Kidney transplantation in the elderly—the Norwegian experience

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Abstract

Background. Elderly patients are the fastest growing population requiring renal replacement therapy. With increasing scarcity of organs, old patients are likely to remain in dialysis. We have had an active transplant program with elderly patients (i.e. ≥70 years) and present results from our experiences.

Methods. From 1990 throughout 2005, we performed 301 first kidney transplantations in elderly patients. Data were compared with 513 senior patients aged 60–69 years and 512 control patients, aged 45–54 years, transplanted during the same time period. Time in dialysis prior to transplantation, number of patients receiving a living donor (LD) kidney, donor age, HLA mismatch, rejections, patient- and graft survival data were collected.

Results. The 5-year actuarial patient survival was 56% in elderly patients, 72% in senior patients; P < 0.001 versus elderly and 91% in control patients; P < 0.001 versus elderly. Death censored graft survival was similar in the different groups, 89% in elderly, 88% in senior and 90% in control patients. LD was used in 35%; 17% in elderly patients, 34% in senior patients; P < 0.001 and 47% in control patients; P < 0.001. Pre-emptive transplantation was performed in 19% of the patients; 10% in elderly patients, 18% in senior patients; P = 0.003 and 25% in control patients; P < 0.001.

Conclusions. Our data show no difference in death censored graft survival between the age groups. Given the poor prognosis during dialysis treatment, selected elderly patients may successfully be offered a kidney transplant.

Keywords: elderly patients; graft survival; kidney transplantation; patient survival; rejection

Introduction

Elderly patients are by far the fastest growing population requiring renal replacement therapy both in Europe and the United States [1,2]. Kidney transplantation is generally accepted as the best treatment option for patients with end-stage renal disease (ESRD) [3,4]. Evidence has accumulated that elderly patients often benefit from kidney transplantation despite limited life expectancy [4–11]. Thus transplantation may be a treatment option even at high age. Most reports of transplantation in elderly patients comprise patients older than 60 or 65 years. By contrast, experience with transplantation in patients above 70 years of age is very limited in the literature and the largest studies are based on registry data from multiple centres reflecting various transplantation protocols.

Due to a relatively low incidence of ESRD and a high LD transplant rate for decades, the Norwegian waiting list for kidney transplantation has until recently been kept relatively constant below 50/mill inhabitants. We have accepted patients for kidney transplantation following an individual medical evaluation without a formal upper age limit. More than 10 years ago, we reported that transplantation was feasible even in patients beyond 70 years of age [5]. Living donors are also accepted and particular spousal donors are becoming increasingly more common in this age group. Rikshospitalet is the only transplantation centre in Norway serving approximately 4.7 million inhabitants. With one large centre and a liberal policy with transplantation in old patients, our material is to our knowledge the largest single centre material on kidney transplantation of old patients.

The rising number of patients developing ESRD being put on the transplant waiting list has, in our country, led to discussion of selection criteria for transplantation. A common question is whether high age per se should be a contraindication for acceptance for transplantation. This study was designed to investigate whether kidney transplantation appears to be a sound treatment option for elderly patients (≥70 years of age), or whether it is appropriate to set an upper age limit for transplantation.
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Fig. 1. The proportions of senior and elderly kidney recipients have increased markedly during the last 15 years.

Subjects and methods

Patients and study design

Data of all patients who received their first kidney transplant at Rikshospitalet from 1990 throughout 2005, with follow-up data until 1st of June 2007, were retrieved from the Norwegian Renal Registry and selected by age criteria. The patients were divided into three groups according to their age at transplantation. The elderly recipients ≥70 years were compared with a group of senior recipients of 60–69 years of age and with a control group consisting of adult recipients of median age, e.g. between 45 and 54 years. Three hundred and one patients were in the elderly group, 513 were senior and 512 were controls. The proportion of elderly recipients increased over time. In the first 5-year period, 8.9% of all recipients were older than 70 years at the time of transplantation, 2.1% older than 75, while the proportions in 2005 were 15.0% and 4.8%, respectively (Figure 1).

