean minimal urine pH value during ammonium chloride loading, or at the time of diagnosis of complete dRTA, was higher in group 2 than in group 1 (6.09 vs. 5.36). When only patients with dRTA were considered there was, however, no difference (6.13 in group 1 and 6.09 in group 2). The pre-load pH in fasting urine did not differ between the groups (6.13 vs 6.26). None of the patients had pRTA.

As shown in Table 1 the urinary excretion of calcium and urate as well as the urine volume were significantly higher in group 2. Urinary calcium was above the reference limit in three patients in group 2 but in none of the patients in group 1. Urinary urate was not above the upper reference limit in any of the patients. There were no significant differences between the two groups in their excretion of citrate, oxalate, phosphate or magnesium. Hypocitraturia was, however, common both in group 1 and 2 (69% and 82%, respectively). Fifteen of the 18 patients with dRTA (83%) had a low urinary excretion of citrate. AP(CaOx)index(s) was significantly higher in group 2. Three patients in group 2 but none in group 1 had an index above 2.0. There was a tendency towards a higher AP(CaP)index(s) in group 2 ($P = 0.054$). In contrast neither AP(CaOx)index, AP(CaP)index nor the Ca/Cit ratio differed significantly between the groups (Table 1). As shown in Fig. 1

Table 1 Urine variables and calculated indices in 27 patients with primary Sjögren's syndrome and without (group 1) or with (group 2) a history of urolithiasis

Variable	Reference values	No urolithiasis = group 1 Mean value (SD)	Urolithiasis = group 2 Mean value (SD)	Significance of difference (Student's *t*-test, *P* value)
1. Calcium (mmol/24 h)	<6.0 mmol/24 h	3.14 (1.79)	5.16 (2.65)	0.026
2. Magnesium (mmol/24 h)	>3.0 mmol/24 h	3.76 (2.09)	4.78 (2.41)	0.253
3. Oxalate (mmol/24 h)	<0.40 mmol/24 h	0.28 (0.11)	0.37 (0.22)	0.146
4. Citrate (mmol/24 h)	>2.5 mmol/24 h	1.76 (1.59)	1.43 (1.70)	0.611
5. Urate (mmol/24 h)	1.7–5.3 mmol/24 h	1.24 (0.63)	2.20 (0.76)	0.002
6. Phosphate (mmol/24 h)	–	26.6 (17.5)	30.0 (14.1)	0.597
7. Urine volume (l/24 h)	1.35 l	1.70 (0.70)	2.43 (0.89)	0.025
8. Urine Ca/Cit	<3.0	3.68 (3.94)	6.56 (5.31)	0.118
9. AP(CaOx)index	<1.30	0.68 (0.39)	1.02 (0.65)	0.106
10. AP(CaOx)index(s)	<1.25	0.78 (0.48)	1.59 (1.13)	0.021
11. AP(CaP)index (pH 7)	<105	21.9 (12.8)	30.9 (20.1)	0.166
12. AP(CaP)index(s)	<55	28.9 (24.3)	52.2 (35.8)	0.054

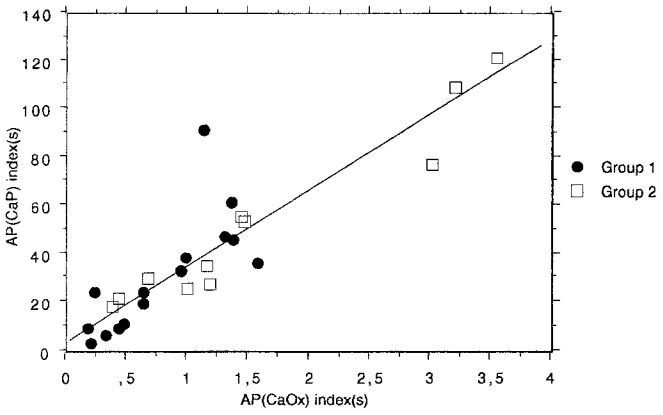

Fig. 1 AP(CaP) index(s) vs AP(CaOx) index(s) in 27 patients with primary Sjögren's syndrome, and without (group 1) or with (group 2) a history of urolithiasis ($R = 0.81$, $P = 0.0005$)

