Long-term risks of kidney living donation: Review and position paper by the ERA-EDTA DESCARTES working group

LONG-TERM RISKS OF KIDNEY LIVING DONATION: REVIEW AND POSITION PAPER

BY THE ERA-EDTA DESCARTES WORKING GROUP

Umberto Maggiore[1], Klemens Budde[2], Uwe Heemann[3], Luuk Hilbrands[4], Rainer Oberbauer[5], Gabriel Oniscu[6], Julio Pascual[7], Soren Schwartz Sorensen[8], Ondrej Viklicky[9], Daniel Abramowicz[10] for the ERA-EDTA-DESCARTES working group

[1]Department of Nephrology Azienda Ospedaliero-Universitaria di Parma Parma, Italy, [2]Department of Nephrology, Charité Medical University Berlin, Berlin, Germany, [3] Department of Nephrology, Technical University of Munich, Munich, Germany,[4]Department of Nephrology, Radboud University Medical Centre, Nijmegen, The Netherlands, [5]Department of Nephrology, Medical University of Vienna, Austria, [6]Transplant Unit, The Royal Infirmary of Edinburgh, UK, [7]Department of Nephrology , Hospital del Mar Barcelona, Spain, [8]Department of Nephrology, Rigshospitalet, University of Copenhagen, Copenhagen, Denmark, [9]Department of Nephrology, Institute for Clinical and Experimental Medicine Prague, Czech Republic,[10]Department of Nephrology, Antwerp University Hospital, Antwerp, Belgium

Running title: the long-term risk of living donation

Index words: kidney transplant, live donor, living donor, long term risk, outcome.

Address for correspondence:
Umberto Maggiore, M.D.
SS Trapianti Rene Pancreas
U.O. Nefrologia
Azienda Universitario-Ospedaliera di Parma
Via Gramsci 14 – 43126 Parma, ITALY
Fax +39-0521-033185, Phone +39-0521-033209
E-mail: umberto_maggiore@hotmail.com

Abstract

Because there is currently lack of evidence-based recommendations, and it is likely that they will appear in the near future, but surely not regarding how to manage immunosuppression for kidney transplant recipients, as ERA-EDTA Working Group on kidney transplantation, we wrote a pragmatic article in order to help nephrologist coping with immunosuppression management for kidney transplant recipients affected by COVID-19. We also give advice on antiviral-drug concerning drug-to-drug interaction, on adjustment for renal function, and on the use of additional immunosuppressive and immunomodulatory drugs to counteract hyper-inflammatory syndrome.

In this position paper DESCARTES board members critically review the literature in an effort to summarize the current knowledge concerning long-term risks of kidney living donation, to help physicians for decision-making purposes, and for providing information to the prospective live donors. Long-term risk of ESRD can be partially foreseen by trying to identify donors at risk of developing “de novo” kidney diseases during life post-donation, and by predicting lifetime ESRD risk. However, lifetime risk may be difficult to assess in young donors, especially in those having first-degree relatives with ESRD. The study from Norway also found an increased risk of death after living donor nephrectomy, which became visible only after more than 15 years of post-donation follow-up. However these findings are likely to be largely the result of an overestimation due to the confounding effect related to a family history of renal disease. DESCARTES board members emphasize the importance of optimal risk-benefit assessment and proper information to the prospective donor, which should also include recommendations on health-promoting behavior post-donation.

Introduction

Kidney transplantation with living donor organs is associated with longer graft and patient survival compared to deceased donor organs. Until recently, we have been reassured by the fact that the long-term risk of ESRD or death in living kidney donors is similar to, or even smaller than the general population [1, 2]. However, because living donors are selected among the healthiest, their long-term outcomes should be better, rather than equal to the general population. Two recent studies have tried to compare donors with healthy subjects rather than with the general population [3, 4]. The findings of these studies have raised some concerns related to the long-term safety of living donation. Further studies on the long-term risks of living donation have since been published. In this position paper DESCARTES (Developing Education Science and Care for Renal Transplantation in European-States) board members critically reviewed the most recent literature concerning the long-term risk estimates of living donation. The present manuscript represents an effort to summarize the current knowledge that may help physician for decision-making purposes, and for providing information to the prospective live donors.

Balancing risks and benefits of living donation

There is unanimous consent that all transplant teams should make every possible effort in helping the prospective donors to make an informed decision by providing them with quantitative risk estimates [5, 6]. If the risks are unknown, adequate and informed decision making is almost impossible. When prospective donors are faced with an unknown risk they cannot rationally decide, and the transplant team has a difficult task in balancing the risk and benefit of living donation [5, 6].

