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Renal Tubular Dysfunction in Primary Sjögren's Syndrome: Clinical Studies in 27 Patients

P.P. VIERGEVER*, T.J.G. SWAAK**

Summary **Kidney involvement in Sjögren's syndrome (SS) including renal tubular disorders are well recognized but little is known about frequency and extent of such dysfunction in the general population of patients with primary SS, due to a lack of group studies. We studied 27 patients with primary SS and without other possible causes of tubular dysfunction. Increased urinary β2M excretion, due to proximal tubular dysfunction, was present in 26% of patients. Inadequate urine acidification after oral NH_4 Cl, proving distal tubular dysfunction, was found in 12% of the patients studied. Concentrating ability, tested by thirst, was decreased in 44% of patients studied. Abnormal renal tubular tests correlated with presence of ANA ($p = 0.05$) but not with other clinical parameters. In conclusion demonstrable renal tubular dysfunctions occur in over half the patients with primary SS. Literature concerning this subject is discussed.**

Key words: **Primary Sjögren's Syndrome, Kidney Renal Tubular Dysfunction, Renal Tubular Acidosis, Urine β2 Microglobulin Urine, Concentrating Ability, Urine Acidification Ability.**

INTRODUCTION

Dysfunction of the renal tubules is known to occur in many rheumatic disorders (1,2) including primary Sjögren's syndrome (SS), which is defined as SS without the presence of an associated rheumatic disorder. Previous reports of such dysfunctions, however, mostly concern symptomatic case reports, studies of small groups of patients with unclear selection criteria, and/or mixed populations of both primary and secondary SS (3-25).

We decided to investigate tubular function in a large and clearly defined group of patients with primary SS only. This would provide more insight into the frequency and extent of renal tubular dysfunction in this disorder.

PATIENTS AND METHODS

Patients

Thirty eligible patients were selected from the outpatient population of a referral rheumatological center. All patients were characterized by the subjective signs of xerostomia and keratoconjunctivitis. Keratoconjunctivitis was further proven by a positive Schirmer test and split-lamp examination. If the diagnosis was sustained by a positive minor gland biopsy (26,27) the diagnosis SS was accepted. In that case (≠7) in which no biopsy was performed, salivary gland involvement had to be proven by scintigraphy and sialography. Patients with other rheumatic disorders (occurring up to one year after tubular testing) were excluded, as were those with known past or present renal disease or another possible cause of renal tubular dysfunction (28). Finally 27 patients agreed to cooperate.

Methods

Laboratory investigations included: ESR, peripheral blood count, Na, K, Ca, PO_4, creatinine in serum and in 24-h urine, albumin, protein electrophoresis, determination of specific immunoglobulin fractions, venous pH, HCO_3-, β2-microglobulin (β2M) in serum and in 24-h urine, glucose and protein in urine (dipstick), urine microsediment and testing for presence of ANA (immunofluorescence) and for presence of circulating immunecomplexes (C1q-binding assay).

Dysfunction of the proximal renal tubules was investigated by measuring the 24-h urinary β2M excretion in alkalinized urine. An excretion of > 370 μg/24-h β2M

*Department of Internal Medicine, Zuiderziekenhuis, Groene Hilledijk 315, 3075 EA Rotterdam; **Department of Rheumatology, Dr Daniel den Hoed Clinic, Groene Hilledijk 301, 3075 EA Rotterdam, The Netherlands.

is abnormal (29,31). Serum β2M levels depend also on GFR. Normal values used were: Sβ2M < 2.00 mg/l for GFR > 100 ml/min, Sβ2M ≤ 2.50 mg/l for 70 ml/min < GFR ≤ 100 ml/min and Sβ2M ≤ 3.00 mg/l for GFR ≤ 70 ml/min (2). β2M levels were measured by competitive immunoassay (Phadezym®, β2 microtest, Pharmacia diagnostics, Uppsala, Sweden).

The classic acidification test of Wrong and Davies (30) was used to assess the urine acidification ability, a distal tubular function. Failure of urine pH to fall below 5.3 after a standardized dose of NH_3 Cl was considered to be abnormal, provided systemic acidosis occurred.

The concentrating ability of the kidney was evaluated by a 15-h period of thirsting. This should normally result in SG urine > 1.022 (3), as we also confirmed afterwards in 12 normal controls whose age distribution was comparable with that of the SS patients studied. SG measurements were performed using a hydrometer.

