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Clinical studies of renal disease in Sjögren's syndrome

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SUMMARY When 17 patients with Sjögren's syndrome, without apparent clinical manifestations of renal disease, were examined renal function studies frequently indicated abnormalities in their renal phosphate handling. The percentage tubular reabsorption of phosphate (%TRP) was decreased in six (35·3%), and maximal tubular reabsorption rate for phosphate ($TmPO_4$/GFR) was low in eight (47·1%). In contrast, indices of renal calcium handling and serum parathyroid hormone levels were normal, suggesting that the abnormalities of phosphate metabolism were due not to extrinsic, but rather to intrinsic disease processes occurring in the kidney in Sjögren's syndrome. When the patients were divided into two groups according to the presence or absence of a renal tubular acidification defect (RTAD), patients with RTAD were younger ($p<0·005$), had longer disease duration ($p<0·01$), lower creatinine clearance ($p<0·05$), and higher incidence of low %TRP ($p<0·05$). Thus the patients with lower creatinine clearance generally had disease of longer duration at diagnosis and tended also to have defects in concentrating and acidifying the urine.

Key words: renal tubular acidosis, interstitial nephritis, urine concentrating ability, renal phosphate handling, urine β_2 microglobulin, creatinine clearance, percentage tubular reabsorption of phosphate, tubular reabsorption rate for phosphate.

Sjögren's syndrome is sometimes associated with renal tubular acidosis[1–7] or tubular concentrating defect.[1 7–10] Tu *et al* have pointed out the pathological similarity between the lesion in the salivary gland and in the kidney,[11] suggesting that the lesion in interstitial nephritis, consisting of lymphoid cellular infiltration,[5 6 11] could be part of the multiple organ-system infiltration characteristic of Sjögren's syndrome.

We have analysed renal function in patients with Sjögren's syndrome, particularly noting their renal handling of phosphate and circulating levels of parathyroid hormone (PTH). In addition, we have sought inter-relationships between different parameters of renal function in the hope of obtaining greater insight than would be possible by analysing each parameter individually.

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Patients and methods

PATIENTS

Medical records of all inpatients with Sjögren's syndrome admitted between 1979 and 1985 were reviewed. In addition, two patients (Nos 6 and 11) were included from our outpatient clinic. Patients were excluded if the diagnostic criteria described below were not fulfilled. Patients were also excluded if adequate data were not available to assess renal function; thus 17 were selected out of a total of 22 patients (Table 1). The diagnosis of Sjögren's syndrome was made in these 17 patients (age 28–70, mean 51) by the presence of all of the following: keratoconjunctivitis sicca, decreased lacrimation, and xerostomia.[10 12] Keratoconjunctivitis sicca was demonstrated by typical corneal staining with fluorescein on slit lamp examination. Decreased lacrimation was diagnosed by less than 5 mm of moistening in 5 min in Schirmer's test. Parotid saliva was collected from each patient under resting conditions and after stimulation with fruit chewing

gum for 5 min, and xerostomia was diagnosed as less than 10 ml of salivary secretion. All patients had typical morphological features compatible with Sjögren's syndrome both on lip biopsy and sialography/scintigraphy,[13–16] where greater than grade 3 by Chisholm and Mason's classification[16] was considered positive. Other associated disease conditions, as well as drugs administered before, during, and after seven days of blood sampling are listed in Table 1.

LABORATORY EXAMINATIONS

Serum calcium was adjusted for changes in serum albumin using Payne's equation.[17] Serum gammaglobulin was measured by routine electrophoresis on a cellulose acetate membrane. Immunoglobulin isotypes were determined by single radial immunodiffusion on thin layer gels. Creatinine clearance was adjusted for body surface area. Percentage phenolsulphthalein excretion (PSP) 15 min after intravenous injection of phenolsulphthalein was measured, and a value below 25% was judged to be low. Specific gravity and osmolality of urine collected at hourly intervals after 15 hours of complete fluid restriction were measured by the Fishberg test, and values below 1·022 for specific gravity or 700 mmol/kg for osmolality were judged to be low.[9] Urine protein and sugar were measured semiquantitatively by commercial test tape (AMES Miles-Sankyo Co Ltd, Tokyo, Japan), in which 1+ approximately corresponded to 300 mg/l and 3+ to 3000 mg/l of protein. Urine β_2 microglobulin was measured by solid phase radioimmunoassay using the Phadebas β_2 microtest kit (Pharmacia Diagnostics, Uppsala, Sweden).