Meanwhile, the physicians should recognize that donors may also benefit, which adds another perspective for justifying living organ donation [7]. In order to recommend a person as an acceptable organ donor, a physician should first ascertain that the benefits for the potential donor are sufficient to offset the risks [7]. Such a framework can minimize conflict of interests for the physician [7]. Although organ donation provides no physical benefit for donors, it may afford psychological gratification [7, 8]. The psychological benefit can be very large and at least as important as the physical benefit of the recipient. Typical examples are represented by a parent

who wants to see the child return to a normal life, the spouse seeing the loved one sharing the joys of life, or the altruistic donor who starts a chain of transplantations allowing a number of patients to undergo successful transplant procedures that would otherwise be impossible to accomplish. Importantly, the vast majority of donors are satisfied after donation and would do it again, supporting the living donation procedure [9]. Unjustified dismissal of potential donors might harm both the recipient and the donor [8, 10].

Key to a meaningful balancing of benefits and risks is a comprehensive knowledge of the short-term as well as long-term risks of donor nephrectomy. In this paper we especially focus on the evidence of any association between nephrectomy and the long-term risk of ESRD (End Stage Renal Disease) or death in the individual kidney donor.

Does harmful hyperfiltration occur in living donors?

Traditionally, the most basic concern over kidney donation has been the fact that nephrectomy halves the renal mass, raising the question whether the remaining kidney suffers in the long-term from being overloaded with the extra work of the missing kidney.

Worries arose from the rat model of progression of renal diseases, whereby a substantial renal ablation (5/6 nephrectomy) causes glomerular hypertension (i.e. increase of glomerular transcapillary pressure). Glomerular hypertension causes albuminuria and eventually focal segmental glomerulosclerosis, leading to progressive renal failure [11]. Despite initial worries on the negative impact of extreme kidney mass reduction in humans [12], a recent prospective study of 21 adult living kidney donors, before, one, and six years after donation, suggests that the rat model of progression of renal disease does not apply to donor nephrectomy [13]. This study showed that the remaining kidney undergoes the expected adaptive hyperfiltration (about 40% increase of GFR) [13]. Hyperfiltration occurs because of hyperperfusion and hypertrophy which happens in parallel with hyperfiltration. However, the morphometric analysis, and the mathematical modeling of glomerular dynamics suggested that hyperfiltration occurred with no clear-cut contribution of glomerular hypertension [13]. This encouraging finding seems to be confirmed by a recent prospective follow-up control-study [14, 15], carried out on about two hundred donors and healthy controls. At 36 months after donation, measured GFR (iohexol) continued to improve in donors, whereas controls had an expected age-related decline in renal function [15]. Unfortunately, these prospective studies have relatively short-term follow-up. Long-term follow-up of several decades can currently be accrued only by retrospective studies, with their inherent bias and difficulty in controlling for confounding issues.

Important to note in this respect is the fact that, with the availability of an effective renin-angiotensin-aldosterone system (RAAS) blockade, glomerular hypertension and proteinuria due to

hyperfiltration can be treated effectively [16]. Although no clinical studies in living donors exist, it can be assumed that the majority of donors who eventually will develop proteinuria and hypertension would nowadays be treated with RAAS blockers.

Retrospective studies on the long-term ESRD risk

To avoid bias in retrospective studies, it is critical that they include an appropriate control group of non-donating healthy subjects. Controls must represent the counter-factual experience of life without donation: what would have happened to donors if they had not donated. The best representatives of counter-factual life without donation are the non-donating siblings who share the same genetic and environmental background as the donors.

Indeed, the long-term effect of nephrectomy has been originally investigated by studies which compared donors with their non-donating siblings [17, 18]. In these landmark studies, there was no difference in albuminuria and blood pressure between donating and non-donating siblings after more than 10 and 20 years of follow-up. Creatinine clearance was only 10 to 20% lower in donors. However, the drawback of these studies is the low numbers, the largest one [18] recruiting only 50 non-donating siblings.

The only alternative for using siblings is to identify non-donating controls sharing nearly the same baseline risk factors as the donors. Large health surveys performed on the general population provide ideal pools from which these controls can be sampled. Sampled controls must share the most important baseline risk factors, a procedure that may require the use of various and complex statistical tools. If, and only if, the matching procedure grants an identical distribution of the most important baseline prognostic factors between donors and matched controls, then the observed difference in outcome can be regarded as being caused by living donor nephrectomy.

