Exploring the Complex Ethical Challenges Associated with Living Donor Kidney Transplantation

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Abstract

Living donor kidney transplantation is regarded as the best treatment for selected patients with end-stage renal disease, associated with improved survival and quality of life. However, it should be recognized as a distinct medical procedure during which an organ is procured from a healthy individual for the benefit of another patient. Seven decades after the first successful procedure, ethical constraints persist, even though the procedure has become routine worldwide. The perceived risks for donors are considered low and ethically acceptable; however, recent studies have identified increased long-term risks of end-stage renal disease for living donors compared to healthy non-donors, raised hypertensive disorders during pregnancy, and a possible increase in mortality. Additionally, in most centers, there is a growing acceptance of donors with minor abnormalities, which were previously declined, yet long-term follow-up data on these donors remains scarce. Furthermore, various risks and benefits must be evaluated, including the potential risks from refusing donations and possible lifesaving opportunities arising from conditions identified during the evaluation process. A thorough assessment of the candidate donor's risks is essential. While current literature helps us mitigate significant risks for the candidate donor, it is important to elaborate on these risks with greater precision. Maintaining ethical practices and ensuring informed consent requires an updated registry of all living donors and candidates, along with long-term follow-up that includes ongoing data reviews.

Keywords: Informed Consent; Kidney Transplantation/ethics; Living Donors; Personal Autonomy

INTRODUCTION

Living kidney donation constitutes a distinct medical procedure in which an organ is taken from a healthy individual to benefit another patient and, more broadly, the wider society. The tension between bodily integrity and human solidarity is fundamental to the ethics of transplantation. Joseph Murray elucidated this in his Nobel Lecture on December 8, 1990: "The only remaining problem was the ethical decision concerning the removal of a healthy organ from a normal person for the benefit of someone else. For the first time in medical history, a normal healthy person was to be subjected to a major surgical operation, not for his benefit".[1] He referred to the first successful kidney transplant from a living donor between identical twins, Herrick, which took place on December 23, 1954. This pioneering procedure was carried out by Murray and his team at Peter Bent Brigham Hospital in Boston, Massachusetts. This marked a milestone in the history of transplantation.

Seven decades after this procedure became routine, ethical constraints still persist, albeit each year, more than 35 000 people worldwide become living kidney donors.[2] Overall, perioperative mortality has declined significantly in the past decade compared to earlier periods, now down to fewer than one event per 10 000 donations.[3] Long-term increased risks of end-stage renal disease have been emphasized in two pivotal studies,[4,5] along with potential higher mortality rates.[4] Additionally, there have

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been reports of increased complications related to pregnancy, which adds to the overall uncertainty.[6] It is essential to assess the risks associated with donor nephrectomy to protect this population.

The global shortage of organs has led to an increase in kidney transplants from living donors. In recent decades, Portugal has emerged as a global leader in organ donation and transplantation. Portugal has one of the highest rates of incident and prevalent treated end-stage renal patients worldwide, with 240.9 per million population (pmp) and 2055 pmp as of December 31, 2023, respectively. It also has a significantly lower rate of living donor kidney transplants at 7 pmp, compared to deceased donor transplants, which stands at 53.6 pmp.[7-9] When comparing internationally, data from the Global Observatory on Donation and Transplantation indicates that in 2023, we ranked sixth in transplants per million population, following the United States, Spain, Finland, the Netherlands, and France. While we placed fourth in deceased donor kidney transplants, our ranking was significantly lower for living donor transplants, where we held the 35th position out of 89.[8] While optimizing and enhancing deceased organ donation must consistently remain a priority, boosting our living donor program is also a national priority. Addressing the ethical issues related to living donor kidney transplantation is therefore a significant concern.