Patients and donors were HLA-typed by serology, confirmed by genomic typing when needed, and matching was performed using ‘broad’ specificities. Patients were regularly screened for HLA-antibodies by microlymphocytotoxic technique against T cells. If latest serum was positive against more than 5% of panel, patients were termed PRA positive. Recipient selection was primarily based on matching for HLA-DR, secondarily on waiting time. Age-matching was applied to some extent; mainly to avoid extreme differences.

Multi-organ recipients were excluded from the analysis. All retrievable data relevant for graft and patient survival were obtained from the Norwegian Renal Registry. Causes of death and graft loss were also retrieved. Standard immunosuppressive therapy has been relatively constant during the years of the study. From 1990 to 1999 most patients received triple immunosuppression with ciclosporin (CsA), azathioprine and steroids. In 2000, the patients received intravenous basiliximab, CsA and steroids, whereas the patients transplanted from 2001 throughout 2005 received CsA, mycophenolate mofetil (MMF) and steroids.

Statistics

Two-sided unpaired t-test or Mann–Whitney test was used as appropriate to compare groups. χ²-test or Fisher’s exact test was used to analyse categorical data. Survival data were assessed with the Kaplan–Meier method and Cox regression analysis (univariate and forward stepwise regression), unless otherwise stated counting death with functioning graft as graft failure. Patient survival was defined as time from transplantation to death or end of study. The analysis was implemented using SPSS® 15.0.

Results

Recipient and donor characteristics

Pre-emptive and LD transplantations were less frequent in the elderly and senior groups. The elderly and senior patients also had a longer pre-transplant dialysis history than the control group. Mean donor age was significantly higher in the elderly group (52.6 years versus 49.6 years in the senior group; \( P < 0.01 \) and 45.8 years in the control group; \( P < 0.001 \)). There was no difference between the groups regarding donor sex or donor cytomegalovirus (CMV) serostatus. Recipient and donor characteristics are summarized in Table 1.

<table>
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<th>Table 1. Recipient and donor characteristics at transplantation</th>
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<td>Median age in years (quartile range)</td>
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<td>Pre-emptive transplantation (%)</td>
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<td>Living donor (%)</td>
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<td>Median pre-transplant dialysis in months (range)</td>
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<td>HLA-A mismatch (mean)</td>
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<td>HLA-B mismatch (mean)</td>
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<td>HLA-DR mismatch (mean)</td>
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<td>HLA DR 0-mismatch (%)</td>
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\( ^{1}P < 0.0167, \^{11}P < 0.005, \^{111}P < 0.001 \).

\( P \)-values indicate comparison with elderly.

Due to comparison of three groups Bonferroni correction is used to get an overall level of significance of 0.05.
Rejection and graft function

The elderly group showed significant lower frequency of acute rejections the first 12 weeks post transplantation compared to the two other groups (elderly = 35%, senior = 44%; \( P = 0.005 \), control = 45%; \( P = 0.002 \)). Figure 2 shows a Kaplan–Meyer plot of rejections the first 12 weeks. In spite of the difference in rejection frequency, there was no difference between the groups with respect to s-creatinine levels during follow-up. Comparison of creatinine values are shown in Table 2. Conversion to eGFR by the modified MDRD formula did not show any difference between the groups (data not shown).

Patient survival

Elderly and senior patients had a higher incidence of death with functioning graft during follow-up (elderly = 45%, senior = 31%; \( P < 0.001 \), control = 13%; \( P < 0.001 \)). Five-year actuarial patient survival was 56% in the elderly group, 72% in the senior group; \( P < 0.001 \) and 91% in the control group; \( P < 0.001 \). Patient survival plot comparing the age groups is shown in Figure 3. In the elderly group, there was no significant difference in survival between the subgroup 70–74 years of age (\( n = 199 \)) and the subgroup \( \geq 75 \) years of age (\( n = 102 \)). Three months patient survival was 92% in the elderly, compared to 95% (ns) in senior and 99% (\( P < 0.001 \)) in the control group.

The following variables for patient survival were analysed in a multivariate Cox regression model (forward stepwise): age of recipient and donor, sex of recipient and donor, living donor versus deceased donor, number of HLA mismatch (tested separately for HLA-A, -B and -DR), mode of dialysis, time in dialysis, PRA positivity, CMV positive donor and CMV positive recipient. The results of the Cox regression analysis are presented in Table 3.

