Renal Tubular Function in Systemic Lupus Erythematosus*

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SUMMARY

Renal function is commonly assessed by measurement of glomerular filtration rate (GFR). However, defects in tubular function may still exist in the presence of a normal GFR. In 12 patients with systemic lupus erythematosus (SLE), 6 of whom had previously been shown to have renal impairment, glomerular and tubular function were studied separately. In 4 patients, all parameters of renal function tested were normal. Impaired tubular function was found in 8 of the 12 patients, including 5 with normal GFR. Defects were noted in the ability to acidify urine in 7 patients and tubular reabsorption of phosphate was reduced in 2. A poor correlation was noted between the presence of renal tubular acidosis and the serum γ-globulin level. The pathogenesis of the defect in urinary acidification in SLE and its prognostic significance are discussed.

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Subclinical disorders of renal tubular function have been described in a variety of hypergammaglobulinaemic conditions, including 'auto-immune' diseases such as Sjögren's syndrome,[1,2] systemic lupus erythematosus (SLE),[3] alveolitis[4] and chronic active hepatitis.[5] The reported abnormalities of renal tubular function include impairment of acid excretion and urinary concentration. It has been suggested that the hypergammaglobulinaemic state may be causally related to the tubular dysfunction. The purpose of this investigation was to examine various parameters of tubular and glomerular function in patients with SLE, and to study the relationship between the defects of renal function and the presence of hypergammaglobulinaemia.

PATIENTS AND METHODS

Twelve patients (Table I), 6 of whom were known to have renal disease, were studied. There were 10 females and 2 males, aged between 19 and 61 years. All conformed to Harvey's diagnostic criteria for SLE.[6] This permitted the inclusion of a patient who had discoid lupus erythematosus; haemolytic anaemia, polyarthritis and

TABLE I. CLINCAL FEATURES

Patients	Estimated duration disease (months)	Estimated duration renal disease	Other major manifestations	Drugs
1	336	0	Thrombocytopenia	Ampicillin
2	24	0	Pleurisy	None
3	120	0	Pneumonia, Raynaud's phenomenon	Prednisone 5 mg
4	8	0	Pleurisy	Prednisone 30 mg
5	180	0	Arthritis	Prednisone 10 mg
6	96	0	Discoid LE	Prednisone 20 mg
7	360	20	Discoid LE, anaemia, arthritis	Prednisone 10 mg
8	23	11	Pneumonia	Prednisone 60 mg
9	10	1	Arthritis, pleurisy	Prednisone 60 mg
10	1	1	Arthritis	Prednisone 60 mg
11	16	15	Convulsions, arthritis	Prednisone 15 mg
12	62	50	Arthritis, adenopathy	None

nephritis, but no LE cells. Fourteen healthy volunteers, aged 19 to 40 years, acted as controls.

The protocol used during the investigation followed essentially that of the one-day renal function test of Edwards *et al.*[7] This entailed the collection of a mid-stream urine specimen for microscopy and culture, 2 arterial blood samples, and 2 3-hour timed urine specimens, followed by a 2-hour urine collection. Parameters of renal function measured included the creatinine clearance, phosphate clearance, protein excretion and the maximal urinary concentration attained after the subcutaneous injection of 5 units of pitressin tannate in oil. In addition, the ability to handle an acid load was tested according to the short oral ammonium chloride loading test of Wrong and Davies.[8] Urine pH, titratable acid (TA), ammonium and bicarbonate were measured in the last 2 urine collections, and acid-base studies were performed on arterial blood collected before, and during the test. Total hydrogen ion excretion was estimated as the sum of TA and ammonium, minus bicarbonate.

Activity of the immune process was assessed by estimation of total haemolytic complement. Urine pH was measured at room temperature with a glass electrode pH meter. TA was determined according to the method of Wrong and Davies,[8] urinary ammonia by the micro-diffusion method of Conway,[9] and urine bicarbonate by the method of Van Slyke and Neill,[10] employing the Henderson-Hasselbalch equation. Urea, creatinine and calcium were measured with the Technicon auto-analyser. Urine osmolality was determined by means of an advanced osmometer. Serum proteins were analysed by paper electrophoresis. Total haemolytic complement was measured according to a modification of the method of Kent *et al.*[11]

RESULTS

Creatinine clearance was reduced in 3 patients (Fig. 1), the lowest being 26 ml/min/1,73 m². Urinary protein excretion was increased in 5 patients, 2 of whom had the nephrotic syndrome. Defects in tubular function were also present (Fig. 1). Tubular reabsorption of phosphate

