The Korean Journal of Internal Medicine
Vol. 16, No. 2, June, 2001

Urinary Stones following Renal Transplantation

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Background : *The formation of urinary tract stones following renal transplantation is a rare complication. The clinical features of stones after transplantation differ from those of non-transplant patients. Renal colic or pain is usually absent and rarely resembles acute rejection.*

Methods : *We retrospectively studied 849 consecutive kidney transplant patients in The Rogosin Institute/The Weill-Cornell Medical Center, New York who were transplanted between 1980 and 1997 and had functioning grafts for more than 3 months, to determine the incidence of stone formation, composition, risk factors and patient outcome.*

Results : *At our center, urinary stones were diagnosed in 15 patients (1.8%) of 849 functioning renal grafts for 3 or more months. Of the 15 patients, 10 were males and 5 were females in their third and fourth decade. Eight patients received their transplant from living donors and 7 from cadaveric donors. The stones were first diagnosed between 3 and 109 months after transplantation (mean 17.8 months) and 5 patients had recurrent episodes. The stones were located in the bladder in 11 cases (73.3%), transplanted kidney in 3 cases and in multiple sites in one case. The size of stones varied from 3.4 mm to 40 mm (mean 12 mm). The composition of stones was a mixed form of calcium oxalate and calcium phosphate in 5 cases and 4 patients had infected stones consisting of struvite or mixed form of struvite and calcium phosphate. Factors predisposing to stone formation included tertiary hyperparathyroidism (n=8), hypercalciuria (n=5), recurrent urinary tract infection (n=5), hypocitraturia (n=4), and obstructive uropathy (n=2). Many cases had more than one risk factor. Clinically, painless hematuria was observed in 6 patients and dysuria without bacteriuria in 5 patients. None had renal colic or severe pain at any time. There were no changes in graft function at diagnosis and after removal of stones. Five patients passed stones spontaneously and 8 patients underwent cystoscopy for stone removal.*

Conclusion : *Urinary stone formation following kidney transplantation is a rare complication (1.8%). Hyperparathyroidism, hypercalciuria, recurrent urinary tract infection and hypocitraturia are the most common risk factors, but often there are multiple factors which predispose to stone formation. To detect stones and determine their location and size, ultrasonography appears to be the most useful diagnostic tool. Prompt diagnosis, the removal of stones and stone-preventive measures can prevent adverse effects on renal graft outcome.*

Key Words : *Urinary stones (calculi); Kidney transplantation; Calcium oxalate; Hyperparathyroidism*

INTRODUCTION

Urinary stones following renal transplantation is a rare complication. Less than 150 cases of this complication

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have been reported in the literature since the earliest report by Hume et al. in 1966[1]. Many of the clinical features of urinary stones after transplantation differ from those of non-transplant patients. Typical renal colic or pain is usually absent because of denervation of the transplant kidney and ureter. Rarely, the presentation resembles acute rejection or acute tubular necrosis[2, 3]. We retrospectively reviewed our renal transplant recipients to study the incidence of urinary stone disease, risk factors for stone formation, composition of the stones and clinical outcome.

MATERIALS AND METHODS

Study subjects included 849 consecutive kidney transplant recipients in The Rogosin Institute/The Weill-Cornell Medical Center New York who were transplanted between 1980 and 1997 and had functioning grafts for 3 or more months. At surgery, all patients underwent a ureteroneocystostomy where the ureter is tunnelled into the bladder. Most patients were treated with triple immunosuppressive therapy consisting of prednisone, azathioprine and cyclosporine. Some received mycophenolate mofetil instead of azathioprine. All stones were diagnosed by ultrasonography and confirmed by radiography and cystoscopy. Patients with stones were studied for routine biochemical investigations using standard laboratory procedures. Serum iPTH was measured by radioimmunoassay by the Smith-Kline Laboratories, Lake Success, New York. Twenty-four hour urine specimens were collected in jars containing 25 mL of 6N HCl for creatinine, calcium, citrate, oxalate and uric acid excretion. In a small number of patients, analysis of the 24-hour urine was performed as the UroRisk Diagnostic Profile by Mission Pharmacal Reference Laboratory, San Antonio, Texas. The stones were chemically analysed by Louis C. Herring Laboratories, Orlando, Florida. In our study, hyperparathyroidism was defined as hypercalcemia (> 10.5 mg/dL), along with inappropriately elevated serum intact parathyroid hormone level (> 54 pg/mL). Hypercalciuria was defined as a 24-hour urinary calcium excretion of more than 300 mg in a male and 200 mg in a female while on an unrestricted diet. Hyperoxaluria was defined as more than 40 mg of oxalate, hyperuricosuria as more than 750 mg of uric acid and hypocitraturia as less than 300 mg of citrate in a 24-hour urine collection.

