

Living Kidney Donor Transplantation and Global Kidney Exchange

Ignazio R. Marino,¹ Alvin E. Roth,² Michael A. Rees^{3,4}

Abstract

Global kidney exchange offers an opportunity to expand living donor kidney transplants internationally to patients with immunologic barriers. The concept has been proven to be successful in a limited number of transplants. However, a number of misconceptions have created obstacles to its development. We suggest that a systematic application of this innovative tool would offer opportunities to treat thousands of patients worldwide who are presently denied a transplant and often even access to dialysis.

Key words: Exchange program, Living donor renal transplantation, Paired kidney donation

Introduction

The progressive increase in the number of donor-recipient pairs for living donor kidney transplant has resulted in a growing number of transplants that cannot be performed due to immunologic incompatibility between donor and recipient.

At present, ABO blood group incompatibility or a positive crossmatch constitutes about 30% of the reasons for the rejection of an organ from a living donor for a specific recipient. Desensitization techniques and aggressive immunosuppressive therapies have made these

transplants possible but with an increased risk of infectious complications and rejection. However, these procedures are still limited to certain specific cases.

To overcome these incompatibility barriers, kidney paired donation (KPD) has been proposed as a feasible alternative and has been conducted in several countries with excellent results. The idea of KPD and transplantation was introduced first by Felix Rapaport in 1986.¹ A few years later, KPD was adopted and expanded in South Korea, Europe, and the United States.²⁻⁸

One factor that has positively influenced the effectiveness of a KPD program is the pool size of incompatible pairs. In pool sizes of over 100 pairs per year, there have been significant improvements in the possibility of detecting good combinations compared with smaller pool sizes.⁹ For this reason, several KPD programs have evolved to include multiple transplant centers, both regionally and nationally. Furthermore, the implementation of more than 2-way exchanges and the inclusion of altruistic donors to initiate transplant chains have delivered dramatic growth in the number of transplants achieved.^{10,11}

The United States can offer greater possibilities for transplant in that it has a large genetically heterogeneous population; such features increase the chances of identifying compatible donors for difficult-to-match patients.

In the United States, several organizations have developed KPD programs in accordance with the standards set by the United Network for Organ Sharing, a national competent authority. The United Network for Organ Sharing is a private, nonprofit organization that manages the Organ Procurement and Transplant Network system in the United States under a contract with the federal government. One such organization is the Alliance for Paired Kidney Donation (APKD), which operates the only international

From the ¹Thomas Jefferson University, Philadelphia, Pennsylvania; ²Stanford University, Palo Alto, California; the ³University of Toledo, Toledo, Ohio; and the ⁴Alliance for Paired Kidney Donation, Toledo, Ohio, USA

Acknowledgements: The authors have not received any funding or grants in support of the presented research or for the preparation of this work and have no declarations of potential conflicts of interest.

Corresponding author: Ignazio R. Marino, Thomas Jefferson University, Philadelphia, PA, USA

E-mail: ignazio.marino@jefferson.edu

Experimental and Clinical Transplantation (2022) Suppl 4: 5-9

paired kidney exchange program in the United States, serving patients from 15 countries.

Global kidney exchange (GKE) programs can also offer opportunities to expand living donor renal transplant internationally to patient-donor pairs who have limited access to sufficient financial means or are from countries with little or no opportunities for KPD. The juxtaposition between countries with funds but no available kidneys and those with available kidneys but no funds or no kidney exchange prompted the proposition of GKE as an exchange program that allows mutual assistance between patients in different nations.¹²

