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Authors

Freise, Jonathan
Nunez, Miguel
Chi, Thomas
et al.

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Therapeutic Living Donor Nephrectomy for Proximal Ureteral Pathology: A Longitudinal Case Series

Jonathan Freise, Miguel Nunez, Thomas Chi, Marshall Stoller, Chris Freise, and Garrett R Roll

OBJECTIVE To raise awareness that patients with proximal ureteral stricture who elect for nephrectomy can consider donating the kidney. We present a series of patients undergoing therapeutic living donor nephrectomy (TLDN), a scenario in which a patient undergoing nephrectomy for an underlying medical problem donates the kidney to a person with end-stage renal disease. This practice is underutilized, and only a single TLDN with proximal ureteral stricture has been previously described. We aim to help define the indications, risks, and benefits for patients.

METHODS This is a retrospective case series of seven therapeutic donors with proximal ureteral pathology and stone disease. Patient characteristics, donor work up, operative details, and donor and recipient outcome were collected.

RESULTS All seven donors had proximal ureteral pathology, and six of the seven had nephrolithiasis or ureterolithiasis. After electing for nephrectomy, the mean time to TLDN was 57.9 days. No recipients experienced delayed graft function . Mean follow up was 40.1 months (range 8-131), and the most recent follow-up mean creatinine was 1.08 (mg/dL). Graft and recipient survival is 100%. No recipients developed recurrence of ureteral stricture or stones.

CONCLUSION This is the first series demonstrating patients with proximal ureteral stricture, even with concomitant stone disease, may donate kidneys for transplantation. Recipient outcomes suggest this practice is safe, and appropriately selected patients that have already elected for nephrectomy should receive counseling about this opportunity. Importantly, patients who donate a kidney receive waiting list priority if they ever need a kidney transplant in the future. UROLOGY 00: 1−6, 2022. © 2022 Elsevier Inc.

Therapeutic living donor nephrectomy (TLDN) is the process in which a patient with an underlying medical disease who elected to undergo nephrectomy chooses to donate the kidney to a patient with end stage renal disease rather than having the kidney sent to pathology. The United Network for Organ Sharing (UNOS) committee and Organ Procurement and Transplantation Network (OPTN) coined these patients as "therapeutic organ donors". An astounding discrepancy between available organs and patients in need exists,[1,2] so identifying patients who could participate in TLDN could expand the pool of organs.

The process of TLDN,[3,4] has broad applicability to iatrogenic ureteral injuries, strictures, and nephrolithiasis. Proximal ureteral obstruction and stone disease often occur concurrently, and this represents 1 subset of patients undergoing nephrectomy who can be considered.

We share our experience with seven therapeutic donor and recipient pairs, describing our expedited diagnostic work-up and recipient selection, as well as donor and recipient outcomes. We demonstrate that TLND for proximal ureteral obstruction and stone disease, even after multiple interventions on the kidney, is safe and outcomes are excellent without recurrence of stone disease or stricture in recipients. A standard extravesicular ureteroneocystostomy or ureteropyelostomy is usually possible and long-term function is excellent.

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From the Department of Surgery, University of California San Francisco, San Francisco, CA, United States; the School of Medicine, University of California San Francisco, San Francisco, CA, United States; the Department of Urology, University of California San Francisco, San Francisco, CA, United States; and the Department of Surgery, Division of Transplantation, University of California San Francisco, 505 Parnassus Avenue, Box 0780, Floor 08, Room 896, San Francisco, CA 94143, United States

Corresponding author. E-mail: Garrett.roll@ucsf.edu

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MATERIALS AND METHODS

The Committee on Human Research at University of California, San Francisco approved this retrospective chart review (IRB# 20-31396).

The urologist reviewed all potential treatment options with the patient and the patient elected for nephrectomy prior to introducing the concept of donating the kidney to someone else. Potential TLDN candidates were then referred to the transplant team for evaluation. A brief screen for medical contraindications that may affect kidney quality was performed by a kidney transplant nurse coordinator and transplant surgeon. As the scheduling of nephrectomy was ongoing, a prompt diagnostic work-up based on UNOS and OPTN guidelines,[5] including screening for transmissible diseases, age-related cancer screening, serologic testing, and psychosocial evaluation was performed. Work-up also included a nuclear Technetium-99m (99mTc) Mercaptoacetyltriglycine (MAG3) renal scan to determine differential renal function between the kidney planned for removal and the remaining kidney. Potential donors were then presented at our multidisciplinary selection meeting.