GFR was calculated using endogenous creatinine clearance and is expressed as corrected for 1.73 m^2 standard body surface. Renal biopsy was not performed in any case because of risks involved and absence of clinical consequences.

Statistics

Numerical data are expressed here as mean (range), and for these data the Wilcoxon rank sum test was used. In other instances, we used the two-tailed Exact probability test. Statistical significance was accepted for $p \leq 0.05$.

RESULTS

Clinical data

Table I summarizes the relevant characteristics of the group of 27 patients studied. As can be seen there, many patients had longstanding complaints of SS. Associated Raynaud's phenomenon was often present. Paraproteinuremia occurred in several cases, all with exclusion of lymphoreticular malignancy. A history of kidney stones was obtained in 3 cases.

Serological abnormalities such as elevated ESR, increased serum β_2M, presence of ANA and circulating immune complexes were found to be frequently present. The GFR was normal in all, with respect to age. No patients had overt metabolic acidosis, decreased HCO_3-, electrolyte abnormalities, glucosuria proteinuria urine sediment abnormalities.

Table I: *Basic characteristics of the studied patients with primary SS (n=27)*

Sex (F:M)	22 : 5
Age (years)	53 (29-75)*
Disease duration (n≥ 5y; n> 5y)	10 ; 17
Raynaud's phenomenon (n)	9
Kidney stones (n)	3
ESR (mm 1st h)*	18 (3-70)
ESR (n > 20 mm 1st h)	9
γ globulin (g/l)*	11 (7-19)
Paraproteins (n × type)	2 × IgMκ, 2 × IgGλ
ANA + (n)	6
Circulating immunecomplexes	4
Serum β2M (μg/l)*	1.86 (1.05-4.20)
Serum β2M (n above normal)*	4
GFR (ml/min)	84 (54-118)
Acidosis (n)	0
Electrolyte abnormalities (n)	0
Proteinuria	0
Glucosuria	0
Urine sediment abnormalities	0

* Expressed as mean (range)

Tubular function test

An increased 24-h urinary β2M excretion was found in 7 patients (1265 (414-4403) μg/24-h β2M) with a normal excretion (185 (82-323) μg/24-h β2M) in the other 20 patients.

Urine acidification was decreased in 3 patients with lowest achieved urine pH of 5.5, 5.6 and 6.0, respectively. In 2 patients vomiting of the ingested NH_4 Cl resulted in failure of this test; the remaining 22 patients had a normal acidification test (all urine pH ≤ 5.1).

The thirsting test was refused or interrupted by 8 patients, because of their troublesome xerostomia. Of the remaining 19 patients, 8 showed an inadequate urine concentrating ability (SG 1.025 (1.023-1.033)).

In one case a combined decreased acidification and concentration of urine was observed. Another patient showed increased urinary β2M excretion with decreased urine concentrating ability. In total 16 of 27 patients showed signs of tubular dysfunction when tested, but notably this did not result in clinically overt signs of renal tubular dysfunction in this group. Patients with normal tubular function tests were compared with those showing abnormal results (Table II).

ANA was found to be significantly more frequently present ($p=0.05$) in the latter group. Otherwise no significant differences were observed. Circulating immunecomplexes and increased serum β2M levels also tended to be more frequently present (but $p<0.20$).

Table II: *Demographic, laboratory and immunological findings in patients with primary SS as divided for the absence or presence of abnormal tubular function tests (n=27)*

	Normal tubular tests (n=11)	Abnormal tubular test(s) (n=16)
Sex (F:M)	8:3	14:2[ns]
Age (years)	53 (39-73)*	52 (29-75)[ns]
Disease duration (n5y;n>5y)	3;8	7;9 [ns]
Raynaud's phenomenon (n)	4	5 [ns]
Kidney stones (n)	0	3 [ns]
ESR (mm 1st h)	15 (3-42)	20 (4-70) [ns]
ESR (n > 20 mm 1st h)	3	6 [ns]
γ globulin (g/l)	10 (8-16)	11 (7-19) [ns]
Paraproteins	2	2
ANF (n)	0	6 §
Circulating immunecomplexes (n)	0	4 [ns]
Serum β2M (μg/l)	1.79 (1.05-2.06)	1.95 (1.045-4.20) [ns]
Serum β2M (n above normal)	0	4 [ns]
GFR (ml/min)	84 (54-118)	84 (58-115) [ns]

* Data are expressed as: mean (range), § p=0.05, ns= not significant.