Table 1 gives the findings of the two large matched-cohort studies performed so far that have raised recent concerns on the safety of donor nephrectomy. Overall, the estimates of the long-term effect of nephrectomy on the risk of developing ESRD were fairly consistent between the two studies. Indeed, the ESRD risk increased by about 11 times in the Norwegian study by Mjoen *et al* [3] and 8 times in the US study [4] (**Table 1**). These estimates definitely reflect a large ***relative*** increase in risk. However, as long as the reference risk is not taken into account, relative risk estimates do not give practical information about what matters the most to live donors namely, the increase in the long-term ***absolute*** risk. The reference absolute lifetime risk for ESRD in controls was in fact very small in both studies (0.06% and 0.04%, in the Norwegian and US study respectively). Indeed, eleven times or eight times a close-to-zero reference hazards yields only

minor increases in the absolute risk: the difference between donors and controls in the average absolute risk was in fact less than 0.3% after 15 years in the US study (**Table 1**) (i.e. above 300 living donations need to be done to have one donor developing nephrectomy-related ESRD after 15 years) [3, 4].

Anyhow, because of lack of overlap between donors and controls, in both studies controls could not be matched for some major baseline risk factors such as family history of renal disease, geographical area and year of inclusion in the study. These factors should be matched in the study design in order to ensure that controls have the same baseline distribution of genetic and environmental determinants of renal disease, and that they share the same temporal trends of ESRD. Inadequate control for these confounding variables is undoubtedly a potential source of relevant bias in both studies. For example, in the Norwegian study, no matching for family history of renal disease could be performed despite 80% of the donors being first–degree relatives of the recipients. The resulting uneven distribution of this important baseline risk factor might have led to overestimating the long-term adverse consequences of nephrectomy. Indeed, most of the donors developing ESRD did so because of new-onset immunologically-mediated renal disease (i.e. genetic and environmentally-determined diseases) rather than because of progressive chronic renal failure and focal segmental sclerosis (i.e. renal disease caused by reduced renal mass).

Identifying the prospective donors who are at increased long-term ESRD risk

Despite the risk of bias, the two studies discussed above nonetheless suggest that nephrectomy is associated with, albeit low, long-term risk of ESRD. While the effects of reduced renal mass can hardly explain the observed increased long-term ESRD risk, it is clear that a reduced post-donation renal reserve will advance the progression to ESRD when “de novo” kidney diseases develop [19]. Whereas rare events on the remaining kidneys such as renal cancer or trauma cannot be foreseen, it is important to address if kidney donors have an additional risk beyond these unforeseen events. Therefore, the problem of assessing the long-term ESRD risk comes down to identify prospective donors at increased risk of developing renal diseases after donation.

These donors are mainly those with minor medical abnormalities (e.g. hypertension, obesity) or borderline characteristics (e.g. older age, borderline-normal GFR) at the time of donation. However, an increased risk may also be present in those with a normal pre-donation work-up, especially in the case of young donor age. Indeed, it is particularly difficult to predict the medical consequences in the long-term (i.e. >30 years) for prospective donors below the age of, say, 25 to 35 years. Young donors who are at risk of developing renal diseases will be difficult to identify, as they may well have a normal pre-donation medical evaluation [20]. In fact, evaluation and donation may occur decades ahead of the manifestation of a primary renal disease (e.g.

microhematuria/albuminuria or hypertension in IgA nephropathy) or of the development of risk factors for renal failure, such as diabetes [20]. Young age might be a special concern in first-degree relatives of the donors. In fact, a study performed on the Norwegian general population by Skrunes *et al* [21] showed that subjects with a first-degree relative with ESRD caused by non-hereditary diseases such as glomerulonephritis, pyelonephritis, diabetes, or hypertension, have a long-term risk of ESRD which is almost 4 times higher compared to subjects with no family history of renal disease. The findings from this large cohort study confirm those from previous studies [22, 23]. Therefore, nephrologists should inform the young prospective donors having a first-degree relative with renal disease (e.g. brother with ESRD because of glomerulonephritis) that consanguinity in young donors can be regarded *per se* as a risk factor for the development of renal diseases despite a normal medical work-up. African American race is an additional baseline risk indicator that might be taken into account when assessing young related donors with normal work-up [20, 24].

In this context it is also important to know that risk can be modified, e.g by healthy lifestyle, by regular medical surveillance of renal function, proteinuria and blood pressure, and by timely and aggressive treatment of newly developed risk factors such as hypertension or albuminuria e.g. with RAAS blockers. Patients have to be educated that by such measures the increased risk after living donation could be counterbalanced, although to date no study confirms this contention.

