Urologia Internationalis

Research Article

Urol Int 2024;108:399–405
DOI: 10.1159/000539091

Received: January 17, 2024
Accepted: April 24, 2024
Published online: April 29, 2024

Bladder Stones in Renal Transplant Patients: Presentation, Management, and Follow-up

Maxwell Sandberg[a] Adam Cohen[a] Megan Escott[a] Davis Temple[b] Claudia Marie-Costa[b] Rainer Rodriguez[b] Alex Gordon[c] Anita Rong[b] Brian Andres-Robusto[b] Emily H. Roebuck[b] Wyatt Whitman[a] Christopher J. Webb[d] Robert J. Stratta[d] Dean Assimos[a, e] Kyle Wood[e] Maajid Mirzazadeh[a]

[a]Department of Urology, Atrium Health Wake Forest Baptist Medical Center, Winston Salem, NC, USA; [b]Wake Forest University School of Medicine, Winston Salem, NC, USA; [c]Edward Via College of Osteopathic Medicine, Blacksburg, VA, USA; [d]Section of Transplantation, Department of Surgery, Atrium Health Wake Forest Baptist Medical Center, Winston Salem, NC, USA; [e]Department of Urology, University of Alabama Birmingham Medical Center, Birmingham, AL, USA

Keywords
Bladder stones · Kidney transplant · Nephrolithiasis · Calculus

Abstract
Introduction: The study aim was to analyze the presentation, management, and follow-up of renal transplant patients developing bladder calculi. ***Methods:*** Patients who underwent renal transplant with postoperative follow-up at our institution were retrospectively analyzed (1984–2023) to assess for the development of posttransplant bladder stones. All bladder stones were identified by computerized tomography imaging and stone size was measured using this imaging modality. ***Results:*** The prevalence of bladder calculi post-renal transplantation during the study window was 0.22% (N = 20/8,835) with a median time to bladder stone diagnosis of 13 years post-transplant. Of all bladder stone patients, 6 (30%) received deceased donor and 14 (70%) living donor transplants. There were 11 patients with known bladder stone composition available; the most common being calcium oxalate (N = 6). Eleven (55%) patients had clinical signs or symptoms (most commonly microhematuria). Fourteen of the bladder stone cohort patients (70%) underwent treatment including cystolitholapaxy in 12 subjects. Of these 14 patients, 9 (64%) were found to have nonabsorbable suture used for their ureteroneocystostomy closure. ***Conclusions:*** The prevalence of bladder stones post-renal transplant is low. The utilization of nonabsorbable suture for ureteral implantation was the main risk factor identified in our series. This technique is no longer used at our institution. Other factors contributing to bladder stone formation in this population warrant identification.

karger@karger.com
www.karger.com/uin

Karger
OPEN ACCESS

Correspondence to:
Maxwell Sandberg, maxwellsandberg@msn.com

Introduction

The formation of bladder calculi (stones) is a rare complication following renal transplantation, with a reported prevalence of 1–3% [1, 2]. While kidney stones in the transplant population are well described [3, 4], there is a paucity of information regarding the development of bladder stones in this group. In the general population, bladder stones may be asymptomatic or manifest with symptoms including abdominal pain, gross hematuria, urinary frequency, dysuria, or with urinary tract infection (UTI). However, symptomatology for renal transplant recipients is not well characterized. Moreover, the presence of bladder stones may require surgical removal in the setting of immunosuppression, which may predispose patients to potential complications. Thus, there is a need to better characterize the natural history and risk factors of such stones in this unique patient population. The study aims were to determine the prevalence of bladder stones developing in this cohort at a single, high volume renal transplant center, and characterize the presentation, management, and follow-up of those afflicted.