Although the promise of GKE is significant, it has been met with ethical criticism concerning the possible exploitation of financially disadvantaged groups. Results, however, have demonstrated that these concerns did not come to fruition and that the program has been extremely successful, with more than 50 transplants achieved to date with 100% graft and patient survival for up to 5 years for international recipients. All international donors have shown normal renal function and blood pressure in up to 5 years of follow-up.¹⁰ In 2020, Ambagtsheer and associates stated that implementation of GKE is a means to increase access to transplantation ethically and effectively.¹³ These conclusions by the European Society of Transplantation Committee on Ethical, Legal, and Psychological Aspects of Transplantation were crucial to promoting an open discussion about the value of GKE. Together with the strong endorsement of GKE by Minerva and associates¹⁴ in *Lancet* and the positive position statement from the American Society of Transplant Surgeons,¹⁵ Ambagtsheer and colleagues¹³ successfully dispelled previously raised doubts. The more than 1000 kidney exchange transplants accomplished per year in the United States are due in part to the continued exploration of matching strategies, including nonsimultaneous chains. Global kidney exchange can be expected to benefit from continued exploration and refinement.

Requirements for Global Kidney Exchange Participation

The requirements for transplant centers to participate in the international GKE program include the following. (1) The transplant program for living donor nephrectomy and kidney transplant must be approved by a corresponding national competent authority. (2) Transplant programs must

have well-documented experience in donor nephrectomy that are performed by minimally invasive techniques and according to best practices (intra- or extraperitoneal laparoscopic or robotic surgery). The technique should be based on clinical grounds and according to the surgeon's preference in technique, based on the criteria of vascular anatomy, size of the abdominal cavity, previous surgery, and technical implications for the recipient. (3) Transplant programs must accept the rules that have been laid down in the program, including the ability to offer first-rate posttransplant/donation long-term care. (4) To harmonize immunologic criteria, immunology laboratories that participate in the program must be accredited by the European Federation for Immunogenetics or the American Society for Histocompatibility and Immunogenetics or by other organizations accredited by the different participating countries.

The matching between pairs is performed based on the algorithm identified by APKD; APKD provides its protocol with appropriate documentation to the other parties. The protocol includes details on algorithms and criteria on which it is based for the purpose of identifying compatible pairs. The allocation software is managed by APKD in accordance with and in compliance with the regulations issued by the competent US authority.

A match run is carried out as often as whenever a new pair is enrolled in the program, with the pool of remaining pairs active after each national match run is performed. Before the inclusion of a pair into the program, all work-up must be completed. The work-up includes clinical studies, immunologic characterization, angio-computed tomography scans to assess vascularization, specific informed consent, and authorization or approval by an independent body (eg, ethics committee, third party committee) as well as other legal requirements, according to national regulations.

A secure platform is available to share information on match run results and the medical records of the donors or other necessary information, in accordance with data protection regulations.

The final combined pairs are chosen on the basis of the assessment of virtual crossmatch outcomes. Once all transplant teams accept the offer identified through virtual crossmatching, blood samples of donors are shipped to the HLA laboratories of the transplant hospital to perform a laboratory crossmatch to evaluate the feasibility of the kidney transplant procedure. The laboratory crossmatch is

performed by using flow cytometry and/or complement-dependent cytotoxicity.

Global Kidney Exchange Programs: Essential Components and Examples of Use

Users of GKE have identified several new barriers that must be overcome to successfully expand, in addition to traditional immunologic barriers such as blood type and donor-specific anti-HLA antibodies. First, financing kidney exchanges between countries requires different solutions that consider the cost differential between dialysis and kidney transplant. Second, kidney exchange remains illegal in some countries; in other countries, laws have limited relationships between participants that are legal. However, other countries have stated that chain-initiated nondirected donation is not legal. Third, regulations have limited the cross-border transportation of living donor kidneys in many countries so that kidney exchange is only possible by having donors travel to recipient centers.

Financing kidney transplant is an essential component of any solution designed to deliver more kidney transplants to address the growing global burden of end-stage renal disease. Government payers, commercial payers, and self-pay options predominate among payment strategies to address kidney replacement treatment options such as dialysis and transplant. For the most part, none of these options work well outside of national borders, especially as it relates to living donor kidney transplant. The following 3 examples serve to demonstrate the financial challenges associated with GKE.

