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Suggestions on how to make suboptimal kidney transplantation an ethically viable option

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Abstract: To overcome kidney donation, the pool of potentially eligible donors has been widened by using suboptimal organs harvested from living donors or cadavers. These organs may engender health complications as age, risk factors, and pathologies of donors fail to meet the standard donor criteria.

After examining a wide array of literature on suboptimal kidney transplants, we evidenced two major issues: the lack of standardized terminology and the lack of long-term data on the health outcomes of both suboptimal living donors and recipients. Consequently, surgeons are still unable to provide patients with thorough information to obtain a well-informed consent. Suboptimal kidney transplantation still remains in its experimental stage, thereby raising many ethical and medico-legal concerns.

We suggest that one possible solution to overcome some of the ethical shortcomings of suboptimal kidney donations is to provide living donors and recipients honest, accurate, and thorough information about its health risks. To this aim, we advocate adopting a widely standardized terminology that would embrace the whole concept of suboptimal kidney transplantation, increasing the number of future publications on the health outcomes of living donors and recipients, spurring ethical reflection to improve the experience of suboptimal kidney transplantation and reduce the waiting-list for kidney transplantation.

Keywords: Kidney transplantion; Bioethics; Medico-Legal

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1 Introduction

An ever increasing shortage of kidneys for transplants has led many countries to expand the pool of potential donors, thereby extending the selection criteria for organs by virtue of suboptimal organs.[1] This strategy has been supported by the therapeutic aims of the procedure, by the rigorous criteria governing the determination of death and, finally, by the good survival rates of living donors. Despite the potentially promising outcomes of suboptimal kidney transplants, we maintain that two major issues should be addressed.

The first pertains to the lack of a standardized terminology. Indeed, in the literature, terms such as expanded criteria donors (ECDs), marginal kidneys, marginal donors, suboptimal kidneys, suboptimal donors, and others, are wrongly used as synonyms for very diverse clinical conditions. To better illustrate this point, we have listed the definitions of some of the most consolidated terms.

Expanded criteria donors (ECDs) is a term associated with the removal of a kidney for transplantation either from 60+ year-old cadavers with no medical conditions or from cadavers older than 50 with two of the following conditions: history of hypertension, death from a cerebrovascular accident, terminal serum creatinine levels > 1.5 mg/dL.[2]

The term marginal kidney, instead, generally conveys the idea of organs that have undergone physiological deterioration of glomerular, vascular, and tubular structures due to either aging or pathologies including atherosclerosis, hypertension, tobacco use, dyslipidemia, obesity, and diabetes. It can also refer to an organ that has been harvested from a standard donor manifesting renal parenchymal disease or to the presence of critical anomalies of the renal arteries or urinary tract.[3]

Similarly heterogeneous is the definition of marginal donors. It can indeed describe either a suboptimal cadaveric renal allograft or a non-heart beating donor. However, it can also be applied to an elderly living kidney

donor or to a living donor affected by hypertension, obesity, or diabetes. In addition, it can also refer to a living donor with a medical history of malignant pathologies, contagious infectious diseases, or renal cysts. [4]

As for the term marginal living donor (MLD), some authors use it to describe a living donor affected by various diseases or characterized by particular risk factors. [5] On the other hand, the European Association of Urology (EAU) considers marginal donors either 70+ year-old subjects without risk factors or 70- to 80-year olds with diabetes mellitus, hypertension, proteinuria > 1 g/24 h, and renovascular damage.[6]

A description very similar to MLD is given by the term complex living kidney donors (CLKDs). As the name suggests, the term is used to classify a living donor affected by a myriad of possible risk factors including race (black), sicklemia, genetic and cardiovascular risk factors, an ongoing kidney disease, a possible onset of chronic renal disease due to nephron-mass reduction, or even a combination of all these factors.[7]

Finally the term donation after cardiac death (DCD) is used to contrast with donation after brain death (DBD). [8] Actually, DCD is the equivalent of non-heart beating donation, whereas DBD is the equivalent of heart-beating donation after brain-dead —the first is theoretically considered a suboptimal donation.

