Discussion
Renal function decline with age: consequences for living kidney donation. A mini-review on renal senescence

Submitted

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Abstract

With ageing, structural and functional changes occur within the kidney and renal function slowly declines. Despite this age-related renal function decline, it has become more and more common to accept elderly living donors. Due to the persistent shortage of organs for transplantation purposes, reluctance towards these so-called marginal donors is declining. This has contributed to a gradual increase in mean age of the living kidney donor population over the past decades.

The consequences of this altered policy are not fully clear yet. Is donor renal safety compromised when we allow donation at older age? In this mini-review, we discuss the current literature on elderly living donors and provide data from our own living kidney donor population.
Introduction

With the persistent shortage of organs for transplantation purposes, several efforts have been undertaken to expand the potential kidney donor pool. Selection criteria for living kidney donors have been extended over the past decade. For instance, it has become more and more common to accept elderly living donors, as reluctance towards these so-called marginal donors is declining and many centres no longer employ an upper limit for donor age [1]. In our centre, mean donor age has increased from forty years in the eighties, to fifty years nowadays.

Most studies investigating the consequences of this altered policy focus mainly on potential hazards for the recipient. Higher donor age has been associated with unfavourable graft function and survival, though not invariably so [2-5]. Still, for the recipient, transplantation from an elderly living donor source is superior to dialysis as well as to transplantation from a deceased donor [6,7]. Benefits for the recipient must be in balance with risks for the donor. Fortunately, laparoscopic donor nephrectomy is generally a safe procedure, which also appears to be true for elderly donors [8]. Less is known however about remnant renal function in the elderly living kidney donor, which is just as essential to investigate if not even more so. In particular long-term data are lacking so far.

In this mini-review, we discuss the current literature on elderly living donors and provide additional data from our own living kidney donor population. Hereby, we aim to provide supportive evidence for use of elderly donors and thus to optimize the donor pool without compromising long-term donor safety.

Age related renal function decline

With ageing, structural and functional changes occur within the kidney and renal function slowly declines. This can be attributed to loss of functional nephrons and arteriosclerosis, leading to decrease in renal blood flow and GFR and effective renal plasma flow (ERPF) [9]. The individual variability in the extent of decline in filtration and flow is large. Several cross-sectional studies in the general population have shown that the GFR decline on average amounts to 5-10 ml/min/decade [10,11]. In prospective living kidney donors, assumed to present a healthy subset of the population, results are more or less similar, though some reports are conflicting. Unfortunately, there are very few longitudinal data available. Most studies show an age-related decrease for both male and female donors [12,13]. In contrast, stable renal function has been

Figure 1. Predicting a GFR below 60 ml/min/1.73 m² short-term after donation.

A population of 125 kidney donors was divided into quartiles of baseline GFR prior to donation. The probability of GFR below 60 ml/min/1.73 m² is calculated by means of a logistic regression model including baseline GFR and age, with Nagelkerke $R^2=0.49$ and $p<0.001$. The sensitivity and specificity of this model were 61% and 93%, respectively.
reported in females; however, this was in a relatively young population of merely 62 donors [14]. On cross-sectional analysis, we observed a significant negative relation of age with GFR in both male and female donors, ranging between 20 and 76 years old [13]. As a result of the age related decline in renal function, older donors have a lower GFR to start with and post-donation GFR is lower on the short-term, too. In line, with increasing age, donors were found to be more likely to reach glomerular filtration rate (GFR) below 60 ml/min/1.73 m² short-term after donation, as shown in figure 1 [15]. It should be noted that also for a given pre-donation GFR, the probability to end up with a GFR below 60 ml/min/1.73 m² was larger in older donors. So, apparently, the early adaptive response of the remaining kidney to contra-lateral nephrectomy was less effective in older donors than in younger donors.

**Effect of ageing on renal reserve capacity**

With the age-related decrease in renal function, it seems logical that renal reserve capacity may decrease concomitantly. Indeed, an impaired renal response to vasodilator stimuli has been reported in healthy older subjects, related to the severity of arteriosclerosis [16]. In our population of kidney donors, the largest report on reserve capacity so far, we did not observe a relation between reserve capacity and age before donation, tested either by low-dose dopamine, amino-acid infusion, or a combination of dopamine and amino-acids [15]. So somewhat at variance with our expectations, renal reserve capacity was well preserved in older subjects. This may be explained by the very healthy population that kidney donors represent.

