Invited Comment

Age and renal transplantation: an interim analysis

Gabriele Schratzberger and Gert Mayer

University Hospital, Department of Internal Medicine, Division of Nephrology, Innsbruck, Austria

Keywords: age; donor; kidney; recipient; renal transplantation

Introduction

The life expectancy of the population in general is increasing consistently, as is the age of the dialysis population. Consequently, donors and recipients are getting older, and renal transplantation has become a therapy that is not limited to the youngest segment of subjects with terminal renal failure. Reluctance to use organs from elderly subjects has decreased with increasing demand (and possibly with increasing age of transplant physicians), and age-matching programmes have been developed to better serve the dialysis population. The medical aspects of this changing attitude continue to be explored. However, the answers obtained may be the starting point for a discussion of oncoming ethical problems.

Effect of donor age on outcome (Figure 1)

In the period from 1977 to 1982, a donor age > 30 years was a major reason for declining a cadaver kidney allograft offer [11]. While 15% of kidneys retrieved from 16–20-year-old donors were not transplanted, the discard rate was 30 and 56% for donors aged 31–40 or 51–60 years, respectively. Donors older than 60 years were so rare that they were not even mentioned. Since then the demand for organs has increased and the criteria for organ acceptance have changed dramatically. Only 5 years later, more than half of the kidneys transplanted in the United States were from donors over the age of 50, in 5% the donor age was even over 60 years [12] and the discard rate had decreased to 25% in the latter group [13]. In the Eurotransplant registry the number of patients receiving a transplant from a donor > 65 years increased from 195 in 1997 to 285 in 1998 and 345 in 1999 [14].

All these developments took place despite publications dating back to 1974 [15] documenting clear evidence of an inferior outcome of grafts from elderly donors. In the early postoperative period an increased rate of primary non-function and delayed graft function was reported, both of which are well-known risk factors for allograft survival in general [16,17]. The impact on long-term outcome, however, was even more dramatic. In 1994 Alexander and co-workers [13] reported the 2-year transplant survival with regard to donor age in more than 30 000 transplantations performed between 1987 and 1991. When adjusted for various covariates (number of previous transplantations, donor and recipient race, presence of diabetes mellitus, percentage of panel-reactive antibodies (PRA), cold ischaemia time and HLA mismatch), the lowest risk for graft failure at 1 year was seen in kidneys obtained from donors aged 16–45 years. With each decade of increase in donor age the relative risk rose by 15–20%. The magnitude of this effect, however, increased exponentially with time, reaching an odds ratio for failure after 2 years of 3.25 in donors older than 70 years, as compared to a group of 30-year-old donors. Terasaki et al. [18] reported a higher prevalence of delayed graft function, an increased need for post-operative dialysis and a higher serum creatinine at discharge in recipients from older donor kidneys. The projected transplant half-life decreased from 10.2 years if the donor was 16–20 years old to 5 years for grafts retrieved from donors who were 60 years of age. An especially prominent effect of donor age on long-term outcome was also described by Gjertson in 1996 [19]: in grafts surviving the first post-operative year, donor age accounted for 30% of the variability in outcome; the effect at 1 year was also significant but at 4.1% much less striking. In an analysis by Nickerson et al. [20] the adjusted odds ratio for an increase in serum creatinine of more than 20 mmol/l between 6 and 24 months post-transplantation was 1.09 for every year increase in donor age. Even in living donation, some [21] but not all [22] authors have argued that donor age determines long-term outcome.

In summary, donor age has turned out to be the most powerful predictor of long-term renal allograft
function. Histopathological studies reveal a 20–25% loss of volume particularly in the cortex, fibrous intimal thickening of arteries, loss of glomeruli due to global sclerosis with enlargement of the remaining glomeruli, patchy tubular atrophy and interstitial fibrosis [23] in ageing kidneys. Kumar et al. [24] performed pre-transplant biopsies of kidneys from donors older than 55 years. Age-associated glomerulosclerosis was present in 85%, patchy interstitial fibrosis in 64%, thickening of the arteriolar wall and mesangium in 47%, chronic inflammatory cells in the interstitium in 29% and cystic changes in 6% of the kidneys. Unfortunately, however, until now we have been unable to correlate age-associated changes in pre-transplant biopsies with post-operative function, and in general it must be noted that the association between function and donor age in individual cases is very weak. This is not completely surprising. The

Fig. 1. Influence of donor age on graft survival. Several studies from 1991 to 1999 [4,5,9,11,16,30–33] were combined in this dot blot, picturing the size of the study cohort and the actuarial (not censored for death) allograft survival separated into two groups. The first group (shaded dots) shows the distribution of graft survival from donors younger than 60 years within the first 5 years after transplantation. The second group (solid dots) shows the corresponding pattern in donors over the age of 60 at the time of transplantation.