Interestingly, in countries like the US and the UK, the concept of suboptimal kidneys is even more ambiguous. For instance, the guidelines laid down by the U.S. Department of Health and Human Services for the clinical evaluation of potential living donors contain no definition for suboptimal kidney.[9] In the UK, instead, the guidelines for the informed consent process established by the British Transplantation Society rightly state that terms like marginal, non-standard, extended or expanded criteria grafts are unsatisfactory at providing patients with accurate information on the possible risks associated with organ transplantation.[10] Consistently, The British Transplantation Society and The Renal Association guidelines for living donor kidney transplantation do not include a standard definition of suboptimal kidney, despite providing a detailed analysis of all the risk factors capable of compromising the quality of an organ.[11]

Some studies have suggested that so long as the criteria for defining a marginal donor are not fully standardized, the methods for establishing the quality of an organ will continue to differ among transplant centers.[12] In line with this theory, we maintain that such heterogeneous definitions prevent researchers from elaborating epidemiologically robust and internationally comparable data on the risks of suboptimal kidney transplantation —a limitation that deprives both living donors and recipients from receiving accurate and thorough information about the related risks. Notwithstanding the challenge of creating a homogeneous and an unambiguous classification of the different types of suboptimal kidneys, it behooves us to consider, for the purpose of our work, two mega-groups called marginal living kidney donors (MLKDs) and marginal deceased kidney donors (MDKDs). By and large, the former encompasses living donors who are not classifiable as Standard Criteria Donors (SCDs) on the basis of age, risk factors, and pathologies. The latter instead refers to the harvesting of cadaveric suboptimal kidneys from both DCDs and DBDs.

Unfortunately, classification and nosology are not the only causes for concern. Indeed, the limited clinical data on the health risks associated with suboptimal kidneys in renal transplantation cannot be ignored nor can the notion that a marginal transplant is preferable to dialysis or to possible death while on the waiting list.[13]

This brings us to the last crucial aspect of our present work, *i.e.*, the importance of addressing two major ethical questions regarding the increasing use of suboptimal kidneys to tackle organ shortage. The first question regards whether it is ethically licit, and, if so, on what terms, to harvest an organ from a donor whose age, risk factors, and pathologies fall far of the standard criteria donor. The second question regards whether suboptimal kidneys in renal transplantation ought to be used at all.

2 A brief clinical update: little evidence, many questions unanswered

Most of the current literature on the health conditions of kidney donors after explantation deals with standard donors. Some of these clinical studies have though yielded somewhat limited and discrepant results. For instance, some investigators have revealed that immediately after explantation healthy donors show a 25-40% reduction in glomerular filtration rate (GFR) and a higher risk of developing gout by age 20, compared to non-donors.

However, since these results are based on rather short-term follow-ups, it is still unclear whether the long-term effects of reduced GFR levels could eventually give rise to more serious complications including cardiovascular diseases and end-stage renal disease. Nor is it known whether age, race, and comorbidity could influence GFR reduction after donation.[15] Post-explantation complica-

tions have also been detected in women, in whom gestational hypertension or pre-eclapsia is much more common than in non donors.[14]

By contrast, similar lines of research have observed that the age-related deterioration of renal function in donors is the same as that of non donors, that nephrectomy does not compromise future pregnancies, and that the risk of developing arterial hypertension in donors at age 20 is not much higher than the risk in non donors. However, some authors recommend that obese patients with a BMI > 35 kg/m^2 be discouraged from organ donation, not least when other comorbid conditions exist.[16] On the other hand, these same authors while indicating that no risks are known for donors with borderline blood pressure values and with a familiarity for hypertension, they do cite one study reporting that non donors with a BMI > 30 kg/m^2 who underwent unilateral nephrectomy were at a higher risk of developing proteinuria and renal failure, as evidenced in the long-term follow-ups.[17]