Methods

This was a retrospective analysis of all patients who underwent renal transplantation and follow-up at Atrium Health Wake Forest Baptist Medical Center from 1984 to 2023, or had a kidney transplant elsewhere and were followed at our institution during this interval. After obtaining Institutional Review Board approval (IRB00093774), patient information from an institutional renal transplant database was used to identify those individuals who developed bladder calculi following kidney transplantation. Computerized tomography (CT) imaging was used to make the diagnosis of bladder calculi and measure stone size which was defined as maximal diameter of the stone(s). Follow-up CT scans were used to track bladder stone size over time after initial diagnosis in those where observation was initially undertaken. The majority of asymptomatic patients underwent CT imaging for evaluation of peri-graft fluid collections, and hydronephrosis detected with ultrasonography. Prostate volumes were calculated from CT scans using the ellipsoid formula (length*width*height*[π/6]). Patients with any known bladder stones before transplant were excluded as were those with inadequate follow-up laboratory data. Patients who had foreign body suture associated with the development of bladder stones had it extracted at the same time as stone removal. Lower urinary tract symptoms were defined as obstructive symptoms, urgency, and frequency with urination.

Symptoms/signs associated with bladder stone(s) were classified as fever, costovertebral angle tenderness, microhematuria, dysuria, abdominal pain, groin pain, and gross hematuria. Microhematuria was defined as >3 red blood cells/high-powered field on urinalysis. The suture used during ureteral anastomosis for each transplant was also recorded as either nonabsorbable or absorbable. All bladder calculi were of mixed composition and characterized by the predominant stone type. Basic metabolic panel and complete blood count data were analyzed with utilization of values closest to the date of stone identification. All statistical analyses were descriptive to determine medians, means, and frequencies of patient variables which were carried out using IBM SPSS Statistics Version 28 (Armonk, NY, USA).

Results

Data from 8,835 kidney transplant patients who met inclusion criteria were reviewed. Of all patients, 20 (0.22%) were found to have developed bladder stone(s) posttransplant (Table 1). The median time to bladder stone diagnosis was 13 years after renal transplant. The median number of bladder stones formed was 1, with a mean maximum size dimension on CT scan of 10.6 mm per stone. Eleven of 20 (55%) patients had symptoms or signs of bladder stones; most common being microhematuria. Nine (45%) had nonabsorbable suture used for their ureteral anastomosis, and 7 out of 9 (78%) were living donor transplants. Most patients (14/20; [70%]) underwent surgical treatment for their bladder stones; cystolitholapaxy and removal of any foreign body suture being the most common procedure. Calcium oxalate was the most common stone composition (N = 6; 30%). There were 3/20 (15%) of patients who developed renal graft failure after the diagnosis of their bladder stone(s), at a median of 17.5 months following transplantation. At latest follow-up, 14/20 (70%) of patients had died, at a median of 2 years after bladder stone diagnosis and 18 years following renal transplantation.

Nineteen of 20 (95%) of patients had urologic evaluation after the identification of their bladder stone(s) (Table 2). There were 3 (15%) with imaging confirmed vesicoureteral reflux of their transplant graft. One patient had a stricture of their transplant ureter. Looking at micturition symptoms, 10/20 (50%) had obstructive voiding symptoms, 9/20 (45%) urgency, 10/20 (50%) increased urinary frequency, and 3/20 (15%) urinary retention. Of note, 2 patients with a history of urinary retention were males and 1 was female. The median prostate volume of males in the study was 30 cc. Nine of 20 (45%) received medical therapy for management of voiding symptoms, all males. Medical therapy was with prescription medications, and all 9 patients were on tamsulosin, with a minority also on combination therapy