Percentage tubular reabsorption of phosphate (%TRP) was calculated from the formula $1-C_{PO4}/C_{cr}$; where C_{PO4} represents renal clearance of phosphate, and C_{cr} creatinine clearance. $TmPO_4/GFR$ (maximum tubular reabsorption rate for phosphate) was calculated from a nomogram using plasma phosphate concentration and %TRP.[18] To determine NH_4Cl loading, ammonium chloride was given at 0·1 g/kg body weight, and urine was collected at the start and at hourly intervals for six hours. Urine pH determinations were carried out within 30 min of voiding. Diagnosis of renal tubular acidification defect (RTAD) was made when the urine pH did not fall below pH 5·3 in any of the specimens.[5] Plasma parathyroid hormone (PTH) was measured by radioimmunoassay using antibody recognising the C terminal 1–34 portion of the molecule (C-PTH) (Eiken Chemicals Co, Tokyo, Japan). Blood samples for plasma PTH measurement were obtained in the outpatient clinic. Bone histology on the iliac crest bone biopsy specimen was evaluated as described previously.[19] Normal values shown in the tables are standardised average values used at Kobe University Hospital. Statistical analysis was carried out using Student's *t* test modified for a small sample,[20] and also by a non-parametric Fisher-Yates test of significance in 2×2 contingency tables.[21]

Results

Patients with Sjögren's syndrome had hyperglobulinaemia predominantly of IgG type, in which serum gammaglobulin was 28·1 (6·6)% (22·3(7·8) g/l), and serum IgG, IgM, and IgA were 23·9(7·6), 2·0(1·4), and 3·5(1·1) g/l respectively. (Values are mean (SD)). All patients had blood gas determinations. Patients 1, 4, and 5 were judged to have pH values indicating renal tubular acidosis, while the rest had normal values. The plasma sodium, potassium, chloride, bicarbonate, urea, and creatinine were within normal limits, except for patients 1, 4, and 5 who had decreased potassium levels. Patient 1, receiving no potassium supplement had a potassium level of 3·3 mmol/l. Patient 5, who had 2·8 mmol/l potassium, had renal function studies performed both with and without supplementing potassium; the results were similar. Patient 4 had a potassium level of 1·9 mmol/l, rising to normal with supplemental potassium. These patients also had increased chloride levels because of renal tubular acidosis. Liver function tests were all normal. Proteinuria was present in two out of 15 patients (13·3%); in all the patients urine sediments were normal on repeated examination. The average creatinine clearance was 66·8(15·1) ml/min, a significant decrease when compared with that of healthy controls ($p<0·01$) (Table 1). PSP excretion at 15 min was lowered in five out of 14 patients examined (35·7%). Urine concentrating ability, as measured by the Fishberg test, was defective in nine out of 11 patients examined (81·8%). Urine β_2 microglobulin excretion was increased in four out of 11 patients (36·4%). Renal calcium excretion was normal, as determined by daily calcium excretion, the urine calcium/urine creatinine ratio, and urine calcium per body weight, except for patient 1 who showed increased urinary calcium excretion. Serum calcium levels were also normal, except for patients 1 and 5, who had a low calcium level because of overt renal tubular acidosis. Serum phosphate level was low in two out of 18 patients (11·1%) (Table 1). Percentage tubular reabsorption of phosphate (%TRP) was less than 79% in six out of 17 patients (35·3%). $TmPO_4/GFR$ was less than 2·5 in eight out of 17 patients (47·1%). Serum alkaline phosphatase was increased in seven out of 17 patients (41·2%). Renal