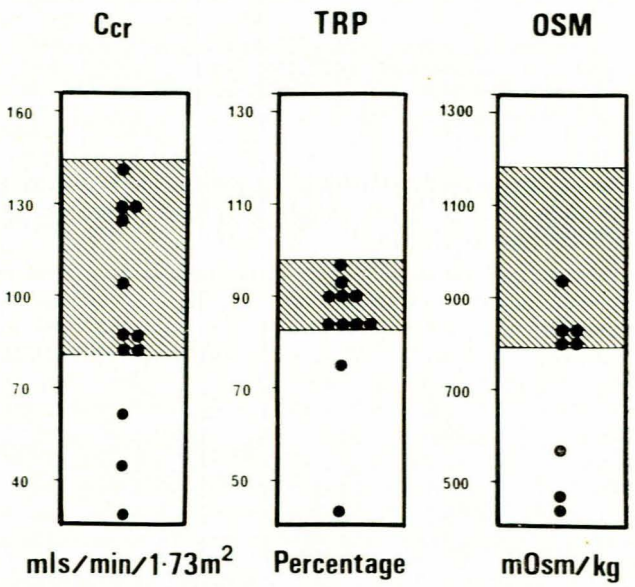

Fig. 1. Creatinine clearance (Ccr), tubular reabsorption of phosphate (TRP) and maximum urinary osmolality (OSM) 8 hours after injection of pitressin. Shaded areas represent mean ± 2 SD of control values.

was reduced in 2 patients, neither of whom showed evidence of hyperparathyroidism. Three patients were unable to concentrate urine normally, as judged by the maximal urine osmolality attained 6 - 8 hours after the administration of pitressin tannate in oil.

The pattern of acid excretion in the presence of systemic acidosis, induced with ammonium chloride, is shown in Fig. 2. All 6 patients with clinical renal disease had an impaired ability to lower urinary pH to normal levels (normal range 4,68 - 5,19). In the 4 patients who were unable to reduce pH below 5,40, TA production was decreased. Ammonium excretion was also decreased in 2 of these patients, but was normal when corrected for urine pH. The 1 patient with systemic acidosis present before acid loading died subsequently from progressive renal failure. In 1 patient, who was able

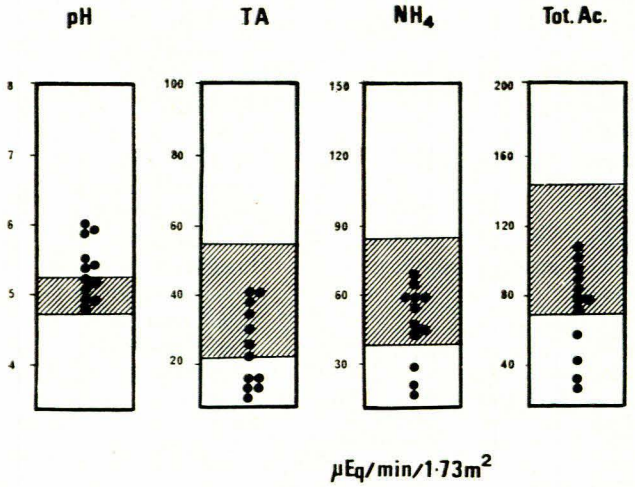

Fig. 2. Lowest urinary pH, greatest amount of titratable acid (TA), ammonium (NH_4), and total acid (Tot. Ac.) excreted after an acid load. Shaded areas represent mean ± 2 SD of control values.

to lower urine pH to 5,12, total hydrogen ion production was reduced as a result of impairment of excretion of both TA and ammonium.

Glycosuria was found in 1 patient, who was known to have diabetes mellitus, and who had no defect in renal function. Urinary tract infection was detected in 1 patient, who demonstrated a trivial defect in acidification. Total serum globulin was elevated in 7 patients and in 3 of these impaired acid excretion was present (Table II). Serum γ-globulins, however, were raised in only 2 patients. Thus an inconstant relationship existed between renal tubular acidosis and serum γ-globulin levels. Alpha$_2$-globulin was raised in the patient who demonstrated a pattern of acid excretion similar to that found in chronic renal failure.

Total haemolytic complement was reduced in 7 patients (Table II), 2 of whom had no evidence of renal disease. The other 5 had defects in acidification, the disorder being minimal in 2 cases. Of the 3 patients with low complement levels and more severe defects, 2 have subsequently died, 1 of renal failure. The other (who was azotaemic and hypertensive) died at home, so the cause of death could not be established. The third patient is being maintained on chronic dialysis. Renal biopsies were performed on 4 of the patients who were known to have renal disease before entering this study, confirming the clinical diagnosis of lupus nephritis.