ETHICAL CHALLENGES IN LIVING KIDNEY DONATION

Living kidney donation directly contradicts the primary principle of medical ethics, *“primum non nocere,”* and poses a considerable ethical challenge. Most of the ethical issues related to transplantation have been discussed in the context of principlism theory by Beauchamp and Childress.[10] It comprises four principles: 1) autonomy (respecting personal choices), 2) beneficence (producing benefits), 3) nonmaleficence (avoiding harm), and 4) justice (distributing benefits and burdens equitably). Although imperfect and not without critics, principlism remains the dominant approach to medical ethics.[2] It provides a set of tools for guiding the living donor evaluation and is, therefore, the ethical theory outlined here.

THE PRINCIPLE OF AUTONOMY

The principle of autonomy states that an individual, in this situation, a living kidney donor candidate, has the right to make their own choices. But this concept is inextricably linked to that of informed consent. Informed consent requires that a person be informed of an intervention’s nature, risks, and probable outcomes before giving their consent. The donor must be competent to understand the relevant information.

Potential living donors should be provided with all relevant information concerning the donation procedure, including the evaluation process, risks of the procedure and of the evaluation itself (such as the discovery of an unknown health problem), other available treatments for the recipient, such as the deceased organ transplant or the dialysis programs, and the expected outcome for both the recipient and the donor.[11-13] Research revealed significant variation in the written and oral information provided among different countries, transplant centers, and even providers at the same centers, particularly regarding long-term risks.[14] Although achieving complete standardization of information may not be possible, research has highlighted the necessity of a standardized process to ensure fair educational and decision-making opportunities, thereby preventing disparities across transplant centers.[14,15] More recent findings of a slightly absolute (i) increased risk of end-stage renal disease compared with healthy non-donors, (ii) increased complications of donor’s pregnancy, and (iii) possible decreased survival for a long time, must be transmitted and discussed with the potential donor.[4,5,11-13,16] The uncertainties about outcomes in certain medical conditions must also be considered.[16] Some uncertainties prevail and probably will increase in future years as accepting complex medical donors is an increasing practice.[17] Developing communication strategies to clarify these uncertainties is a major challenge, as well as keeping living donor registries up to date, following up long-term, including all donors, and facilitating research and investigations, namely in developing countries.[6,14,17,18] Furthermore, the panorama of living kidney donation is rapidly changing. Last decade’s new strategies to increase living donation include ABO incompatible transplants and Kidney paired exchange programs with several variations, including non-directed or “altruistic” donation, each with specific ethical dilemmas. Communicating all the possibilities and implications is a major challenge in a living donor consultation.[18]

In Portugal, the informed consent process is not considered complete without an evaluation with an independent donor advocate or a representative of the local ethics committee to further ensure the donor’s safety and obtain proper ethics authorization. This practice aligns with international guidelines recommending an independent living donor advocate to verify that donor candidates have the necessary information to make a voluntary and informed decision about donating, confirm consent for donation, and function independently from the recipient candidate’s team.[12] Other countries might employ different procedures, such as conducting an external review of planned donations, to ensure that independence, advocacy for donor rights, and voluntarism are respected.[12]

The donors should be informed that they can withdraw consent at any time before the procedure without any recrimination. In that situation, the evaluation team must ensure that medical and individual reasons for not proceeding with a donation remain confidential.[12,13] The decision to donate should be voluntary and not coerced.

Exhaustive psychosocial evaluation is mandatory.[11,12] Another important issue is how the donor's autonomy should be restricted in case of excessive risk. The increasing shortage of organs led to the evaluation of a broader range of potential living donors that would not have been evaluated before: the complex medical donors.[17] Donors with an increased risk of complications above the predefined threshold risk established by each Unit should not donate, regardless of the relationship with the receptor.[12] However, defining acceptable risk in many situations is often challenging, and precise metrics may not be applicable. A multidisciplinary team discussion, including the psychosocial team, is necessary.

End-stage renal patients are excluded as transplant candidates when no expected benefits are foreseen due to serious comorbidities.

