Why Do Kidneys from Older Donors Display an Inferior Survival?

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Introduction

The increasing gap between the supply and demand of kidneys for transplantation has resulted in an increasing use of older donors. Between 1988 and 1995, UNOS registered a 172% increase in the number of cadaveric donors over 50 years of age,[1] which is an increase from 12% to 25% of total cadaveric kidney donors. For 1998, the Eurotransplant registry indicates that up to 25% of cadaveric transplants came form donors who were older than 55 years of age.[2]

The use of kidneys from older donors is associated with an increased risk of delayed graft function, an increased need for postoperative dialysis treatments, and a higher serum creatinine concentration at discharge.[3] At 5 years, a 25% difference in graft survival rate has been reported between transplants from young and old donors. The projected graft half-life decreased from 10.2 to 5 years if the donor was between 16 and 20 years of age or 60 years of age, respectively. Finally, in a large multivariate analysis, donor age was identified as the most important factor that determines long-term outcome.[4] In this article, we discuss the factors that are associated with an increased loss of kidney grafts from old donors.

The Loss of Older Donor Kidneys

We analyzed the acute rejection incidence of kidneys received from donors older than 50 years of age and those received from donors younger than 50 years, and found that the cumulative incidence of acute rejection episodes was significantly higher in patients who received a graft from an older donor, while the timing of the rejection episodes was not different (Fig. 1).[5] Other investigators have also noted an increased incidence of acute rejection episodes in kidneys from older donors.[6] When the acute rejection rate and the rate of graft loss in kidney transplants from old donors (≥50 years of age) versus young donors (<50 years of age) was examined in the 3 pivotal Mycophenolate mofetil trials, there was a higher incidence of biopsy-proven acute rejection or treatment failure of kidneys from older donors in both the tricontinental and the European study. In the tricontinental trial, the incidence was 44% versus 39% (acute rejection or treatment failure), and in the European trial, the rate was 47% versus 40%, respectively. However, there was no difference in the acute rejection rate, or in the rate of graft loss, in the United States trial (36% in both arms) (Dr. Ramos, personal communication, Roche Pharmaceuticals, Palo Alto, CA).

When we analyzed the influence of advanced donor age on graft survival, a significantly increased rate of graft loss was found in kidneys from older donors that had experienced 1 or more acute rejection episodes. This adverse outcome was observed in the first 5 years after transplantation, whereas after 5 years, the differences were not significant.[5]

Ferguson modeled the likelihood of graft failure over time as a function of the acute rejection history of kidney grafts, irrespective of the donor age. He demonstrated that the risk of graft loss related to rejection is greatest in the early posttransplant period.[7] In patients with no acute rejection episodes, the risk of graft loss decreased sharply at a few months posttransplantation and reached a low level at 2 years. Patients with a single acute rejection episode reached the same low-level graft loss after 3 to 4 years. However, for patients with multiple rejection episodes, the risk of graft loss was several times that of the other patients for up to 6 years

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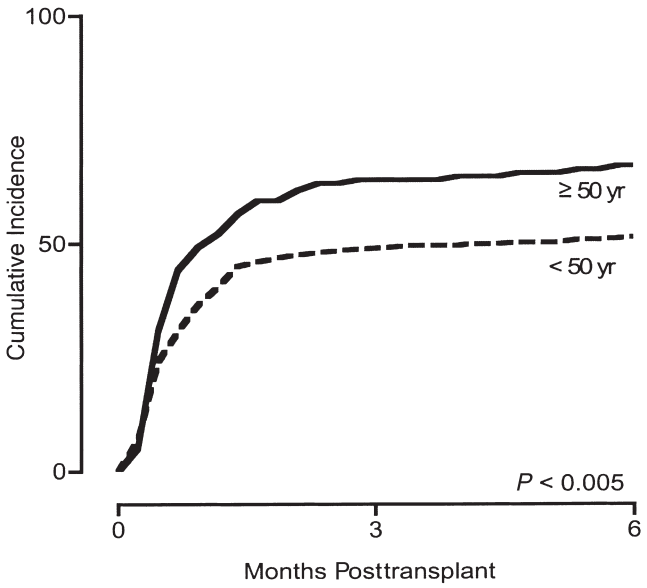

Figure 1. Cumulative incidence of first acute rejection episodes, according to donor age in first cadaveric renal transplants.

posttransplantation, at which point it also stabilized at a relatively low level. Therefore, the risk of late graft failure, in conjunction with the acute rejection history, is finite and limited to the first 5 or 6 posttransplant years. Results from our study on the factors associated with the loss of old donor kidneys[5] are consistent with the hypothesis that increased graft loss is related to the early acute rejection history of these grafts.

