Challenges and Advances in Kidney Paired Donation: National and Global Perspectives

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Abstract
The concept of Kidney Paired Donation (KPD) was first described by Rapaport in 1986, enabling two ABO- or HLA-incompatible donor-recipient pairs to exchange donors and form compatible pairs (CPs). The first transplant using this concept occurred in South Korea in 1991, followed by Europe in 1999, the USA in 2000, and Portugal in 2013. Kidney exchange programs can range from simple two-pair exchanges to more complex arrangements involving three or more pairs and can include DD (deceased donor). International initiatives, such as the South Alliance for Transplant and Scandiatransplant, have successfully increased transplant numbers. Including CPs seeking higher immunological compatibility, or incorporating DD into transplant chains, further increases the number of transplants. More recently, the concept of Global Kidney Exchange has emerged, enabling exchanges between high- and low-income countries while ensuring medical care for pairs from low-income regions. This approach may enhance genetic diversity but raises important ethical and legal considerations. Participation in KPD programs increases the number of patients transplanted and reduces waiting times. Its success depends on the number of registered pairs, making access to information for nephrology consultants and its dissemination to the whole medical and non-medical community a priority.
This narrative review explores the evolution of KPD, the challenges of different kidney exchange types, and their implementation in Portugal. It also presents future perspectives, emphasizes public education and awareness, and provides a practical, accessible information source for the Portuguese population.
This narrative review was based on a targeted literature search conducted in PubMed and ScienceDirect up to May 2025, complemented by institutional documents and official data from the Portuguese Institute of Blood and Transplantation and the Global Observatory on Donation and Transplantation. Peer-reviewed articles, guidelines, registry-based studies, and institutional reports were selected when they addressed the clinical, immunological, organizational, logistical, ethical, or legal aspects of KPD. A total of 47 scientific publications and institutional documents were included in a qualitative narrative synthesis, with particular emphasis on the Portuguese experience.

Keywords: ABO Blood-Group System; Blood Group Incompatibility; Directed Tissue Donation; Histocompatibility; Kidney Transplantation; Living Donors; Waiting Lists.

INTRODUCTION: KIDNEY TRANSPLANTATION AND THE CREATION OF KIDNEY PAIRED DONATION

Chronic kidney disease (CKD) is a growing health problem, affecting 11%-13% of the worldwide population and up to 20% of individuals over 65 years of age. Between 1990 and 2019, both CKD incidence and disability-adjusted life years (DALYs) doubled, mainly due to population ageing and the rising prevalence of diabetes, metabolic syndrome, and hypertension. CKD is associated with substantial morbidity, mortality, and cardiovascular risk, and it is projected to become the fifth leading cause of death globally by 2040, rising from 27th in 1990 and 11th in 2016.[1–5]

Living donor (LD) kidney transplantation (KT) remains the best treatment for end-stage renal disease (ESRD), offering superior survival, quality of life, cost-effectiveness, and environmental benefits when compared to dialysis.[6,7] In 2022, 39% of transplants reported to the Global Observatory on Donation and Transplantation (GODT) were from LD.[8]

Since the first successful kidney transplant in 1954, both LD and DD programs have expanded worldwide, unevenly,

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reflecting differences in legal frameworks, ethical standards, and healthcare systems.[8-10]

Despite this growth, waiting lists for transplantation continue to increase each year. Additionally, the number of patients on the waiting list for re-transplantation has increased in recent years, and a new transplant continues to be beneficial compared to dialysis.[6,7] These candidates contribute to an increase in highly sensitized (HS) patients on the waiting list. To address organ shortages, alongside improvements in surgical techniques, increasing living kidney donation is widely used.

In 2017, 5% of transplants in Germany, 10% in Spain, 26.4% in Scandinavia, 30% in the United Kingdom (UK), and more than 50% in the Netherlands were LD transplants. [9,10]

Over time, candidate selection criteria for transplant have broadened to include older donors and individuals with selected medical or psychosocial risk factors. This expansion must be accompanied by a prioritization of donor safety and their informed consent. Thus, it is essential to understand the short- and long-term risks of living donation, as well as the impact of expanding these criteria on graft survival. [8,10,11]

At the same time, innovative transplant strategies have emerged to address organ shortages. In addition to conventional compatible LD approaches, such as ABO-incompatible (ABOi) KT, HLA-incompatible (HLAi) KT, KPD programs have emerged to address the growing need for this organ. KPD was first proposed in 1986 by Rapaport and implemented in 1991 in South Korea, and enables incompatible donor-recipient pairs to exchange donors and achieve compatible transplants. Since then, KPD programs have diversified in design and scope, becoming an essential component of transplantation systems worldwide and representing a crucial option for patients facing immunological barriers to transplantation.[12,13]

In this context, this narrative review explores the evolution of KPD, its implementation in Portugal, the challenges associated with it, and future perspectives, with particular emphasis on the role of education and awareness in ensuring its success.