Prediction of the risk to develop ESRD in the general healthy population

As outlined above, prospective donors at increased risk of renal disease after donation might be identified among those with various minor medical abnormalities or borderline characteristics. So far, no study was specifically designed to assess the effect of individual donor risk factors in the context of all other risk factors which may exert an additive effect in increasing the overall risk to develop ESRD after donation [25]. However, a recent retrospective study which pooled the follow-up from various US cohorts (5 million subjects in total) estimated, via complex simulation models, what is the predicted lifetime risk of ESRD of every healthy individual. The model was based on ten demographic and clinical characteristics namely, age, gender, race, estimated GFR, systolic blood pressure, antihypertensive medications, BMI, non-insulin dependent diabetes mellitus, urine albumin to creatinine ratio, and smoking history [26]. The risk calculator, which is based on model estimates and is freely available on the Web (www.transplantmodels.com/esrdrisk). It is useful to calculate the pre-donation lifetime risk in all donors, and might be particularly useful in the settings of prospective donors who present with various minor medical abnormalities, such as borderline-normal eGFR, hypertension, and high normal urine albumin to creatinine ratio. Such a calculation makes the risk of donation better quantifiable and may help the donor to make an informed decision. For example, according to the risk calculator, a white hypertensive female subject aged 40

with eGFR of 80mL/min/1.73m2, with 130mmHg systolic blood pressure on anti-hypertensive medication, and with an otherwise unremarkable work-up, has a predicted pre-donation lifetime risk of ESRD of 0.73%. The predicted pre-donation risk for ESRD is 0.10% after fifteen years. Unfortunately, the post-donation risk cannot be calculated with the calculator, therefore the effect of donor nephrectomy cannot be predicted. However, based on this [26] and on a previous study [4], it is likely that, on average, the ESRD risk is increased by nephrectomy by about 3 to 5 times or by +0.30% absolute risk fifteen years after donation (e.g. from 0.10 to 0.40%, that is well below an absolute risk of 1% despite donor nephrectomy; for a quick reference concerning the post-donation change in the average risk, see Table S5 from Supplementary Appendix of Grams et al [26]).

Besides not predicting post-donation risk, the calculator has two additional limitations. Firstly, the prediction model for lifetime risk is based on a simulation study. In fact, the actual length of follow-up that was accrued to generate these simulations ranged only between 4 and 16 years. Therefore predictions may be less accurate for young donors, precisely those in whom these long-term predictions (>30 years) are of greatest interest in respect to lifetime ESRD risk estimations [27, 28]. Recently, Ibrahim *et al* published a study on the long-term risk of ESRD in a cohort of white live donors [29] who were followed-up for an average of 17 (range 2 to 51) years. The authors examined the baseline determinants of the risk of developing chronic renal disease decades after donation and developed a -not yet validated- risk calculator based on a population of white donors (http://jasn.asnjournals.org/content/27/9/2885/suppl/DCSupplemental). The estimates of the combined ESRD or eGFR<30mL/min risk from this study appear consistent with the predictions for 15-yrs ESRD risk alone that can be obtained from subjects with similar characteristics using the live donor risk calculator by Grams et al [26]. Secondly, the live donor risk calculator does not take into account a family history of renal disease [30], which, as outlined above, is the most important ESRD risk indicator in young donors with normal work-up at evaluation. Unfortunately, data on family history of renal disease were not available from the cohort and therefore could not be included in the prediction model [31].

Reliable long-term ESRD risk predictions in older donors

As outlined above, the long-term ESRD risk estimates that are currently available to guide decision making are more reliable when applied to older as opposed to younger donors [27]. Recent studies provide further support to this notion by showing that the post-donation hazard of ESRD (i.e. the risk of ESRD during every year of post-donation follow-up) progressively increases after 10 years post-donation when renal failure is caused by either diabetes or hypertension [32]. This late progressive increase, which might not have been detected by the studies published so far [3, 4] because of the insufficient length of follow-up, is less of an issue when evaluating the suitability of

older donors [27]. In fact, current screening protocols invariably search for risk factors such as abnormal fasting blood glucose, albuminuria, hypertension, and reduced renal function. Older donors who are fate to develop advanced renal failure because of diabetic nephropathy or hypertensive nephrosclerosis might already have developed these abnormalities at the time of evaluation. For example, by the age of 65 virtually all the subjects that will eventually develop ESRD or near-ESRD due to diabetes during their remaining lifespan will show increase fasting blood glucose and albuminuria at the time of their living donor workup. If they had to develop diabetes later in life they will not have enough time to develop advanced renal disease because of the limited life expectancy. Therefore, unlike their younger counterparts, older candidates will have their lifetime ESRD risk greatly decreased by current screening protocols [27]. Indeed, evidence published so far shows that living donation from older donors appears safe [25, 33-36], and that the recipient outcomes are generally good [37, 38]. Therefore we believe that the practice of evaluating older donors should be encouraged.