Still, other studies show that the percentage of GFR decreases by 8 ml/min/1.73 every 10 years after age 40, that renal blood flow diminishes by 10% every 10 years [18, 19], and that renal cortical mass progressively decreases with aging.[20] Finally, it should also be taken into consideration that donors have a perioperative mortally rate equal to 0.03%.[21]

Even more tentative is the literature on the health outcomes of MLKDs. Indeed, a systematic review comprising 45 studies demonstrated that donors undergo long-term follow-ups only in very few cases (> 1 year). Furthermore, the majority of these studies are retrospective and without a control group.[22] Another recent review [23], which analyzed 152 studies and 5 of the major international guidelines, revealed that obesity, hypertension, vascular variants, advanced age (up to age 70), and women in childbearing years are not contraindications for living donation. On the other hand, the authors concluded that the quality of the evidence, analyzed by the GRADE (Grading of Recommendations Assessment, Development and Evaluation) system, was rather poor in relation to the health outcomes of hypertensive, obese, and elderly donors, as well as of subjects expressing vascular variants. It was even more so for women in their childbearing years.

The problem of prognostic uncertainty in MLKDs also emerges in the CARI (Caring for Australasians with Renal Impairment) guidelines. Indeed, although they show that living organ donation is considered justifiable, they also suggest the need for more accurate data on the long-term consequences of donors. Accordingly, they describe four types of assessments: (1) medico-psychosocial evaluation of long-term donors, (2) evaluation of prospective studies of subgroups of donors including hypertensive, obese, and elderly donors, (3) long-term data collection on the health status of living kidney donors, and (4) assessment of how transplantation centers handle ethical questions and the process of informed consent.[24]

Equally revealing for the purpose of our study were two 10-year follow-up studies of donors affected by impaired glucose tolerance (IGT). Both studies demonstrate that this subgroup of donors has a higher chance of developing diabetes mellitus compared to healthy donors. In particular, the first study shows that over the 10 year period 9.8% of MLKDs developed diabetes compared to 2.4% of controls.[25] Likewise, the second study showed that 16% of MLKDs developed diabetes compared to 2% of controls.[26]

The long-term outcomes of patients receiving organs from MLKDs or MDKDs are only relatively more promising. Indeed some studies indicate that whereas the survival rate of patients receiving organs from MDKDs is lower than that of patients receiving organs from standard donors, it is nonetheless still better than that of patients remaining on dialysis.[27] Despite this, kidney transplant failure, *i.e.*, return to dialysis or nephrectomy, is more frequent in MDKD recipients [28-30]. Similarly, renal function in patients older than 60 receiving ECD kidneys is worse than that of patients receiving standard kidneys.[31]

A worse scenario is also depicted in studies of MDKDs. They report that kidneys from MDKDs are more likely to fail in 70% of the cases compared to kidneys harvested, for example, from a 35-year old donor who dies in a car accident.[32] Further, MDKD recipients have a much shorter mean life expectancy compared to recipients receiving a kidney from a standard donor (5.1 years *vs* 10 years, respectively).[33]

Finally, our consideration that the use of suboptimal kidneys raises a number of health concerns for transplant patients is corroborated by authors documenting the health outcomes of subjects receiving ECD kidneys. Indeed, they found that these patients have a much higher risk of developing viral-induced cancer [34] and cardiovascular diseases.[35] For other authors, these types of renal grafts could even have a deleterious impact on the recipient.[36]

On the basis of what has been reported in the literature so far, we fully support Niemi and Mandelbrot's thesis that the more medically complex a donor is, the higher the odds of unsuccessful transplants will be. Consequently, in such bleak scenario, the patient's health can only worsen, albeit the entity of the complications is not yet fully known.[37]

Thus, in our opinion, and as suggested in the works cited, it would be paramount to reinforce the need for bioethical reflection on suboptimal transplantation to safeguard the long-term health and well-being of both donors and recipients. Lastly, it would be just as important to hone the informed consent process to obtain a truly informed consent to suboptimal kidney transplantation .

