Glomerular and Tubular Function in the Transplanted Kidney

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INTRODUCTION

Glomerular filtration (GFR) as measured by the serum creatinine level and the creatinine clearance is commonly used as an index of renal function in the transplanted kidney (Massry et al, 1967; Henderson et al, 1968; Györy et al, 1969). Assessment of tubular function is seldom performed, even though disturbances have been described (Massry et al, 1967).

The purpose of this study was to examine selected parameters of tubular function as well as glomerular filtration rate in the transplanted kidney.

PATIENTS AND METHODS

Thirteen renal cadaver allograft recipients aged 24 to 49 years were studied 3 to 46 months after transplantation. Bilateral nephrectomies had been performed in 9 of these patients prior to transplantation. Oliguria lasting 2 to 14 days occurred in 4 patients. During the first four weeks 10 patients received local graft irradiation and 3 antilymphocyte globulin. At the time of investigation all patients were still receiving azathioprine and prednisone. Diuretics were stopped for 48 hours and other non-essential drugs for 24 hours before the test. No episode of rejection had occurred in the previous two months.

Fourteen healthy volunteers aged 19 to 40 years with both kidneys intact acted as controls.

The protocol used during the investigation followed essentially that of Edwards et al (1964). Included was the collection of two arterial blood samples, two 3-hour timed urine specimens and then one 2-hour urine specimen. Parameters measured were the creatinine clearance, phosphate, alpha-amino-nitrogen and protein excretion, and the maximal urinary concentration after injection of pitressin. The ability to handle an acid load was tested (Wrong & Davies, 1959). Urine pH and acid excretion were
measured in the last 2 urine collections. Standard laboratory methods were used for biochemical analyses. Alpha-amino-nitrogen was measured by the method of Rubenstein and Pryce (1959).

RESULTS

The creatinine clearance (Ccr) was significantly lower in the grafted patients (Figure 1), averaging 65% of the mean value of the control subjects. Urine protein excretion was increased in 5 patients, being greater than 1 mg/min in 3 of these patients.

![Figure 1. Renal function in transplanted kidneys. Shaded areas represent mean ± 2 SD of control values. Ccr = creatinine clearance; TRP = tubular reabsorption of phosphate; α-amino N2 = urinary α amino nitrogen; OSM = urinary osmolality following pitressin.](image)

Various defects in tubular function were also present (Figure 1). Tubular reabsorption of phosphate (TRP) was reduced in 7 patients, two of whom had other evidence suggesting hyperparathyroidism. In no patient was the serum calcium elevated. Urinary alpha-amino-nitrogen excretion was increased in 3 patients. Glycosuria was present in a patient with steroid induced diabetes.

Urine osmolality following parenteral pitressin was below the control range in 4 patients. However, when allowance was made for comparing patients having single kidneys with controls have two kidneys (Györy et al, 1969), the ability to concentrate urine was defective in only two patients.

The ability to lower urine pH in the presence of a systemic acidosis induced by ammonium chloride loading, was markedly impaired in three patients (Figure 2), studied at 3, 17 and 45 months after transplantation. Systemic acidosis was not present before the test. In these patients titratable acid excretion (TA) was impaired; Ammonium (NH4) excretion was

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normal and when corrected for urinary pH was supranormal in one patient. Total acid excretion (NH$_4$ + TA - HCO$_3$) was reduced in two patients. Despite a plasma potassium concentration of 3.6 mEq/l on the study day we suspected depletion of the total body potassium because in the previous three months plasma potassium had ranged between 2.9 and 3.4 mEq/l. A repeat test 10 days after discontinuing frusemide and administering spironolactone and oral potassium chloride, showed a normal response to ammonium chloride loading (Figure 2), urine pH dropping to 5.17, titratable acid production rising into the normal range and ammonium excretion increasing.

![Figure 2. Lowest urinary pH and greatest amount of titratable acid (TA) and ammonium (NH$_4$) excreted following an acid load. Shaded area represents mean ± 2 SD of control values. Effect of K replacement is shown in 1 patient. Tot AC = total acid excretion following acid load (ammonium + titratable activity - bicarbonate)](image)

In a further four patients a minor defect in acid excretion existed in that a pH of 5.2 or lower was not achieved. One of these patients (EB), investigated 30 months after transplantation showed a defect in titratable acid excretion, with normal ammonium excretion and reduced total acid excretion. Urinary phosphate excretion was normal or elevated in all the patients studied.

**DISCUSSION**

Of the 13 transplant recipients only 4 had completely normal tubular function, one of whom had mild proteinuria. GFR was relatively well preserved in most of the recipients, averaging 65% of the mean control values. Ogden (1967) studying live donors found that the GFR after unilateral nephrectomy averaged 71% of the pre-operative value in the same patients.

When comparing the concentrating ability of patients with single kidneys
with subjects having 2 kidneys, account must be taken of the increased water and solute load per nephron in the single kidney, (Györy et al, 1969). Making appropriate corrections we found that two recipients had defective urinary concentration.

The one patient who had a marked amino-aciduria also had a grossly impaired tubular reabsorption of phosphate, a raised serum alkaline phosphatase and bony changes due to secondary hyperparathyroidism. As tubular function was otherwise normal the amino-aciduria and phosphaturia probably resulted from excessive parathyroid hormone secretion (Muldowney et al, 1968). The abnormally high excretion in this patient was presumably due to the increased phosphate buffer available (Pitts et al, 1948).

In the three patients with an inability to lower urinary pH below 6.1, and in patient EB, the pattern of acid excretion coupled with an absence of systemic acidosis under basal conditions produced a picture clearly resembling the incomplete syndrome of renal tubular acidosis (Wrong & Davies, 1959). The decreased titratable acid production in these patients could not be accounted for by a lowered GFR and a diminished load of phosphate buffer, as occurs in generalised renal failure (Wrong & Davies, 1959). Furthermore ammonia production was normal or elevated in contrast to the situation in patients with generalised renal failure. Excessive parathyroid hormone secretion may also produce renal tubular acidosis (Muldowney et al, 1968), however there was no overt evidence of hyperparathyroidism in the above patients. In one patient the renal tubular acidosis was clearly a result of potassium depletion and corrected by potassium replacement. We therefore recommend that patients on high dosage steroids receive potassium supplements and that a potassium sparing diuretic be used when diuretics are indicated.

The pathogenesis of renal tubular dysfunction in the transplanted kidney is obviously multifactorial and various mechanisms have been postulated including ischaemic damage, rejection and immunosuppressive therapy. In particular azathioprine has been suspect (Massry et al, 1967). Supporting this contention is the work (Rabkin et al, 1971) with amphibian skin which suggests that this drug does produce a disturbance in cellular sodium transport, which may in part explain the disturbance in sodium metabolism seen after transplantation (Henderson et al, 1968).

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