METHODOLOGY

This manuscript was designed as a narrative review addressing the evolution, models, clinical relevance, ethical challenges, and future perspectives of kidney paired donation (KPD), with particular emphasis on the Portuguese experience. The aim was to provide a clinically oriented and educational synthesis of the available evidence, rather than a systematic review or meta-analysis. A targeted literature search was conducted in PubMed and ScienceDirect up to May 2025. This was complemented by institutional documents and official data from the Portuguese Institute of Blood and Transplantation (IPST), the Global Observatory on Donation and Transplantation (GODT), and other relevant transplant organizations. Search terms included combinations of “kidney paired donation”, “kidney paired exchange”, “living kidney donation”, “ABO incompatibility”, “HLA incompatibility”, “highly sensitized patients”, “compatible pairs”, “non-directed donors”, “deceased donor chains”, “global kidney exchange”, and “Portugal”.

Eligible sources included peer-reviewed articles in English, international guidelines or consensus documents, registry-based studies, institutional reports, and official documents addressing the legal, organizational, immunological, logistical, ethical, or clinical aspects of KPD. Sources were prioritized when they provided information on KPD models, national or international program implementation, clinical outcomes, allocation strategies, ethical concerns, or the Portuguese National. Articles were first screened by title and abstract. Potentially relevant articles were then reviewed in full text and selected according to their relevance to the objectives of the manuscript. A total of 47 scientific publications and institutional documents were selected for qualitative synthesis. The selected literature was organized into predefined thematic domains: immunological barriers to living donation, KPD models, international and Portuguese experience, clinical benefits, logistical and ethical challenges, and future strategies to expand participation and improve equity.

Given the narrative and educational scope of this review, no formal PRISMA flow diagram, risk-of-bias assessment, or quantitative evidence grading was performed. This limitation was considered when interpreting the evidence, and the manuscript focuses on a balanced synthesis of key concepts, areas of consensus, and unresolved controversies in the field.

THE PORTUGUESE EXPERIENCE: FROM LIVING DONATION TO KIDNEY PAIRED DONATION

Portugal has one of the highest prevalences of CKD in Europe and worldwide. Estimates vary according to the population studied and the diagnostic criteria applied, ranging from approximately 9.8%-11.3% in studies using strict clinical definitions and excluding ESRD, to 20.7%-20.9% when all CKD stages are considered in broader population-based assessments. The prevalence of CKD in stages 3-5 is estimated at 6.1%, and the country continues to report a persistently high number of patients undergoing hemodialysis.[5,14–16]

The Portuguese transplant system, established in 1993 and based on the Spanish model, promotes preventive measures, organ donation, safe transplantation, and structured follow-up. It is coordinated by the IPST, which oversees organ donation, allocation, and post-transplant follow-up on a regional basis. By law, all Portuguese citizens or residents not registered in the National Registry of Non-Donors (RENNDA) are considered potential donors.[17,18]

Despite limited financial resources, Portugal ranked third in Europe and fourth worldwide for DD transplantation in 2023, but 35th globally for LD transplantation.[18,19]

Living organ donation has been legally permitted since 2007, and the National Kidney Paired Donation Program (PNDRC) was established in 2010, with the first transplant performed in 2013. Enrollment in the PNDRC is restricted to designated transplant centers (Centro Hospitalar Universitário Santo António, Centro Hospitalar de São João, Centro Hospitalar Universitário de Coimbra, Centro Hospitalar Lisboa Central, and Centro Hospitalar Lisboa Ocidental), with referral pathways available for non-participating institutions.[20,21]

Eligibility criteria for PNDRC include ABOi, positive complement-dependent cytotoxicity and/or flow cytometry crossmatch, and the presence of donor-specific antibodies (DSA). Pair selection is conducted at least four times annually and reviewed by an expert committee.[21,22] Since 2022, compatible pairs (CPs) and non-directed donors have also been included when improved compatibility is anticipated, increasing opportunities for incompatible pairs. In the same year, non-directed donors have also been included with preferential allocation to the PNDRC and subsequent assignment to HS patients if no match is identified after two pairing attempts.[20,21] The implementation of a national digital platform has further enhanced secure communication and data sharing among transplant centers.

Portugal performed its first international KPD in 2019 and participates in international collaborations through the South Alliance for Transplants. In 2022, the International KPD was established to facilitate matching for unsuccessful pairs within the national program.[18,21]

COMPATIBILITY

Incompatibility between donor and recipient is one of the main barriers to living kidney transplantation, and its management was the foundation for developing KPD. About one-third of potential LD pairs are incompatible due to ABO blood group or HLA mismatches.[12,13,23]

ABOi arises from naturally occurring antibodies against blood group antigens present on red cells and multiple tissues, including the kidney.[9,23] ABOi transplantation carries a high risk of hyperacute rejection and graft loss.[9,24]

HLAi occurs when the recipient has specific antibodies directed against the donor human leukocyte antigen types. These donor-specific antibodies (DSA) usually arise after prior blood transfusions, pregnancies, or transplants. A positive crossmatch test confirms the presence of clinically relevant DSA and predicts acute rejection and transplant failure.[9] The panel reactive antibody (PRA) quantifies recipient sensitization, with values above 85% defining HS patients. For example, a PRA of 80% means the patient is incompatible with 8 of 10 donors.[25] Among HLA loci, HLA-DR compatibility has the greatest impact on transplant outcomes. HLA-DQ mismatches have been associated with an 18% increase in graft loss and rejection risk. [26]