DISCUSSION

Twelve patients with SLE were selected for this study. In 6, renal impairment had been demonstrated previously. At the time of the study, all parameters of renal function tested were normal in 4 patients. Impaired tubular function was found in 8 of the 12 patients, including 5 with normal glomerular filtration rates (GFR). Five of the 12 patients exhibited proteinuria; all had abnormal tubular function, while in only 3 was the GFR diminished. The reduced reabsorption of phosphate found in 2 patients cannot be explained by parathyroid overactivity, or by a reduction in the GFR. In 1 patient, the defect could have been secondary to prednisone treatment, since it has been shown in dogs that corticosteroids may inhibit the tubular reabsorption of phosphate.[12] TA production was reduced in 4 of the 6 patients who failed to lower their urine pH to normal levels. Ammonium production was normal in these patients, when corrected for urine pH. One patient showed low TA and ammonium excretion, but produced urine with a pH in the normal range.

Several immune disorders have been described in association with a renal tubular acidosis. These include multiple myeloma,[13] Sjögren's syndrome,[1,2,14] hyperglobulinaemic purpura,[15] chronic active hepatitis[5] and SLE.[3] In all these conditions, except multiple myeloma, where a proximal renal tubular acidosis occurs, the tubular acidosis is of the distal variety. Distal renal tubular acidosis is characterized by a failure to produce urine of low pH. The tubules are unable to excrete hydrogen ions against a concentration gradient. In this

TABLE II. SERUM PROTEINS

Patient	LE	Globulins* (g/100 ml)	Gammaglobulins*	Complement* (C'H50 u/ml)	Tubular function
1	+	2,2	1,6	46	Normal
2	−	3,9	1,8	294	Normal
3	+	3,3	1,6	161	Normal
4	+	3,3	ND	217	Normal
5	+	3,6	1,9	50	Normal
6	−	4,0	1,9	217	Defective
7	−	2,5	1,4	217	Defective
8	+	1,7	1,4	86	Defective
9	+	3,7	2,6	0	Defective
10	+	4,1	2,6	128	Defective
11	+	2,5	1,4	109	Defective
12	−	2,5	1,0	24	Defective

* Normal: globulin: 1,5 - 3,0 g/100 ml; gammaglobulin: 1,0 - 1,8 g/100 ml; complement: 160 - 210 C'H50 u/ml.

variety of renal tubular acidosis, TA excretion is impaired. In the complete form, which is associated with a basal systemic acidosis, ammonium excretion is also reduced, but it is normal when corrected for urine pH. This was seen in 1 of our patients (case 12), who subsequently died of progressive renal failure. At the time of the study, her creatinine clearance was 45 ml/min/1,73 m^2 and, in view of the report by Elkinton,[16] that acidosis does not usually occur until glomerular filtration rate is below 20 ml/min, it is unlikely that her acidosis was due to generalized renal failure. In the incomplete variety of renal tubular acidosis, found in 5 of our patients, no systemic acidosis occurs and ammonium production, when corrected for urine pH, is supranormal. Three of these patients with distal renal tubular acidosis exhibited another defect of distal tubular function, namely a failure to concentrate urine normally.

In generalized renal failure, although urinary pH is usually low, total acid excretion is reduced as a result of impaired ammonium excretion and, to a lesser extent, reduced TA excretion. The lowered TA production in patients with generalized renal failure is secondary to the reduced filtration of phosphate. One of our patients (case 10) exhibited this pattern of acid excretion, but he had relatively good renal function as judged by the creatinine clearance of 82 ml/min/1,73 m^2.

As renal tubular acidosis may also be secondary to hyperparathyroidism, hypokalaemia, hypercalcaemia and pyelonephritis, each patient was screened for evidence of these conditions. In 2 patients with minimal defects in acidification and normal GFRs, the disorder may possibly have been secondary to a urinary tract infection in one, and hypokalaemia in the other.

