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FULL REVIEW

Donation from old living donors: how safe is it?

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ABSTRACT

As the rate of living kidney donor (LKD) transplantations increases, the selection of extended criteria donors such as old donors (>60–65 years) becomes more common. The pool of these old donors is probably wider than we think, especially if we tolerate a lower glomerular filtration rate (GFR) than the gold standard of 80 mL/min/1.73 m^2. Several important studies with large cohorts of living donors including old subjects have been published these last few years and give insights on the outcome in this subpopulation. The risk of death and end-stage renal disease (ESRD) is similar to that of matched controls from the general population. Post-donation GFR, as a result of glomerulopaenia, is lower in old than in younger donors but pre-donation as well as the rate of function loss is not different between young and old donors. Nearly 80% of donors over 60 have <60 mL/min GFR post-donation, the risk of cardiovascular mortality and progression to ESRD in the long term, as in the general population, is under question. Despite reduced renal function of the old kidney, the results of transplantation from an old living donor appeared to be equivalent to deceased transplantation from a younger donor. Finally, transplantation from an old living donor appeared to be a reasonably safe procedure for both the donor and the recipient and the age *per se* is certainly not a contraindication to donation.

The development of transplantation from a living kidney donor (LKD) has benefited from the extension of the donor definition, but it could be further expanded by the extension of donor selection criteria, including the donor age. Indeed, the success of LKD transplantation, the organ shortage and death on the waiting list have led some transplant teams to accept these extended criteria for an old LKD [1]. There is no official upper limit for LKD age but in many publications, a donor is considered as old if over 60 or 65; there is even a report of donation in 219 persons over 70 [1]. In the USA, the mean age of the LKD has increased over time, but those over 65 years remain few, 0.7% in 1988, 0.9% in 2000 and 1.5% in 2008 [2]. Some European centres have reported a much higher proportion, >20% of donors over 60 in Rotterdam [3], 16.8% over 60 and 7.7% over 65 in Norway [4].

Donation from an old LKD raises several questions, first regarding the recipient and donor outcomes. Are the results acceptable for the recipient? What is the risk, mortality and long-term renal function for the donor? The present recommendations for donor selection give a major weightage to the level of renal function, with a threshold of glomerular filtration rate (GFR) that has to be over 80 mL/min/1.73 m^2. With such a criterion, we can wonder how many old donors would be selected. But should not we, to increase the pool, tolerate a lower GFR threshold, variable according to the age of the donor? At first view, donation nephrectomy and its

consequences on renal function could be seen as taking an unreasonable risk in an old person, but is it more reasonable to deprive of one of his (her) kidney a young man or woman, who has a long lifespan and is susceptible to develop pathologies that we do not even suspect, than this old person whose risk factors for chronic kidney disease (CKD) are likely to be already present. Discussions are starting to emerge on this point.

ARE THE RESULTS ACCEPTABLE FOR THE RECIPIENT?

It is clear that the age of the donor has an impact on the transplant outcome. In a recent meta-analysis for which the objective was to compare graft survival (GS) and graft function in recipients of a kidney from an old (60–85 years) or a young LKD (30–55 years), the DONOR network reported that GS was significantly lower at 5 years when the donor is >60 (72 versus 80%, $P < 0.05$) [5]. Recipient survival was also decreased. The GFR at 1 year was significantly altered in recipients of an old kidney but the absolute difference was small, 3 ml/min. Importantly, the study showed that GS differences disappeared with time and in the 2000s, the results were similar for old and young donors. In an observational study realized in five centres in Ontario, Canada, the same group found later that death adjusted and unadjusted GS was not statistically different between transplantations from old and young LKD [6]. Another study having included 1063 LKD kidney transplantations also reported that increased age was related to reduced GS after 4 years and the difference was already significant for LKD over 40 [7]. Delayed graft function was more frequent when the donor was >60 (6.8 versus 2.5%). Older kidneys (>60 years) had a lower pre-transplant and baseline post-transplant function, and presented a more rapid decline in GFR after 1 year. They also more commonly developed low-to-moderate proteinuria that was by multivariate analysis the only determinant and not the level of GFR - of graft loss. An old donor can donate to a young or an old recipient and subgroups were made where the difference between the age of the donor and the recipient was 5 years, <5 years or >5 years. It was shown that receiving a kidney from an older donor was a disadvantage and from a younger donor an advantage in young recipients but not in recipients over 50. Comparison with deceased donor transplantation sheds another light on these data in that transplantation from an LKD, even when the donor is old, gives better results than deceased donor transplantation. In a series of 219 transplantations from >70-year-old LKDs (70–84), graft loss was significantly higher than in LKDs 50–59 but similar to matched standard 50–59 deceased donor allografts [1]. Similar results have been reported with LKD over 60 compared with <60 standard criteria deceased donors [6]. A study from the US Network for Organ Sharing calculated the kidney allograft half-life according to the age of the donor and the recipient and found minimal differences, outside the situation of a 13–39-year-old donor giving a kidney to a 13–39-year-old recipient who reached better GS [8].