Graft survival

Five-year graft survival was 53%, 70% and 84% in the elderly, senior and control groups, respectively. The inferior graft survival in the elderly patients reflects a natural higher risk of death with functioning graft with higher age. There was no difference in five-year survival censored for death with functioning graft between the groups; 89% in elderly, 88% in senior; ns and 90% in control; ns. Graft survival censored for death with functioning graft is shown in Figure 4.
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Fig. 4. Kaplan–Meyer survival plot illustrating no difference in death censored graft survival.

Figure 4. Three-month graft survival was 89% in elderly, 92%; ns in senior and 96%; P < 0.001 in controls.

Causes of death and graft loss

Four hundred and sixty-six of the patients died, with or without a functioning graft, during the observation time (158 deaths in the elderly, 208 in senior and 100 in control). Cardiovascular disease (CVD) (31% of deaths in the total material) and infection (23% of deaths in the total material) were the leading reasons of deaths and the highest incidence was found in the elderly group where 34% of deaths were caused by CVD and 27% by infection. The reasons for graft loss were death with functioning graft (elderly = 81%, senior = 72%; P < 0.05, control = 48%; P < 0.001), rejection (elderly = 9%, senior = 22%; P = 0.001, control = 39%; P < 0.001), primary non-function (elderly = 4%, senior = 2%; ns, control = 3%; ns) and vascular thrombosis (elderly = 1%, senior = 0%; ns, control = 4%; ns).

Discussion

To our knowledge, this study is the largest single centre study addressing long-term outcome of kidney transplantation in patients of old age although many reports have addressed the issue. In the United States (1994–2000), only 0.3% of the kidney recipients were older than 75 years at the time of transplantation and 6.4% aged between 60 and 75 years [2], compared to 4.1% ≥75 and 17.5% between 60 and 75 years of age at our centre. Our data reflect a very liberal policy regarding age and transplantation in Norway and historically few problems with organ shortage.

Graft survival was similar in the three different age groups when censored for death with functioning graft. A good graft outcome in old recipients is consistent with the findings of several other authors [2,8,12,13]. Obviously the mortality is increased in the higher age groups. The question is to address a possible survival benefit in old recipients. A comparison of survival in dialysis patients and transplant recipients from our centre [6] showed a 62% survival in transplant patients over 60 years versus 13% in dialysis patients after 4 years. A better survival in transplanted patients was published from the USRDS, on average 60% after 5 years in recipients over 75 years of age receiving live donors and 40% in recipients of deceased donors [2]. Likewise, Munshi et al. [14] described a 5-year survival rate among dialysis patients 65–74 years old of less than 20%. In a Dutch study of 122 dialysis patients aged more than 65 years the 5-year survival rate was 27% [15]. The 2005 ERA-EDTA Registry report quotes a 5-year survival of 34% in incident dialysis patients 65–74 years of age [16]. However, any such comparisons between populations are obviously biased by selection of healthier patients being referred for transplantation. With no possibility for randomisation, the best comparisons so far have been performed between dialysis patients remaining on the waiting list for transplantation and those who actually receives a transplant. In patients ≥75 years who were wait-listed for transplantation but not transplanted the USRDS data showed a 5-year survival rate of 29.7%. Data from the USRDS registry have also shown a survival advantage for elderly patients (60–75 years) 1 year after transplantation compared to those remaining on dialysis [4]. Also in Europe a survival advantage has been found for elderly (>60 years) recipients when compared with wait-listed patients remaining on dialysis [9]. The patients remaining on dialysis had a death rate twice as high as transplant recipients; life expectancy was 8 years after transplantation versus 4 years in the dialysis group. Recently, Rao et al. [10] published data indicating that the survival of transplanted patients ≥70 years of age is superior to patients on the waiting list 1.8 years post-transplantation. When discussing high age a comparison of survival versus the normal age matched background population is of some interest. In the Norwegian population, life expectancy of a 70-year-old person is 12.2 years (male) and 15.5 years (female) (data from the Norwegian statistical bureau). The expected lifetime for patients in the age group 70–74 years is 3.8 years for dialysis patients and 6.7 years for transplanted patients according to ERA-EDTA Registry 2005. In our opinion, a 5-year survival rate of more than 50% in patients transplanted beyond 70 years of age is certainly acceptable compared to the prognosis of elderly patients in dialysis. In addition, transplanted patients generally have far better quality of life than dialysis patients. Our data show almost the same survival rates as earlier reports, despite better medical therapeutic alternatives. This could be a result of a more liberal policy accepting old patients with increasing co-morbidity during the last 10 years.