Table 1. Bladder stone demographics

Variable	
Total patients	20
Age at transplant, years	32 (24–54)
Gender	
Male	16
Female	4
Type of primary transplant, *n* (%)	
Deceased	6 (30)
Living	14 (70)
More than 1 transplant, *n* (%)	12 (60)
Median time after transplant to stone identification, years	13 (5–18)
Mean number stone size (range)	10.6 (2–23)
Symptomatic stone, *n* (%)	11 (55)
Fever	0
Costovertebral angle tenderness	0
Groin pain, *n* (%)	1 (9)
Nausea	0
Abdominal pain, *n* (%)	1 (9)
Microhematuria, *n* (%)	5 (50)
Gross hematuria, *n* (%)	2 (20)
Dysuria, *n* (%)	4 (40)
Received treatment for stone, *n* (%)	14 (70)
Type of treatment, *n* (%)	
SWL	0
Ureteroscopy	0
PCNL	0
Cystolitholapaxy	12 (86)
Other	2 (14)
Stone free after treatment, *n* (%)	12 of 14 (86)
Predominant stone composition, *n* (%)	
Calcium oxalate	6 (30)
Calcium phosphate	2 (10)
Struvite	2 (10)
Uric acid	1 (5)
Other	0 (0)
Unknown	9 (45)
Developed graft failure (after stone), *n* (%)	3 (15)
Median time to graft failure after transplant, months	17.5 (9–26)
Mortality, *n* (%)	14 (70)
Median time to death after stone identification, years	2 (0.75–5)
Median time to death after transplant, years	18 (8–22)
Median magnesium, mg/dL	1.8 (1.6–1.9)
Median phosphorous, mg/dL	2.9 (2.5–3.5)
Median serum creatinine, mg/dL	1.6 (1.3–2.5)
Median hemoglobin, g/dL	13.4 (11.5–15.2)
Median platelet count	186,000 (128,750–255,750)
Median absolute neutrophil count	5,100 (3,500–8,500)
Median absolute lymphocyte count	1,500 (900–2,000)
Median monocyte count	700 (400–700)
Suture, *n* (%)	
Absorbable	5 (25)
Nonabsorbable	9 (45)
Missing data	6 (30)

Table 1 (continued)

Variable	
Immunosuppression, *n* (%)	17 (85)
Mycophenolate/tacrolimus, *n* (%)	6 (32)
Prednisone/tacrolimus, *n* (%)	2 (11)
Tacrolimus, *n* (%)	2 (11)
Cyclosporine, *n* (%)	2 (11)
Cyclosporine/prednisone, *n* (%)	1 (5)
Cyclosporine/mycophenolate, *n* (%)	1 (5)
Cyclosporine/mycophenolate/tacrolimus, *n* (%)	1 (5)
Alemtuzumab/mycophenolate, *n* (%)	1 (5)
Prednisone/mycophenolate/rituximab, *n* (%)	1 (5)

The above table lists all stone-relevant variables reviewed in the study population. Continuous variables are reported as medians with interquartile ranges in parentheses with the exception of stone size which is a mean with range. Categorical variables are reported as total numbers with percentages of the total in parentheses. Complete blood count and basic metabolic panel laboratory data were taken as close to the date of stone identification as possible.

Table 2. Urologic histories

Urologic variable	Total number
Urologic follow-up	19 (95)
Reflux	3 (15)
Stricture	1 (5)
Obstructive symptoms	10 (50)
Urgency	9 (45)
Frequency	10 (50)
Urinary retention	3 (15)
Median prostate volume (cc)	30 (21–38)
Micturition medication	9 (45)
History of UTI	7 (35)
Urologic surgery	8 (40)
Radical nephrectomy	2 (25)
Mitrofanoff procedure	1 (13)
Laser vaporization of prostate	1 (13)
Orchiectomy and nephroureterectomy	1 (13)
Radical prostatectomy	1 (13)
Bladder augmentation	1 (13)
Inflatable penile prosthesis	1 (13)

The above table lists all urologic history reviewed in the study population. Variables are reported as total numbers with percentages of the total in parentheses with the exception of prostate volume which is a median with interquartile ranges.

with finasteride. Seven patients had culture confirmed UTIs. Eight patients had a prior history of urologic surgery before bladder stone identification, and their operations are listed in Table 2. The most common operation was radical nephrectomy ($N = 2$). Seventeen of 20 (85%) patients were on immunosuppression at the time of bladder stone identification. The most common regimen was mycophenolate and tacrolimus ($N = 6$), and the total complement of immunosuppressive medications is listed in Table 2.