Altogether, these data suggest that when a young patient has several potential donors, it is preferable to select a young one but they also suggest that although giving lower results for transplantation of a kidney from an old donor is a good option. LDT from an old donor should certainly not be excluded when a patient has old donors only or when an old donor is the only solution for a young hyperimmunized recipient. In addition, the age of the donor should not be a contraindication to paired exchange. The UNOS study used its data to plead for extension of the age criteria in order to increase the number of transplants performed in living donor paired exchange programs [8]. Finally, by increasing the pool of donors, transplantation from an old LKD could be a solution to organ shortage. It could spare the recipient years on dialysis and in addition, it allows pre-emptive transplantation. In this way, it could be life-saving. Indeed, the reduction of time from end-stage renal disease (ESRD) to wait-listing has been reported as having a significant and dose–response advantage on graft and patient survival in deceased as well as in LKD transplantation, while the time between the wait-listing and transplantation has a negligible effect [9].

WHAT IS THE RISK OF DONATION FOR THE OLD LIVING DONOR?

The old donor is selected based on the same criteria as a young one, with the risk of finding more often exclusion criteria, minor abnormalities or cardiovascular risk factors such as hypertension or obesity that will lead to contraindication, alone or if associated. The existing national guidelines do not have specific rules for old LKD.

Mortality

Several studies with large cohorts of patients have now been published on short- and long-term mortality after living donation. A study by the Minneapolis team in the eighties reported a 0.03% mortality in the perioperative period. A recent analysis of the 1999–2008 US OPTN database also found this percentage of 0.03% mortality in the first month for an overall mortality of 2.8% over the study period [2]. In a huge cohort of 80 347 LKD (1994–2004), Segev *et al.* [10] reported the results according to the age of the donor that was, with the gender, black race and presence of hypertension, the main determinant of mortality at 3 months. Three-month mortality ranged from 3.0 of 10 000 for LKD between 18 and 39 to 6.6 for those over 60 years and did not change during the last 15 years. These rates were compared with those of cholecystectomy (18 of 10 000) and nephrectomy outside donation (260 of 10 000). The long-term risk of death also increased with age (16.6 of 10 000 LKD for the ≥60 group versus <7.4/10 000 for the <50 group, $P = 0.08$), and with a mean follow-up of 6.3 years (3.2–9.8), was not significantly different when LKD were compared with 9364 subjects from the NHANES III cohort, matched for age, gender, race and comorbidities, even in the donors over 60 years of age. Another study focused on LKD >70 who were also compared

with matched NHANES participants and the mortality was found similar to controls up to 10 years of follow-up [1].

Renal function

Old donors are generally selected based on the same criteria as younger donors regarding renal function (GFR over 80 mL/min/1.73 m^2, proteinuria <300 mg/day). The method for evaluating renal function in the LKD will not be discussed but it is important to emphasize that equation estimations (even CKD-EPI) are not considered reliable [11, 12]. Age, gender and body mass index (BMI) when taken into account may explain their low predictive value [12]. Under-evaluation of GFR could lead to excessive exclusion of potential donors. GFR measurement using one of the reference techniques is certainly mandatory in potential donors over 50 and in any potential donors around 80 mL/min/1.73 m^2, before excluding them from donation.

The risk of ESRD in the long term has been evaluated by several studies, which reported that its incidence in LKDs was no higher than that of the general population [13]. A publication described the profile of 102 LKD who developed kidney failure and were listed for transplantation [14]. They were rather young with a mean age of 32 and 44% were African-Americans.

The evolution of renal function after donation has been documented by several major recent publications on large cohorts. They are not always focused on old patients but their group is big enough to be informative. In 569 LKDs, 422 <60 and 117 >60 years of age, the post-donation estimated GFR (eGFR) was lower in the older patients, <60 mL/min/1.73 m^2 in 80% of them versus 31% in the younger patients, but as the eGFR was also lower before donation the percentage of renal function loss was strictly identical in both the groups, around 35% [3]. None of the donors had <30 mL/min/1.73 m^2. Similar results were found in another study of 196 LKDs, whose renal function was measured 3 months after donation using iothalamate GFR (iGFR) [11]. Ninety-one percent of the 60–69 donors and 61% of the 50–59 had <60 mL/min/1.73 m^2, versus <16% of the donors aged <49. Note that the eGFR, either MDRD or Cockroft–Gault, or the endogenous 24-h-creatinine clearance correlated badly with iGFR and overestimated the number of donors having a level of renal function that would classify them in class III CKD. Regression analysis found pre-nephrectomy GFR and age to be significant factors predicting post-nephrectomy GFR and the profiles of GFR decrease according to age were parallel pre and post-donation.