The first GKE transplant involved an immunologically compatible husband and wife from the Philippines who were denied funding for a transplant in the Philippines by the government payer (PhilHealth).^{12,16} The husband-wife pair had no financial resources for travel, kidney transplant, or postoperative medications given their personal situation and the absence of a Philippine government payer for these costs (PhilHealth did not approve payment for this couple to receive a kidney transplant and also did not provide adequate payments for dialysis). The solution was a philanthropic solution whereby the APKD provided funding for travel and the transplant procedure and created an escrow account to pay for an estimated 10 years of recipient and donor follow-up care upon return to the Philippines.

The second GKE transplant involved an immunologically incompatible donor and recipient who were cousins. They had government funding for a transplant in Mexico through the Mexican Institute of Social Security (known as IMSS by its Spanish acronym) but had not found a match from the Mexican deceased donor system in 5 years, and there was no viable kidney exchange program in Mexico.¹⁷ This pair raised sufficient financial resources to pay for travel to the United States and raised one-third of the cost of an uncomplicated kidney transplant in the United States. The IMSS agreed to provide postoperative medications and donor-recipient long-term follow-up care upon return to Mexico. The solution was a combination of government-financed postoperative care and private/philanthropic funding whereby the APKD partially subsidized the transplant procedures and fully managed financial aspects of potential complication costs.

Two GKE transplants involved an immunologically incompatible pair of friends from Denmark and an immunologically incompatible mother-daughter pair from Mexico who were able to privately pay for travel, transplant, and postoperative care but were not able to manage the financial risk of a significant complication. The solution involved private/philanthropic funding whereby the patient paid for an uncomplicated kidney transplant in the United States, with APKD philanthropically fully managing the financial aspects of potential complication costs.

The 5 examples given above involved pairs from the Philippines, Mexico, and Denmark. The Philippines and Mexico do not offer kidney exchange to their citizens, so these patients had no choice but to look for an international option. In Mexico, it is possible that a living donor kidney could have been shipped from the United States to Mexico, but the patient's transplant team in Mexico did not want to participate in the exchange. US regulations prevent a living donor kidney from being procured in Mexico, Denmark, or the Philippines and shipped to the United States. Thus, in each of these examples, the only option was for international pairs to travel to the United States and pay for transplant costs at US-based prices. Denmark offers kidney exchange through ScandiTransplant, but the program has less than 50 pairs participating, so matching for hard-to-match patients is limited. For the Danish patient, who had panel reactive antibody levels greater than 90%, the only reasonable option was to look for a bigger kidney exchange pool outside of ScandiTransplant, such as the APKD pool in the United States.

Discussion

Worldwide estimates suggested that between 5 and 7 million people died prematurely in 2010 because they did not have access to renal replacement therapy such as dialysis or kidney transplant. This estimate is double the deaths occurring every year for tuberculosis, malaria, and AIDS combined. In sub-Saharan Africa alone, every year, 3 million patients die because of lack of access to dialysis.¹⁸

In Europe, with a total population of 588 million inhabitants (if Iceland, Norway, and Turkey are included), about 90 000 people are on kidney deceased donor wait lists, and it is estimated that 6000 patients die every year while waiting for an organ. Recently, the World Health Organization (WHO) reported that every year the number of solid-organ transplant procedures performed in the world is about 150 000.¹⁹

As we write, more than 100 000 patients are on kidney transplant wait lists in the United States, but fewer than 20 000 deceased donor kidneys will be transplanted in a year. Disparities in access to treatment are even worse when we compare Europe or the United States with the least industrialized countries, where millions of patients with kidney failure die every year because, as mentioned above, they do not have access to renal replacement therapy or even access to willing living kidney donors who are emotionally related.