Table 1 *Patient profile and renal function studies*

Patient No	*Age/ sex*	*Mean duration of disease (years)*	*Associated disease**	*Medications†*	*Creatinine clearance (ml/min)*	*PSP‡ test at 15 min (%)*	*Fishberg concentration test*	*Urine*		*Serum phosphate (mmol/l)*	*Alkaline phosphatase (IU/l)*	*%TRP*	*$TmPO_4$/GFR*	*NH_4Cl loading test*
								Protein	*β_2 Microglobulin (μg/l)*					
1	28/F	4	HypoK, RTA	—	52·0	41·2	Low	+++	ND	0·7	190	73·1	1·7	Abnormal
2	46/F	3·5	HyperT	—	80·0	34·2	Normal	−	29·5	1·3	62	97·3	5·0	Abnormal
3	37/F	5	—	P,A	60·5	21·0	Low	−	120	1·1	131	77·1	2·6	Abnormal
	40/F	8	—	P	33·3	22·3	Low	±	ND	0·7	138	71·5	1·7	Abnormal
4	34/F	2	CT,HypoT,HypoK,RTA	K,T	67·6	34·1	Low	−	960	1·1	108	89·0	3·4	Abnormal
5	35/F	10	RA,OM,HypoK,RTA	—	52·0	5·3	Low	+	13 896	0·8	533	72·0	1·8	Abnormal
6	62/F	8	MCTD	A	59·8	ND	ND	−	ND	0·8	123	72·4	2·1	Abnormal
7	44/F	2	—	—	95·2	39·4	ND	−	ND	1·2	80	88·0	3·4	Normal
8	56/F	0·5	—	—	68·0	17·3	Low	−	70	1·0	70	86·2	2·6	Normal
9	67/F	2	—	—	54·4	17·5	Low	−	960	0·9	75	75·5	2·0	Normal
10	65/F	1	—	—	83·1	14·5	ND	−	190	1·0	76	89·2	3·1	Normal
11	61/F	3	—	—	85·5	ND	ND	−	ND	1·1	100	86·0	3·0	Normal
12	58/F	1	CT, NormoT	—	61·3	33·6	Normal	−	ND	1·2	71	79·8	2·9	Normal
13	48/F	6	CT	—	65·6	39·3	Low	−	62	1·0	62	79·2	2·4	Normal
14	70/F	1	CT, NormoT	—	79·4	41·0	Low	−	125	1·0	90	79·0	2·4	Normal
15	59/F	6	RA	—	64·2	25·1	ND	−	ND	1·4	69	95·3	4·9	Normal
16	68/F	1	RA	—	82·1	ND	ND	−	760	0·9	104	77·2	2·2	Normal
17	47/F	1	AC	—	57·8	40·7	Low	−	73	1·1	113	90·4	3·3	Normal
Mean (SD)	51(13)	3·6(2·9)			66·8 (15·1)§	28·4 (11·6)				1·0 (0·2)	122 (108)	82·1 (8·2)	2.8 (1·0)	
Normal range					105·2–107·0	25–50%		—	5–235	0·8–1·5	36–100	Above 79·0	2·5–3·5	

*HypoK=hypokalaemia; RTA=renal tubular acidification; hyperT=hyperthyroidism; CT=chronic thyroiditis; HypoT=hypothyroidism; RA=rheumatoid arthritis; OM=osteomalacia; MCTD=mixed connective tissue disease; NormoT=euthyroidism; AC=acrosclerosis.
†P=10 mg prednisolone daily, orally; A=aluminium gel; K=25 mmol potassium daily, orally; T=15 mg thyroid powder daily.
‡PSP=phenolsulphthalein.
§Significance at $p<0·01$ by Student's *t* test.

tubular acidification (RTA), as determined by ammonium chloride loading, was defective in six out of 17 patients (35·3%).

As renal handling of phosphate is mainly regulated by parathyroid hormone (PTH), serum PTH was measured by radioimmunoassay, to determine whether the abnormal phosphate metabolism was due to extrinsic hormonal control or not. PTH as determined in 10 patients with Sjögren's syndrome in the outpatient clinic was normal. Two patients included in the main study were drawn from this group (Table 2). As the present study was retrospective, however, PTH determination in patients under study could not be done. Bone histology examination, performed only in symptomatic patients, showed osteomalacia in patient 5 and mildly active osteoporosis in patient 6. Aminoaciduria as sought in patients 1, 4, and 5 was not detectable. Some of the patients had chronic thyroiditis; however, only patient 4 required thyroid supplementation. It is apparent from Table 1 that a hyperthyroid state (patient 2) or chronic thyroiditis (patients 4, 12–14) did not contribute to the renal dysfunction observed in these patients.