According to the meta-analysis of the DONOR network, LKDs have higher microalbuminuria after donation than controls [15], while overt proteinuria is uncommon. In the Minneapolis series of 255 donors evaluated 12 years after donation, proteinuria was found in 1.2% [13]. Microalbuminuria was present in 12.7%. Fehrman–Eckholm reported microalbuminuria in 21% of 573 LKDs with a mean age of 61.5 years evaluated 14 years after donation [16] and she noted that its occurrence was significantly associated with increasing time post-donation.

Interesting work on the LD kidney physiology and histology has been done in the past years to describe what can be expected of an old kidney. Rook *et al.* [17] measured the modification of the reserve capacity (RC) 4 months after donation. In 178 LKDs, including 57 aged 54–75, RC after dopamine injection was found to be 11% ± 10 before donation, independent of donor's age. After donation, RC decreased to 5% ± 7 with a higher and significant reduction in the donors over 53. The BMI was the other independent determinant of the magnitude of RC decrease. A comparison of the response with nephron reduction of 24 LKDs over 55 and 33 under 45 concluded that young and old kidneys had the same capacity of glomerular hyperfiltration and cortical hypertrophy [18]. Parameters of glomerular function (GFR, renal plasma flow, filtration fraction, whole kidney Kf) and of glomerular structure (glomerular volume, filtration surface area, basement membrane thickness, filtration slit frequency, hydraulic permeability, single nephron Kf) were not different and the only factor that could explain the lower GFR of the old donor was glomerulopaenia. In a review on the anatomical and functional changes in the ageing kidney, including many studies in the LKD, senescence was associated with an increase in the number of sclerotic glomeruli leading to a compensatory increase in the volume of the functional glomeruli [19]. This compensation reaches a threshold around the age of 60. Glomerulopaenia can eventually be aggravated by vascular lesions related to hypertension, carbohydrate abnormalities, obesity, that old donors are more prone than young donors to develop with time.

The Mayo Clinic has analysed kidney biopsies obtained before implantation in 1203 adult LKDs [20]. Those with microalbuminuria, diabetes and isotopic GFR under the age-specific fifth percentile were excluded. Biopsies were blindly scored for chronic lesions, interstitial fibrosis, tubular atrophy, arteriolar and glomerulosclerosis. Two hundred fifty-seven donors were between 50 and 59, 92 between 60 and 69 and 11 were >70. Their iGFRs were 97 ± 14, 90 ± 12 and 86 ± 11 mL/min, respectively. Older LKDs were more likely to have hypertension, higher cholesterol and higher glycaemia that remain nonetheless in the normal range. The prevalence of nephrosclerosis (sum of the lesions of sclerosis) ≥2 increased with the age of the LKDs: from 2.7% for donors 18–29 to 44% between 50 and 59, 58% between 60 and 69 and 73% over 70. Adjustment for kidney function and comorbidities did not explain the age-related increase in the prevalence of nephrosclerosis. Finally, nephrosclerosis appeared to be a lesion largely associated with age that cannot be predicted by our usual medical evaluation.

The impact of CKD and cardiovascular risk factors

The long-term slight decrease in renal function is related to senescence of the remaining kidney, but it is susceptible to accelerate in the presence of cardiovascular risk factors, diabetes, obesity and hypertension, which are expected to be more common in the old LKDs before and after donation. As said before, obesity has been associated with lower GFR post-donation [13, 17] and is also known as a risk factor for proteinuria in the uninephrectomized subject, living donor or not [21]. Surprisingly, hypertension post-donation is generally not noted as a significant factor associated with low renal function in the long term.

There has been some questions in the literature about the risk associated with reduced renal function after donation. The cardiovascular toxicity of microalbuminuria and proteinuria is well recognized. Levey *et al.* [22] have proposed a table estimating, for the general population, the risk of cardiovascular mortality, ESRD, acute kidney failure and progressive CKD. Conversely, a study performed in 8705 persons over 65 living in three French cities, followed for 6 years, concluded that only those with eGFR <45 mL/min had increased cardiovascular mortality and poor renal outcome [23]. It is admitted that blood pressure is higher after nephrectomy [24]. A meta-analysis having included data for one million adults with no previous vascular disease showed that in middle and old age, blood pressure, even in the normal range, is strongly associated with cardiovascular mortality [25]. Therefore, long-term mortality could be increased in the LKD as a direct consequence of donation.