After nephrectomy, in line with prior studies, reserve capacity decreased. Remarkably, after donor nephrectomy, older age had become a limiting factor for renal reserve capacity. After donation, infusion of low-dose dopamine did no longer induce a rise in GFR in older donors [17]. Figure 2 shows regression analyses for age with baseline GFR and dopamine-stimulated GFR, both before and after donor nephrectomy in 178 living kidney donors from our centre. It shows that before donation, for the whole continuum of age, dopamine-stimulated GFR ran parallel with baseline GFR. At two months after donor nephrectomy, GFR did not respond to dopamine in the higher range of donor age. Possibly, older donors need to address their renal reserve to adapt to the new single kidney situation and to maintain renal function. The long-term consequences of this donation-induced loss in renal reserve are currently unknown.

**Age-related hyperfiltration**

In humans, intra-glomerular pressure cannot be measured directly, but filtration fraction (FF) can be used as a surrogate marker. When GFR and ERPF are measured simultaneously, FF can be obtained as the ratio GFR/ERPF. FF hereby represents the proportion of plasma that is actually filtered and is assumed to provide a reflection of intra-glomerular filtration pressure. The use of filtration fraction can be a valuable tool for interpretation of renal hemodynamics in man. With ageing, both ERPF and GFR decrease. However, ERPF proportionally decreases more than GFR. Consequently, filtration fraction, which is thus the GFR divided by the ERPF, increases with ageing [18].

Animal studies have supported the impact of an elevated filtration pressure as a pathogenetic factor for progressive renal function loss [19]. Recently, human data supporting the role for an increased filtration fraction as a poor prognostic
factor in progressive renal function loss have become available as well [20,21].

Theoretically, after kidney donation, the age-related higher filtration fraction could be associated with a larger decrease in renal function for two main reasons. First, the higher filtration fraction may indicate that the kidney already addressed its reserve capacity, in response to vascular lesions and loss of functional nephrons. So less reserve would be present for the adaptive response after nephrectomy. Second, the higher glomerular pressure that underlies the higher filtration fraction could result in long-term glomerular capillary damage and renal function loss. So far, however, no data are available on the predictive effect of pre-donation filtration fraction for long-term renal outcome after donation.

Assessment of age-related renal function decline with equations
The gold standard for measurement of renal function is by the clearance of specific tracers. As it is laborious and expensive, creatinine-based measures are used in clinical practice. Creatinine clearance from 24 hour urine collection has been criticised for the inaccuracy due to collection orders. Accordingly, renal function equations, such as MDRD and Cockcroft-Gault, are advocated for cheap and easy estimation of glomerular filtration rate (eGFR) or creatinine clearance. These equations were empirically developed from data in patients with renal disease, and aim to predict renal function from serum creatinine. They also include body weight, age and gender (Cockcroft-Gault) or age and gender alone (MDRD) to account for differences in muscle mass and hence creatinine generation between individuals. However, the accuracy of renal function equations tends to be poor in subjects without renal disease. True
GFR is considerably underestimated by eGFR when GFR is in the normal range or only mildly impaired [12]. These renal function equations have not been well-validated in older subjects. In 52 very old --but otherwise healthy-- subjects, aged 70 to 110 years, true GFR was found to be relatively preserved. The Cockcroft-Gault severely underestimated true GFR [22]. As age is in the algorithm, the performance of renal function equations may well be age-dependent. This was investigated by Verhave et al. in a large population-based study in subjects without renal disease. In older subjects, the MDRD equation performed better than the Cockcroft-Gault, with marked underestimation of renal function by the latter in older subjects [10]. Apparently, the systemic error or renal function equations is age-dependent. Therefore, assessment of age-related renal function decline is strongly influenced by the method used to estimate renal function. This is illustrated in figure 3 that shows regression lines for true GFR and estimated GFR by MDRD and Cockcroft with age in 250 prospective living kidney donors from the University Medical Center Groningen. It shows that the loss in renal function per decade was overestimated by CG and underestimated by MDRD.

Cystatin C has been proposed as an alternative marker for renal function, that does not have the limitations of creatinine [23]. In elderly subjects with serum creatinine in the normal range, Fiser et al. found cystatin C to be a better marker of renal function impairment than serum creatinine [24]. However, Van den Noortgate et al. found similar performance for creatinine and cystatin C in elderly [25]. Most studies on cystatin addressed populations with cardiovascular or renal risk or established disease. Some larger studies have investigated the general population but validation by gold standard renal function measurements is lacking so far.