To overcome these barriers, ABOi and HLAi transplantation were developed. ABOi outcomes now approximate those of compatible transplants, though short-term rejection remains higher.[9,23] HLAi transplantation, however, is associated with inferior long-term results and requires intensive desensitization protocols.[25,27]

KPD emerged as a simpler, safer, and more cost-effective alternative. [22,25] By allowing incompatible pairs to exchange donors, KPD avoids the risks of aggressive desensitization while expanding access. Programs increasingly combine both approaches, using KPD as first-line and reserving desensitization for those unlikely to find a CP. The Australian program and Johns Hopkins Institute successfully combine KPD with desensitization. Additionally, they allow the inclusion of ABOi pairs with relatively low isoagglutinin titers, thereby increasing the quantity and variability of available donors and the program's success.[25] European guidelines recommend KPD as the preferred option due to better outcomes and cost-efficiency, unless there is clinical urgency or a low probability of finding a compatible donor that justifies desensitization. [22,25]

Kidney compatibility extends beyond ABO and HLA compatibility. Several factors, including age, size, previous infection with specific viruses (such as Epstein-Barr virus (EBV) and cytomegalovirus (CMV)), other HLA antigens, and epitopes/eplets, can also affect compatibility.[26] By increasing compatibility between the donor and recipient in all these aspects, we also enhance long-term graft survival. [28]

Thus, immunological incompatibility not only defined the limits of traditional living donation but also directly shaped the rationale and growth of KPD.

From a clinical perspective, KPD should not be viewed just as an alternative to desensitization, but as a strategy that can expand access to LD transplantation while avoiding the complexity and burden associated with intensive immunological interventions. Current European recommendations support KPD as the preferred approach whenever a CP can be identified, particularly for recipients with ABOi or HLAi. Nevertheless, desensitization remains an important option for HS-patients and for candidates with a low likelihood of obtaining a match. Rather than representing competing strategies, KPD and desensitization may be considered complementary approaches, with the optimal choice depending on the recipient's immunological profile and the likelihood of successful matching. This distinction is particularly relevant in smaller national programs, such as Portugal, where pool size, matching frequency, and international collaboration directly influence the probability of successful transplantation.[9,25,27]

TYPES AND MODELS OF KIDNEY PAIRED DONATION

KPD encompasses several models, including N-way exchanges, domino chains, advanced donation programs,

and trans-organ exchanges. The availability and implementation of these models vary across countries, reflecting differences in legislation, healthcare systems, and cultural values.[9]

The simplest model of KPD is the two-way exchange, in which two incompatible pairs swap donors, permitting two compatible transplants. Three-way exchanges (Fig. 1) extend the cycle to three pairs, and some countries allow four-way or larger cycles, such as the Netherlands, Portugal, and Belgium. While more complex cycles expand opportunities, they also create significant logistical challenges, especially when surgeries are performed simultaneously.[9,29]

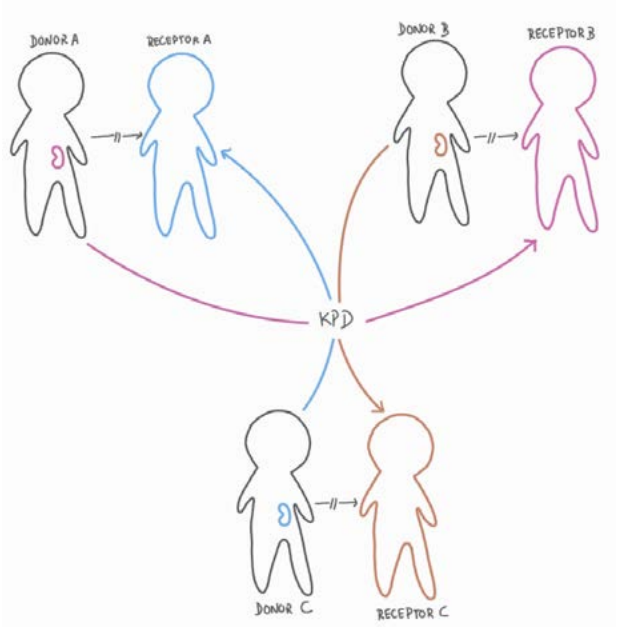

Figure 1. Three-way exchange in kidney paired donation

Domino-chains (Fig. 2) are initiated by a non-directed donor who gives to a recipient in an incompatible pair, and the donor then continues the chain. The sequence may conclude with a donation to the DD waiting list or by creating a bridge-donor for future chains.[30] This approach, common in the United States of America (USA), the UK, and the Netherlands, increases transplant numbers but carries risks if bridge-donors withdraw.