Fig. 2. Influence of recipient age on graft survival. Several studies from 1991 to 2002 [1–10] were combined in this dot blot, showing the size of the study cohort and the actuarial (not censored for death) allograft survival separated into two groups. The first group (shaded dots) shows the distribution of graft survival in recipients younger than 60 years within the first 5 years after transplantation. The second group (solid dots) shows the corresponding pattern in recipients over the age of 60 at the time of transplantation.
Baltimore Longitudinal Study of Aging showed that one-third of the participants did not show any change in glomerular filtration rate (GFR) over time [25]. Epstein concluded that the common denominator for the functional changes occurring with ageing is more a diminution in the kidney’s ability to respond appropriately to the challenges of either deficits or excesses. These alterations attain clinical significance only when renal function is challenged by superposition of comorbid conditions like hypertension or heart failure [26–28]. Not surprisingly therefore, the medical history of the donor provides information about the expected post-transplant course independent of donor age. Kidneys from patients dying of cardiovascular events or stroke fail more often than do organs from donors dying of subarachnoid haemorrhage [29]. What the transplant community would need is therefore a marker for organ damage. Clearly, damage, in general, is more likely to occur in elderly grafts although donor birth age alone is not a very specific indicator.

Effect of recipient age on outcome (Figure 2)

In general, advanced recipient age is no longer a contra-indication for renal transplantation. In a report from the EDTA-ERA registry the number of transplantations performed in patients older than 60 years increased from 2.9% in 1983 to 9.9% in 1992 [7]; in 1999, 12.5% of all transplantations reported to the Eurotransplant registry were performed in recipients older than 65 years [14]. Clearly, graft loss due to death is more common in the elderly, occurring at a rate of 1.1/100 patient years in recipients aged 18–49 and at 4.1/100 patient years in recipients older than 65 years [34]. Moreover, after living donation, patient survival at 5 years is 93% in recipients <60 years, but only 72% in recipients >60 years. On the contrary, death-censored graft survival seems to be better in elderly recipients. In a study by Roodnat et al. [35] the overall relative risk for allograft failure increased by only 1.44% for each year of recipient age, even though patient survival decreased by 5% per year. Tesi et al. [6] reported a 5-year patient survival rate of 68.1% in elderly but 89.1% in younger recipients. Death-censored graft survival, on the contrary, was 11% better in the older group, so that crude graft survival was almost identical. In a large analysis by Gjertson [19], 1-year graft survival was 84.2% in recipients older than 65 years and 87.3% in the age group 43–65 years. Uncensored 5-year graft survival was 69.4 and 72.5%, respectively. These differences, although statistically significant, are quite small in absolute terms, and age accounted for only 2.1% of the variance in 5-year graft outcome. Recent data, however, indicate that elderly recipients might be more prone to developing chronic allograft nephropathy. Using data from the USRDS, Meier-Kriesche et al. [34] demonstrated that 8-year death-censored graft survival is significantly decreased in the older age groups, being 67% for ages 18–49 years vs 62% for ages 50–64 and 51% for ages >65 years. In multivariate analysis, recipient age was a strong and independent risk factor for chronic allograft failure in Caucasians. These findings were reinforced by an analysis that was restricted to living donor transplants without rejection. It has been argued that age-related factors, like increased concentrations of transforming growth factor β or lipoproteins in the serum, might contribute to accelerated senescence [34,36,37].

Even though the effect of recipient age on short- and mid-term transplant outcome does not seem dramatic, it remains a matter of discussion whether this is also true for ‘very old’ recipients. At least some [38], but not all [39], authors have concluded that the effect of age on the risk of graft failure is best described as an exponential rather than a linear function, and most outcome studies have used age as a categorical rather than a continuous variable. Nonetheless, even in the ‘very old’, transplantation can be a valuable option in informed subjects, especially if a living donor is available, thus overcoming the argument of ‘organ wasting’. However, identification of high-risk patients is mandatory. Doyle et al. [8] conducted a retrospective single-centre study to determine graft and patient survival in first-time kidney transplant recipients aged 60 years or more in order to identify pre-transplant risk factors to predict clinical outcome: graft survival at 1 and 5 years was 86 and 60%, respectively, and patient survival was 90 and 68%, respectively, both being decreased when compared to recipients aged 18–59. Specific age-related risk factors identified were non-skin malignancy (increase in risk 5-fold), vascular (but not coronary artery) disease (2.2-fold) and a current history of smoking (7.9-fold increase, but no more increased risk if smoking had stopped within 2 months prior to transplantation). Furthermore, in recipients older than 70 years the risk was 2.7-fold higher than in subjects between the ages of 60 and 64. However, when patients with the above-mentioned risk factors were excluded, both patient and graft survival were equivalent to those in younger subjects [8]. In addition, cardiovascular disease, infections and malignancies play an increasing role with age [40] not as mortality in general; the risk of severe infection appears to increase exponentially in elderly recipients (as opposed to linearly in patients on the waiting list) [39] and is at least partially dependent on the intensity of immunosuppression [41]. Even though the risk of malignancy also increases exponentially rather than linearly, the almost 50% decrease in cardiovascular risk more than offsets the potential danger [39,42] as transplantation increases the life expectancy of the elderly with end-stage renal disease, as compared to that of patients on dialysis, even if only subjects on the waiting list are used as a control group [39]. In patients older than 60 years, the annual death rate on the waiting list was 10%, but decreased to 7.4% in transplant recipients. The absolute benefit was thus even greater than that observed in the age group 20–39 years, even though in these, more projected life years could be gained by transplantation (17 vs 4 years) [43].
Age matching in renal transplantation