In a population of living kidney donors, cystatin C was not superior to creatinine-based renal function estimates but appeared to perform similarly [26,27]. Unfortunately, these analyses did not investigate whether cystatin C would be useful for donor screening purposes.
Assessment of renal function is an important component of donor evaluation. The method of choice should meet certain requirements, enabling a selection process that minimises short and long-term donor safety. There is no place for renal function equations in donor screening. Fortunately, most centres use 24-hour creatinine clearance or isotopes for screening purposes [1]. Whether there is a place for cystatin C based equations in future evaluation of (elderly) donors remains uncertain. At the moment, renal function measurements by use of isotopes or inulin remain the method of choice for evaluation of elderly subjects or when renal function estimate is low [28].

**Adaptive changes after donor nephrectomy**

After donor nephrectomy, considerable adaptive responses occur in the remaining, contra-lateral kidney, aimed at preservation of renal excretory capacity. Considering age-related renal function loss, it could be anticipated that renal hemodynamic adaptation may be impaired in older donors. However, there is evidence that indicates that post-nephrectomy may occur independent from age at nephrectomy [29]. The effect of age on the renal adaptive response to nephrectomy was recently investigated in subjects who underwent nephrectomy for donation or renal carcinoma. Subjects were at least half a year after nephrectomy, to allow adaptive responses to be largely complete. In subjects older than 57 years, the adaptive rise GFR in response to unilateral nephrectomy was preserved as compared to subjects below 55 years, albeit at a lower absolute level of GFR. Furthermore, the magnitude of the adaptive increase was found to be similar to or slightly smaller than the response to unilateral nephrectomy in younger subjects [29]. Similar to results from our and other centres, the increase in single kidney GFR found in this study was 38-42% [15].

**Potential renal risks of overweight with ageing**

With ageing, body mass index is known to gradually increase. Population based studies show a mean increase in body...
weight of approximately seven kilos over a decade with a concomitant rise in the prevalence of overweight and obesity [30]. In transplant recipients, weight gain after transplantation is notorious and has been associated with graft loss and mortality [31]. Bosma et al. found that a higher filtration fraction, as a marker for hyperfiltration, was an independent predictor for graft loss and mortality [20]. In the general population, overweight is a well recognized risk factor for renal damage and even end stage renal disease [32]. Overweight and obesity are associated with hyperfiltration, as apparent from an increase in GFR, ERPF and filtration fraction [33]. Part of this renal risk may thus be explained by overweight-induced hyperfiltration, as hyperfiltration, on the long-run, may be harmful for the kidney. Of concern for living kidney donors, overweight was particularly found to be a renal risk factor after nephrectomy [34]. We found that despite profound changes in renal hemodynamics short-term after donor nephrectomy, the relation between body mass index and filtration fraction persisted. Even more so, long-term after donor nephrectomy, an increase in body weight was associated with an increase in filtration fraction [Rook et al., currently under review]. The consequences of a possible interaction between age and overweight on a renal risk profile have not been established, but deserve further consideration, as weight excess is in principle accessible to intervention.

Long-term follow-up of elderly donors

Several studies provided long-term follow-up of kidney donors. Table 1 shows donor age and remarks for some recent studies with long-term follow-up. Donor health is usually excellent and there are no signs of accelerated loss of renal function in the single post-donation kidney [35-38]. However, none of these studies specifically addressed older donors,
possibly because 20 years ago, older donors were not as common as today. Furthermore, most studies are hampered by a large proportion of subjects lost to follow-up and by retrospective designs [39].

Recently, we invited a cohort of 55 kidney donors who donated between 2000 and 2002 for long-term renal follow-up. The response rate was 69%, with no differences with regards to age, pre-donation renal function or BMI between donors with or lost to follow-up. We analysed for a potential effect of age at donation on GFR and ERPF. In the single kidney, both GFR and ERPF had markedly increased 6 years after living kidney donation compared to short-term after donation. Age did not affect the changes in renal hemodynamics in this long-term follow-up, as shown in figure 4 [Rook et al., analyses currently ongoing]. These preliminary data provide further support that kidney donation, as performed under the prevalent screening and selection policy at time of donation, is safe for the older kidney donor.

**Conclusion**

Effects of age on renal risk after living kidney donation are of clinical relevance, as –due to persistent donor shortage– older subjects are increasingly accepted for kidney donation, to the extent that many centres do not use an upper age limit for donation any more. Elderly donors represent a healthy selection of the population and in this selected population, the risks of older age are apparently limited, also in the case of kidney donation. Whereas it was usual to consider calendar age in judgement of prospective kidney donors, this policy is now gradually being abandoned. It might be more relevant to take renal function as a marker of biological age, of course taking relevant co-morbidity into consideration as well. Whereas under the current donation policies, kidney donation by older donors is generally safe, monitoring of short-term and long-term outcome in donors and recipients remains warranted to obtain and maintain an optimal risk-benefit ratio in this evolving field.
References