Global kidney exchange offers an exchange program, using APKD's algorithm, to match one incompatible pair with another, so that patients in many countries could be helped. This way, underserved, international patients who have one or more willing emotionally related donors, but cannot afford a transplant in their own countries, can cross borders to exchange donors with incompatible pairs from industrialized countries. In industrialized countries, one additional transplant can save hundreds of thousands of euros and provide 10 additional years of life compared with dialysis. Another major problem that industrialized countries are now facing is the increasing number of patients (approximately one-third of patients on kidney transplant wait lists) who return to dialysis after a failed transplant and need a second or third transplant. Most of these patients become hyperimmunized after receiving the first kidney transplant; with the system currently in place, these patients have very poor chances to be retransplanted, particularly in countries with small or limited kidney paired exchange program. A collaborative effort between

world geographic areas with different genetic profiles may also contribute to solving the emerging problem of hyperimmunized patients who have little chance to get retransplanted after a failed kidney graft.

Global kidney exchange leverages the cost savings achieved through earlier transplant over dialysis to fund the cost of kidney exchange between patient-donor pairs with immunologic barriers in the industrialized world and patient-donor pairs with barriers to health care access in less industrialized countries. In countries that provide universal citizen access to treatment for end-stage renal disease, the cost of dialysis is generally more than twice the cost of renal transplant when time frames greater than 1 year are considered. As an example, the cost of hemodialysis in Europe exceeds 80 000 euros per year. In contrast, the cost of a kidney transplant procedure is roughly 100 000 euros. When we consider these estimates and calculate the average lifespan of a patient undergoing dialysis being 10 years, we can surmise that the person will have poorer quality of life and a cost to the health care system of close to 1 million euros. On the other hand, with a successful kidney transplant, we may have the same person enjoying an excellent quality of life, going back to full activity, and have a much longer lifespan, with a cost to the health care system of only the price of medication (approximately 18 000 euros per year). Therefore, beyond the fundamental value of the improved quality of life of patients undergoing kidney transplant, which remains a priority for any society, the cost difference between a dialysis patient and a transplant patient constitutes a crucial issue for any health care system, bringing significant financial savings. At the same time, this also guarantees the long-term economic sustainability of GKE.

As another example, when we compare a patient on dialysis versus a patient who has undergone a kidney transplant, the lifespan is shorter, the quality of life is worse, and the cost for the health care system in 10 years is 802 000 euros compared with 269 000 euros with successful kidney transplant. Therefore, an opportunity exists for health care payers in industrialized countries to financially support 2 kidney transplants and still reduce their overall cost, rather than having a patient stay on dialysis. We propose that kidney exchange could be extended to overcome poverty barriers in the least industrialized countries, as well as immunologic barriers in the industrialized world, by enabling exchanges between them. As proposed in a previous study, both transplant and subsequent immunosuppression costs

could be paid for by the industrialized world's health care provider for the patient with ESRD.¹²

In conclusion, GKE provides personalized solutions by capturing relevant genetic, immunologic, physiologic, and social information to match patients with kidney failure and their willing donors to identify opportunities for living donor kidney transplant instead of dialysis or death.

With GKE, a modality that can equally benefit rich and poor, industrialized world health care is made available to impoverished patients in less industrialized countries, while at the same time fighting unethical transplant tourism. In fact, with GKE, the exchange of a kidney for transplant is an altruistic gift and never an unethical and illegal commercial exchange. Moreover, with such a controlled system, every single donor and every single recipient of the GKE program can be scrutinized before the transplant procedure is performed and their data can be entered in a registry that can be accessed by transplant professionals to ensure ethical treatment of living donors and improved transition of care across national borders.

Because one of the main motivations of GKE is to make transplantation more available in low- and middle-income countries, it would be helpful if the WHO revisited the ethics of GKE, ideally with an open discussion involving representatives of all WHO countries interested in this procedure.¹⁹