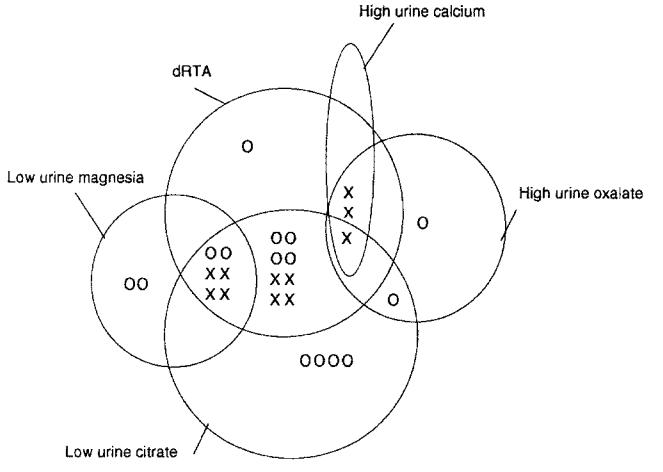

Fig. 2 Factors related to an increased risk of calcium stone formation (dRTA, hypercalciuria, hyperoxaluria, hypocitraturia and hypomagnesuria) in each of 27 patients with primary Sjögren's syndrome. *O* patients without a history of urolithiasis (group 1), *X* patients with a history of urolithiasis (group 2)

there was a good correlation between AP(CaOx)index(s) and AP(CaP)index(s) ($r = 0.81$, $P = 0.0005$).

Serum ionized calcium was normal in all patients except in one from group 1 (1.42 mmol/l), and there were no significant differences between the two groups.

A family history of urolithiasis was present in three of the patients in group 1 (19%) and in six of the patients in group 2 (55%) ($P > 0.05$).

Figure 2 shows the presence of dRTA, hypocitraturia, hypercalciuria, hyperoxaluria and hypomagnesuria in each patient. Eleven patients had urolithiasis (group 2). In group 2 hypocitraturia and dRTA were present in nine patients, of whom four patients also had hypomagnesuria and one patient also had hyperoxaluria and hypercalciuria. Two patients had dRTA, hyperoxaluria and hypercalciuria.

When the 18 patients with dRTA were compared with the 9 patients without dRTA, the former had a significantly higher Ca/Cit ratio ($P = 0.029$) and urinary urate ($P = 0.023$), whereas AP(CaOx)index(s), AP(CaP)index(s), AP(CaOx)index and 24-h urine volume did not differ. When the 11 stone formers with dRTA were compared with the 7 patients with dRTA but without a history of stone disease, no differences were recorded in any of the urine variables, nor were there any differences between the seven patients with and the nine patients without dRTA in group 1.

Discussion

Patients with primary Sjögren's syndrome (SS) frequently develop dRTA [24, 28, 36], which causes an increased risk of calcium stone formation [6]. The high urine pH in patients with dRTA might theoretically be a powerful determinant for precipitation of calcium phosphate [29], which was also the major constituent in most of the stones formed by our patients. Whereas most authors report that calcium phosphate stones are common in patients with dRTA [8], others have found a higher frequency of calcium oxalate stones or mixed stones [6].

In the present investigation 18 of 27 patients with SS had dRTA, 11 of whom had a history of calcium stone disease (group 2). None of the patients without dRTA had formed stones. Patients with dRTA have four urine abnormalities that might imply an increased risk of calcium stone formation: they always have a high urine pH, usually hypocitraturia and sometimes hypercalciuria and hyperuricosuria [5, 6, 21]. Among our 18 patients with dRTA the mean minimal urine pH was 6.09 in group 2 and 6.13 in group 1, a finding that does not support the assumption that urine pH is the major discriminating factor. These observations are in close agreement with those reported by Caruana and Buchalew who recorded a pH of 6.11 in 34 patients with urolithiasis and dRTA [6]. As shown in Fig. 2, 9 of our 11 patients with urolithiasis and dRTA had hypocitraturia, which is in accordance with most previous reports [5, 6, 23]. Although urine calcium was significantly higher in the 11 stone formers, only 3 had hypercalciuria (Fig. 2). In dRTA patients (without SS) hypercalciuria has been reported in between 3% and 36% [5, 6, 8, 12, 37]. In a group of patients with SS, urolithiasis and dRTA, it was concluded that hypercalciuria was the most important risk factor for calcium stone formation in four of five patients [20]. Although our stone formers had a significantly higher urate excretion, none had urate values above the upper reference limit. Hyperuricosuria has previously been reported in 23% of stone-forming patients with dRTA [5, 6], and urine urate was higher in patients with dRTA than in control patients in another study [21].

