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Kidney paired donation in developing countries: A global perspective

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Abstract

Purpose of review: We review the key principles of kidney paired donation (KPD) and discuss the status and unique considerations for KPD in developing countries.

Recent findings: Despite the advantages of KPD programs, they remain rare among developing nations, and the programs that exist have many differences with those of in developed countries.

There is a paucity of literature and lack of published data on KPD from most of the developing nations. Expanding KPD programs may require the adoption of features and innovations of

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successful KPD programs. Cooperation with national and international societies should be encouraged to ensure endorsement and sharing of best practices.

Summary: KPD is in the initial stages or has not yet started in the majority of the emerging nations. But the logistics and strategies required to implement KPD in developing nations differ from other parts of the world. By learning from the KPD experience in developing countries and adapting to their unique needs, it should be possible to expand access to KPD to allow more transplants to happen for patients in need world-wide.

Keywords

solid organ transplantation; deceased donor; living donor

Introduction

According to the global observatory on donation and transplantation data, a total of 151,299 solid organ transplants were performed across the world in 2021.¹ Only a small amount of these data came from emerging nations, as some transplant programs in developing countries are still evolving and lack robust data reporting. Deceased donation requires a strong infrastructure and logistics, hence in the early phase of building a transplant program living donation programs are often established in many resource restricted regions of the world.² However, there are some inherent barriers to living donation such as biological incompatibility between donor-recipient pairs (DRPs). ABO incompatible (ABOi) and HLA incompatible (HLAi) transplantation are feasible under careful *a priori* protocols, but these approaches add clinical complexity and financial barriers exist due to the need for greater levels of immunosuppression, increased risk of complications (e.g., infection, rejection and graft loss), and associated costs.³⁻⁵ Additionally, the logistics involved in crossing these barriers can be challenging to developing programs. Kidney paired donation (KPD) is a strategy to overcome incompatibility barriers by exchanging donors to create compatible combinations. In this article, we review the key principles of KPD and the status and unique considerations for KPD in developing countries.

Overview of kidney paired donation

Kidney paired donation was first proposed by Rapaport⁶ in 1986 and first performed in South Korea in 1991⁷ (Figure 1). Subsequent KPD program growth was slow, with KPD appearing in Europe in 1999 and in the United States in 2000. Since then, much progress has been made overcoming policy, legal, logistical, clinical and psychosocial barriers to KPD. The first national registry of paired donors was developed in 2001 through the Alliance for Paired Donation in the United States, which provided a central registry of potential donors and facilitated nationwide sharing of living donor kidneys. KPD is designed to surmount a number of barriers, classically including biological incompatibility (ABOi and/or HLAI). KPD programs can also help overcome chronological incompatibility allowing for various types of asynchronous donation (i.e. donors may donate before a recipient's transplantation); geographic incompatibility by helping donors donate remotely in geographically distant locations to the transplant center; in addition to improve HLA, size and age mismatch. Figure 1 summarizes the main landmarks in the evolution of KPD over three decades.

Two types of donors are possible, directed (donation to known recipient) and non-directed (donation to unknown recipient). The use of the term “altruistic donor” was previously used for a non-directed donor but is no longer favoured, as all donors demonstrate altruism in their willingness to donate. Figure 2 summarizes the structures of KPD used in practice, the logistics of which can range from straightforward to quite elaborate. In the simplest form of KPD, two designated donors can “swap” recipients to provide a better match (Figure 2A). Multiple donor-recipient pairs can be added into this swap to facilitate multiple better-paired exchanges (Figure 2B).