It has been suggested that the hypergammaglobulinaemia found in 'auto-immune' diseases may be responsible for the disturbance in acidification described in these disorders.[17,1] Impairment of acid excretion could be due to reabsorption of filtered globulins by the tubular cells. Since the proximal tubule is the major site of protein reabsorption, one would expect a proximal tubular acidosis to occur. However, it is possible that globulins could reach the distal tubular cells by leaking out of peritubular capillaries, damaged by the immune process. In cases of multiple myeloma associated with the Fanconi syndrome, protein-like inclusion bodies have been demonstrated in the proximal tubular cells.[18] In patients with distal tubular acidosis, however, inclusion bodies have not been demonstrated in the distal tubules. The possibility that hypergammaglobulinaemia may impair circulation in the distal peritubular vessels either by increasing viscosity or by producing a vasculitis, has also been postulated.[2] However, no histological evidence of vascular damage has been noted.[2,3] It has been suggested[14] that there may be specific antibodies, reacting with tubular cells. In Sjögren's syndrome[2,14,19] where peritubular infiltrates of round cells are prominent in the kidney, immunoglobulin and complement deposits have been described in the tubular cells of patients with renal tubular acidosis. However, different workers[20,21] have failed to detect immunoglobulins in tubular cells of patients with hypergammaglobulinaemia due to other causes.

The occurrence of renal tubular acidosis in the absence of hypergammaglobulinaemia in many of our patients, leads us to believe that hypergammaglobulinaemia is not the main factor producing this disturbance of renal function. This is in agreement with the work of Tu and Shearn,[3] who also studied a group of patients with SLE. However, Morris and Fudenberg[17] demonstrated a high incidence of renal tubular acidosis in patients with hypergammaglobulinaemia and Talal *et al.*[14] found significantly raised globulin levels in patients with renal tubular acidosis.

It has been shown that a fall in serum complement in SLE may herald the onset of an active phase of the disease.[22,23] It is commonly associated with renal involvement and thus may be a guide to prognosis in SLE.[24] In our study, the combination of low serum complement and renal tubular acidosis carried a particularly poor prognosis, as 2 patients died, and the third is requiring chronic dialysis.

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REFERENCES

1. Shearn, M. A. and Tu, W. H. (1968): Ann. Rheum. Dis., **27**, 27.
2. Shioji, R., Furuyama, T., Onodera, S., Saito, H., Ito, H. and Sasaki, Y. (1970): Amer. J. Med., **48**, 456.
3. Tu, W. H. and Shearn, M. A. (1967): Ann. Intern. Med., **67**, 100.
4. Mason, A. M. S., McIllmurray, M. B., Golding, P. L. and Hughes, D. T. D. (1970): Brit. Med. J., **4**, 596.
5. Seedat, Y. K. and Raine, E. R. (1965): S. Afr. Med. J., **39**, 595.
6. Harvey, A. M., Shulman, L. E., Tumulty, P. A., Conley, C. L. and Schoenrich, E. H. (1954): Medicine (Balt.), **33**, 291.
7. Edwards, K. D. G., Stewart, J. H., Asheley, B. C. E. and Whyte, H. M. (1964): Proceedings of the Australian Association of Clinical Biochemists, **1**, 101.
8. Wrong, O. and Davies, H. E. P. (1959): Quart. J. Med., **28**, 259.
9. Conway, E. J. (1947): *Micro-diffusion Analysis and Volumetric Error*, London: Crosby Lockwood.
10. Van Slyke, D. D. and Neill, J. M. (1924): J. Biol. Chem., **61**, 523.
11. Kent, J. P., Bukantz, S. C. and Rein, C. R. (1946): J. Immun., **53**, 37.
12. Roberts, K. E. and Pitts, R. F. (1953): Endocrinology, **52**, 324.
13. Constanza, D. J. and Smoller, M. (1963): Amer. J. Med., **34**, 125.
14. Talal, N., Zisman, E. and Schur, P. H. (1968): Arthritis Rheum., **11**, 774.
15. Mason, A. M. S. and Golding, P. L. (1970): Brit. Med. J., **3**, 143.
16. Elkinton, J. R. (1963): Med. Clin. N. Amer., **47**, 935.
17. Morris, R. C. and Fudenberg, H. H. (1967): Medicine (Balt.), **46**, 57.
18. Engle, R. L. and Wallis, L. A. (1957): Amer. J. Med., **22**, 5.
19. Talal, N. (1971): Ann. Intern. Med., **74**, 633.
20. McCurdy, D. K., Cornwell, G. G. and De Pratti, V. J. (1967): *Ibid.*, **67**, 110.
21. Wilson, D., Williams, R. C. and Tobian, L. (1967): Amer. J. Med., **43**, 356.
22. Schur, P. H. and Sandson, J. (1968): New Engl. J. Med., **278**, 533.
23. Williams, R. C. and Law, D. H. (1958): J. Lab. Clin. Med., **52**, 273.
24. Townes, A. S., Stewart, C. R. and Osler, A. G. (1963): Bull. Johns Hopk. Hosp., **112**, 202.