An internal match run identified potential recipients from the local transplant deceased donor waiting list. Patients with ESRD were screened for their willingness to accept high kidney donor profile risk donors. Candidates with years of expected waiting time prior to reaching the top of the waiting list were preferred, as were non-obese candidates. Patients with a history of nephrolithiasis or significant dysfunction of the lower urinary tract were also excluded. In recent years, patients with serologic evidence of exposure to Epstein Barr Virus (EBV) were favored to allow belatacept based immunosuppression. Final recipient selection took place at the kidney transplant selection meeting, and the recipient then underwent routine preparation for living donor kidney transplantation. The candidates were informed about the possibility of TLDN and informed consent was obtained. The goal timeframe for work-up was guided by the recipient's planned nephrectomy date.

RESULTS

Therapeutic Living Donors

Seven patients (D1-7) planned for nephrectomy and then elected to move forward with TLDN and their characteristics are listed in Table 1. The mean donor age was 53 years, 5 were female, and the mean body mass index (BMI) was 32 kg/cm^2. 4 patients donated a left kidney. On MAG3 lasix renogram mean function of the kidney to be donated was 43.2%. Donor estimated glomerular filtration rate (eGFR) was considered in the context of donor and recipient age and comorbidities, and recipient waiting time. The anticipated eGFR of the donor after surgery was not considered because this patient was electing for nephrectomy out of medical necessity, unrelated to donation. All 7 donors had proximal ureteral pathology, and 6 of the 7 had nephrolithiasis or ureterolithiasis. A representative example of the appearance of these kidneys is shown in Fig. 1, a coronal reconstruction of computed tomography (CT) scan from patient D7. two patients had their kidney removed for ureteral strictures, two patients for complications related to nephrolithiasis, and three patients donated for iatrogenic ureteral injuries. Donors had undergone multiple procedures including percutaneous nephrostomy and retrograde ureteroscopy prior to nephrectomy. 3 patients, D1, D3, and D5 had a nephrostomy tube, D3 and D5 had the tube at time of nephrectomy. After the patient elected

Table 1. Donor characteristics and outcomes.

Patient	D1	D2	D3	D4	D5	D6	D7
Age at time of donation (y)	47	64	37	55	56	54	57
Gender	Female	Female	Male	Male	Female	Female	Female
Height (cm)	165.1	175.3	172.7	177.8	162.6	162.6	162.6
Weight (kg)	53.5	62.6	169.6	120.7	90.7	72.8	72.6
BMI (kg/m^2)	19.6	20.4	56.9	38.2	34.3	27.5	27.5
Left vs Right kidney donated	Right	Right	Right	Left	Left	Left	Left
Pre-operative eGFR (ml/min)	>60	67	109	78	81	104	74
MAG study	49% right 51% left	47% right 53% left	35.1% right 64.9% left	58% right 42% left	56% right 44% left	55% right 45% left	60% right 40% left
History of nephrostomy tube	Yes	No	Yes	No	Yes	No	No
Reason for donation	Iatrogenic ureteral injury	Ureteral stricture	Iatrogenic ureteral injury	Ureteral stricture	Nephrolithiasis c/b iatrogenic ureteral avulsion	Nephrolithiasis c/b ureteral stricture	Iatrogenic ureteral injury c/b nephrolithiasis and stricture
First urology visit to donation (d)	651	147	272	861	68	195	76
Decision to donate to nephrectomy (d)	68	53	61	100	48	29	46
Most recent eGFR (ml/min)	68	54.5	79	54.5	52	87.5	51

Abbreviations: eGFR = estimated glomerular filtration rate.
c/b = complicated by.

Fig. 1. Coronal reconstruction of D7 CT scan prior to left nephrectomy demonstrating an enlarged left kidney, some renal parenchyma scarring and a dilated collecting system.

to undergo therapeutic nephrectomy, the mean time to their TLDN was 57.9 days. No therapeutic living donors experienced perioperative complications, and no patients who underwent attempted TLDN and were unable to donate the kidney at our institution. TLDN follow up was per the urology nephrectomy standard of care. All donors with nephrolithiasis underwent metabolic stone evaluation and were followed at our comprehensive stone clinic for prevention. Two patients, D5 and D6, did have an episode of stone recurrence months after their nephrectomy, for which D5 underwent shock wave lithotripsy, and D6 underwent stone extraction without lithotripsy. Neither patient has had additional recurrence of nephrolithiasis to date. Most recent mean eGFR is 63.8 ml/min.