But we do not know whether all these results apply to the LKD.

The few studies analysing cardiovascular complications in cohorts of LKDs compared with matched controls from the general population are reassuring. The DONOR network used healthcare administrative data for 2028 LKDs in Ontario, Canada, followed for a median duration of 6.5 years, who were compared with 20 280 controls selected from the healthiest segment of the general population [26]. The risk of the composite outcome, death and major cardiovascular events, myocardial infarction, stroke, any vascular surgery, was significantly lower in the donors than in the non-donors (2.8 versus 4.1%). A higher risk for both was associated with older age but in non-donors as well.

WHAT IS THE POOL OF THE OLD LIVING DONORS?

The selection of the LKD is much dependent on renal function. We meet old people with low GFRs in our outpatient clinics, but we have less knowledge of renal function in the old population that is supposed to be in good health. The study known as the Three French Cities study reported eGFR (MDRD) in 8705 people aged 65 or more [23]. Among them, 10.2% had over 90 mL/min/1.73 m^2 and 76.9% were between 60 and 89 mL/min/1.73 m^2. A study from the Nijmegen Biomedical study also provided age and gender references for eGFR in a population without expressed risk (no hypertension, no diabetes, no cardiovascular nor renal disease) [27]. GFR was estimated by the MDRD formula in 1660 males and 2072 females, with 869 in each group having ≥65 years of age. The data showed that old to very old subjects eventually have good to excellent renal function. Finally, the pool of old donors with sufficient GFRs for donation is probably wider than we imagine.

The GFR above 80 mL/min /1.73 m^2 is usually considered as the gold standard for LKD selection, but the UK recommendations propose a different threshold adapted to the age of the donor [28]. It is defined as the GFR value at donation that will allow the donor to have at least 30 mL/min/1.73 m^2 at the age of 80. This value is 86 mL/min/1.73 m^2 up to the age of 40, 77 at the age of 50, 68 at the age of 60, 59 at the age of 70, 50 at the age of 80. These numbers result from an evaluation of GFR decrease of the remaining kidney with age. They have not been validated by clinical studies to date, and we have to be cautious as the evaluation of renal function decrease is based on age only and does not take into account that the donor can develop, in the long term, risk factors for CKD.

The pool could be further expanded if we extend our selection criteria and consider donors with minor abnormalities. Most European centres are reluctant to use obese donors, but they are accepted in the USA. Although obesity increased the risk of complications, hypertension and reduced GFR [21], the safety results are considered acceptable [29]. Larger studies are certainly needed.

IS IT LESS REASONABLE FOR AN OLD PERSON TO DONATE THAN FOR A YOUNG ONE?

Steiner [30] expressed the provocative point of view that we take more risk when selecting a young donor than an old one. His arguments are that it is likely that we know all the risk factors of CKD and cardiovascular diseases in an old LKD. According to the USRDS, half of the new cases of ESRD in the USA (45% secondary to type 2 diabetes, 27% to hypertension, 8% to glomerulonephritis) occur after the age of 65. Racial variations in the outcome and incidence of CKD after donation have also been reported [31] and indeed, it is known that black people are more prone to develop hypertension, diabetes, CKD and ESRD. The cumulative lifetime risk of ESRD for a 20-year-old in the USA has been calculated by computer simulation stratified by race and gender [32]. It has been found to be 7.8% for a black woman, 7.3% for a black man versus 1.8 and 2.5% in white women and men, respectively. Lifestyle can also lead to the acquisition of risk factors for CKD, such as obesity or sedentariness. They are likely to be already present in the old subject but not in the young one. A normal evaluation in a young donor is seemingly reassuring, but a normal evaluation in the old one has a stronger predictive value.

CONCLUSION

It is undisputable that living donor transplantation can be a solution to answer the organ shortage and is the best option for a patient, whatever the donor. One of the reasons is that in sparing the recipient years on dialysis, transplantation is associated with reduced mortality. This is true provided that donation does not harm the donor. Major studies have been published during these last few years on the outcome after donation of old donor kidneys. They suggest that the procedure is safe both for the donor and for the recipient. The mortality rate has been evaluated and estimated in one study as lower than that of common surgery such as cholecystectomy. Most of the old donors have reduced renal function after donation, with an eGFR level that classifies them in

class III CKD, an improper staging in the context of a person with a normal kidney, and the question has arisen of its consequences on CKD progression, cardiovascular complications and mortality. Data have been accumulated now which do not support an increased risk. More studies focused on old donors are still needed, but we can already consider that age *per se* is not a contraindication to kidney donation.

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