The frequency of domino matching varies: monthly in Poland, quarterly in the UK and the Netherlands, and approximately every 4 months, or when a new non-directed donor registers, in Portugal and Spain. This practice is not permitted in France, Greece, and Switzerland.[9,12] Some programs have also explored domino exchanges initiated by DD, first implemented at a national level in Italy, thereby expanding matching opportunities for HS and long-waiting candidates.[30]

Advanced Donation Programs, active in the USA since 2011, allow donors to donate at a convenient time while their intended recipient receives a transplant later, through a planned exchange. Voucher-based systems (Fig.3), including family-voucher models, further expand this concept by granting conditional priority to designated recipients. However, transplantation cannot be guaranteed, particularly for blood group O or HS patients.[13,30,31] These programs address the issue of chronological incompatibility and allow donors to recover before assuming caregiving roles.[32]

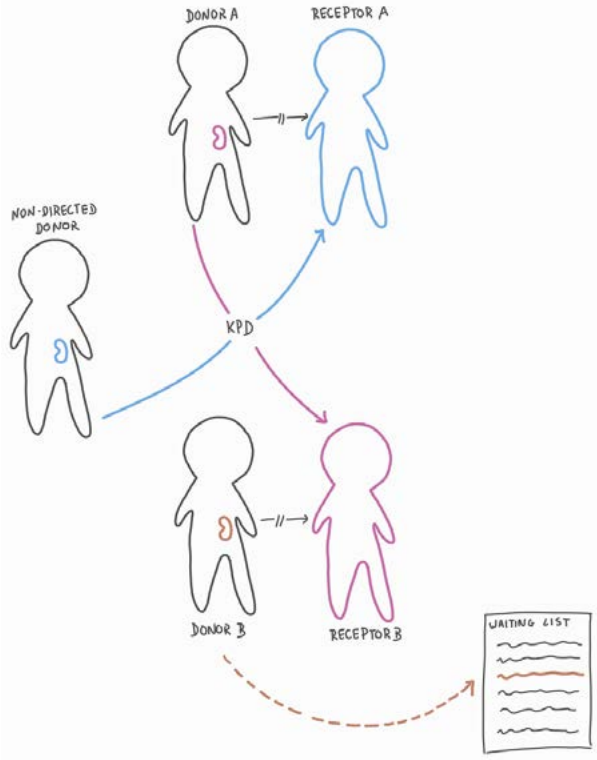

Figure 2. Domino exchange in kidney paired donation

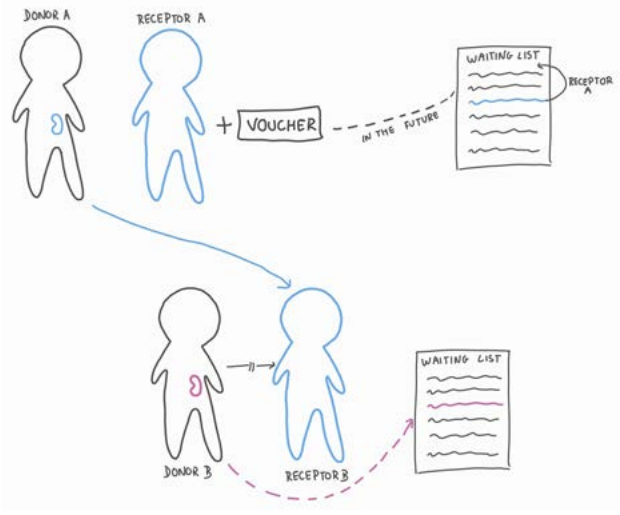

Figure 3. Voucher-based systems in kidney paired donation

Trans-organ exchange involves donors initially evaluated for one organ donating a different organ, such as a kidney instead of a liver, enabling transplantation for the original recipients. Despite its potential to increase transplant volume (20-30 transplants monthly), this strategy raises important ethical concerns due to the higher morbidity and mortality associated with liver donation. It is considered acceptable only under strict informed consent.[1,13,33]

GLOBAL PERSPECTIVES ON KIDNEY PAIRED DONATION

In Europe, Switzerland performed the first KPD transplant in 1999, followed by the Netherlands (2004), which pioneered four-way exchanges and the integration of non-directed donors.[34] The UK launched its national program in 2007, now the largest in Europe, while Spain followed in 2009 and has since built the continent's second-largest program.[35] Matching algorithms in these programs often prioritize HS patients and consider unacceptable HLA antigens, reflecting European consensus recommendations.
KPD programs have developed heterogeneously worldwide, reflecting differences in legislation, healthcare systems, and cultural norms.
In the USA, KPD was introduced in 2000 and rapidly expanded through major organizations, including the Alliance, the National Kidney Registry (NKR), and United Network for Organ Sharing (UNOS). KPD represents about 12% of all USA LD transplants, with innovations such as domino chains and voucher systems.[13,35,36] Canada implemented its national KPD program in 2009, incorporating domino chains from the beginning. Interestingly, in Canada, it is the donor, not the kidney, that travels to the recipient's transplant center. By 2020, 765 KPD transplants had been performed. However, only 38% of blood group-incompatible and 45% of HLA-incompatible candidates enrolled in the program were successfully matched.[12,37]
In Latin America, KPD is legally permitted in several countries but remains underdeveloped, with a decline in living donation occurring alongside an expansion of DD transplantation. Socioeconomic inequalities and limitations in healthcare infrastructure continue to restrict equitable access to living donation. In Asia, KPD is prohibited in Japan due to cultural and ethical considerations, but is active in countries such as South Korea and India. [38]
International collaborations are increasingly relevant. Eurotransplant (Austria, Belgium, Croatia, Germany, Hungary, Luxembourg, the Netherlands, and Slovenia) and Scandiatransplant (Sweden, Denmark, Norway, Finland, Iceland, and Estonia) prioritize a shared database over national ones and facilitate donor exchanges across multiple European countries. The South Alliance for Transplants (Spain, Italy, and Portugal) focuses on establishing national chains and cycles and then forms international chains and cycles with the remaining unmatched participants. The UK and Ireland, as well as France and Switzerland, follow a third model, allowing pairs from partner countries to enroll in their national programs.[9] Cross-border organ sharing in Europe has contributed to an increase in transplants among patients with PRA >95% who had been waiting more than five years for a transplant.[25]