References

- Rapaport FT. The case for a living emotionally related international kidney donor exchange registry. *Transplant Proc.* 1986;18(3)(Suppl 2):5-9.
- Kwak JY, Kwon OJ, Lee KS, Kang CM, Park HY, Kim JH. Exchange-donor program in renal transplantation: a single-center experience. *Transplant Proc.* 1999;31(1-2):344-345. doi:10.1016/s0041-1345(98)01655-8
- Thiel G, Vogelbach P, Gürke L, et al. Crossover renal transplantation: hurdles to be cleared! *Transplant Proc.* 2001;33(1-2):811-816. doi:10.1016/s0041-1345(00)02802-5
- de Klerk M, Keizer KM, Claas FH, Witvliet M, Haase-Kromwijk BJ, Weimar W. The Dutch national living donor kidney exchange program. *Am J Transplant.* 2005;5(9):2302-2305. doi:10.1111/j.1600-6143.2005.01024.x
- Delmonico FL, Morrissey PE, Lipkowitz GS, et al. Donor kidney exchanges. *Am J Transplant.* 2004;4(10):1628-1634. doi:10.1111/j.1600-6143.2004.00572.x
- Roth AE, Sonmez T, Unver MU. Kidney exchange. *Quart J Econ.* 2004;119(2):457-488.
- Roth AE, Sönmez T, Unver MU, Delmonico FL, Saidman SL. Utilizing list exchange and nondirected donation through 'chain' paired kidney donations. *Am J Transplant.* 2006;6(11):2694-2705. doi:10.1111/j.1600-6143.2006.01515.x
- Rees MA, Bargnesi D, Samy K, Reece L. Altruistic donation through the Alliance for Paired Donation. *Clin Transpl.* 2009;235-246.
- Ashlagi I, Bingaman A, Burq M, et al. Effect of match-run frequencies on the number of transplants and waiting times in kidney exchange. *Am J Transplant* 2018;18(5):1177-1186. doi:10.1111/ajt.14566
- Rees MA, Roth AE, Marino IR, et al. The first 52 global kidney exchange transplants: overcoming multiple barriers to transplantation (Abstract in press). *29th International Congress of The Transplantation Society (TTS 2022), Buenos Aires, Argentina, September 10-14, 2022.*
- Rees MA, Kopke JE, Pelletier RP, et al. A nonsimultaneous, extended, altruistic-donor chain. *N Engl J Med.* 2009;360(11):1096-1101. doi:10.1056/NEJMoa0803645
- Rees MA, Dunn TB, Kuhr CS, et al. Kidney exchange to overcome financial barriers to kidney transplantation. *Am J Transplant.* 2017;17(3):782-790. doi:10.1111/ajt.14106
- Ambagtsheer F, Haase-Kromwijk B, Dor FJ, et al. Global kidney exchange: opportunity or exploitation? An ELPAT/ESOT appraisal. *Transpl Int.* 2020;33(9):989-998. doi:10.1111/tri.13630
- Minerva F, Savulescu J, Singer P. The ethics of the global kidney exchange programme. *Lancet.* 2019;394(10210):1775-1778. doi:10.1016/S0140-6736(19)32474-2
- American Society of Transplant Surgeons. ASTS position statement on global kidney exchange. October 2017. Accessed April 26, 2020. <https://asts.org/about-asts/position-statements#.XqLLytNKjAY>.
- Bozek DN, Dunn TB, Kuhr CS, et al. Complete chain of the first global kidney exchange transplant and 3-yr follow-up. *Eur Urol Focus.* 2018;4(2):190-197. doi:10.1016/j.euf.2018.07.021
- Carrillo I. Un Puente de vida (English translation: A bridge of life). *Newsweek en Español.* 15th ed. April 14, 2017. <https://web.stanford.edu/~alroth/NewsweekEnEspanol.pdf>
- Liyanage T, Ninomiya T, Jha V, et al. Worldwide access to treatment for end-stage kidney disease: a systematic review. *Lancet.* 2015;385(9981):1975-1982. doi:10.1016/S0140-6736(14)61601-9
- World Health Organization. Seventy-fifth World Health Assembly A75/41 Provisional agenda item 27.2; April 12, 2022. Human organ and tissue transplantation. Report by the Director-General. https://apps.who.int/gb/ebwha/pdf_files/WHA75/A75_41-en.pdf