In less obvious situations, the living donation should additionally be questioned when we expect low results for the receptor because of comorbidities or a high risk of recurrence of the primary renal disease with graft loss. A transplantation failure causes significant emotional stress for the donor-recipient pair, family, and the team involved. In both scenarios, there are instances of paternalism. Often, this involves a person in authority (such as a medical doctor) conditioning decisions for a subordinate person (like a living donor) to act in the subordinate person's best interest. From another perspective, in some instances, the principles of beneficence/nonmaleficence, based on the best interest argument, prevail over the principle of autonomy.

In some challenging cases, such as those involving complex vascular donor anatomy or rare disorders in the recipient, referring patients to specialized centers for "high-risk" cases can help to balance the tensions between paternalism and patient autonomy. This should only be done with the patient's full understanding and consent and with appropriate safeguards in place to address the increased risks. Transparent audits, support for medical personnel, and a focus on improvement rather than punitive measures in the case of below-average outcomes should be included.[19]

THE PRINCIPLES OF BENEFICENCE AND NONMALEFICIENCE

The principles of beneficence and nonmaleficence are often discussed together in medical practice, focusing on the benefits and potential harms of a particular treatment. When considering the pair donor-recipient, the living donor kidney transplant is the best treatment for the recipient,[6,20,21] but it can harm another individual. Although the risks of nephrectomy are small, they are real, including short-term complications such as infections, pain, and even death,[22] and long-term risks do exist.[4,5,18]

Many people who donate a kidney to a relative experience important psychological benefits from donating, including lasting increases in self-esteem and happiness after donating.[23-26] However, a small number of donors had an adverse outcome.[27] Concern for donor health, defined broadly from a medical and psychological perspective, is a central ethical consideration when physicians subject healthy individuals to a procedure with medical–physical, and psychological - risks. Minimizing possible harmful aspects depends on careful selection, informed consent, and follow-up of donation candidates.

An expanded view of the risks and benefits of living donation must include a discussion of the harms of refusing to allow it.[28] In their elegant study, Reese *et al* reported that potential donors who were discarded for donation were more likely to report that their lives were worse and that they experienced more stress, anxiety, and emotional changes. This highlights the importance of looking at the benefits of donation.[29] This additional point in the equation will redefine the beneficence/nonmaleficence discussion.[30] Many potential donors do not donate.[31] In addition to tackling the reasons for non-donation and enhancing those strategies, future efforts should include more in-depth psychosocial assessment, characterization, and support for this group. This group is expected to be quite diverse, but we anticipate that the findings will help improve the care provided to living donors.

In a qualitative study of 56 living donors, Rasmussen *et al*[32] pointed out some tangible benefits identified by donors that are currently overlooked in living donor evaluation, including reduced caregiving burden, increased wage earnings, and improved donor independence. They argue that these qualitative findings should inform quantitative research on the tangible benefits of donation, as these additional benefits may alter present living donor risk-benefit calculations. Further research in this area will be welcomed and reinforce the practice of living kidney donation.

Another often overlooked benefit is the potential for lives saved while assessing living donor candidates. This evaluation can lead to the early diagnosis of various abnormalities, including previously undetected life-threatening illnesses, which should be considered one of the key advantages of living donation programs.[33]

THE PRINCIPLE OF JUSTICE

Finally, the principle of justice reflects a concern for the fair distribution of the limited resources in the healthcare system. It is particularly important in transplantation, where demand far exceeds supply. The presence of international guidelines, particularly the Kidney Disease: Improving Global Outcomes (KDIGO) Clinical Practice Guideline on the Evaluation and Care of Living Kidney Donors,[12] helps guide clinicians in the selection, evaluation, and follow-up of living donors. It ensures that all donors undergo almost identical tests and appointments. In practice, each Unit should set its acceptable risk threshold that can be consistently reproduced,[12] although this is not always true.[34]

The principle of justice can also be applied to the entire society. Improving living donor programs will reduce the competition for deceased donor organs. Lately, the waiting list for a deceased-procured organ has been reduced, and so has the economic burden of dialysis.[35] Portugal has one of the highest rates of incident and prevalent treated end-stage renal disease,[8,9] as well as deceased donor kidney transplants worldwide.[36] However, there is potential for a significant increase in living donor kidney donations. It is crucial to emphasize that establishing living kidney transplant programs should not undermine the deceased donor program, as that would be inequitable for patients without living donors. Instead, by developing both programs simultaneously, patients can benefit more from this scarce resource.