When the patients were divided into two groups according to the presence or absence of renal tubular acidification defect (RTAD) (Table 3) those with RTAD were younger ($p<0·005$) and had longer disease duration ($p<0·01$). The patients with RTAD had lower creatinine clearance ($p<0·05$), increased incidence of low %TRP ($p<0·05$), while serum phosphate and $TmPO_4/GFR$ were not significantly different in the two groups. The Fishberg test, PSP test, serum alkaline phosphatase, urine β_2 microglobulin excretion, and serum gammaglobulin level were equally abnormal in the two groups.

Table 2 *Plasma C terminal parathyroid hormone (C-PTH) level in Sjögren's syndrome*

Patient No	*C-PTH (ng/ml)†*
4*	0·29
5*	0·29
18	0·32
19	0·27
20	0·31
21	0·26
22	0·22
23	0·28
24	0·39
25	0·29

*Corresponds to the patient numbering in Table 1.
†Normal value <0·50.

Table 3 *Comparison of patients with or without renal tubular acidification defect (RTAD)*

	Patient		
	With RTAD	*Without RTAD*	*Statistical significance*
Patients (n)	6	11	
Age (years)	40 (12) (n=5)	59 (9) (n=11)	p<0·005*
Mean duration of disease (years)	5·4 (3·0)	2·2 (2·0)	p<0·01*
Gammaglobulin (%)	31·4 (5·9)	26·3 (6·8)	NS*
Serum phosphate (mmol/l)	1·0 (0·2)	1·1 (0·1)	NS*
Patients with low serum P (%)	33·3	0	NS†
%TRP	78·9 (10·2)	84·2 (6·4)	NS*
Patients with low %TRP (%)	71·4	18·1	p<0·05†
$TmPO_4/GFR$	2·6 (1.2)	2·9 (0.8)	NS*
Patients with low $TmPO_4/GFR$ (%)	60·0	36·4	NS†
Patients with proteinuria (%)	50·0	0	p<0·05†
Creatinine clearance (ml/min)	58·0 (14·5)	71·1 (13·1)	p<0·05*
Patients with low PSP excretion at 15 min (%)	50·0	33·3	NS†
Patients with low Fishberg test (%)	83·3	83·3	NS†

Values are mean (SD).
Statistical significance was obtained with *Student's *t* test or †Fisher-Yates non-parametric test.

Discussion

The results show that renal function was considerably defective in the patients with Sjögren's syndrome even when they were without apparent clinical manifestations of renal disease. The abnormalities were not confined to distal tubules, but proximal tubules were also, though less frequently, involved. This finding confirms previous results on the renal tubular acidosis or tubular concentrating defects observed in Sjögren's syndrome,[1–10] and shows that there is no selectivity in the anatomical site of involvement in the kidney of Sjögren's syndrome.

It was found that, although indices of renal handling of phosphate such as %TRP or $TmPO_4/GFR$ were frequently abnormal, indices of calcium metabolism and serum PTH levels were both normal. This would indicate that the abnormalities of phosphate metabolism seen in these patients were not due to extrinsic hormonal control, but were caused by an intrinsic pathological process within the kidney. These findings are thus compatible with

previous pathological results which showed that interstitial nephritis with lymphoid cellular infiltration is the main lesion in the kidney in Sjögren's syndrome.[5 6 11]

The present results show that among the various parameters of renal function urine concentrating ability is most vulnerable to damage in Sjögren's syndrome. This was observed irrespective of whether the patients had RTAD or not. It thus appeared that renal concentrating ability was primarily involved during the course of the disease and thus could be a sensitive indicator of renal damage in Sjögren's syndrome.

It was observed that the patients with lower creatinine clearance values generally had disease of longer duration at diagnosis; and tended also to be unable to concentrate and acidify the urine, indicating that a selective mechanism of injury directed specifically at the renal tubular acidification system is not present. Instead, it is likely that renal tubular acidosis is the result of an extension of a generalised pathological process within the kidney. Our results are compatible with the conclusion that the abnormalities of renal function, such as those observed with regard to phosphate metabolism, are due not to extrinsic, but rather to an intrinsic disease process in the kidney. The present results thus support the previous pathological finding that interstitial nephritis with lymphoid cellular infiltration is the main lesion in the kidney in Sjögren's syndrome. It is likely that the local injuries in the kidney and in the salivary gland have a similar basis, as proposed by Tu *et al.*[11] If this is the case, it may be predicted from these and other studies that renal involvement in Sjögren's syndrome is reversible depending on the stage of the disease process or on the treatment.

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