The effect of nephrectomy on long-term risk of death

Mjoen *et al* [3] found that nephrectomy increases long-term mortality of live donors and that this effect is visible only after 15 years of follow-up, a time span that could not be explored by previous studies [3]. This surprising finding is difficult to explain by the consequences of nephrectomy alone. **Table 2** lists the mechanisms that might be theoretically responsible for the increased long-term risk of death, which are grouped by those that relate to an increased risk of renal failure after donation, and those that relate to abnormalities that develop because of post-donation low-normal GFR. In previous paragraphs we have already mentioned the importance of identifying prospective donors at risk of developing post-donation "de novo" kidney diseases, as these may lead to *chronic* renal failure that is obviously associated with an increased risk of death. On the other hand, as shown in **Table 2**, there is no evidence so far that nephrectomy increases the risk of developing, in the long-term, *acute* renal failure episodes (e.g. because of kidney stones [39] or AKI [40]). More intriguing are the subtle abnormalities that develop after nephrectomy because of the resulting low-normal GFR, such as increased arterial blood pressure [15, 41], and increased levels of PTH [14, 15], homocysteine [14, 15], and uric acid [42]. Whether or not the latter laboratory abnormalities adversely affect the long-term risk of death is a controversial issue [43-45]. However, even though they may indeed develop after donation, they are minor and non-progressive and therefore can hardly explain the increased long-term risk of death. On the other hand, an increase of plasma endothelin [46], of ADMA (asymetric dimethylarginine), a strong cardiovascular risk factor [47], an increase in left ventricular mass, and a decrease in aortic distensibility, have all been described early post-nephrectomy [48, 49]. The clinical relevance of these findings appear to be questioned

by the results of the study by Garg *et al* who showed no increase whatsoever in the risk of cardiovascular events in living donors up to 10 years post-donation [50].
Overall, the evidence published so far does not provide a clear rationale for the increased risk of death observed over long-term follow up in the study by Mjoen *et al* [3].

Risk of bias of the estimated effect of donor nephrectomy on mortality

Just like with the risk of ESRD, the long-term risk of death must be assessed by retrospective studies examining the counterfactual experience without donation: what would have happen to donors if they had not donated? The longest follow-up ever, 45 years after nephrectomy, was examined in a study by Narkun-Burgess *et al* [51]. In this study, the long-term effect of nephrectomy was examined by comparing US Army personnel who lost a kidney due to trauma during World War II (62 subjects, the majority of whom were white) with a group of Army enlisted men who bought National Life Insurance policies during their World War II military service. Nephrectomy had no adverse effect on survival, which was identical between uninephrectomized servicemen and controls, with an almost entire lifespan follow-up. It is worth noting that in this study subjects were young at the time of nephrectomy (average age 25yrs old), but they did not have a family history for renal disease [51].
The study by Segev *et al* [52] was the first comparing survival of US donors (over 80,000) with 1:1 matched healthy rather than general population. The study showed that nephrectomy did not have any adverse effect on mortality. However, median follow-up was only 6 years (interquartile range 3-10). In contrast to this US study, the Norwegian study by Mjoen *et al* [3], which had a much longer follow-up, found that nephrectomy causes a 30% increase in mortality in the long-term (i.e. 1.3 relative risk). At first glance, a relative risk of 1.3 might look a small risk increase. In fact, because the reference risk (mortality) was high among the controls (almost 15 percent 25-yrs cumulative mortality), the increase in absolute risk was large. After 20 to 25 years, nephrectomy was associated with an increase of 5% in the absolute risk of dying. We hold the opinion that this «plus 5% mortality» might be an overestimation due to the confounding effect related to a family history of renal disease (80% of the donors were first degree relatives of the recipients). Indeed, not only the baseline risk of ESRD is increased in patients having a first-degree relative with ESRD, but so is also the baseline risk of death [21]. In the study performed in the Norwegian whole population by Skrunes *et al* [21] the relative risk of death associated with a family history of renal disease was 1.10 (i.e. 10% increase). This might look a trivial increase, but as shown in **Figure 1**, the impact is far from being negligible. If we apply, under the proportional hazard assumption, the relative risk of 1.10 associated with a family history of renal disease to the matched-controls of the study of Mjoen *et al* [3], their baseline risk increases substantially. This increase, depicted as an

upward shift of the mortality function line in **Figure 1**, reflects the potential bias in this study. As a consequence, the true adverse effect of nephrectomy on mortality is difficult to determine and further studies on this issue are required before making definite conclusions.