Research indicates that women are less likely than men to receive kidney transplants, yet they constitute most of the kidney donors.[37,38] Gender inequality in transplantation is unfair and needs to be tackled. Transplant centers must investigate the underlying causes of this disparity, and educational programs should be actively promoted. It is essential to consider both biological and sociocultural factors. The biological factors often cited include the sex distributions of various potential biological risk factors for diseases, such as smoking, along with a higher incidence of hypertension and ischemic heart disease, which may result in the more frequent exclusion of male candidates. Conversely, while women show a higher prevalence of chronic kidney disease compared to men, the incidence of end-stage renal disease is higher in males than in females.[37] Notably, even women can often be more incompatible with their spouse or child due to the immunological consequences of pregnancy; they may become living donors, albeit that.

Socio-cultural aspects should be considered, as they hold significant importance in many cultures. It is expected that women's heightened altruism will arise from their traditional role as caregivers within the family.[38-40] Family expectations often place the burden of being a living donor on her, while men are more commonly expected to keep working and provide for the family. Furthermore, access to living donor transplants can differ among various populations due to professional motivations, availability of information, and financial concerns. Identifying and addressing these disparities is a crucial task for living donor programs.

There is a consensus in European countries that international and national laws should strictly maintain the general prohibition on organ commercialism. In Portugal, law 36/2013,[41] for the transposition of the EU directive 2010/53/EU[42] on living organ donation practice, has determined that living organ donation must be voluntary and unpaid. No case of suspected commercialism in the transplantation field has ever been identified in Portugal.

However, donors should not incur financial losses and should receive compensation for additional expenses such as travel costs or lost income.[43]

LONG-TERM FOLLOW-UP OF DONORS AND NATIONAL REGISTRIES

Long-term follow-up of all donors and national and international registries are essential. Collecting follow-up information on donors' health status is vital for understanding the risks and consequences of donation. This information is crucial for individual donors who may need timely intervention if health issues arise. It also plays a significant role in educating potential donors and assisting them in making informed decisions about whether to donate. The literature concurs that we do not fully understand the long-term medical outcomes following kidney donation. This underscores the urgent need for continued data collection efforts, as it is only through such efforts that we can bridge this knowledge gap and ensure the safety of living donors.[6,17,18,44,45] The best way to address concerns about long-term risks in previous donors, especially those with medical complexities, is through longitudinal prospective cohort studies. These studies would compare clinical outcomes in organ donors with non-donor controls, evaluating the donation's effect on these outcomes. Defining appropriate controls presents a significant challenge. Additionally, low event rates in living kidney donors hinder the detection of meaningful differences in clinical outcomes. Ongoing prospective studies are encountering difficulties in recruiting and retaining enough control subjects. The Living Donor Collective Project in the US aims to ensure long-term follow-up of living donors and potential candidates who did not proceed with donation.[46] If successful, the information gathered will be invaluable.

Retrospective cohort studies are a more efficient and cost-effective method for examining donor risk and are the main source of our current knowledge of LKD outcomes. However, most retrospective cohort studies suffer from low inclusion rates, short observation period rates, and limited racial diversity, making them susceptible to selection bias and limited conclusions.

A national donor follow-up registry offers a more comprehensive assessment of risks to living kidney donors than other studies since it focuses on the same community. It should provide outcome data on a much larger and more diverse population of LKDs than retrospective or prospective cohort studies. This approach offers sufficient power to determine if baseline characteristics predict worsened long-term health outcomes in subgroups of LKDs. In contrast to data linkage studies, a registry would not be limited to a small number of hard outcomes but could examine the broader scope of important health outcomes.[47] Additionally, it ensures quality assurance at all transplant centers, maintaining public trust in the system of living organ donation.[47]

Some countries have successful models for tracking the long-term outcomes of living organ donors, especially those with universal healthcare systems. For example, all living donors in Switzerland are documented in the Swiss

Organ Living Donor Health Registry.[48] This registry collects information from general practice doctors one year after donation and then every two years. In Norway, donors receive free, lifelong medical follow-up, and details about each donor are stored in the Norwegian Living Kidney Donor Registry,[49] Australia and New Zealand also have similar universal healthcare systems and registries.[50] In Portugal, all LKD receive free lifelong medical follow-up, but a similar comprehensive registry does not yet exist.