3 Consent is not always informed

The issue of informed consent in transplantation of suboptimal kidneys has to be dealt with from two different perspectives: that of the MLKD and that of the MLKD or MDKD recipient.

In theory, as highlighted in the Amsterdam Statement [38], informed consent ought to play a major role in the decision-making process of donors. In particular, MLKDs should receive thorough information regarding the actual short- medium- and long-term health risks associated with this surgical procedure. Indeed, only if the information is truly exhaustive can the informed consent be considered valid and effective [39].

In practice, however, consent is often based on little or inaccurate information. For instance, a study involving 292 living kidney donors reveals that even though 90% of the sample became aware of the short-term medical risks, only 69% understood the adverse psychological implications of donations, only 52% understood the long-term health risks, and only 32% understood the financial implications. Noticeably, 40% reported receiving undue psychological pressure to donate.[40]

Furthermore, in developing standard international guidelines for living kidney donations, some authors suggest that the risk-benefit ratio should not solely be based on scientific evidence, but also on personal judgment. By doing so, donors would be able to decide on their own as to whether the procedure is "worth" going through or whether their motivations and their strong relationship with the recipient outweigh the risks.[16] Accordingly, transplant surgeon should limit themselves to providing accurate and thorough information about the procedure, despite being fully aware of the possible health-related risks.

Undeniably, the information cannot be as complete and exhaustive as one would wish. As already mentioned, the clinical data available so far are often contradictory and only refer to carefully selected living donors who, despite not being affected by comorbidity, have developed some complications notwithstanding.

That said, our criticism of the way suboptimal kidney living donor transplantation is currently handled is based on the consideration that these types of surgical procedures do not seem to respect the true principles of bioethics. In brief, in bioethics, the principle of totality, or therapeutic principle, holds that every surgical intervention performed on the human body is actually performed on the totality of the person. Therefore, it will be justified only if it can be beneficial for the totality of the organism, or if it is done as an altruistic act. For instance, in cases of homoplastic transplantation, the principle of totality has to be intertwined with the principle of solidarity e sociality. Hence, on the one hand the donor must not suffer any substantial or irreparable harm to his/her life and, on the other hand, a healthy outcome for the recipient must be assured to justify his/her sacrifice. However, because of the lack of scientific data on the long-term health outcomes of MLKD transplants, the principle of totality conflicts with the principle of solidarity, thereby rendering MLKD donation ethically debatable.

We are adamant that these ethical challenges can be overcome by increasing the scarce body of knowledge and by adopting a widely shared ethical reflection. In the meantime, we suggest several ways to deal with the absence of a standardized process. First, it would be necessary to opt for MLKD transplantation only in emotionally related subjects. Secondly, it would be highly helpful to evaluate this surgical option on a case-by-case basis and to establish compatibility by running cross-matching tests. Third, both donors and recipients should be able to make informed decisions only after receiving accurate and thorough information including the fact that the long-term health outcomes are still limited. In this regard, the donor should be made aware that suboptimal kidney transplants are less likely to benefit the recipient, thereby increasing the possibility that his or her sacrifice could be made in vain. Fourth, alibis should be granted to protect donors from psychological pressures or coercion in case of withdrawal.[41] Lastly, their resolve and motivation —be it based on kindred, kinship, or religion— should be painstakingly scrutinized by a team of physicians and psychologists unfamiliar with the process of kidney explants and transplants.