Non-directed donors can either donate directly to an unknown patient on a center’s waitlist or can start a chain in which multiple DRPs are involved, with the final donor donating to the waitlist (Figure 2D). KPD may also allow the incorporation of deceased donation into chains wherein a deceased donor kidney is transplanted to a patient listed on a KPD registry to start a chain of transplants (Figure 2C). Donor vouchers and advanced donation allow living donor candidate to donate a kidney temporally separated (by months to years) from the receipt of a kidney by their intended recipient; this is performed to overcome chronologic incompatibility. These strategies may allow donor candidates to donate at a time that is convenient for them, have time to recover and then serve as the recipient’s caretaker or provide a kidney while healthy, even if their recipient does not yet need renal replacement therapy. Specifically, voucher donors may choose a single recipient for a future transplant (directed donation), or name multiple recipients if one of them needs a kidney transplant in the future (semi-nondirected donation). The most developed of these programs is the Advanced Donation Program started by The National Kidney Registry (NKR).^{8,9} This innovative use of KPD can further be enhanced by the participation of blood-type O recipient and non-O donor pairs.

These three distinctive categories of KPD participation (non-directed, advanced, and voucher donors),¹⁰ do not exist in India and they are not included in the The Transplantation of Human Organs Act in India and the developing world.

The status of KPD in developing nations

There is no published data of KPD from most of the developing nations. Table 1 shows transplant activity, including deceased donation, living donation, and kidney exchange among developing countries. The World Bank has categorized developing nations based on their income status into low-income countries (LICs) and low-middle income countries (LMICs). The four nations which report kidney exchanges are India, Iran, Nepal, and Pakistan, which all are categorized as LMIC and there have been no reports from LICs to date.

The Iranian model of kidney transplant established in 1988 is a unique example of a compensated and regulated living unrelated kidney donation. Through this model, a total of 436 paired kidney donors and recipients were benefited¹¹. This model can increase transplantation, but careful attention must be paid to risks of coercion and protection of donor safety and well-being. In Pakistan, living donation practices are restricted to a few transplant centers, and there is only a single case report of KPD, where an exchange

was performed to overcome the ABO incompatibility barrier.¹² The majority of the KPD reports from developing nations belong to India, the seventh largest and the second most populous nation in the world. Interestingly, most reports from India are from a single center reporting 300 KPDs and performing non-simultaneous kidney exchanges without non-directed donation.^{13,14} This center recently performed their longest KPD chain of 10 DRPs and has become a champion for the development of KPD within India and the rest of the developing world.^{15,16} In 2015, the kidney exchange matching rate of Indian single center KPD programs was 62% which shows the percentage of pairs undergoing KPD within the registered pairs. This rate is significantly higher than the matching rates of national KPD programs in Australia, Canada, The Netherlands and the UK (49%, 44%, 37% and 27%, respectively).¹⁷

Global Kidney Exchange

In 2010, 5–7 million people died worldwide because they did not have access to renal replacement therapy.¹⁸ DRPs from LICs and LMICs participate in the Global Kidney Exchange (GKE) program to overcome financial incompatibility.¹⁹ Although the GKE has generated considerable support, it has also generated critics and rebuttals.^{20–32} International bodies such as the World Health Organization (WHO), The Transplantation Society (TTS), Council of Europe's Committee on Organ Transplantation and the Declaration of Istanbul Custodian Group have expressed concerns over the absence of transparency in the selection of the compatible DRPs in the LICs and LMICs, stating GKE as transplant colonialism. GKE provide some donor supply, but the European Platform on Ethical, Legal and Psychosocial Aspects of Organ Transplantation has expressed concerns that GKE violates the non-payment principle, exploits donors in LICs and LMICs, and detracts from the aim of self-sufficiency and logistical simplicity (transcultural issues, travel visas). Some of the concerns surrounding GKE can be mitigated by allowing independent international committee review by organizations such as WHO and TTS. More research is required to establish the willingness of DRPs to participate in GKE, inclusion criteria for participating, management of escrow funds, and common global legislation. A few examples of Filipino and U.S. GKE pairs have been successful and remain well at 3 years follow up, making a strong case for this type of program expansion.³³ Minerva et al. strongly advocates for the expansion of GKE based on the principle that all human lives have equal value, and opposes the concerns of organ trafficking, exploiting the poor, and involving coercion and commodification / exploitation of donors and suggest that GKE promotes global justice. So far 54 patients have been transplanted in GKE including 19 international patients and 35 Americans.³⁴

Challenges and opportunities for KPD in developing countries

Despite the advantages of KPD programs, they remain rare in the developing world, and the programs that exist have many differences with those of developed countries.