RESULTS

Urinary stones were diagnosed in 15 of 849 transplant patients (incidence: 1.8%). Underlying kidney diseases included chronic glomerulonephritis in 7 cases, hypertension in 2, reflux nephropathy in 2, pyelonephritis in 1, systemic lupus nephritis in 1 and two cases had unknown etiology. None formed urinary stones prior to transplantation. Of the 15 patients, 10 were males and 5 were females. The ages were from 28 to 67 years old (mean 41.5 years old). Eight patients received their renal transplant from living donors and 7 from cadaveric donors. The stones were first diagnosed between 3 and 109 months after transplantation (mean 17.8 months). The duration of follow-up was from 11 to 149 months (mean 58 months). Since the initial episode of stone disease, five patients had recurrent episodes of stone formation over the follow-up period. The stones were located in the bladder in 11 cases (73.3%), the transplanted kidney in 3 cases and in multiple sites in one case. Three patients had stones in the suture materials at ureteroneocystostomy site. The size of stones varied from 3.4 mm to 40 mm (mean 12 mm). The composition of stones was mixed form of calcium oxalate and calcium phosphate in 5 cases while 4 patients had infected stones consisting of struvite or mixed form of struvite and calcium phosphate (Table 1). Clinically painless hematuria was observed in 6 patients and urinary frequency and dysuria without bacteriuria in 5 patients. Four patients were incidentally diagnosed with stones without any significant symptoms or signs. Factors predisposing to stone formation included tertiary hyperparathyroidism in 8 cases, hypercalciuria in 5, recurrent urinary tract inection in 5, hypocitraturia in 4 and obstructive uropathy due to ureteral stenosis in 2 cases. Five cases had more than one risk factor. In no cases were there changes in graft function at diagnosis and after removal of stones. Five patients passed their stones spontaneously and 8 patients underwent cystoscopy for stone removal. Only two patients had been on conservative management. Parathyroidectomy was performed in 2 cases for tertiary hyperparathyroidism (Table 2).

Table 1. Composition of stones

Composition of stones	Number of patients
Calcium oxalate & phosphate, mixed form	5
Pure calcium oxalate	1
Predominant calcium phosphate	3
Struvite (Mg ammonium phosphate)	2
Struvite & calcium phosphate, mixed form	2
Composition not studied	2

Table 2. Outcome of stone patients

Management of stone	Number of patients
Spontaneously passed	5
Cystoscopically removed	8
Parathyroidectomy	2*
Medical treatment only	2

*: Two patients underwent parathyroidectomy after stone removal for tertiary hyperparathyroidism.

DISCUSSION

The formation of urinary stone following renal transplantation is a rare complication. In a review of the literature, the incidence of stones in renal transplant calculi varies from 0.2% to 5.7%, usually less than 1%[4-11]. Shoskes et al. reported 2 cases of 1,000 renal transplants (0.2 %)[12], Lancina et al. reported 16 cases of 794 functioning renal grafts (2%)[13]. Motayne et al. reported 7 cases of 112 patients who underwent a stapled ureteroureterostomy using a commercially available stapling device[14]. We observed 15 cases of stone disease following transplantation (1.8%). The location of stones is usually in the transplanted kidney[4-6, 10, 13, 15]. Klein et al. describe 7 vesicular calculi on the non-absorbable suture at the site of ureteroneocystostomy[16]. In our study, most stones were found in the bladder (73.3%), and three patients had stones on the suture materials at the ureteroneocystostomy site. The composition of renal allograft calculi predominantly consists of calcium oxalate and/or calcium phosphate as in non-transplant patients[2, 3, 7-10, 17]. But it appears that infected stones (struvite and mixed form of struvite and calcium phosphate) occur more frequently after transplantation than in non-transplant subjects[2]. We also found a mixed form of calcium oxalate and calcium phosphate stones in 5 cases and, in one case, pure calcium oxalate. Four patients with infected stones had recurrent episodes of urinary tract infection. There have been a few cases of uric acid stone reported in kidney transplant patients[5, 13, 15]. However, we have not seen a simple case of pure uric acid stone in these series. The rarity of uric acid stone is a remarkable contrast to high incidences of hyperuricemia and gout in kidney transplant patients treated with cyclosporine[18]. The low incidence of uric acid stone, in spite of hyperuricemia, may be explained by impaired renal excretion of uric acid and high urinary pH (partial renal tubular acidosis) in these patients.

