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Received: 12 November 2018 | Revised: 10 March 2019 | Accepted: 1 April 2019

DOI: 10.1111/ajt.15386

CASE REPORT

AJT

Bi-organ paired exchange—Sentinel case of a liver-kidney swap

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Organ transplantation is the optimal treatment for patients with end stage liver disease and end stage renal disease. However, due to the imbalance in the demand and supply of deceased organs, most transplant centers worldwide have consciously pursued a strategy for living donation. Paired exchanges were introduced as a means to bypass various biologic incompatibilities (blood- and tissue-typing), while expanding the living donor pool. This shift in paradigm has introduced new ethical concerns that have hitherto been unaddressed, especially with nondirected, altruistic living donors. So far, transplant communities have focused efforts on separate liver- and kidney-paired exchanges, whereas the concept of a transorgan paired exchange has been theorized and could potentially facilitate a greater number of transplants. We describe the performance of the first successful liver-kidney swap.

KEYWORDS
clinical research/practice, donors and donation: living, donors and donation: paired exchange, ethics and public policy, kidney transplantation/nephrology, liver transplantation/hepatology

The use of paired kidney exchange allows for transplantation of incompatible donor and recipient pairs. Similarly, paired liver exchange has allowed for liver transplantation between incompatible pairs.[1] A novel bi-organ exchange has been proposed in the past.[2] In this type of exchange, different organs (eg, liver for a kidney), would provide for transplantation of 2 recipients with different kinds of end-organ failure. The potential for a bi-organ exchange would exist in a situation where medical circumstances would prevent a donor's kidney donation to their intended recipient, when no medical contraindications exist for liver donation. If another donor-recipient pair could be found where medical circumstances precluded this donor's liver but not kidney donation, the liver and the kidney could be exchanged between these pairs. Below, we report on the first case of such an exchange (Figure 1).

We were approached by a patient (donor-L) whose mother was on dialysis and was waitlisted for kidney transplantation. The mother had nephrotic syndrome from biopsy-proven fibrillary glomerulonephritis and the daughter was deferred from kidney donation because of concern over her risk of being afflicted with the same condition later in life, especially given documented cases of an autosomal dominant inheritance.[3] Donor-L proposed a bi-organ exchange based upon the Dickerson article.[2] Donor-L had no proteinuria/hematuria and had adequate renal reserve. Magnetic resonance imaging and computed tomography scan demonstrated liver anatomy conducive to donation. Because of donor-L's small physique and her recipient's blood type, finding an exchange donor took 18 months. The eventual kidney donor (donor-K) desired to donate a portion of her liver to her sister, who had primary biliary cirrhosis. Evaluation revealed that donor-K's left lobe was <30% of her liver volume. Right lobe donation was ruled out because of insufficient residual mass in her left lobe. Donor-K's left lobe did not have enough mass for the intended recipient (graft weight/standard liver volume = 32%). After discussion of the possibility of a bi-organ exchange, donor-K desired evaluation for possible kidney donation. Following standard evaluation for donor-K, involving a team separate from the medical personnel who evaluated donor-L, donor-K and was cleared. The novel nature of the bi-organ exchange was explained to all 4 patients. All parties were provided with our center's Scientific Registry of Transplant Recipients outcomes for liver and kidney transplantation respectively. The informed consent forms for the liver-kidney swap were modified from those used for our living donor renal transplant/living

Abbreviations: GW/SLV, graft weight to standard liver volume ratio; LDLT, living donor liver transplant; LDRT, living donor renal transplant; RHF, right heart failure.