Recipients Characteristics

The mean age of recipients (R1-7) at time of transplantation was 63.9 years; five of 7 recipients were female (Table 2). The mean BMI was 26.4 kg/cm^2. Patients were on preoperative dialysis for a mean of 3.6 years prior to transplantation, with a mean preoperative calculated panel-reactive antibody (cPRA) of 36.3.

Recipient Outcomes

4 recipients received simulect induction, while three received thymoglobulin induction (Table 3). The mean cold and warm ischemia times were 253 and 24 min, respectively. In 4 cases a ureteral stent was placed at time of transplantation, and all recipients had a standard extra vesicular ureteroneocystostomy or ureteropyelostomy using running 6-0 Maxon suture. Patient R4 had a 1liter blood loss from subcapsular hematomas, and R7 had a capsular injury that did not bleed. No patients experienced delayed graft function or rejection. The average length of stay was 3.9 days. Mean follow up was 40.1 months (range 8-131), and the most recent follow-up mean creatinine was 1.08 (mg/dL). Graft and recipient survival has been 100%. No recipients developed recurrence of ureteral stricture or any stones. Patient R4, presented with mild hydronephrosis, elevated creatinine, and a distended bladder 14 weeks after transplant. This was relieved with a foley catheter and benign prostatic hyperplasia (BPH) was subsequently treated with resolution of renal

Table 2. Recipient characteristics.

Patient	R1	R2	R3	R4	R5	R6	R7
Age at transplant (y)	32.4	62.6	66.6	80.9	71.9	68.8	70.5
Gender	Female	Male	Female	Male	Female	Female	Male
Height (cm)	162.6	167.6	162.6	175	160	142.2	157.5
Weight (kg)	74	69.2	55.7	84.3	69.6	60.1	58
BMI (kg/m^2)	28	24.6	21.1	27.5	27.2	29.7	23.4
Etiology of kidney disease	IgA nephropathy	Autosomal recessive polycystic kidney disease	Diabetes and hypertension	Unknown	Diabetes and hypertension	Hypertension and NSAIDs	Diabetes
Blood type	A+	B+	A+	O+	B+	O+	A+
cPRA	0	0	44	0	85	89	0
Type of renal replacement therapy	Hemodialysis	Hemodialysis	Hemodialysis	Hemodialysis	Peritoneal dialysis	Peritoneal dialysis	Peritoneal dialysis
Duration of renal replacement therapy prior to transplant (y)	6	3	6	1.5	4	2	3

Abbreviations: cPRA = calculated panel-reactive antibody.

Table 3. Recipient outcomes.

2q	R1	R2	R3	R4	R5	R6	R7
Induction (Thymoglobulin or simulect)	Simulect	Simulect	Simulect	Simulect	Thymoglobulin	Thymoglobulin	Thymoglobulin
Ureteral stent placement at time of transplant	No	Yes	Yes	No	No	Yes	Yes
Cold ischemia time (m)	210	553	300	214	117	180	199
Warm ischemia time (m)	21	21	30	18	17	27	30
Surgical complications	No	No	No	Subcapsular hematomas	No	No	Intraoperative capsular disruption
DGF	No	No	No	No	No	No	No
Length of stay (d)	3	3	3	7	3	3	5
Most recent creatinine (mg/dL)	1.02	1.07	1.16	1.67	0.81	0.75	1.09
Most recent eGFR (ml/min)	72.5	>60	52	41	>60	>60	73.5
Follow-up (m)	131	57	24	23	32	12	8
Graft survival to date	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Rejection	No	No	No	No	No	No	No
ureteral complication or stone formation	No	No	No	Foley catheter placement for hydroureter of transplant kidney, no further intervention	No	No	No

Abbreviations: DGF = delayed graft function.
eGFR = estimated glomerular filtration rat.

obstruction. None of the recipients have required cystostomy, ureteroscopy, ureteral stent replacement or percutaneous nephrostomy tube.

DISCUSSION

The concept of TLDN is underutilized, and possibly under-reported to date. To our knowledge this series represents the largest in the literature. The first published series in 2019 describes four patients.[6] In that series, with a mean of 47 months follow-up, 2 patients donated for loin pain hematuria syndrome, 1 after traumatic relative ureteral avulsion, and 1 after a new diagnosis of small renal mass. Our results extend on these indications for TLDN, including proximal ureteral stricture, nephrolithiasis, and iatrogenic ureteral injuries, all of which can be indications for nephrectomy.[7]