Discussion

After analysis of a large renal transplant patient cohort, we found a low prevalence of bladder calculi postoperatively (0.22%). Estimates of the prevalence of bladder calculi in the general population vary, but are thought to be approximately 8–19% in males and 3–5% in females in Western nations [5]. Moreover, bladder stones account for about 5% of all urinary tract stones formed [6]. While no definitive answer exists as to why the prevalence is much lower in those subjected to renal transplantation, some have hypothesized that the lower glomerular filtration rate in this cohort inhibits stone formation [3]. As noted, bladder stones are more frequently identified in males than females in the general population [7, 8], and the prevalence in our transplant population was also similar to the general population, 4:1 (male to female). We did not find any patient or stone specific variables in female patients that uniquely separated them from males who also formed bladder stones. In addition to being lower than the general population, our bladder stone prevalence was lower than what has been previously reported for renal transplant patients [1, 2, 4]. One potential explanation for this discrepancy is the smaller size of prior studies compared to the current study, which included over 8,800 transplant patients. However, only about one-half of the patients with bladder stones in our series were symptomatic at presentation. Therefore, in the absence of routine CT imaging surveillance, the true prevalence in our study population was likely higher.

Bladder stone diagnosis occurred at a median time of 13 years posttransplant. Publications by Kim et al. [4] and Hahnfeld et al. [1] report shorter time to bladder stone diagnosis, at a mean of 17.8 months and 50.3 months, respectively, while others have reported an interval of bladder stone detection in line with our findings [9]. All bladder stones were of mixed composition; calcium oxalate being the most common which others have reported [2, 10]. We also tracked immunosuppression regimens of all patients with bladder stones. It has been reported that the development of bladder stones is associated with cyclosporine use and is higher in combined kidney pancreas transplants compared to kidney transplants alone [11]. All patients in our study underwent kidney transplant only, but 25% of the cohort were on cyclosporine at the time of stone identification.

In our study, the graft failure rate in bladder calculi patients was 15%, which is slightly higher than prior reports of graft failure for renal transplant patients with bladder calculi [10], but in line with graft failure rates overall for renal transplant recipients [12, 13]. The time to graft failure was short at a median of 17.5 months after transplant, whereas accepted times for graft failure are often longer for both deceased and living donor recipients, many times over 10 years [14]. While we cannot be certain as to the cause of the short time to graft failure, it is possible that bladder calculi or associated factors for their generation have a negative effect on renal graft function.

A variety of laboratory parameters were also collected. Prior work has shown that hyperparathyroidism, hypocitraturia, hypercalciuria, and a prior history of stones in the transplant recipient are risk factors for the subsequent development of bladder and kidney stones [4, 15]. For our study, the median values for all basic metabolic panel and complete blood count data were within normal limits aside from creatinine. Being that these were transplant patients it is unsurprising that the median creatinine level in the study population would be elevated and we do not feel any definitive conclusions can be drawn from the laboratory data analyzed. We also noted that 9 bladder stone patients had nonabsorbable suture used to anastomose the transplant ureter to the bladder. It is well established that patients who have nonabsorbable suture used for ureteral anastomoses during renal transplant have a higher incidence of bladder calculi, with these sutures acting as nidus for both UTIs and calculi [1]. In our series, this was performed by only one surgeon who eventually discontinued this practice. Others have reported this occurrence, but also the development of bladder calculi on absorbable suture [2]. Other factors associated with development of bladder calculi following transplant include the presence of retained ureteral stents which was not a factor in our series [16].

In terms of presentation, symptoms/signs varied, but microhematuria and dysuria were most often seen. In their study, Lipke et al. [2] reported hematuria, UTI, and dysuria as symptoms associated with bladder calculi in renal transplant patients. An assessment for UTI was not uniformly done at the time of stone identification in our series. Seven patients had a history of UTI, indicating there may be an association between UTI and bladder stone formation in renal transplant recipients. Due to the low number of patients with urinary symptoms included in our analysis, a valid assessment for associations cannot be made. In prior studies as in ours, the most common approach for removal of bladder calculi associated with foreign body suture was cystolitholapaxy with lithotripsy and endoscopic suture removal [1, 16]. Only 2 patients who received treatment had a recurrence of their bladder stones during the study window. Risk factors for recurrence were not identified.