Similarly, delicate issues are also posed by the information given to MKLD or MDKD recipients. Given the profound health implications in these types of transplants, the information should be given in much more detail than in standard kidney transplantation. By doing so, patients will be able to make an educated decision by judiciously weighing their options of either accepting a suboptimal kidney, remaining on dialysis or the waiting list. Accord-

ingly, patients should be informed that the kidney that has been allocated to them is not an ideal organ but an organ that was discarded according to standard selection criteria. Major emphasis should also be placed on informing patients that suboptimal kidney transplants may more likely fail, thereby increasing their risk of having to return to hemodialysis or of experiencing worse health conditions. On the other hand, they should also learn about the consequences of rejecting the offer of a suboptimal kidney including the risks correlated with long-term dialysis and long waiting lists, as well as the possibility of death. In case it should be deemed necessary to receive a dual kidney transplant from a marginal donor to boost nephron function, patients should be made aware of the potential increase in surgical risks, as opposed to single kidney transplants.

Most important, patients should know that consenting to accept a suboptimal kidney transplant does not mean having reached a "point of no return". Contrarily, they will be allowed to remain on the waiting list for a more suitable organ, thereby having the option to decline a suboptimal kidney in case a standard organ should be made available. Receiving such detailed information would consequently guarantee MKLD or MDKD recipients their right to self-determination in the decision-making process.

Thus, the questions we raised about whether it is morally licit to harvest a suboptimal kidney for donation although it may not be a suitable match for the recipient and about whether suboptimal kidneys should be used at all in kidney transplantation still remain unanswered. We can only say that such impossibility is based on one common denominator: a dearth of definite data on the long-term prognosis of both MLKDs and MLKD and MDKD recipients.

Accordingly, we hold that this type of transplant, both from the bioethical and medico-legal points of view, is still in its experimental stage. Therefore, both donors and recipients should be made fully aware that their decision to undergo this type of transplant is not simply therapeutic but therapeutic and experimental at the same time.

4 Conclusions

Many questions about the long-term health effects of suboptimal kidney transplantation clamor for further investigation. Indeed, to this day, kidney transplantation with organs harvested from MLKDs or MDKDs is still in its experimental stage with an uncertain long-term prognosis for both donors and recipients. One possible explanation is that the current evidence is often weak and at times contradictory. Furthermore, the lack of a shared terminology for the concept of suboptimal kidney renders very difficult the process of comparing the results in the current literature.

Owing to the limited data on the long-term prognosis of donors, we thus believe that donation from MKLDs is a questionable issue. Indeed, increasing the number of valid prospective studies will not only deepen our knowledge of the clinical course of both MLKDs, and MLKD and MDKD recipients, but also prompt a more profound ethical reflection.

In the meantime, we maintain that MLKDs should be considered only when the donor has a close emotional bond with the recipient and should be evaluated on a case-to-case basis. In these circumstances, providing donors and recipients with thorough and accurate information about the limited and contradictory clinical data is paramount to ensure an educated informed consent. Further, donors should also be fully informed about the concrete beneficial outcomes of the transplant so at to evaluate the authenticity of their altruistic gesture. It is only in this way that donors will be guaranteed a pressure-free environment where they can express their conscious and educated consent and receive more valid ethical and scientific responses to their act of solidarity.

As for the kidney transplants obtained from MLKDs or MLKDs, we came to the conclusion that there are no particular ethical implications so long as the recipient is fully informed about the higher risk of failure associated with substandard kidney transplants as opposed to standard ones.

Accordingly, it is hoped that the recipient's decision to accept a suboptimal kidney will not be swayed in any way by caveats underscoring the shortage of organs and the lengthening of waiting lists. Indeed, such argument on the part of transplant surgeons and coordinators could represent a form of solicitation, whereby the patient would see for himself/herself no other choice but to opt for surgery, with death being the only other choice.

Lastly, we hope that the international scientific community will embrace a shared terminology for suboptimal kidney transplantation. Indeed, a standardized terminology would enable scientists to compare the results of different clinical studies, thereby obtaining more robust data on the long-term health outcomes of suboptimal transplants. Eventually, such data would engender patient-focused information that would be extremely useful to support both MLKDs and MLKD and MLDD recipients in their decision-making process.

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