Previous studies have shown that acute interstitial rejection episodes do not have a negative impact on the graft prognosis, whereas acute vascular rejections have a significantly negative impact.[8] Histopathological studies of acute rejection biopsies from older donor grafts show an increase in acute rejection episodes attributable to an increase in interstitial, or Banff grade I, rejection episodes. These studies also show that both vascular and interstitial rejection episodes in kidneys from old donors are detrimental (Fig. 2) and suggest an age-related limited ability of the tissue to repair after injury. The study from Moreso et al. is consistent with this view,[9] observing an increased graft loss of kidneys from older donors if such kidneys had experienced acute rejection episodes or delayed graft function. A study from Edmonton suggests, however, that graft loss in older donor kidneys is a continuous process, independent from additional insults. In a time-dependent analysis of risk factors for graft loss, Prommool et al.[10] found that delayed graft function and acute rejection were risk factors for graft loss in the first 5 years, but thereafter donor age was the most important factor. Both studies[9,10] differed from ours, however, in that a substantial fraction of patients received prophylactic treatment with antilymphocyte antibodies, which may be beneficial to prevent early acute rejection. Kidneys from older donors thus seem more immunogenic than kidneys from younger donors—and older kidneys are less able to mount a tissue repair response following injury.

The Aging Kidney

The findings that approximately one-third of patients in the Baltimore Longitudinal Study of Aging did not show any change in the glomerular filtration rate[11] and that some inbred rat strains do not develop age-related renal damage[12] suggest that

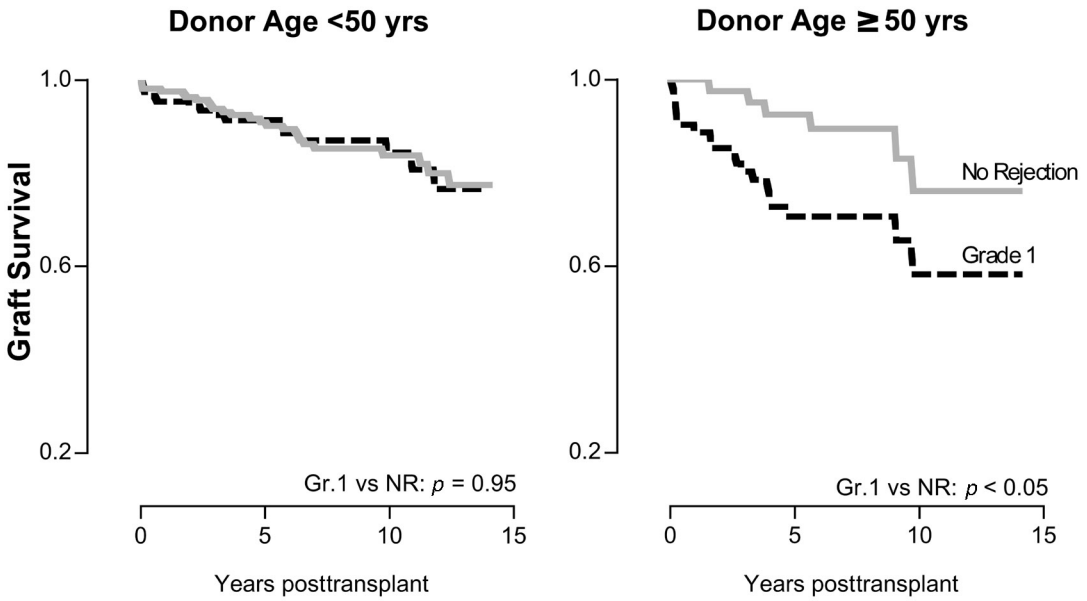

Figure 2. Kidney graft survival according to grade I acute rejection history and donor age in first cadaveric transplants. There is no difference in survival of kidneys from donors <50 years of age that had no rejection or rejection grade I, whereas the graft survival is worse in grafts from donors ≥50 years of age that have experienced an acute rejection episode.

the renal dysfunction of the elderly may be due to an accumulation of injuries induced by minimal and clinically undetected renal disease, rather than the consequence of the aging process itself. On the other hand, aging is a normal biological process characterized by atrophy and the gradual loss of functioning cells.