CHALLENGES OF KIDNEY PAIRED DONATION

Despite its proven benefits, KPD faces multiple challenges that limit its expansion and effectiveness. These can be grouped into legal and cultural barriers, logistical complexity, donor withdrawal, equity concerns, and limited awareness.[8]

1. Legal and cultural restrictions

In several countries, living donation is legally restricted to genetically related or emotionally connected individuals, blocking the use of other exchange programs, such as those in Germany or Japan.[38]

2. Logistical challenges and allocation systems

Logistical complexity and allocation policies play a central role in ensuring equity. In Portugal, allocation is organized nationally for urgent, pediatric, and multiorgan cases, while other patients are managed regionally. The system considers HLA and ABO compatibility, PRA, dialysis time, and age. Since 2007, to protect blood group O candidates, priority has been given to isogroup matching, except in urgent cases.[6,7,20]
KPD allocation systems continue to evolve, with most European programs allowing clinician input in final match selection, while others rely on ranked match lists or staged crossmatch strategies. In the Czech Republic, Poland, and Portugal, the program generates a ranked list of possible matches for clinicians to select from. In Spain, once a chain or cycle is formed, centers exchange clinical data and perform crossmatch testing, and the medical team decides whether it proceeds to transplantation.[6,9]
The Mayo Clinic uses an algorithm that identifies potential matches and forms chains, starting with a non-directed donor and ending with a LDs kidney being offered to a candidate on the DD waiting list. The final decision is made by a specialized team, ensuring that no compatible pair is matched with a donor who is less compatible than their original donor.[28]
Prioritization of HS patients remains critical, although patients with very high PRA values (>80%) continue to face reduced matching probabilities (6.5% lower).[25] Some studies suggest that only those with a PRA>95% are disadvantaged.[7,27]
It is important to develop algorithms that improve match efficiency in KPD programs. In 2012, the Nobel Prize in Economic Sciences was awarded to a matching algorithm that improves the number of successful pairings. Artificial intelligence (AI) may contribute by generating dynamic

exchange models that anticipate chain failures, improve equity, and predict rejection or graft survival by analyzing medical records.[39] These tools could double the number of successful transplants and reduce incompatibility rates among HS recipients by up to 45%.[12,13]
Mathematical algorithms are becoming increasingly complex and optimized, making it easy to access real-time data on potential matches and view computed tomography images across centers.[27]

3. Donor withdrawal and chain disruption

Donor withdrawal represents another significant challenge, particularly in non-simultaneous exchanges and chains involving bridge-donors. Dropout rates range from 1.5% to 5%, with causes including the donor's health, voluntary withdrawal, or intraoperative organ refusal.[25,40] While simultaneous transplants reduce dropout risk, they increase logistical demands and limit chain size. As the number of pairs involved increases, the need to coordinate multiple centers also grows, both to accommodate all transplants and maintain anonymity.[9,34] Covering the expenses associated with KPD, including travel, accommodation, and postoperative care, may help increase participation. Although there is a broad consensus that donations must be voluntary and not financially compensated, this does not preclude reimbursement for legitimate expenses and income losses incurred by donors.[8,34]
Transporting organs rather than donors may mitigate some barriers, as studies suggest that a CIT of less than 14 hours does not significantly affect transplant outcomes. Some studies even indicate that CIT values below 20 hours or above 16 hours do not affect graft or patient survival.[11,13,41] In the UK, only double or triple exchanges are allowed, reducing the likelihood of transplant failure due to immunological, clinical, or logistical complications. Moreover, triple exchanges that include at least one double-pair match are preferable. This ensures that, if the triple exchange fails, at least two pairs can still proceed to transplant. In Spain, multiple laboratories conduct two rounds of HLA testing: a first round for the preferred chain or cycle, and a second round for alternative chains or cycles, allowing the realignment of broken pairs. In the Netherlands, a single centralized laboratory performs all tests and repeats them as needed until an optimal solution is found, avoiding positive crossmatch results.[9]
Finally, it is important to consider the potential psychological complications associated with participation in KPD. Preventative strategies and psychological support mechanisms are crucial for anticipating and effectively addressing these challenges.[8]