Program structure is one of these differences: multicenter, regional, and national KPD programs (Swiss, Australia, Canada, Dutch, UK, USA) are more common in the developed than the developing world, whereas single center programs are more common in Brazil,

India, Pakistan, and Nepal.^{12,13,35–46} Bangladesh, Qatar, and many others have not started KPD programs.

System inefficiency often exists in developed countries due to bureaucracy and regulations: kidney exchanges frequently take weeks to months to obtain legal permission in India despite the fact that only closely-related family members (i.e. parents, spouse, siblings, children, and grandparents) are allowed to donate a kidney.⁴⁷

Protecting the privacy of a donor, including maintaining anonymity when requested, is common practice among developed countries but uncommon in developing nations. Anonymous allocation during KPD is a standard practice in the Netherlands, Sweden, and other parts of Europe but, this is not the case in countries such as India, Korea, and Romania.^{14,48,49} In areas where anonymity is not maintained, the intended donor/recipient pair must meet and share medical information once a potential exchange is identified, but before formal allocation of pairs occurs. The original donor/recipient pair may refuse the proposed exchange option for any reason and continue to be on the wait list. In India, non-anonymous KPD allocation is standard practice and has the goal of increasing trust and transparency between the transplant team and the administrative team.^{14,49} Countries differ in philosophical approaches to optimizing trust and transparency, and objective data on most effective practices would benefit the global community.

Donor age group matching is most commonly expected among all variables by DRP. Medical fitness of DRP should be established before allowing DRP to meet each other to avoid chain collapse. DRP meetings need to be arranged on virtual platforms given the diverse geographic regions. Transplant teams should solve any concerns surfacing after DRP's meeting and allow DRP to reject offers and remain waitlisted for the next match run if desired.

Compared to developed nations, donor-recipient matching has been commonly performed manually in countries such as India. Recently, the Alliance for Paired Donation shared their computer software for KPD allocation for use in India.^{14,49} With increasing automation in allocation, kidney exchange length should be gradually increased from two-way to three-ways and so on, depending on the logistical capacity of the program. Simultaneous transplant surgery should be encouraged over non-simultaneous surgery due to risk of donor renege, but this can limit the length of chains. Geographic differences of DRPs can make simultaneous surgery difficult. The geographic separation of recipient and matched donor may be addressed with transition from donor travel to the shipment of donor kidneys, as in Canada⁵⁰ and the United States.^{51,52} The logistical demands of donor versus travel must be reconciled regionally, based on resources and infrastructure.

Reimbursement for lost wages, travel costs, and lodging in the donation process are more frequently allowed in programs from developing nations. In a global perspective analysis, lost income was reimbursed in 17 countries, while travel, accommodation, meal and childcare costs were reimbursed in 19, 17, 14 and 12 countries, respectively.⁵³ Ten countries had comprehensive programs where all major cost categories were reimbursed to some extent.⁵³

The way forward

Expanding KPD in developing countries may benefit from adopting features of successful KPD programs (Table 2). Table 3 offers some potential solutions for developing nations. Increasing the engagement with national and international societies should be encouraged to ensure endorsement and sharing of best practices.

Ethical, legal, and policy considerations should respect donor autonomy during all phases of the evaluation and donation process and remain patient-centric. Nations desiring to implement a KPD program are expected to have a learning curve in managing complex logistics and would benefit from starting with simple single-center simultaneous two-way KPD and gradually expanding to more complex strategies such as advance donation. Graft survival, patient survival, and rejection rates with KPD have been shown to be similar to direct donation.^{8,13,27} Therefore, KPD should be encouraged and promoted in centers where cost is a major consideration since incompatible transplant is substantially more expensive before and after transplantation. Likewise, overcoming the incompatibility barrier of a DRP through KPD will be particularly beneficial to countries with low rates of deceased donor transplantation.⁴⁶