The differential function based on the MAG3 scan was generally worse in the kidney available for transplant, (mean 43.2%, and as low as 35%) due to previous interventions resulting in some degree of scarring of the parenchyma. Visually these kidneys appear to be less than perfect at the time of nephrectomy. Despite this, recipient renal function has been excellent, possibly optimized by patient selection. Potential recipients were screened for their willingness to accept high kidney donor profile risk donors as a surrogate for risk tolerance, and candidates with years of expected waiting time were preferred so the risk they shouldered from the TLDN kidney could be balanced with benefit. Obese recipient candidates were avoided to minimize the metabolic demands on the allograft. Young patients were also avoided unless the donor was also young and the MAG3 scan showed excellent function. Candidates with a history of nephrolithiasis or significant dysfunction of the lower urinary tract were also excluded due to theoretic risk ureteral stricture and stone formation after transplant. Calcineurin inhibitor avoidance using belatacept was used in recent years, so patients without evidence of EBV exposure were avoided.

At the time of nephrectomy the kidney is often encased in dense adherent fat and has areas of parenchymal scarring. Fig. 1 shows a coronal CT scan from patient D7, who had nephrolithiasis complicated by stricture, and is an illustrative example of pre-operative imaging demonstrating this appearance. Surgeons should not be dissuaded by the appearance of the kidney but should be aware of the risk of bleeding from subcapsular hematomas.

In this series, many of the donors had been dealing with ureteral pathology for years prior to their decision to remove the affected kidney and most had been referred to a tertiary referral treatment center for consideration of treatment options after previous failed attempts. D1 suffered an iatrogenic injury during hysterectomy requiring Boari flap and ureteral reimplantation. D1 subsequently underwent laparoscopic lysis of adhesions for ureteral nerve entrapment with only mild improvement. D2 had a long history nephrolithiasis requiring stent exchanges and dilations but flank pain and hematuria continued. D3 suffered a right ureteral injury during open inguinal hernia repair requiring nephrostomy tube placement. Complete ureteral obstruction developed, and ureteral reimplantation was attempted but aborted. D4 had an idiopathic ureteral stricture and massive hydroureter that required frequent technically challenging stent exchanges. D5 had a history of nephrolithiasis complicated by complete ureteral avulsion requiring nephrostomy. D5 was deemed to be a poor candidate for autotransplantation given small bladder capacity and anatomy. D6 suffered from a ureteral stricture from nephrolithiasis, and D7 had an iatrogenic ureteral injury and development of stricture and nephrolithiasis requiring frequent stent exchanges.

We previously demonstrated in a 2018 multi-institutional study of 40 patients with prior ureteroscopic management for proximal stone disease with development of ureteral stricture that 10 (25%) patients ultimately required nephrectomy.[8] Significant ureteral stricture disease requiring reconstruction can require long term patient commitment. As can be seen in the above description most of the patients in this series who ultimately donated their kidney had experienced some type of significant ureteral stricture or injury. Consistent with our previous study, the patients in this had already undergone several interventions on the affected kidney, sometimes over years, to try and address or repair their ureteral pathology. The associated time, morbidity, cost, and stress associated with this journey was a deciding factor for patients in moving toward nephrectomy. This was compounded by the fact that for many of them, the function of their affected kidney had been negatively affected over time, begging the question for them of whether reconstruction was worth the investment of energy, time, and additional morbidity. A few of these patients came to our treatment center with motivation already in place that they would like to donate their injured kidney, bringing in the idea of altruism to their decision making. However, counseling regarding ureteral repair and reconstruction was undertaken (including consideration of autotransplantation, ileal ureter substitution, complex flap reconstruction, uretero-ureteral diversion, etc.) prior to the patient deciding that they would opt for nephrectomy. In these cases, the relationship between the patient and the urologist should be well established prior to considering nephrectomy to ensure that the patient has considered every option to preserve the native kidney. To that end, we advocate that it is advisable to have distinct surgeons responsible for the nephrectomy care and the transplant care. 2 distinct teams help avoid any ethical concerns or conflict of interest and ensure the option to donate the kidney is only introduced after the patient has been extensively counseled and has elected for nephrectomy.

In all cases, extensive urologic counseling was performed that included shared decision making outlining risks and benefits of reconstruction options, including ureteral substitution and autotransplant. Autotransplantation is frequently performed at our center and was offered to appropriate patients in this series.[9] Years of frustration with failed therapies and interventions was a recurring theme for the patients in this series that elected for nephrectomy. For many donors, limiting further inconvenience was another priority driving their decision. Most of the donors had not previously considered TLDN until it was offered as an option, and were excited about the option to help another person in need once they learned it was an option. Additionally, patients considering nephrectomy are very reassured to learn that proceeding with TLDN means they will be granted priority on the kidney transplant waiting list if their remaining kidney fails in the future.