4. Equity and ethical concerns

Equity and ethical concerns arise when CPs or DD kidneys are included in KPD programs because certain recipients may be disadvantaged, particularly those with blood group O. Allocation policies must therefore balance efficiency with transparency and fairness. Risk assessment tools such as the Kidney Donor Risk Index (KDRI), the Kidney Donor Profile Index (KDPI), and the Living Kidney Donor Profile Index (LKDPI) support informed decision-making. While the KDRI and KDPI are calibrated for DD and used primarily in US allocation systems, the LKDPI is specifically designed for LD transplantation and incorporates both donor-specific and donor-recipient compatibility factors, making it particularly relevant in KPD settings. LKDPI is calibrated on a scale comparable to the KDPI, allowing comparison across donor types when multiple potential donor-recipient combinations are available.[26,42,43] The LKDPI has been used in some programs to compare donor quality and to justify a potential gain, or at least equipoise, when considering the inclusion of CPs, despite its recognized limitations.[28] However, a study using data from the Australia and New Zealand Dialysis and Transplant Registry and the Scientific Registry of Transplant Recipients, concluded that the LKDPI does not adequately discriminate death-censored graft survival and therefore should not be used to justify or promote the participation of CPs in KPD programs.[44]

5. Limited awareness and participation

The effectiveness of KPD depends on pool size. Lack of awareness among patients, professionals, and the public remains a major barrier, particularly in regions with low donation rates.

HOW TO INCREASE THE NUMBER OF TRANSPLANTS

The success of KPD programs depends on the size of the donor pool, as matching probability increases with the number of participating pairs. Programs enrolling more than 100 pairs per year show significantly higher match rates.[22,45] Several strategies have therefore been developed to expand participation and increase transplant activity.

1. Early presentation and awareness

Early introduction of KPD during transplant evaluation, combined with a clear explanation of its benefits, can increase participation.[28] Raising awareness among patients, healthcare professionals, and the general public through educational initiatives and campaigns is essential to expanding the program. Although evidence on the most effective communication strategies remains limited.[8]

2. Inclusion of compatible pairs, non-directed donors, and bridge-donors

Including CPs and non-directed donors increases donor pool diversity and improves match rates.[21] This may benefit incompatible pairs, particularly blood group O candidates, and may also allow compatible recipients to access

younger donors, improved HLA compatibility, or anatomically simpler kidneys (Fig. 4).[12,23]

Adding just one CP to the database increased the number of incompatible pairs by 30%, and when several CPs were included, the increase was 50% in an Australian program.[23] The NKR reported that the inclusion of CPs in their program raised the match rate from 37.4% to 75.4%.[41] However, eligibility criteria are required to ensure that CPs are not disadvantaged, as KPD programs were primarily designed to address incompatibility.[23]

One method of maintaining engagement and reducing CP dropout is to reassess participation every 3 months. Studies of recipients entering the program with a CP have shown that all benefited from a significant reduction in graft failure risk, primarily due to the donor's younger age and the avoidance of CMV and EBV incompatibilities.[28] In these cases, the average waiting time was 70 days, though it could reach up to 6 months. Recipients with blood type O or a PRA of ≥98% had significantly longer waiting times, typically exceeding 3 months.[28]

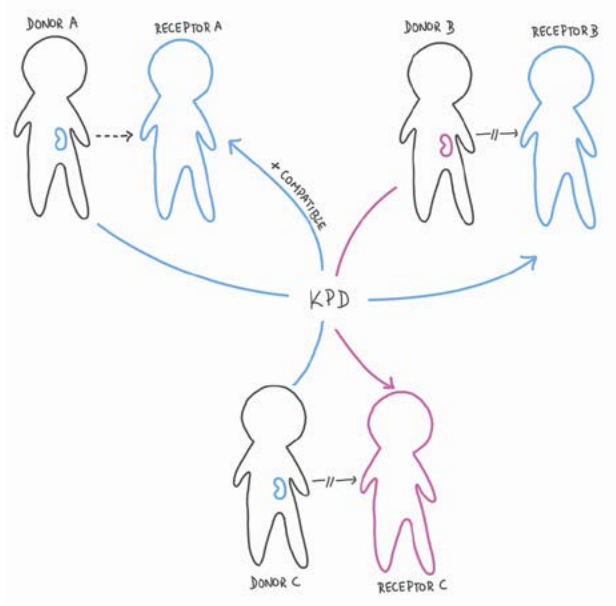

Figure 4. Inclusion of compatible pairs in kidney paired donation

Surveys indicate a high theoretical willingness among CPs to participate, though this may decrease later in the evaluation process. The main deterrent is anticipated transplant delay, particularly when benefits are uncertain. Still, other factors include having another relative who may need a kidney, higher education or income, little exposure to dialysis, preference for a known donor, fear of donor withdrawal, and travel demands. Early counseling addressing expectations and concerns may improve adherence.[23]

Increasing the frequency of matching rounds may reduce waiting times but can compromise overall efficiency.[37] Offering priority in cases of early graft loss due to logistical issues or donor-related causes is currently implemented by the NKR, with minimal expected impact on overall equity due to low early rejection rates (0.5% in the first month and 1.6% in the first year).[37,41]

Policies regarding CP inclusion vary across countries. While Belgium and France restrict KPD to incompatible pairs, countries such as the UK and Portugal allow and encourage CP participation when matched donors offer equal or superior compatibility.[9]