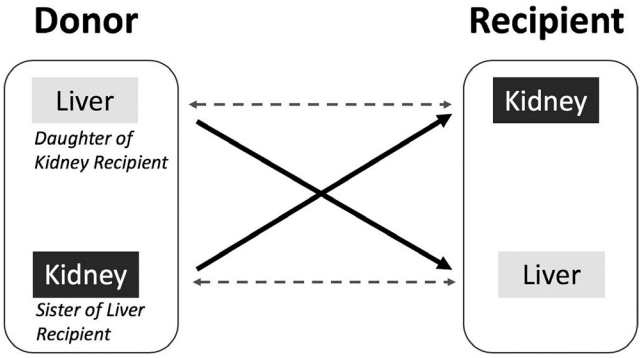

FIGURE 1 Diagrammatic representation of the liver-kidney exchange

donor liver transplant (LDRT/LDLT) and paired kidney exchange programs. Recipient outcomes posttransplantation were expected to be similar to the usual kidney/liver recipient, and in the interest of patient confidentiality, neither the recipients' diagnoses nor the donors' ages were shared between the pairs. Donor-K and her intended liver recipient were aware that donor-L had originally intended to serve as her mother's kidney donor but was unable to proceed due to genetic factors, a fact that heavily influenced donor-K's decision to participate in the exchange (a sense of social connection).

Our team debated the ethical underpinning of this swap. A discussion with the chair of the ethics committee at the time concluded that a full committee review was unnecessary. The ethical concepts of beneficence and autonomy were the main factors at play. For the totality of the bi-organ exchange, the donor risks and the benefits to recipients would not differ as compared to nonexchanged LDLT and LDRT (ie, had each donor been allowed to directly donate to their intended recipients). The advantage to the recipients gaining transplants that otherwise may not have occurred remains constant. Denying donor-L the opportunity to donate, given she was fully informed of the risks (which were not higher than that of nondirected liver donation) and had consented to the procedure, would have violated her autonomy as a patient. Since this was not a clinical trial/research study, institutional review board approval was not appropriate.

The 2 donor operations were carried out simultaneously, with their recipient operations following. Baseline demographics, and pre- and postoperative laboratory values are summarized in Table 1. Donor-K donated her left kidney and donor-L her right hemiliver. The kidney recipient underwent kidney transplantation with bilateral nephrectomies due to significant proteinuria (spot urine protein: creatinine ratio 6.5 g/g). Her immediate postoperative course was uneventful. At the 6-month protocol kidney allograft biopsy, borderline inflammation was seen and the patient was treated with oral pulse steroids. She then developed BK viremia at month 9, and her immunosuppression was lowered accordingly. A rise in her serum creatinine at 1 year prompted a cause biopsy showing acute cellular rejection 1a. Appropriate medication changes were made, and her renal allograft function has stabilized. She remains free of any significant proteinuria, with no glomerular pathology seen on either of her biopsies.

The liver recipient had previously undergone a transjugular, intrahepatic portocaval shunt for variceal hemorrhage, complicated by hepatic encephalopathy and severe pruritus with a model for end-stage liver disease–sodium score of 19 at time of listing. Postoperatively, she developed right heart failure (RHF) from unrecognized pulmonary artery hypertension (presenting with rising aspartate aminotransferase/alanine aminotransferase and lactate levels and an echocardiogram demonstrating right heart strain). This resolved with venoarterial extracorporeal membrane oxygenation and IV epoprostenol. She eventually transitioned to oral sildenafil. She was followed by the cardiology service upon discharge, and a right heart catheterization showed normalization of right-sided pressures with discontinuation of her sildenafil at 1 year posttransplant, with normal liver and renal function (she sustained a brief period of acute tubular necrosis during her episode of RHF, requiring dialysis).

Both donors continued to do well at follow-up (Table 1) and neither one experienced any unexpected surgical complications. Specifically, donor-L underwent a liver ultrasound after 2 months, showing the expected degree of regeneration in the remnant left lobe, with normal liver function. While both recipient-donor pairs had insisted on anonymity at first, both parties subsequently requested to meet at 6 months. Throughout our ongoing contact with the patients, the overwhelming sentiment from all involved was that everyone got what they desired (even with the liver recipient who had a protracted recovery course), and that everything had gone smoothly. Neither donor had any regrets about their donations, nor did they harbor any feelings of unfairness about the swap. The nondirected nature of the donations failed to diminish the satisfaction either donor experienced from knowing they had benefited their respective recipients.