Once the decision to donate was made, every effort was made to expedite the pre-transplant evaluation as much as possible and accommodate the planned nephrectomy date so TLDN does not significant delay treatment of the donor's underlying medical issue. Importantly, there is a UNOS requirement that all living donors are required to undergo a psychosocial assessment as part of transplant evaluation, which needs to be done expeditiously. The mean time to donation from decision was 57.9 days. Our work-up, based on UNOS and OPTN policies,[5] also included a MAG3 renal scan for our patients.

All seven donors underwent laparoscopic TLDN. Importantly, the renal vein is cleared below the level of the adrenal vein to increase length, and the renal artery is similarly mobilized to the aorta, both of which can be challenging in this population. The cold ischemic time (Table 3) reflects the fact that the recipient operation was done in sequence rather than parallel to ensure the kidney was transplantable prior to starting the recipient operation. Additionally, back table preparation of these kidney can require some extra time.

Our institutional transplant practice is to place a ureteral stent in selected cases. Four of seven patients presented here had ureteral stent placement at the time of transplantation. A standard extravesical ureteroneocystostomy was done when any length of soft ureter tissue was present, even if it was edematous, or the reconstruction was done directly to the renal pelvis. The ipsilateral native ureter is an option for reconstruction, but we reserve it for failure of the primary reconstruction, which was not required in this series. Importantly, there has not been recurrence of the primary disease process that necessitated TLND in any of the recipients.

No donors had a peri-operative complication.

All seven recipients had a successful outcome. The success of kidney transplantation is generally judged by a creatinine below approximately 2.0 (mg/dL) and an eGFR around 60 (ml/min), achieved by most of the seven patients described here. Renal function worse than that needs to be viewed in the context of recipient age, access to transplant outside of TLDN, and expected survival on the waiting list without TLDN. Patient R4 is the only recipient with a relatively low eGFR, and he is an excellent example of a patient with an eGRF less than 60 (ml/min) who is considered by transplant providers to have had an excellent outcome. This is because at his age the mortality while waiting on dialysis is very high and TLDN offered him the opportunity to shave approximately seven years off his expected waiting time. If patient R4 survived until he was atop the deceased donor waiting list he would have been close to 90 years of age and would not have been a candidate for transplantation. Currently he is alive, off dialysis, with an eGFR of 41, which is expected to be stable for years based on his donor's characteristics.

In the seven recipients in this series, there were no class III or above Clavien-Dindo complications. Patient R4 is a cautionary example because these kidneys can develop capsular disruption during nephrectomy and/or back table preparation, and this patient had multiple subcapsular hematomas that had to be released, resulting in 1 liter blood loss. Patient R7 also had a capsular disruption, though without significant bleeding. Surgeons should be aware of this possibility and proper informed consent should be obtained from the recipient. Care should be taken not to disrupt the capsule during nephrectomy. Fortunately, neither of these 2 patients had a significantly prolonged hospitalization or ongoing bleeding after transplant, and both have excellent kidney function to date. Our experience demonstrates that even in the context of a significant amount of scarring from previous manipulation and surgical treatment, these kidneys can be used safely and effectively to extend the renal donor pool.

Our study is limited by the retrospective nature of the data collection. Frequently, patients were referred to our medical center, and as a result the complete list of previous interventions on the kidney in question was not identifiable in our medical record. This limited our ability to state precisely how many interventions each patient underwent prior to donation. Given the nature of the disease process and what was seen at the time of nephrectomy we are confident that all seven patients underwent multiple invasive interventions.

CONCLUSION

TLDN in patients with proximal ureteral stricture, even in the face of concomitant stone disease is safe and effective for both treating the donor's primary medical problem and increasing the pool of available kidneys for transplantation. Patients with proximal ureteral stricture should be counseled on all reconstructive options outside of kidney donation including ureteral substitution and autotransplantation prior to being introduced to the concept of TLDN. Importantly, a major advantage of TLDN is that the donor will receive priority on the kidney transplant waitlist in the future if their remaining kidney fails. There are likely a very large number of missed opportunities for TLDN currently, which can offer access to transplantation to properly selected patients who otherwise would be expected to have low survival without it. In this series, the long-term follow up demonstrates excellent renal function after transplant and identified no recurrence of stricture or stone disease in recipients. Moving forward, it is important to increase awareness about this unique process as well as have urology and transplant services work together to serve patients with ureteral stricture/injury while simultaneously serving the growing population of patients with ESRD.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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