Bridge-donors represent another strategy to expand transplant chains.[9] Although this approach increases transplant opportunities, it carries a higher risk of donor withdrawal, due to the recipient's pair having already received a kidney, and, until a new chain is created, there may be changes in the donor's health status or a change in motivation. This risk is estimated at up to 7%, and its mitigation includes structured education, psychological assessment, transparency regarding potential delays, and additional follow-up for bridge-donors. Currently, there is no regulation for this type of donation in Portugal.[13,30]

3. Integration with deceased donor programs

In 2016, the OPTN proposed integrating KPD with DD programs, allowing a LD from an incompatible pair to donate to a candidate on the DD waiting list while the paired recipient receives priority for a DD kidney (Fig. 5).[30] A subsequent strategy introduced in 2018 involved direct exchanges between incompatible LD pairs and DD recipients, although in many countries this approach is limited by legal restrictions on allocating DD kidneys to specific individuals.[30]

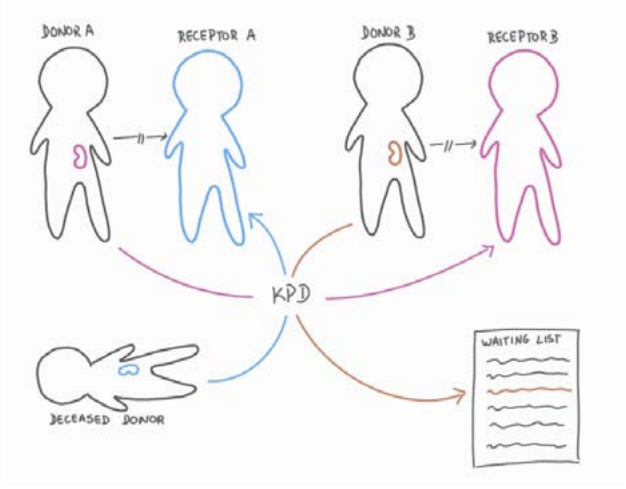

Figure 5. Integration of deceased donors in kidney paired donation

DD kidneys may also initiate transplant chains that end with a HS patient or a candidate with prolonged waiting time receiving a kidney from an LD. The first DD-initiated chain was performed in Italy in 2018, leading to national

adoption in 2019. In the first year, eight DDs enabled 24 transplants involving 16 incompatible pairs.[30] This approach reduces pressure on both KPD and DD waiting lists, particularly as many candidates are listed in both systems.[30]

Equity concerns persist, especially for blood group O candidates without access to compatible LDs. In the Italian program, although most initiating DDs were blood group O, the overall outcome resulted in a net benefit for this group, as additional type O recipients received kidneys at the end of domino chains. CIT remained for less than 6-8 hours, and chain durations ranged from 25 to 94 days.[30] However, delays between transplants increase the risk of donor withdrawal, which limits the feasibility of longer chains. One strategy is to require the LD to donate before their recipient receives priority on the DD list.[25]

Despite its feasibility, DD-initiated KPD requires careful balance between maximizing transplant numbers and ensuring fair allocation, particularly regarding blood group distribution and graft quality. Comparative assessment of LD and DD grafts can be supported using indices such as the KDRI, KDPI, and LKDPI.[29]

4. International collaboration and advanced strategies

Cross-border exchange programs, such as Eurotransplant and Scandiatransplant, demonstrate how international cooperation can enhance matching efficiency. More recently, the Global Kidney Exchange (GKE) has been proposed to connect donor-recipient pairs from high- and low-income countries, expanding genetic diversity and enabling transplantation for HS patients. While medically effective, GKE raises significant ethical concerns related to fairness and potential exploitation, requiring strict oversight.

The first GKE transplant occurred in 2017, facilitated by a pair from the Philippines, enabling multiple transplants in the USA.[1,35,45] Program enrollment requires a comprehensive clinical and immunological evaluation, informed consent, compliance with legal requirements, and ethics committee approval. Postoperative care is shared between the transplant center (the first 3 to 6 weeks) and the recipient's country of origin.[13,35]

Ethical concerns focus on the potential exploitation of vulnerable populations. According to the Istanbul Declaration Custodian Group, exploitation involves taking advantage of vulnerability to create an unequal distribution of benefits. Although GKE may reduce dialysis-related costs in high-income countries, long-term post-transplant care for recipients from low-income countries is not guaranteed.[1,35,45,46] While compensation of legitimate expenses is permitted, financial incentives for donation raise concerns regarding organ trafficking.[1,35,45,46]

International frameworks, including the Council of Europe Convention against Trafficking in Human Organs (2015) and the updated Istanbul Declaration on Organ Trafficking and Transplant Tourism (2018), define organ trafficking as organ removal for financial gain or comparable advantage. Although GKE may reduce global disparities in access to transplantation, its ethical acceptability depends on large-scale implementation, transparency, and continuous monitoring to prevent abuse.[46]

Overall, these strategies illustrate that the expansion of KPD should not be evaluated solely by the number of transplants generated. Each approach involves a balance between efficiency, equity, donor protection, and immunological benefits. The inclusion of CPs, DD-initiated chains, non-directed donors, and non-simultaneous exchanges may increase matching opportunities, particularly for HS patients. However, these strategies require transparent eligibility criteria, safeguards to avoid disadvantaging blood group O or HS candidates, and careful psychosocial support for donors involved. Similarly, predictive indices and matching algorithms may support more structured decision-making, as a complement of individualized clinical and ethical assessment. Therefore, the future development of KPD depends not only on program expansion, but also on governance models capable of ensuring fairness, transparency, donor safety, and long-term trust.