Although urinary urate might be associated with an increased risk of calcium oxalate stone formation, a similar relationship with calcium phosphate stone formation has not been described [7].

A higher AP(CaOx)index(s), which reflects the risk of forming a urine highly supersaturated with calcium oxalate, was recorded in our stone formers, which is in agreement with other reports [25, 26]. Although AP(CaOx)index is only an estimate of the relative risk of calcium oxalate crystallization, it gives indirect information also about the risk of calcium phosphate crystallization due to the strong relationship between AP(CaOx)index and AP(CaP)index. A critical supersaturation with respect to calcium phosphate has, however, been found in other patients with dRTA [25, 26]. In the calculation of AP(CaP)index(s) we used a standard pH of 7.0. Because the ion-activity product of calcium phosphate is strongly influenced by changes in urine pH during the day, this simplification might be a source of error.

Although AP(CaOx)index(s) was different between the groups AP(CaOx)index was not. This can be explained by the higher urine volumes encountered in patients from group 2. Although a high urine volume is commonly recorded in stone formers [32], this finding does not necessarily reflect either the everyday urine flow or the degree of dilution at a higher nephron level. It is important to emphasize, however, that dRTA was often associated with an impaired urine-concentrating capacity in our patients [11]. This mechanism might have contributed to the higher urine volumes recorded for the patients in group 2.

The data obtained show that the urine composition in our patients with SS, dRTA and urolithiasis was similar to that in other patients with dRTA and urolithiasis, and recurrence preventive therapy can be designed as for these patients. None of our patients with hypocitraturia but without dRTA were stone formers. Four of eight patients (50%) with dRTA and hypocitraturia, and five of seven patients (71%) with dRTA, hypocitraturia and some other urine abnormality had formed stones. In addition to dRTA other urine abnormalities might possibly increase the risk of developing urinary calculi in patients with SS.