The clinical features of stone disease after transplantation differ from non-transplant subjects. Because of denervation of the allograft, the common symptoms and signs, such as hematuria and ureteric obstruction, often occur without pain[2, 19, 20]. Sometimes the presentation may resemble acute rejection or acute tubular necrosis[3, 7, 21]. We observed painless hematuria in over half the patients. In four cases, stones were revealed incidentally by ultrasonography without clinical symptoms. Consonant with their radiodense calcium content, renal calculi are usually detected on plain X-ray films of the abdomen. Computed tomography is an excellent, although expensive, modality to detect stones. Ultrasonography appears to be the most useful diagnostic tool to detect stones and determine their location and size. In our study, all stones were diagnosed by ultrasonography, and confirmed by radiography and/or cystoscopy. Factors predisposing to stone formation are hyperparathyroidism, hypercalciuria, recurrent urinary tract infection and hypocitraturia due to renal tubular acidosis. Less common risk factors include outflow obstruction, foreign bodies such as stents, nephrostomy tubes, suture materials and donor lithiasis[2, 3, 7-10, 17, 22-24]. We also found that risk factors for stone formation include hyperparathyroidism, hypercalciuria, recurrent urinary tract infection and hypocitraturia. Brien et al. observed that stone patients had long ischemic time, a delay in onset of normal graft function, high incidence of complications at the site of the transplanted ureter and the urinary bladder, persistent bacteriuria, alkaline urinary pH and postoperative hypercalcemia and hypercalciuria as a consequence of secondary hyperparathyroidism[10].

Following renal transplantation and restoration of adequate kidney function, the secondary hyperparathyroidism resolves spontaneously in the majority of patients and one would expect normalization of the serum calcium[25, 26]. However, David et al. reported hypercalcemia after transplantation in 30% of 64 transplant recipients 1 to 3 years after transplantation[27]. They found that the onset of the hypercalcemia occurred between one day and one year after transplantation and evidence of persistent secondary hyperparathyroidism with raised serum parathyroid hormone was noted in all hypercalcemic patients. Alfrey et al. cited that the high doses of steroids normally administered during the first 1-2 months after transplantation may be responsible for late onset post-transplant hypercalcemia[28]. We think that early reconstitution of normal production of 1,25-(OH)$_2$ vitamin-D by the transplanted kidney, as well as

persistent hyperparathyroidism, facilitates post-transplant hypercalcemia. Many authors have the opinion that hyperparathyroidism is the main cause of post-transplant stones and, therefore, calculus formation is an indication for immediate parathyroidectomy[29-33]. Tertiary hyperparathyroidism developing or manifesting itself after a successful renal allograft may resolve spontaneously[25, 34], but such involution may take several years. The challenge is whether to treat tertiary hyperparathyroidism soon after renal transplantation by subtotal parathyroidectomy or to try a longer period of conservative management[25, 35]. Since target organ damage appears infrequently in post-transplant hyperparathyroidism, a policy of routine parathyroidectomy in asymptomatic hypercalcemic patients seems unwarranted[10, 36, 37]. In our study, most patients with stones had them removed by cystoscopy and 6 patients spontaneously passed stones. Parathyroidectomy was performed in 2 cases with persistent hypercalcemia and recurrent episodes of stone formation. None of these patients had compromise in renal graft function.

In summary, urinary stone formation following kidney transplantation is a rare complication (1.8%). Hyperparathyroidism, hypercalciuria, recurrent urinary tract infection and hypocitraturia are common risk factors, but often multiple factors predispose to stone formation. Ultrasonography appears to be the most useful diagnostic tool to detect stones and determine their location and size. Prompt diagnosis, the removal of stones and stone-preventing precautionary measures help prevent adverse effects on renal graft outcome.

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