The European Commission's EULID project was designed to establish consensus on living donor practices. It stated that " any registry proposal must be realistic and, therefore, simple; its implementation must be feasible".[51] However, the European Union nations have national healthcare systems that ensure healthcare for all living donors and the protection of donors on an individual level. The same is not true for US donors, 18% of whom are uninsured, with higher rates among groups of donors who face more significant long-term health risks, including Blacks and Hispanics.[52]

The Directive 2010/53/EU on standards of quality and safety of human organs intended for transplantation addresses these concerns. It advocates the establishment of National Living Donor Registries to facilitate monitoring and follow-up for Living Organ Donation Practices.[42] It introduced a significant organizational change by establishing central registries in each Member State, overseen by the national competent authority. These registries will need two types of data from transplant centers. The first type concerns the number of living donors and the organs procured, transplanted, or disposed of. The national competent authority will use this data to create an annual report. The second type of data is related to post-transplantation information, focusing on the quality and safety of transplanted organs, including long-term follow-up of living donors. Transplant centers must collect and report this data based on guidance from the national competent authority.[42] The directive was implemented into law through law 36/2013, dated 12th June in Portugal.[41] The competent authority responsible for ensuring compliance with the law is the Direção Geral de Saúde, in collaboration with the Instituto Português de Sangue e Transplantação (IPST). The national registries for living kidney donors, including post-donation follow-up, would be carried out by local transplant Units in the Portuguese Registry of Transplantation (RPT). Unfortunately, this tool has yet to be available. Local registries of long-term follow-up of living donors are maintained at the Transplant Centers without a Central Registry. This hinders a better understanding, monitoring, and analysis of living donor long-term outcomes beyond organ failure and death. The Registry of Centro Hospitalar Universitário de Santo António represents about 50% of the living donors in Portugal.[53,54] It predominantly features individuals from the North of Portugal and only Caucasians, representing center-specific practices and limiting their generality. The authors argue that incorporating comprehensive and detailed national data on all living donors can improve the informed consent process.

Collecting data from living donors over a longer period could significantly enhance living donations. Monitoring the health of living donors throughout their lifetime helps us better understand the risks and benefits of living organ donation for the donor. This aligns with the recent World Health Organization Resolution (WHA 77.4, 2024) on increasing availability, ensuring ethical access, and overseeing the transplantation of human cells, tissues, and organs.[55] Additionally, it can promote the long-term well-being and safety of living donors by identifying risk factors and long-term outcomes, which can then inform living donor policy. This could lead to a more evidence-based approach to expanding opportunities for living donation while safeguarding donors.

CONCLUSION

Living kidney transplantation is the most effective treatment for patients with end-stage renal disease without severe comorbidities.

An assessment, as in-depth as possible, of the candidate donor's risks is mandatory.

Although current literature data allows us to avoid high risks for the candidate donor, efforts should be made to detail these risks more precisely. This can be achieved through retrospective and prospective registries of kidney donors, with comprehensive and long-term data.

Respect for the autonomy of the candidate donor requires that he or she be informed of both the prognosis of the person to whom he or she proposes to give a kidney and of his or her own risks. Only with this clear and complete knowledge can a person provide true informed consent.

Living kidney transplantation, to be correct, requires both great technical differentiation and high ethical demands. Only when these two requirements are present is it possible to overcome the Hippocratic principle *primum non nocere* and subject "a normal healthy person (...) to a major surgical operation, not for his own benefit".[1]

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