In 1991, Donnelly et al. [44] published the results of 141 consecutive first cadaveric transplants and noted that graft failure at 2 years was significantly greater when the donor was more than 5 years older than the recipient. Subsequent studies were unable to replicate these findings, but the number of patients involved was quite low [45,46]. Alexander et al. [13] reported lower allograft survival of elderly kidneys when transplanted into elderly recipients, but the impact of donor age and recipient age on the risk of graft failure was independent. In 1995, Cecka and Terasaki [4] repeated the analysis of the UNOS registry data and identified 1740 kidneys from donors over the age of 60 years among 45,922 cadaver transplantations performed between October 1987 and March 1994. Actuarial graft survival (not censored for patient death) was significantly worse at 1 and especially at 10 years in these kidneys, as compared to donors aged 19–30 years (70 vs 84% at 1 year and 20 vs 45% at 10 years). Data censored for patient death, however, revealed the best survival of elderly kidneys in elderly recipients (1-year graft survival 78%, projected 10-year graft survival 43% as compared to 70% at 1 year and 22% projected 10-year graft survival in recipients aged 19 and 45 years). Moreover, at 1 year, serum creatinine tended to be lower in age-matched elderly grafts. Waiser et al. [47] reported that functional allograft survival (censored for patient death) was 22.5% when a kidney from an elderly donor (age limit 55 years) was transplanted into a young recipient, but 68.7% when it was given to an older recipient. When death with functioning graft was not censored, the corresponding survival rates were 53.3 vs 57.1%.

Basically, these results state that age-matching might be beneficial for elderly kidneys. The parallel increasing demand for kidneys for elderly patients with terminal renal failure prompted the initiation of a controlled trial, the Eurotransplant Senior Program (ESP), with the prime aim of achieving more efficient use of kidneys from donors over 65 years of age and reducing the waiting time for elderly patients by allocating kidneys mainly driven by age matching, disregarding the effects of HLA compatibility and looking for short cold-ischaemia times. To guarantee an acceptable degree of success the programme included only first-time transplant recipients with a panel reactivity of less than 5%. Patients of any age, who received organs from donors older than 65 years that were allocated by the regular allocation programme ETKAS (Eurotransplant Kidney Allocation System), served as controls. Median cold-ischaemia time was shorter in the ESP programme (12 vs 19 h), while the number of HLA mismatches was significantly higher (4 vs 2). Institution of ESP in participating centres doubled the number of organs harvested from donors >65 years, and the discard rate dropped from 22 to 13%. Median waiting time for recipients older than 65 years decreased within a year from 943 to 707 days, and the number of patients on the waiting list also decreased significantly from 905 to 872. There was no difference between the study groups with regard to initial transplant function or graft function at 1 year (censored and not-censored for patient death). Patient survival rate at 1 year was 86% in the ESP cohort; 18 of the 24 deaths reported occurred with a functioning graft. It is interesting to note that the rejection rate observed in each group was quite high (38% in the ESP group and 30% in the control group), even though 43% of the patients in the ESP programme received monoclonal induction and 47% triple immunosuppressive therapy [14]. This result, in particular in the age-matching group, is somewhat surprising as it is generally accepted that immune responsiveness steadily decreases as the age of the recipient increases. This is reflected by a lower percentage of sensitized (>10% HLA PRA) patients, being 46% at age 6–18 vs 30% at age >60 years, a reportedly lower number of rejections at discharge (24 vs 14%) and fewer failures due to rejection in recipients older than 60 years as compared to recipients in the age group between 6 and 18 years (27 vs 48%) [48]. However, the difference is much less impressive when subjects >60 years are compared to the age group between 46 and 60 years.