The concept of double equipoise describes the balance between the recipient's survival benefit with or without LDLT/LDRT and the risk of mortality for the donor.[4] Contrary to deceased donor transplantation, where only the recipient's outcome matters, with living donor transplants, the risk-benefit analysis involves both recipient and donor considerations. If recipient benefits are too low, or if the risk of donor mortality is too high, it would not be ethically defensible for a living donor to undergo an operation. For the purposes of discussion, we are going to focus largely on the mortality risk of donation.

Samstein[5] eloquently addressed the ethical concerns of a transorgan exchange, exploring the perception of a disparity in mortality risk taken on by the liver versus kidney donor. For directed living donor transplants, the transplant center and the patients have accepted the degree of double equipoise. For single organ exchanges, the totality of the benefit for the recipient-donor pair is unchanged and equipoise for the donors is thought to be similar to nonexchange donations. The advantage to the exchange for all is that the recipients gain living donor transplants that otherwise would not occur. While each of the donors separately approached the transplant center with the plan to donate an organ, liver, or kidney, it was donor-L (who took on the incremental risk) who initiated the idea of a bi-organ exchange. In addition to an extensive discussion of the morbidity and mortality involved with their respective donor operations, the risks of paired exchange were explained to all (ie, swap failure,

TABLE 1 Baseline demographics, pre- and posttransplant laboratory values

	Donor-L	Recipient-K	Donor-K	Recipient-L
Age (yr)	21	42	47	52
Sex	Female	Female	Female	Female
Relationship	Daughter-mother		Sisters	
Height, cm	159	150	158	165
Weight, kg	44.8	64	58.7	57.4
BMI, kg/m^2	17.5	28.5	23.6	21
GRBW ratio, %				0.85
GW/SLV				0.4
Blood type/rhesus	O+	B+	O+	O+
PRA		0%		
Cause of end-organ failure (recipients)		Fibrillary GN		PBC
CMV, donor/recipient immune status		D+/R+		D-/R+
HLA mismatches		5 of 6		
Blood pressure, mm Hg	95/65	125/70	113/71	122/55
Serum creatinine, mg/dL	0.65	PD	0.71	0.56
eGFR predonation, mL/min	126		102	89
UPC predonation, g/g			0.14	
Serum ALT predonation, U/L	12			
Serum AST predonation, U/L	21			
Serum albumin preop, g/dL	4.5			1.7
Platelet count preop, $\times 10^9$/L	182			106
INR predonation	1.1			
Serum total bilirubin predonation, mg/dL	0.8			
Induction agent		Basilixumab		None
Maintenance immunosuppression		Tac/MMF/pred		Tac/MMF/pred
Blood pressure at 1 yr, mm Hg			117/79	
Estimated blood loss, mL	120	200	50	1700
Serum creatinine at 1 yr, mg/dL	0.78	1.4	0.97	0.79
Serum ALT at 1 yr, U/L	8			7
Serum AST at 1 yr, U/L	19			16
Serum albumin at 1 yr, g/dL	4.0			4.6
Platelet count at 1 yr, $\times 10^9$/L	217			259
INR at 1 yr	1.0			1.0
Serum total bilirubin at 1 yr, mg/dL	0.8			0.6
UPC at 1 yr, g/g		0.2	Undetectable	

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; CMV, cytomegalovirus; eGFR, estimated glomerular filtration rate (CKD Epi equation); GN, glomerulonephritis; GRBW, graft recipient body weight; GW/SLV, graft weight/standard liver volume; HLA, human leukocyte antigen; INR, International Normalized Ratio; PBC, primary biliary cirrhosis; PD, peritoneal dialysis; PRA, panel reactive antibody; Tac/MMF/pred, tacrolimus/mycophenolate/prednisone; UPC, urine protein:creatinine ratio.

exchange-related donor-derived infections, etc.), which are similar to any single-center kidney exchange. Donor-L went through the same evaluation and consent process that any liver donors (directed/nondirected) would undergo, and the risks taken on by donor-L were not higher than those by other liver donors.