Apart from bias, it is worth noting that approximately 40% of Norwegian donors and controls were smokers. It is known that smoking not only dramatically increases the risk of death but also increases the risk of renal insufficiency [39-41]. We believe that prospective donors have to be informed on the potentially increased long-term risks and educated about counteracting measures, e.g. cessation of smoking.

The effect of nephrectomy on adverse pregnancy outcomes

Pregnancy complications in women with a single kidney after living donation is one of the major concern expressed by young women who are considering donation. In this regard ERBP guidelines [25], which were based on the studies published up to year 2009 [53-56], "recommends informing women of childbearing age that they are selected from a very healthy subpopulation and donation increases their individual risk from below that of the general population, to that of the general population" [25]. A matched-cohort study published after the publication of those guidelines provided further support to the ERBP recommendation, by suggesting that the incidence of gestational hypertension and pre-eclampsia might be increased in kidney donors compared with non-donors [57]. The study found that the absolute risk of gestational hypertension or pre-eclampsia increases from 4.8% to 11.5% because of nephrectomy. The increase in risk of these complications in donors versus non-donors was significantly higher among those aged above 32 years than in younger women. However, nephrectomy did not affect the incidence of any other pregnancy complication (such as caesarean section, postpartum hemorrhage, preterm birth, low birth weight, stillbirths, maternal or neonatal deaths).

Because the available studies point towards a somewhat higher risk of gestational hypertension and preeclampsia, it is important to inform potential donors on this risk. It is however also important to note that such complications can be treated. In fact, overall outcome of pregnancies post donation in those studies was good.

Conclusions

After critically examining the current evidence on long-term risks of living donation, the DESCARTES working group holds the opinion that living kidney donation should be regarded as an acceptable procedure, as the long-term risks for the donor are generally low and in many instances they largely offset the overall benefit for the donor and recipient. Since long-term risks, which vary depending on the donor's profile, can be partially foreseen, the transplant team should make every

effort to assess them in the prospective donor and help the donor take a properly informed decision. The availability of web-based risk calculator (e.g. www.transplantmodels.com/esrdrisk) should be advertised. However, donors should be aware that in some cases lifetime risks may be difficult to predict. This is especially true for young donors with a risky genetic and environmental background. The transplant team should also inform the donor that post-donation healthy lifestyle and outpatient clinic follow-up may offer substantial protection for the donor health in the long-term (see Informed Consent in the *Supplementary Appendix*).

Additional studies are needed to better focus on risks of lifetime ESRD and death risks in the young donors with a risky genetic and environmental background. In addition to efforts of tracking the follow-up of all, and particularly of young donors, new studies could also focus on whether or not the lifetime risks can actually be reduced by the current donor exclusion protocols [27], and modified by appropriate post-donation interventions.

Supplementary Appendix

We provide the critical items of the informed consent concerning long-term risks of living donation based on all current available evidence at the DESCARTES Web page at http://www.era-edtaworkinggroups.org/en-US/group/descartes

References

1. Fehrman-Ekholm I, Elinder CG, Stenbeck M, Tyden G, and Groth CG. Kidney donors live longer. Transplantation 1997; 64: 976-978.
2. Ibrahim HN, Foley R, Tan L *et al*. Long-term consequences of kidney donation. N Engl J Med 2009; 360: 459-469.
3. Mjoen G, Hallan S, Hartmann A *et al*. Long-term risks for kidney donors. Kidney Int 2014; 86: 162-167.
4. Muzaale AD, Massie AB, Wang MC *et al*. Risk of end-stage renal disease following live kidney donation. JAMA 2014; 311: 579-586.
5. Abecassis M, Adams M, Adams P *et al*. Consensus statement on the live organ donor. JAMA 2000; 284: 2919-2926.
6. Steiner R and Matas AJ. First things first: laying the ethical and factual groundwork for living kidney donor selection standards. Am J Transplant 2008; 8: 930-932.
7. Spital A. Donor benefit is the key to justified living organ donation. Camb Q Healthc Ethics 2004; 13: 105-109.
8. Gaston RS and Young CJ. Living donor nephrectomy: understanding long-term risk in minority populations. Am J Transplant 2010; 10: 2574-2576.
9. Erim Y, Kahraman Y, Vitinius F, Beckmann M, Kroncke S, and Witzke O. Resilience and quality of life in 161 living kidney donors before nephrectomy and in the aftermath of donation: a naturalistic single center study. BMC Nephrol 2015; 16: 164.
10. Allen MB, Abt PL, and Reese PP. What are the harms of refusing to allow living kidney donation? An expanded view of risks and benefits. Am J Transplant 2014; 14: 531-537.
11. Hostetter TH, Olson JL, Rennke HG, Venkatachalam MA, and Brenner BM. Hyperfiltration in remnant nephrons: a potentially adverse response to renal ablation. Am J Physiol 1981; 241: F85-93.
12. Novick AC, Gephardt G, Guz B, Steinmuller D, and Tubbs RR. Long-term follow-up after partial removal of a solitary kidney. N Engl J Med 1991; 325: 1058-1062.
13. Lenihan CR, Busque S, Derby G, Blouch K, Myers BD, and Tan JC. Longitudinal study of living kidney donor glomerular dynamics after nephrectomy. J Clin Invest 2015; 125: 1311-1318.

