Age, the riddle of renal transplantation

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In the Western world there is a progressive increase in the number of patients with end-stage renal failure, which is largely due to an increase in patients over 65 years of age. As successful renal transplantation improves both longevity and quality of life compared with long-term dialysis treatment [1], more elderly patients are placed on the transplant waiting list. In the United States Renal Data System, the percentage of recipients of 55 years or older increased between 1988 and 1998 from 17.5 to 32.2% [2]. Also in the Eurotransplant countries, there has been a significant increase in recipients ≥50 or ≥65 years between the periods 1985–1989 and 2000–2004 from 33.1 to 53.2% and from 1.5 to 17.7%, respectively (Figure 1).

The magnitude of improved patient survival is not uniform across patient subgroups [1]. After the first year, including excess initial mortality associated with the transplant procedure, the projected increase in life span of patients aged 60–74 was ~4 years with...
a 61% decrease in their long-term risk of death. Also recipients over 65 years of age who received expanded criteria kidneys lived on average 3.8 years longer than their waiting-listed counterparts, despite lower graft outcomes [3].

**Should kidneys from older donors be transplanted preferentially into old recipients?**

Chronic allograft nephropathy and patient death are the two major causes of late graft loss after renal transplantation [4]. Older recipients are more likely to die with a functioning transplant than younger recipients, whereas death-censored graft failure, defined as a need for re-transplantation or maintenance dialysis, is less common in older recipients [5,6]. Nearly 50% of graft loss in older patients occurred due to death, vs 15% in younger patients [7]. In the elderly, cardiovascular and infectious causes are among the leading primary causes of death. Patients over 60 years of age have an increased risk of dying of an infection after transplantation, but were at a much lower risk of developing an acute rejection episode [8]. The survival of older kidneys was examined in >74,000 UNOS patients in relation to the recipient age [5]. Both recipient and donor age have important effects on graft survival, but the effects of donor age are much stronger than those of recipient age. Compared with recipients 18–29 years old, recipients of 55 years or older were 25% more likely to have uncensored graft failure over a median survival of almost 4 years. On the other hand, donor kidneys from donors of 55 or older were 78% more likely to have graft failure compared with kidneys from 18–29 year olds [5]. Giving older kidneys to older recipients does not appear to have a major effect on graft survival independent of the effects of recipient and donor age per se, as there did not appear to be any consistent interactions of specific recipient–donor combinations. There was no consistent pattern across all of the possible recipient–donor age combinations that would suggest that giving younger or older kidneys to younger or older recipients altered the risk of graft failure [5]. In a multivariate Cox proportional hazard analysis of kidneys from donors of 55 years of age or older, the risk of graft failure was not higher or lower for recipients of different ages. This is in accordance with the data from two single-centre studies that failed to find an independent effect of donor and recipient age differences on graft survival [6,9]. As was the case for graft survival, giving older kidneys to older recipients did not appear to have any major effects on patient survival, or death-censored graft survival, independent of the effects of recipient and donor age per se.

With ageing, the T-cell-dependent antibody response after vaccination, interleukin-2 (IL-2) synthesis, IL-2 receptor density on T lymphocytes, activator protein-1 and T-cell nuclear factor all decrease [10–12]. Many of these data, however, were not obtained in the most relevant age groups for renal transplantation. Although it is thus conceivable that the alterations in immune responsiveness with ageing have an effect on the risk of infection in the elderly, the magnitude of this effect on acute rejection appears to be rather small. In our experience, even with a dual immunosuppressive regimen, the difference in the incidence of acute rejection episodes in patients over 50 years old was modest and only found with kidneys from young donors [13]. No difference in acute rejection was noticed following transplantation of an older donor kidney in patients either over 50 or 60 years of age at the time of transplantation [13,14]. Recent data also indicate an independently increased risk of chronic renal allograft loss in the elderly [15].

Whereas donor age over 30 years was once a major reason cited for discarding cadaveric kidneys, more than half the kidneys transplanted in the USA in 1992 were from donors over 30, 18% were from donors over 50, and 5% were from donors over 60 years of age. Between 1988 and 1995, UNOS registered a 172% increase in the number of cadaveric donors of >50 years of age, which resulted in an increase of older donors from 12 to 25% [16]. In Eurotransplant, up to 48 and 14.4% of cadaveric transplants in the period 2000–2004 came from donors who were older than 49 or 64 years of age, respectively (Figure 2).

The most important reason to be reluctant to allocate kidneys from older deceased donors to younger (especially under 50 years old) recipients is the significantly increased risk of transplant failure [17]. At 5 years, there is already a 25% difference in graft survival rate between transplants from young and old donors, and the projected graft half-life decreased from 10.2 years if the donor was between 16 and 20 years of age to 5 years for grafts that came from donors over 50, and 5% were from donors over 60 years of age. Between 1988 and 1995, UNOS registered a 172% increase in the number of cadaveric donors of >50 years of age, which resulted in an increase of older donors from 12 to 25% [16]. In Eurotransplant, up to 48 and 14.4% of cadaveric transplants in the period 2000–2004 came from donors who were older than 49 or 64 years of age, respectively (Figure 2).