The main ethical objection raised is that there is an increased mortality risk assumed by donor-L vis-à-vis donor-K, who experiences less mortality risk. There was a transition to the lower risk of kidney donation with donor-K (who initially volunteered for donor hepatectomy) to the higher risk of liver donation for donor-L (who originally planned on donor nephrectomy). The decrease in donation risk with the same potential benefit to her liver recipient would not interfere with the double equipoise for donor-K. The crux lies with donor-L, who planned to give a kidney but then accepted the higher mortality risk of liver donation. Since donor-L's intended kidney recipient eventually received a kidney allograft, donor-L's equipoise is actually more

favorable than in the case of a nondirected liver donation (an operation that is performed at our and other centers, and considered ethically sound). Multiple discussions of risks with donor-L took place, and she had ample opportunities to withdraw from donation. Additionally, the >600% incremental increase in mortality risk from 1/3000[6] (kidney donation) to 1/500[7,8] (liver donation) was made abundantly clear to donor-L. Mortality risks aside, one may argue that the morbidity of donor nephrectomy in relation to hepatectomy is remarkably different. While recovery after donor hepatectomy usually exceeds that of donor nephrectomy (6-10 weeks vs 3-4 weeks), recent data would suggest a small but significant increased risk of end stage renal disease among kidney donors,[9] but that the long-term risk of end stage liver disease does not appear to be substantially altered following living liver donation.[10] Moreover, registry data of 15 000 donor nephrectomies revealed an overall postoperative complication rate of 16.8%, with 7.3% of these being Clavien-Dindo grade III or higher.[11] In comparison, liver donation incurs a complication rate of 12%-40%, but only 3.5%-3.8% of which were major (≥Clavien-Dindo grade III).[10]

Another area of contention is that donor-L's recipient received remarkably less from a "life-enhancing" kidney transplant (rather than a truly "life-saving" liver transplant), despite the fact donor-L took on the substantially greater risk of donor hepatectomy. Our counterpoint is that the kidney recipient was spared from an extended dependency on dialysis had she stayed on the deceased donor waitlist (mortality on the kidney waitlist is 6%-8% annually with a significant reduction in quality of life[14,15]). This does not even account for the superior allograft and patient survival outcomes that come with a living vs a deceased donor kidney transplant.[16] In fact, Merion[17] made the observation that the risk to patients on the kidney waitlist is not dissimilar to the liver waitlist mortality and reduction in quality of life for those with moderate model for end stage liver disease scores of 12-17.

To our knowledge, this is the first report of the multiorgan exchange involving a liver-kidney swap. It is obvious that these types of exchanges can increase the donor pool (by Dickerson's simulation, a national bi-organ exchange can potentially yield an additional 20-30 transplants per month over keeping separate liver/kidney exchanges[2]) for transplantation, and one can imagine the enormous impact for mixed organ non-simultaneous extended chains initiated with an altruistic (nondirected) liver or kidney donor. While the initial concept of paired exchanges was to bypass ABO- or histo-incompatibility, a bi-organ exchange would additionally avoid the issue of "organ-type" incompatibility, and could further benefit difficult-to-match recipients participating in kidney paired exchange programs (eg, blood type O and highly sensitized individuals).

DISCLOSURE

The authors of this manuscript have no conflicts of interest to disclose as described by the *American Journal of Transplantation*.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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How to cite this article: Torres A-M, Wong F, Pearson S, et al. Bi-organ paired exchange—Sentinel case of a liver-kidney swap. *Am J Transplant*. 2019;00:1-4. https://doi.org/10.1111/ajt.15386