14. Kasiske BL, Anderson-Haag T, Ibrahim HN *et al*. A prospective controlled study of kidney donors: baseline and 6-month follow-up. Am J Kidney Dis 2013; 62: 577-586.
15. Kasiske BL, Anderson-Haag T, Israni AK *et al*. A prospective controlled study of living kidney donors: three-year follow-up. Am J Kidney Dis 2015; 66: 114-124.
16. Ruggenenti P, Perna A, Gherardi G *et al*. Renoprotective properties of ACE-inhibition in non-diabetic nephropathies with non-nephrotic proteinuria. Lancet 1999; 354: 359-364.
17. Williams SL, Oler J, and Jorkasky DK. Long-term renal function in kidney donors: a comparison of donors and their siblings. Ann Intern Med 1986; 105: 1-8.
18. Najarian JS, Chavers BM, McHugh LE, and Matas AJ. 20 years or more of follow-up of living kidney donors. Lancet 1992; 340: 807-810.
19. Steiner RW, Ix JH, Rifkin DE, and Gert B. Estimating risks of de novo kidney diseases after living kidney donation. Am J Transplant 2014; 14: 538-544.
20. Steiner RW. 'Normal for now' or 'at future risk': a double standard for selecting young and older living kidney donors. Am J Transplant 2010; 10: 737-741.
21. Skrunes R, Svarstad E, Reisaeter AV, and Vikse BE. Familial clustering of ESRD in the Norwegian population. Clin J Am Soc Nephrol 2014; 9: 1692-1700.
22. Freedman BI, Volkova NV, Satko SG *et al*. Population-based screening for family history of end-stage renal disease among incident dialysis patients. Am J Nephrol 2005; 25: 529-535.
23. O'Dea DF, Murphy SW, Hefferton D, and Parfrey PS. Higher risk for renal failure in first-degree relatives of white patients with end-stage renal disease: a population-based study. Am J Kidney Dis 1998; 32: 794-801.
24. Massie A MA, Luo X, Segev D. Quantifying Risk of ESRD in Live Kidney Donors [abstract]. Am J Transplant 2015; 15 (suppl 3).
25. Abramowicz D, Cochat P, Claas FH *et al*. European Renal Best Practice Guideline on kidney donor and recipient evaluation and perioperative care. Nephrol Dial Transplant 2015; 30: 1790-1797.
26. Grams ME, Sang Y, Levey AS *et al*. Kidney-Failure Risk Projection for the Living Kidney-Donor Candidate. N Engl J Med 2016; 374: 411-421.
27. Steiner RW. Moving closer to understanding the risks of living kidney donation. Clin Transplant 2016; 30: 10-16.
28. Steiner RW. The Risks of Living Kidney Donation. N Engl J Med 2016; 374: 479-480.
29. Ibrahim HN, Foley RN, Reule SA *et al*. Renal Function Profile in White Kidney Donors: The First 4 Decades. J Am Soc Nephrol 2016.
30. Spital A. Kidney-Failure Risk Projection for the Living Kidney-Donor Candidate. N Engl J Med 2016; 374: 2093.
31. Grams ME, Garg AX, and Lentine KL. Kidney-Failure Risk Projection for the Living Kidney-Donor Candidate. N Engl J Med 2016; 374: 2094-2095.
32. Anjum S, Muzaale AD, Massie AB *et al*. Patterns of End-Stage Renal Disease Caused by Diabetes, Hypertension, and Glomerulonephritis in Live Kidney Donors. Am J Transplant 2016.
33. Hourmant M, Lerat L, and Karam G. Donation from old living donors: how safe is it? Nephrol Dial Transplant 2013; 28: 2010-2014.
34. Berger JC, Muzaale AD, James N *et al*. Living kidney donors ages 70 and older: recipient and donor outcomes. Clin J Am Soc Nephrol 2011; 6: 2887-2893.
35. Dols LF, Kok NF, Roodnat JI *et al*. Living kidney donors: impact of age on long-term safety. Am J Transplant 2011; 11: 737-742.
36. Lam NN and Garg AX. Acceptability of older adults as living kidney donors. Curr Opin Nephrol Hypertens 2016; 25: 245-256.
37. Young A, Kim SJ, Speechley MR *et al*. Accepting kidneys from older living donors: impact on transplant recipient outcomes. Am J Transplant 2011; 11: 743-750.
38. Englum BR, Schechter MA, Irish WD *et al*. Outcomes in kidney transplant recipients from older living donors. Transplantation 2015; 99: 309-315.
39. Thomas SM, Lam NN, Welk BK *et al*. Risk of kidney stones with surgical intervention in living kidney donors. Am J Transplant 2013; 13: 2935-2944.