CLINICAL BENEFITS OF KIDNEY PAIRED DONATION

By 2019, a total of 22 transplants had been performed in Portugal through the PNDRC. More than 60% of the recipients were previously on hemodialysis, and nearly 30% on peritoneal dialysis. The presence of DSA was the main reason for inclusion in the program (82%), while only three patients presented ABO incompatibility. Three patients had a PRA level above 98%, and 10 had a PRA above 80%. Desensitization was used in selected cases: Rituximab and/or plasmapheresis in 15% of recipients and immunosuppressive induction with anti-thymocyte globulin in 50% of recipients. Postoperative complications were rare (two anastomotic stenoses and one ureterohydronephrosis), no episodes of cellular rejection were recorded, and 100% patient and graft survival were observed during the follow-up period (2-46 months).[22] These results confirm the safety and feasibility of KPD in Portugal, even in HS patients.

While short-term outcomes are already well documented, the increasing number of transplants facilitated by KPD programs underscores the importance of evaluating long-term results. In the USA, the first major study to address this issue, compared outcomes at three, five and seven years post-transplant between recipients enrolled in NKR during its first decade and those who received a LD kidney outside of KPD.[36] Despite involving a higher-risk population, more often Black, female, older, HS, re-transplant candidates, and patients with longer dialysis exposure, NKR recipients achieved mortality and graft survival rates comparable to controls. Although a modestly

increased risk of late graft failure (1.4-fold) was observed, overall, outcomes after even years were similar. These findings highlight the role of KPD in enabling transplantation for challenging patients without compromising long-term survival. However, further studies are needed to confirm potential advantages over conventional living donation.[32,36,47]

Overall, KPD has proven to be an effective means of expanding access to transplantation. It provides outcomes at least equivalent, and in many cases superior, to alternative approaches such as HLAi transplantation, while enabling transplants for complex and HS patients who otherwise face very limited options.

ETHICAL CONSIDERATIONS IN KIDNEY PAIRED DONATION

Ethical issues in KPD revolve around equity, consent, and donor protection.[8] Programs must ensure that enrolling CPs or integrating DD does not disadvantage candidates without such options, particularly those with blood group O or HS. Allocation rules should guarantee fairness and transparency.[23,29,30]

Informed consent is essential, as KPD introduces uncertainty: donors may not know their eventual recipient, and recipients may face delays while waiting for a match. Thorough counselling is needed to ensure donors and recipients understand both the benefits and limitations of participation.[8]

Donor protection remains paramount. The risk of withdrawal in non-simultaneous chains can leave donors exposed to additional psychological pressure. Ethical practice requires minimizing waiting times for bridge-donors and providing psychosocial support throughout the process.[25,40]

Finally, global initiatives such as the GKE raise additional concerns about the potential exploitation of vulnerable populations. While such programs may expand access, strict oversight and full compliance with international ethical standards are necessary to prevent coercion, organ trafficking, or inequitable benefit distribution.[1,35,45,46]

Ethical evaluation in KPD should therefore move beyond the simple confirmation of donor voluntariness and include a structured assessment of fairness, proportionality of benefit, transparency of allocation rules, and the potential psychological impact of exchange participation on both donors and recipients.

CONCLUSIONS AND FUTURE PERSPECTIVES

KPD has emerged as an innovative and effective solution to address the growing challenge of organ shortages for transplantation, associated with a rising prevalence of CKD. By overcoming immunological barriers, it not only increases the overall number of transplants but also delivers long-term outcomes comparable to or even superior to those of traditional LD transplantation, particularly in HS patients or those with complex immunological profiles. The PNDRC serves as a successful example of implementing collaborative strategies to expand access to transplantation, incorporating matching algorithms, secure data sharing, participation of CPs, and international exchange programs. Despite its growing success, KPD programs continue to face considerable challenges, including logistical complexities, donor risks, and the coordination required for simultaneous surgeries. Addressing these issues will require complementary strategies, such as integrating AI to optimize program efficiency and using predictive Indices to guide allocation.

However, the future development of KPD in Portugal should not be measured only by the number of transplants performed, but also by the fairness, transparency, clinical appropriateness, and long-term safety of the strategies used to expand access.

Ethical concerns must remain central, especially regarding fairness, transparency, and international collaboration. Sustained investment in education and public awareness will be essential to increase enrollment and ensure trust in KPD systems.

To support this, an accessible and user-friendly website was designed for use during nephrology consultations or at home. It can be accessed from https://sarsfieldteresa.wixsite.com/transprenalcruzado. This resource may further contribute to awareness and participation, ultimately strengthening the role of KPD as a fundamental pillar in the treatment of end-stage kidney disease.

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