DRPs considering KPD, should be informed of expected time for matching, as waiting times are highly variable depending on donor-recipient blood type combination, recipient sensitization and donor pool size. Selected DRP blood type combinations may be more challenging to match than others (A/B patient and B/A donor, a blood type O donor). Recipients pursuing KPD should also be enrolled in deceased donor kidney waiting lists when available. The cost and complications of maintenance dialysis increases with longer dialysis exposure. For easy to match incompatible DRPs, we prefer KPD due to the better long-term outcomes and costs-savings over desensitization therapy. Donor and recipient candidates should be evaluated according to uniform preoperative multidisciplinary team assessment as per local/national or KDIGO guidelines to minimize risk and prevent chain collapse.^{54,55} Non-standard and technically complex donors should be avoided in the early days of program development. Outcomes should be monitored and continuously reassessed as part of a program quality improvement.

Conclusion:

KPD is in initial stages or has not yet started in the majority of the developing nations. The logistics and innovations required to implement KPD vary across the world. By learning from the KPD experience in developing countries and adapting to their strategies to the unique needs in developing nations, it should be possible to expand access to KPD to allow more transplants happen for patients in need world-wide.

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Year	Event
1986	KPD first suggested by Rapaport ⁵⁶
1991	First KPD program started in South Korea ⁵⁶
1999	First European KPD transplants performed in Switzerland ⁵⁷
2000	First KPD transplants performed in U.S. ⁵⁶ ; First KPD transplants performed in India at IKDRC Ahmedabad ¹³
2001	Hopkins completes KPD transplants and begins first KPD program in U.S. ^{56,58}
2004	Holland establishes first national KPD program ⁵⁹
2006	First KPD program developed in the UK ⁶⁰
2007	The National Kidney Registry, NEAD chain started by Alliance for Paired Donation utilizing first bridge donor ⁶¹ Charlie Norwood Living Organ Donation Act clarifies legality of KPD in U.S. ⁶²
2008	National Kidney Registry completes its first KPD transplants ⁶³
2009	Canadian Blood Services launches the Living Donor Paired Exchange Registry The Spanish National KPD program is developed by Organización Nacional de Transplantes ⁶⁴ Hopkins leads first 16-patient multicenter Domino Chain ⁶⁵
2010	Australian and New Zealand Paired Kidney Exchange Program is established UNOS organizes its first KPD transplants ⁵⁷
2012	National Kidney Registry completes largest historical chain involving 60 participants ⁶⁶
2014	National Kidney Registry sets new record with 70-participant chain ⁶⁷
2016	European Network for Collaboration on Kidney Exchange Programmes Cooperation on Science and Technology Action is developed ^{68,69}
2017	Advanced Donation Program is the first to provide vouchers for future kidney transplants to overcome "chronological incompatibility" between living donors and recipients ⁹
2020	Longest kidney exchange series in India performed involving 10 donor-recipient pairs ¹⁵
2021	Report of non-simultaneous kidney exchange cycles (n=67) in resource-restricted countries without non-directed donation ¹⁴
2023	Largest (n=500) donor-recipient pairs in single center kidney exchange program at IKDRC Ahmedabad India in resource-restricted countries without non-directed donation