DISCUSSION

Kahn et al. in 1962 (3), and Shearn and Tu in 1965 (4), were the first to point towards concentrating disorders and to observe proximal and distal tubular disorders, respectively, in patients with SS. Since these observations, a continuous interest concerning kidney involvement in SS had remained. Most commonly a tubulointerstitial nephritis is observed, with cytotoxic lymphocytes ultimately causing tubular atrophy and fibrosis (7,16-18,22,25,27,32-34). This mechanism of tissue damage resembles the one observed in exocrine tissues like the salivary gland in SS, suggesting the same pathological mechanism. Also, in some cases, immune complexes seem to play a role (35,36).

Despite the amount of earlier literature, there remains a lack of insight into frequency and extent of tubular dysfunction in primary SS, because larger groups of patients have rarely been systemically investigated in this respect. Indeed, a search for literature concerning this subject yielded only the following relevant publications: Siamopoulis et al. (37) studied kidney involvement in general in 36 patients with primary SS. Concerning tubular dysfunction it was found that 5 of 15 patients showed inadequate urine acidification after oral NH_4 Cl, with one case of complete tubular acidosis. Other causes for such dysfunction were not excluded beforehand.

Shiozawa et al. (38) studied a mixed population of 18 patients with SS, 13 of whom were primary. Decreased Tmax PO_4/GFR was found in 5 of 13 and increased urinary β2M excretion in 2 of 9 was investigated. Insufficient urine acidification after oral NH_4 Cl was found in 5 of 13 patients tested, with frank tubular acidosis in 2 cases. Also a decreased urine concentrating ability was present in 8 of 10 patients tested. Patients with tubular defects were found to be significantly younger, with longer disease duration and lower GFR. In this study, however, patients were selected mostly from inpatients records, possibly creating a bias, and again other possible causes for tubular dysfunction were not excluded beforehand.

Finally, Schardijn et al. (31) studied renal tubular functions in 32 patients with primary SS, as we excluding other possible causes of tubular dysfunction. In 7 patients the Tmax PO_4/GFR was decreased and urinary β2M excretion was increased in 5 cases. Urine acidification ability was abnormal in one case. Urine concentration capacity was decreased in 11 patients. Comparison between patients with and without these defects was not made.

This paper concerns the study of a clearly defined group of 27 patients with primary SS, all without another apparent cause for renal tubular disorder. No case of frank tubular acidosis or other clinical overt tubular dysfunction was found, illustrating its infrequent occurrence in primary SS. However, when tested for, an abnormal proximal tubular function, causing increased urinary β2M excretion, was found to be frequently present in 26% of patients. Abnormal distal tubular function, leading to inadequate urine acidification after oral NH_4Cl, was demonstrable in 12% of patients. Finally and most frequently, the urine concentrating ability studied by thirsting was impaired in 44% of those studied. These percentages agree more or less with the find-

ings of the authors mentioned above (31,37,38), especially with those of Schardijn.

Unlike Shiozawa we found no age difference, disease duration or GFR between patients with and without abnormal tubular tests. A bias caused by patient selection may well cause this difference. Indeed, we think that by studying outpatients without any other possible cause of tubular dysfunction, our results, like Schardyn's, may more accurately reflect the frequency and extent of tubular dysfunction in the general population of patients with primary SS.

In a review report (39) the association between SS, renal stones, distal tubular acidosis type I and hypergammaglobulinemia is shown. In our 27 patients a history of renal stones was obtained three times; in 3 patients by X-ray examination and in 2 patients also by surgery. Information about the nature of the stones is lacking (calcium phosphate stones?). However, nephrocalcinosis was excluded in our patients. Only one of the 3 patients was characterized by an incomplete renal tubular acidosis. The question about the coincidence of these findings, still remains; however, at this moment these observations are further evaluated in our RA patients with and without SS.

We found ANA to be significantly more frequently present in patients with abnormal tubular tests. ANA itself is not known to cause tubular dysfunction. It seems probable that the presence of ANA in this setting merely represents a state of more severe autoimmunity causing a greater risk for renal involvement in primary SS. This correlation, however, has not been observed before and awaits confirmation.

It may be concluded that subclinical renal tubular dysfunction can simply be demonstrated in the majority of patients with primary SS, while frank overt clinical dysfunction remains rare. Subgroups at risk remain to be defined, as in this respect data are still scarce and conflicting.

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Correspondence to : A.J.G. SWAAK, M.D., Ph.D.
Department of Rheumatology, Groene Hilledijk 301, 3075 EA Rotterdam, The Netherlands.