Is there something special about immunology in elderly grafts/recipient?

In 1995, Cecka et al. noted that kidneys from donors older than 60 years had a bad outcome particularly in immunized recipients (>10% HLA antibodies). One-year graft survival was 60% compared to 80% when the donor age was 19–30 years. In the case of a rejection episode during initial hospitalization, 53% of all elderly grafts functioned at 1 year as compared to 71% of the organs from younger donors. One explanation for these results is a diminished functional reserve of elderly organs, producing a more pronounced detrimental effect in structural damage. It is widely accepted that the immune system, and thus the immune response, become impaired with age [49]. Many studies have demonstrated that functional and phenotypic changes occur in T lymphocytes with age, while the production of cytokines in response to T-cell activation is altered and changes in macrophage activity may be partially responsible for cellular and humoral immunodeficiency in the elderly. Consequently, the incidence and severity of acute rejections in the elderly should be lower than in younger recipients, again providing an argument to support the concept of age matching in renal transplantation. However, it remains to be determined whether this impression is substantiated by all data. In a study by Palomar et al. [10], rejection episodes of 0.44 and 0.41 per patient were recorded in recipients below and above the age of 60, respectively. Additionally, grading of the severity of rejection according to the Banff criteria revealed no significant difference between the two groups. de Fijter and co-workers [50] studied...
death-censored allograft survival in 514 transplant recipients using cyclosporin A-based (mostly double) immunosuppression. Even though the overall incidence of rejection within the first 6 post-operative months was high (57.5%), 1- and 5-year graft survival were excellent (91.8 and 83.6%, respectively). Multivariate analysis revealed donor age (> or < 50 years), a history of acute rejection and the histological pattern of rejection as significant parameters determining graft survival. Most interestingly, however, the cumulative incidence of acute rejection episodes was much higher (68%) in patients who had received a graft from a donor older than 50 years as compared to that observed in recipients of kidneys from younger donors (53%), almost all of the difference being accounted for by interstitial rejection (Banff grade 1). The higher incidence of acute rejection episodes in older donor kidneys was seen in both younger and elderly recipients (53.9 vs 66.7% in younger and 46.7 vs 64.4% in older recipients) [50]. When the authors analysed the impact of advanced donor age on graft survival, a significantly increased rate of graft loss of kidneys from older donors was observed only in the group of patients who had experienced acute rejection episodes. The adverse outcome in this group of patients occurred in the first 5 post-transplantation years, whereas no significant difference was seen beyond 5 years. In another study, graft survival at 1 year was 73% when the donor was older than 60 years and 84% in younger donor kidneys [9], and the group of patients receiving kidneys from elderly donors had a rejection rate of 30% as compared to 24% in the group of younger donors. Additional data were provided by Waiser et al. [47], who retrospectively studied more than 1200 transplant recipients with regard to donor and recipient age. The combination of a young recipient and a donor older than 55 years yielded the worst outcome at 8 years (graft survival 24.5%). Interestingly, the best outcome was observed when an elderly graft was put into an elderly recipient (69% death-censored and 57% overall graft survival). Notably, however, regardless of recipient age, graft loss due to rejection was higher in elderly donor organs [47]. The principal finding of all these studies is that kidneys from older donors are more likely to undergo acute (interstitial?) rejection episodes in the early post-transplantation period as compared to kidneys from younger donors. This increased frequency is not related to factors such as recipient age or delayed graft function. If confirmed, these results would spawn new ideas (and problems) on the issue of age and renal transplantation. Currently a popular view on the pathogenesis of chronic allograft nephropathy, which is seen more often in elderly donor grafts, is the concept of a reduced nephron number transplanted [51]. Accordingly, as shown by several other authors, the effect of donor age on outcome becomes increasingly prominent with time after transplantation [13]. However, this observation was not confirmed in the study by de Fijter et al. [50]. Another explanation could thus be that increased graft loss of older donor kidneys results from (sometimes even clinically silent) rejection in the early post-transplantation months; also in line with these observations is the finding that in living donor transplants only the occurrence of an acute rejection episode and not donor age per se is independently associated with decreased graft survival [52]. Antigens expressed in injured tissue are more likely to cause an immune response than are those in a healthy environment. An increased immunogenicity in elderly grafts may be explained by an increased age-related presence of pro-inflammatory cytokines, increased expression of HLA in epithelial and endothelial cells, and the recruitment of antigen-presenting cells. If indeed kidneys from elderly donors are more immunogenic and therefore require more intense immunosuppression, this would be true irrespective of the age of the recipient. Such an approach may be acceptable for younger recipients, but it remains to be determined whether this is also true for elderly patients.

**Conflict of interest statement.** None declared.

**References**