A strength of our study was the inclusion of a comprehensive urologic history on each patient. There were 10 patients with obstructive voiding symptoms and three who had documented urinary retention. It is well established that urinary stasis is a risk factor for stone formation [17, 18]. Thus, it makes sense then that our population would have such a high rate of obstructive symptoms. There were 3 patients with documented vesicoureteral reflux involving their transplant graft, another known risk factor for stone formation [19]. The types of prior urologic surgery varied. Two of the procedures (Mitrofanoff, bladder augmentation) could have placed these patients at risk for developing bladder stones. Lastly, as noted, 35% of patients had a history of UTI, and multiple studies have reported associations between UTI, and the development of bladder calculi and upper tract urinary calculi [20, 21].

Our study has several limitations. First, it is subject to the inherent biases of any retrospective review, most notably selection bias. In addition, we included those who had transplants at another institution. We recognize that a full set of patient variables were not available on each patient included in the study, limiting analysis. Moreover, the true prevalence of bladder calculi in our transplant population may be higher given that surveillance imaging of the bladder was not routinely performed.

Conclusions

In summary, the prevalence of bladder stones after renal transplantation is quite low. The majority of patients who are diagnosed have signs and symptoms of such stones. The most common driving factor for stone formation in our series was utilization of nonabsorbable suture for the ureteral anastomosis; a practice that we do not endorse and has been discontinued at our institution. We found a high rate of bladder stones in those who received a living donor graft, but of these 50% had nonabsorbable suture used on their anastomosis. In addition, we saw a high rate of lower urinary tract symptom, in particular obstructive voiding symptoms and prior UTI in our cohort. The reasons for these associations are unclear and warrant further investigation.

Statement of Ethics

This study protocol was reviewed and approved by the Atrium Health Wake Forest Baptist Institutional Review Board, approval number IRB00093774. Written informed consent was not required for this study, and this was approved by the Atrium Health Wake Forest Baptist Institutional Review Board, approval number IRB00093774.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Funding Sources

This study was not supported by any sponsor or funder.

Author Contributions

M.S. organized the project, helped in data collection, and wrote the first draft of the manuscript. A.C. helped in project organization and data collection. M.E. assisted in writing the first draft of the manuscript. D.T., C.M.C., R.R., A.G., A.R., B.A.R., and E.R. helped in organizing and obtaining data collection for the project. W.W. helped in project conceptualization and data collection. D.A., K.W., C.W., R.S., and M.M. were senior organizing authors and assisted in manuscript drafting.

Data Availability Statement

Due to concerns of patient privacy, the data used for analysis in this study is not publicly available. However, upon request a deidentified data set can be obtained from the corresponding author of this manuscript.

References

1 Hahnfeld LE, Nakada SY, Sollinger HW, Rayhill SC, Heisey DM. Endourologic therapy of bladder calculi in simultaneous kidney-pancreas transplant recipients. Urology. 1998;51(3):404–7. https://doi.org/10.1016/s0090-4295(97)00629-8

2 Lipke M, Schulsinger D, Sheynkin Y, Frischer Z, Waltzer W. Endoscopic treatment of bladder calculi in post-renal transplant patients: a 10-year experience. J Endourol. 2004;18(8):787–90. https://doi.org/10.1089/end.2004.18.787

3 Cheungpasitporn W, Thongprayoon C, Mao MA, Kittanamongkolchai W, Jaffer Sathick IJ, Dhondup T, et al. Incidence of kidney stones in kidney transplant recipients: a systematic review and meta-analysis. World J Transplant. 2016;6(4):790–7. https://doi.org/10.5500/wjt.v6.i4.790

4 Kim H, Cheigh JS, Ham HW. Urinary stones following renal transplantation. Korean J Intern Med. 2001;16(2):118–22. https://doi.org/10.3904/kjim.2001.16.2.118