Figure 1:
History of kidney exchange

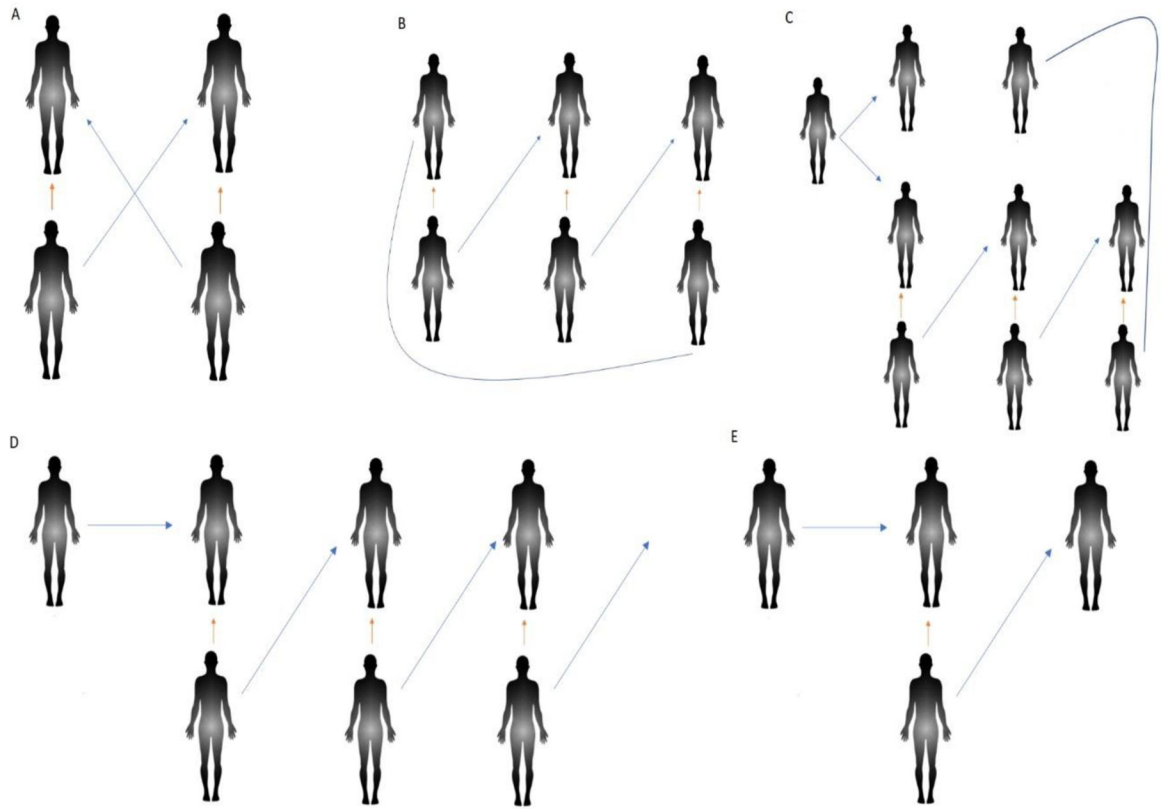


Figure 2.

Overview of kidney exchange (KE): A = Two-way KE; B = Three-way KE; C = Deceased donor (DD) initiated KE where DD donates to first person on waitlist and to KE registry patient. This will create a chain of KE which will end at transplantation of second waitlist patient on DD from the donor of last donor-recipient pair in KE. D = Altruistic donor initiating an open-ended chain of KE which can extend to any numbers; E = Altruistic donor initiating a chain of KE which ends in transplantation of the recipient on waiting list for DD. Blue arrow represent KE and organ arrow represent the incompatibility of donor-recipient pair.

Table 1.

Developing nations with their transplantation activity and pattern

Countries	Reporting year	Population for the year (million)	Total Actual DD	LD Kidney Tx	LD Liver Tx	KE program
<i>Afghanistan</i>	2014	31.3				-
Algeria	2019	42.7	1	268	11	-
Angola	2010	19				-
Bangladesh	2019	168.1	0	205	0	-
Belize	2020	11.7	0	10	0	-
Egypt, Arab Rep.	2015	91.5	0	1417	450	-
El Salvador	2021	6.5	0	27	0	-
<i>Ethiopia</i>	2019	110.1	0	35	0	-
Ghana	2015	27.4	0	3	0	-
India	2019	1,368.70	715	8613	1991	Yes
Indonesia	2013	249.9	0	494	2	
Iran, Islamic Rep	2019	82.8	1078	747		Yes
Kenya	2021	55	0	160	0	-
Kyrgyz Republic	2015	5.9	0	20	2	-
Mongolia	2019	3.2	9	18	31	-
Morocco	2019	36.6	4	36	1	-
Myanmar	2013	53.3	1	2	1	-
Nepal	2015	28.5	0	100	0	Yes
Nicaragua	2019	6.4	2	9	0	-
Nigeria	2019	201	0	165	0	-
Pakistan	2019	204.6	0	1306	285	Yes
Philippines	2019	108.1		283	0	-
Sri Lanka	2020	21.4	98	210	0	-
<i>Sudan</i>	2019	42.5	0	313	0	-
<i>Syrian Arab Republic</i>	2019	18.5	0	275	1	-
Tajikistan	2015	8.5	0	25	0	-
Tanzania	2020	59.7	0	8	0	-