Longitudinal studies of elderly individuals have shown a diminution in renal reserve with aging, along with functional constraints on the kidney's ability to respond appropriately to challenges of either excesses or deficits.[13] Autopsy studies have shown that with increasing age, there is a decrease in the kidney weight, in the number of glomeruli, and in the mean glomerular volume.[14] In a study of 147 zero-hour biopsies from donors aged 6 to 64 years,[15] 38% showed no abnormalities by light microscopy, 44% showed nonspecific lesions, and 18% displayed a specific lesion. Nonspecific lesions were composed of intimal fibrosis of small arteries in 44%, interstitial fibrosis in 8%, and arteriolar hyalinosis in 29%. With age increasing over 40 years, there was a decrease in the fraction of normal biopsies. Kappel and Olsen[16] found an increase in the interstitial volume and an increase in the number of sclerotic glomeruli with aging. Another study also found a correlation between interstitial volume and donor age.[17]

Age-related changes also occur in rats; however, not all rats show the same degree of renal aging. Twenty-four-month-old Sprague Dawley (SD) rats have up to 60% sclerotic glomeruli and display extensive proteinuria, whereas Wistar/LOU or WAG/Rij rats show no age-related proteinuria, suggesting a genetically determined susceptibility in aging. All rat strains show vasoconstriction of both the afferent and the efferent arteriole with aging, and there was no correlation between glomerular hydrostatic pressures or glomerular volume and age-related changes.[18] A study of old and young SD strain rat kidneys found a significant decrease in both the glomerular and the peritubular capillary density in the aging kidney and a reduced endothelial proliferative response.[19] Impaired angiogenesis correlated with the loss of the pro-angiogenic growth factor and the vascular endothelial growth factor, and an increased expression of the anti-angiogenic factor Thrombospondin-119. These changes paralleled and correlated with the presence of glomerulosclerosis and interstitial fibrosis.

Relevance to Transplantation

Two issues have been identified with the use of older donor kidneys.

1. There is an increased incidence of acute interstitial rejection, compared with kidneys from younger donors.
2. Once a rejection episode occurs, the ability to mount a tissue repair process seems impaired.

Foreign tissue antigens tend to be ignored unless the tissue is injured, in which case it is more likely that they provoke and activate an immune response.[20] Grafts from older donors may already have age-related injury and inflammation at the time of procurement and transplantation, which in turn may increase immune recognition. Tissue injury, irrespective of the cause, elicits a stereotypic response, which increases the immunogenicity.[21] The increased immunogenicity may be explained by the presence of proinflammatory cytokines, increased expression of major histocompatibility complex antigens in epithelial and endothelial cells, or the recruitment and activation of antigen-presenting cells.[22-25]

One explanation for the increased loss of grafts from older donors that have experienced acute rejection episodes is that such kidneys have fewer adequately functioning nephrons and that the sum of the damage results in an earlier demise of the graft as compared to younger donor kidneys. It also has been proposed that graft parenchymal cells undergo premature senescence or aging as a result of multiple injuries and repair.[26,27] If progressive loss of renal mass, or senescence, is the mechanism of increased graft loss, then it is to be expected that grafts from older donors show a progressive decrease with time—and that the rate of decline of function correlates with donor age. However, Kasiske found no effect of donor age on the rate of decline in graft function between 1 year and last follow-up.[28]

Our data best fit the hypothesis that increased graft loss of older donor kidneys results from an increased incidence of acute rejection episodes in the early posttransplantation months along with a partly impaired ability to repair the tissue. Others have also found that older donor age, or the presence of 1 or more acute rejection episodes, is a factor associated with decreased death-censored graft survival.[29]

Conclusion

There is an increasing use of kidneys from older donors for transplantation. Such kidneys are more likely to develop delayed graft function and acute rejection episodes whereas they are less likely to mount a completely effective tissue repair response that would allow long-term function. This may be related to an impairment in angiogenesis and/or senescence. As impaired tissue restoration is probably one of the key elements responsible for increased graft loss, tissue injury related to delayed graft function and acute rejection should be avoided.

The "Old-for-Old" donor program, as implemented by Eurotransplant, allocates kidneys from older donors to older, local transplant candidates. This approach has the potential to decrease the likelihood of delayed graft function. However, in our study, delayed graft function and cold ischemia time were not independent risk factors for acute rejection in a multivariate analysis, including donor age.[5] Because older recipients are low immune responders,[30] the "Old-for-Old" program could decrease the likelihood of acute rejection episodes, but in our study this was found only with kidneys from younger donors, and there was no difference in acute rejection following transplantation of an older donor kidney.[5] It should be possible to improve the outcome of older donor kidneys in young recipients by providing more intense immunosuppression in the early postoperative period.

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