5 Trinchieri A. Epidemiology of urolithiasis: an update. Clin Cases Miner Bone Metab. 2008;5(2):101–6.

6 Schwartz BF, Stoller ML. The vesical calculus. Urol Clin North America. 2000;27(2):333–46. https://doi.org/10.1016/s0094-0143(05)70262-7

7 Halstead SB. Epidemiology of bladder stone of children: precipitating events. Urolithiasis. 2016;44(2):101–8. https://doi.org/10.1007/s00240-015-0835-8

8 Takasaki E, Suzuki T, Honda M, Imai T, Maeda S, Hosoya Y. Chemical compositions of 300 lower urinary tract calculi and associated disorders in the urinary tract. Urol Int. 1995;54(2):89–94. https://doi.org/10.1159/000282696

9 Pisapati VNM, Chanamolu D, Kolatham RR, Narendar T. Posttransplant vesical calculi – a case series. Indian J Transpl. 2019;13(3):184–7. https://doi.org/10.4103/ijot.ijot_5_19

10 Cho DK, Zackson DA, Cheigh J, Stubenbord WT, Stenzel KH. Urinary calculi in renal transplant recipients. Transplantation. 1988;45(5):899–901. https://doi.org/10.1097/00007890-198805000-00011

11 Rhee BK, Bretan PN, Stoller ML. Urolithiasis in renal and combined pancreas/renal transplant recipients. J Urol. 1999;161(5):1458–62. https://doi.org/10.1097/00005392-199905000-00011

12 Lam NN, Boyne DJ, Quinn RR, Austin PC, Hemmelgarn BR, Campbell P, et al. Mortality and morbidity in kidney transplant recipients with a failing graft: a matched cohort study. Can J Kidney Health Dis. 2020;7:2054358120908677. https://doi.org/10.1177/2054358120908677

13 Hart A, Smith JM, Skeans MA, Gustafson SK, Wilk AR, Castro S, et al. OPTN/SRTR 2017 annual data report: kidney. Am J Transplant. 2019;19(Suppl 2):19–123. https://doi.org/10.1111/ajt.15274

14 Poggio ED, Augustine JJ, Arrigain S, Brennan DC, Schold JD. Long-term kidney transplant graft survival–making progress when most needed. Am J Transplant. 2021;21(8):2824–32. https://doi.org/10.1111/ajt.16463

15 Bolen E, Stern K, Humphreys M, Brady A, Leavitt T, Zhang N, et al. Urine metabolic risk factors and outcomes of patients with kidney transplant nephrolithiasis. Clin Kidney J. 2022;15(3):500–6. https://doi.org/10.1093/ckj/sfab208

16 Veltman Y, Shields JM, Ciancio G, Bird VG. Percutaneous nephrolithotomy and cystolithalapaxy for a "forgotten" stent in a transplant kidney: case report and literature review. Clin Transplant. 2010;24(1):112–7. https://doi.org/10.1111/j.1399-0012.2009.01133.x

17 Foo KT. Pathophysiology of clinical benign prostatic hyperplasia. Asian J Urol. 2017;4(3):152–7. https://doi.org/10.1016/j.ajur.2017.06.003

18 Nour HH, Mahmoud TF, Alzaabi L. Asymptomatic uncountable urinary bladder stones removal: play the winner. Dubai Med J. 2020; 3(3):122–5. https://doi.org/10.1159/000509044
19 Madani A, Kermani N, Ataei N, Esfahani ST, Hajizadeh N, Khazaeipour Z, et al. Urinary calcium and uric acid excretion in children with vesicoureteral reflux. Pediatr Nephrol. 2012;27(1):95–9. https://doi.org/10.1007/s00467-011-1936-4
20 Ripa F, Pietropaolo A, Montanari E, Hameed BMZ, Gauhar V, Somani BK. Association of kidney stones and recurrent UTIs: the chicken and egg situation. A systematic review of literature. Curr Urol Rep. 2022;23(9): 165–74. https://doi.org/10.1007/s11934-022-01103-y
21 Miano R, Germani S, Vespasiani G. Stones and urinary tract infections. Urol Int. 2007; 79(Suppl 1):32–6. https://doi.org/10.1159/000104439