Countries	Reporting year	Population for the year (million)	Total Actual DD	LD Kidney Tx	LD Liver Tx	KE program
Tunisia	2015	11.3	9	10		-
Ukraine	2015	44.8	3	120	10	-
Vietnam	2015	93.4	17	261	3	-

Countries with no transplantation activity reported: Benin, Bhutan, Bolivia, Burkina Faso, Burundi, Cabo Verde, Cambodia, Cameroon, Central African Republic, Chad, Comoros, Congo Dem. Rep., Congo Rep., Côte d'Ivoire, Djibouti, Eritrea, Eswatini, Gambia, Guinea, Guinea-Bissau, Haiti, Honduras, Kiribati, Korea, Dem. People's Rep. Lao PDR, Lesotho, Liberia, Madagascar, Malawi, Mali, Mauritania, Micronesia Fed. Sts., Mozambique, Niger, Papua New Guinea, Rwanda, Samoa, São Tomé and Príncipe, Senegal, Sierra Leone, Solomon Islands, Somalia, South Sudan, Timor-Leste, Togo, Uganda, Uzbekistan, Vanuatu, West Bank and Gaza, Yemen Rep., Zambia and Zimbabwe.

Abbreviations: DD: deceased donation; LD: living donation; Tx: transplant; KE: kidney exchange. Countries in italics represent low-income countries, and non-italics denotes low-middle income countries according to World Bank classification. The data was retrieved from the official website of global observatory donation and transplantation. - represent no data reported to GODT in the last decade.

Table 2.Key features of kidney exchange programs and approaches described in published literature^{37,63,70–73}

Country	Key features of kidney exchange programs
Australia	High transplant rate for highly sensitized, HLA-incompatible pairs due to accepting ABO-incompatible donor matching with ABO titer 1 : 64 ³⁷
Canada	Non-directed anonymous donors facilitate 62% of transplants ³⁸
Korea	Favourable blood group distribution (non-O > O patients), less sensitized, more compatible pairs and non-directed anonymous donors
United Kingdom	Transplant rate on the rise due to use of altruistic donor chains, embedded 2 way in 3-way or 4 way exchange ⁷⁰
UNOS Kidney Paired Donation, USA	Nondirected donation (NDD) of the kidneys increased significantly in the 20-year ⁷²
National Kidney Registry USA	The largest US exchange network of 103 Member Centers spanning 35 states managed by a nonprofit organization and participate in voucher donation, remote donation, long chain and Donor Shield. ⁷³ NKR facilitates over 450 “Kidney Paired Donation” or “Paired Exchange” transplants annually ⁶³

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Table 3.

Proposed interventions for adapting KPD to developing nations

1. Limit length of KPD to 3-way in initial stages to limit complex logistics; after developing comfort with single-center KPD, shift gradually toward multi-center, regional, state, and national programs to expand the donor pool
2. Include non-directed anonymous donors
3. Include biologically compatible pairs
4. Consider avoidance of anonymous donation in early stages to foster trust in the transplant system
5. Employ computer allocation rather than manual allocation to increase match run frequency
6. Start with simultaneous surgery and consider expanding to non-simultaneous surgeries as experience grows
7. Implement robust protocols to protect recipients such as use of deceased donor allocation priority in the case of paired donors refusing to donate after their recipient has been transplanted
8. Adapt strategies for organ shipping versus donor travelling to a transplant center based on regional feasibility
9. Implement surveillance and monitoring from national and international regulatory bodies to prevent illegal organ trafficking during KPD
10. once established, incorporate selected KPD innovations such as donor voucher programs and advanced and/or remote donation

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