40. Lam N, Huang A, Feldman LS *et al*. Acute dialysis risk in living kidney donors. Nephrol Dial Transplant 2012; 27: 3291-3295.
41. Boudville N, Prasad GV, Knoll G *et al*. Meta-analysis: risk for hypertension in living kidney donors. Ann Intern Med 2006; 145: 185-196.
42. Lam NN, McArthur E, Kim SJ *et al*. Gout after living kidney donation: a matched cohort study. Am J Kidney Dis 2015; 65: 925-932.
43. Pilz S, Tomaschitz A, Drechsler C *et al*. Parathyroid hormone level is associated with mortality and cardiovascular events in patients undergoing coronary angiography. Eur Heart J 2010; 31: 1591-1598.
44. Eikelboom JW, Lonn E, Genest J, Jr., Hankey G, and Yusuf S. Homocyst(e)ine and cardiovascular disease: a critical review of the epidemiologic evidence. Ann Intern Med 1999; 131: 363-375.
45. Zhao G, Huang L, Song M, and Song Y. Baseline serum uric acid level as a predictor of cardiovascular disease related mortality and all-cause mortality: a meta-analysis of prospective studies. Atherosclerosis 2013; 231: 61-68.
46. Nielsen CB, Sorensen SS, and Pedersen EB. Enhanced plasma endothelin in healthy uninephrectomized subjects during basal conditions and after indomethacin. Nephrol Dial Transplant 1994; 9: 5-9.
47. Zoccali C. Traditional and emerging cardiovascular and renal risk factors: an epidemiologic perspective. Kidney Int 2006; 70: 26-33.
48. Yilmaz BA, Caliskan Y, Yilmaz A *et al*. Cardiovascular-renal changes after kidney donation: one-year follow-up study. Transplantation 2015; 99: 760-764.
49. Moody WE, Ferro CJ, Edwards NC *et al*. Cardiovascular Effects of Unilateral Nephrectomy in Living Kidney Donors. Hypertension 2016; 67: 368-377.
50. Garg AX, Meirambayeva A, Huang A *et al*. Cardiovascular disease in kidney donors: matched cohort study. BMJ 2012; 344: e1203.
51. Narkun-Burgess DM, Nolan CR, Norman JE, Page WF, Miller PL, and Meyer TW. Forty-five year follow-up after uninephrectomy. Kidney Int 1993; 43: 1110-1115.
52. Segev DL, Muzaale AD, Caffo BS *et al*. Perioperative mortality and long-term survival following live kidney donation. JAMA 2010; 303: 959-966.
53. Buszta C, Steinmuller DR, Novick AC *et al*. Pregnancy after donor nephrectomy. Transplantation 1985; 40: 651-654.
54. Ibrahim HN, Akkina SK, Leister E *et al*. Pregnancy outcomes after kidney donation. Am J Transplant 2009; 9: 825-834.
55. Reisaeter AV, Roislien J, Henriksen T, Irgens LM, and Hartmann A. Pregnancy and birth after kidney donation: the Norwegian experience. Am J Transplant 2009; 9: 820-824.
56. Wrenshall LE, McHugh L, Felton P, Dunn DL, and Matas AJ. Pregnancy after donor nephrectomy. Transplantation 1996; 62: 1934-1936.
57. Garg AX, McArthur E, Lentine KL, and Donor Nephrectomy Outcomes Research N. Gestational hypertension and preeclampsia in living kidney donors. N Engl J Med 2015; 372: 1469-1470.