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allografts from living donors and deceased donors, in the incidence of both acute rejection and chronic allograft nephropathy [20–22]. One of the factors to explain why living donor transplants have a better graft survival than kidneys from deceased donors is that, by selection, living donors have a normal glomerular filtration rate and conditions that potentially damage renal function have been avoided. This is supported by the fact that approximately one-third of the participants in the Baltimore Longitudinal Study of Aging did not show any change in their calculated creatinine clearance over time [23]. This finding strongly suggests that, if renal dysfunction is found in the elderly, it may be due to an accumulation of injuries induced by minimal and clinically undetected renal disease rather than the consequence of the ageing process itself. On the other hand, ageing is a normal biological process characterized by atrophy and the gradual loss of functioning cells. Longitudinal studies of elderly individuals have shown with ageing a diminution in renal reserve, along with functional constraints on the kidney’s ability to respond appropriately to challenges of either excesses or deficits [24].

The poorer graft survival of older kidneys has been attributed in part to a greater susceptibility to ischaemia–reperfusion injury and delayed graft function, which in turn may make the allograft more susceptible to acute rejection and graft failure [25]. An analysis of 43,000 adult cadaveric transplants revealed a higher prevalence of delayed graft function and an increased need for post-operative dialysis treatments in recipients of old kidneys compared with patients who received a kidney from a young donor [18]. We have recently confirmed that donor age of more than 50 years, as well as a low recipient pre-transplantation blood pressure, a female donor kidney into a male recipient, the peak panel-reactive antibody status and a prolonged cold ischaemia period are independent risk factors for delayed graft function [26]. Delayed graft function had no independent effect on graft survival but was one of two independent risk factors for acute rejection episodes. In theory, one could improve the outcome of old donor kidneys by the prevention of delayed graft function or acute rejection.

According to a large multivariate analysis, 30% of the variability in long-term outcome could be explained by donor age [27]. Kidneys from old donors are more likely to experience acute rejection episodes [13,28–31]. In a previous study, it has been shown that acute vascular rejections have a negative impact on graft prognosis whereas acute interstitial rejection episodes have no impact [32]. As older kidneys experience an increase in interstitial-type acute rejection episodes that are associated with increased graft loss later on, this suggests an age-related limited ability of the tissue to repair after injury [13]. Consistent with this view is a study from Spain in which an increased graft loss was observed of kidneys from old donors, if such kidneys had experienced acute rejection episodes or delayed graft function [25]. In a time-dependent analysis of risk factors for graft loss, delayed graft function and acute rejection were identified as risk factors for graft loss in the first 5 years, but thereafter donor age seemed to be the most important factor [33]. Prophylactic treatment with anti-lymphocyte antibodies was administered to a substantial fraction of these patients [25,33] or only rejections requiring antibody therapy were considered [33].

It is conceivable that early and potent immunosuppressive therapy attenuates the interaction between ageing and renal changes, ischaemia–reperfusion injury and the immune response. Thus, there are suggestions that prophylactic treatment with anti-lymphocyte antibodies may decrease the increased incidence of acute rejection of older donor kidneys. UNOS data have suggested that the poor 5-year graft survival rate of kidneys from donors over age 60 is not improved with better human leukocyte antigen (HLA) matching [18], but the effect of matching for HLA class II antigens on acute rejection remains to be determined [34]. In a retrospective analysis of >1200 transplant recipients, the combination of a young recipient and a donor older than 55 years yielded the worst outcome at 8 years, with a graft survival of 24% [31]. Interestingly, the best outcome was observed if an older donor kidney was allocated to an elderly recipient. It was noted that, regardless of recipient age, graft loss due to rejection was higher with kidneys from older donors [31].

Conclusion

The ‘Eurotransplant Senior Program’ allocates kidneys from older (>65 years old) donors, without prospective matching for HLA antigens, to older (>65 years old) local transplant candidates, and the results look very promising [35]. This approach has the potential to decrease the likelihood of delayed graft function. It should be possible to improve the outcome of older donor kidneys in young recipients by providing more intensive immunosuppression in the early post-operative period. Such an approach may be acceptable for younger recipients, but remains to be determined for the elderly. The therapeutic index for clinical immune suppression appears to be even narrower in the elderly than in younger renal transplant recipients [15]. Medical care of the elderly transplant recipient is best served by a comprehensive (regular) pre-transplant evaluation of risk factors, matching for HLA class II and dedicated medical follow-up after the transplantation [36]. The important perspective remains that a successful transplantation with either a regular or marginal donor kidney is associated with dramatic and substantial improvement of quality of life. The 5-year follow-up data of the Eurotransplant Senior Program are expected next autumn and are eagerly awaited [35,37].

Conflict of interest statement. None declared.
References