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References

1. Adams P, Chalmers TM, Hill LF, Truscot BMcN (1970) Idiopathic hypercalciuria and hyperparathyroidism. BMJ 4:582
2. Backman U, Danielsson BG, Sohtell M (1976) A short duration renal acidification test. Scand J Urol Nephrol Suppl 35:33
3. Bingham S, Williams R, Cole T, Price C, Cummings J (1988) Reference values for analytes of 24-h urine collections known to be complete. Ann Clin Biochem 25:610
4. Brand E, Harris M, Biloon S (1930) Cystinuria: the excretion of a cystine complex which decomposes in the urine with the liberation of free cystine. J Biol Chem 86:315
5. Buchalew VM (1989) Nephrolithiasis in renal tubular acidosis. J Urol 141:731
6. Caruana RJ, Buckalew VM (1988) The syndrome of distal (type 1) renal tubular acidosis. Medicine 67:84
7. Coe FL (1978) Hyperuricosuric calcium oxalate nephrolithiasis. Kidney Int 13:418
8. Coe FL, Parks JH (1980) Stone disease in hereditary distal renal tubular acidosis. Ann Intern Med 93:60
9. Daniels TE, Talal N (1987) Diagnosis and differential diagnosis in Sjögren's syndrome. In: Talal N, Moutsopoulos HM, Kassan SS (eds) Sjögren's syndrome. Clinical and immunological aspects, 1st edn. Springer, Berlin Heidelberg New York, p 193
10. Eriksson P, Denneberg T, Granerus G, Lindström F (1995) Glomerular filtration rate in primary Sjögren's syndrome with renal disease. Scand J Urol Nephrol (in press)
11. Eriksson P, Denneberg T, Larsson L, Lindström F (1995) Biochemical markers of renal disease in primary Sjögren's syndrome. Scand J Urol Nephrol (in press)
12. Harrington T, Bunch T, van der Berg C (1983) Renal tubular acidosis. A new look at treatment of musculoskeletal and renal disease. Mayo Clin Proc 58:354
13. Hodgkinson A (1962) Citric acid excretion in normal adults and in patients with renal calculus. Clin Sci 23:203
14. Johansson G (1979) Magnesium metabolism. Studies in health, primary hyperparathyroidism and renal stone disease. Scand J Urol Nephrol Suppl 51:1
15. Larsson L, Tiselius HG (1987) Hyperoxaluria, Miner Electrolyte Metab 13:242
16. Larsson L, Libert B, Asperud M (1982) Determination of urinary oxalate by reversed-phase ion-pair "high-performance" liquid chromatography. Clin Chem 28:2272
17. Larsson L, Finnström O, Nilsson B, Öhman S (1983) Evaluation of Radiometer ICA1 as a routine instrument for serum ionized calcium and its application for whole blood capillary samples from newborn infants. Scand J Clin Lab Invest 43 [Suppl 165]:21
18. Larsson L, Sörbo B, Tiselius HG, Öhman S (1984) A method for quantitative wet chemical analysis of urinary calculi. Clin Chim Acta 140:9
19. Lawrence R (1974) Assay of serum inorganic phosphate without deproteinisation: automated and manual micromethods. Ann Clin Biochem 11:234
20. Moutsopoulos HM, Cledes J, Skopouli FN, Elisaf M, Youinou P (1991) Nephrocalcinosis in Sjögren's syndrome: a late sequela of renal tubular acidosis. J Intern Med 230:187
21. Nicar MJ, Skurla C, Sakhaee K, Pak CYC (1983) Low urinary citrate excretion in nephrolithiasis. Urology 21:8
22. Nordin BEC, Peacock M, Wilkinson R (1972) Hypercalciuria and renal stone disease. Clin Endocrinol 1:169
23. Norman ME, Feldman NI, Cohn RM, Roth KS, McCurdy DK (1978) Urinary citrate excretion in the diagnosis of distal renal tubular acidosis. J Pediatr 92:394
24. Pokorny G, Sonkodi S, Iványi B, Mohácsi G, Csáti S, Iványi T, Ormos J (1989) Renal involvement in patients with primary Sjögren's syndrome. Scand J Rheumatol 18:231
25. Preminger GM, Sakhaee K, Skurla C, Pak CYC (1985) Prevention of recurrent calcium stone formation with potassium citrate therapy in patients with distal renal tubular acidosis. J Urol 134:20
26. Robertson WG, Peacock M, Nordin BEC (1968) Activity products in stone-forming and non-stone-forming urine. Clin Sci 34:579
27. Shioji R, Furuyama T, Onodera S, Saito H, Ito H, Sasaki Y (1970) Sjögren's syndrome and renal tubular acidosis. Am J Med 48:456

28. Talal N, Zisman E, Shur PH (1968) Renal tubular acidosis, glomerulonephritis and immunologic factors in Sjögren's syndrome. Arthritis Rheum 11:774
29. Tiselius HG (1984) A simplified estimate of the ion-activity product of calcium phosphate in urine. Eur Urol 10:191
30. Tiselius HG (1991) Aspects on estimation of the risk of calcium oxalate crystallization in urine. Urol Int 47:255
31. Tiselius HG, Larsson L (1981) Biochemical evaluation of patients with urolithiasis. Eur Urol 7:31
32. Tiselius HG, Almgård LE, Larsson L, Sörbo B (1978) A biochemical basis for grouping of patients with urolithiasis. Eur Urol 4:241
33. Tompkins D, Toffaletti J (1982) Enzymatic determination of citrate in serum and urine, with use of the Worthington "Ultrafree" device. Clin Chem 28:192
34. Trudeau DL, Freier EF (1967) Determination of calcium in urine and serum by atomic absorption spectrophotometry (AAS). Clin Chem 13:101
35. Tu WH, Shearn MA, Lee JC, Hopper J (1968) Interstitial nephritis in Sjögren's syndrome. Ann Intern Med 69:1163
36. Vitali C, Tavoni A, Sciuto M, Maccheroni M, Moriconi L, Bombardieri S (1991) Renal involvement in primary Sjögren's syndrome: a retrospective-prospective study. Scand J Rheumatol 20:132
37. Wrong OM, Feest TG (1980) The natural history of distal renal tubular acidosis. Contrib Nephrol 21:137