The elderly and senior patients have an increased 3 months mortality compared to the control group. This reflects a higher risk from surgery as expected with higher age. To minimize this risk, it is important to perform individualized and careful pre-transplant evaluation of co-morbidity. With severe co-morbidity one should consider life-long dialysis, particularly since the survival in dialysis has improved during the last decade according to the 2005 ERA-EDTA Registry report.

From the Cox regression analysis, it seems likely that immunological factors are less important for patient survival in the oldest population. Neither HLA mismatch nor PRA positivity meant significant hazard in the elderly group. On the other hand, DR mismatch is a significant risk factor in the senior group and in the total material, and PRA positivity is significant in the control group. The proportion...
of PRA positive recipients is low in all three groups. Interestingly, haemodialysis prior to transplantation turns out as a significant risk factor compared to peritoneal dialysis and pre-emptive transplantation in the control group. However, less than 20% of dialysis patients were treated in PD, and this result should be interpreted with caution. The most important ‘correctable’ risk factors in the elderly and senior groups seem to be time in dialysis and donor age. These findings need further investigation though it seems reasonably to believe that reducing time in dialysis prior to transplantation will improve the results of transplantation in patients ≥ 60 years of age.

Elderly patients have a significant lower incidence of LD transplantation. This reflects a smaller pool of possible suitable donors because of higher age. It could be an ethical dilemma to expose a young donor to the surgical risk and possible long-term risks of living with one kidney, especially when the recipient may have limited survival because of old age or extra-renal co-morbidity. In addition the use of elderly donors raises ethical questions about exposing a healthy elderly relative to the short time risk of nephrectomy when the outcome of the recipient is dubious due to high risk. On the other hand, Kandaswamy et al. [17] found that kidney recipients with extra-renal co-morbidity did benefit from an LD transplant, in fact they had more pronounced benefit of LD than patients without extra-renal co-morbidity. Our experience using both young and elderly LDs over many years is that it is safe both with respect to short-term and long-term risks [18]. Increased use of spousal donors could be a way to raise the number of LD in the oldest patients.

Performing transplantations in elderly recipients also raises another ethical question. Is it justifiable to allocate a kidney from a deceased donor to an old recipient? This will reduce the availability of a deceased donor to younger recipients on the waiting list. One should be careful to generalize our results to other transplant centres with much longer waiting lists. Our experience does, however, indicate that selected elderly recipients perform well after kidney transplantation. In this context with adequate organ supply we believe this practice is ethically sound.

As other authors have previously shown [7,8,19,20], the oldest cohort has a lower rejection rate. There was no difference in prevalence of HLA antibodies between the groups, but the elderly group had better HLA–DR match compared to the other groups. This finding is related to our procedures for recipient selection. Selecting a recipient with no DR mismatch has the highest priority ahead of time on waiting list and a general judgement. In most cases, a younger recipient will be preferred ahead of an older one if the candidates have equal mismatch and equal time on waiting list. As a consequence the oldest recipients will be expected to have better DR matching. When the analysis were made within each HLA–DR match group there still existed a trend towards lower rejection rate in the elderly group, but the difference was not significant.

In a recently published editorial review, Arns et al. [21] conclude that ‘old for old’ renal transplantation is an effective approach to expand the donor pool while maximizing graft survival in older recipients. The Eurotransplant Senior Program showed that long-term patient and graft survival were comparable between elderly patients receiving an organ via the ESP program and patients who received the organ via the ordinary Eurotransplant algorithm [22]. By using this strategy, the ethical dilemma of allocating an organ to an old recipient instead of a younger one could be minimized as many of the organs given to the elderly would not have been accepted for a younger recipient.

All patients placed on the Norwegian transplantation list have met the same criteria for acceptance, regardless of age. Patients > 40 years of age are screened for vascular and coronary heart disease. For all patients with a history of diabetes, regardless of age, coronary angiography is mandatory. If necessary, CABG/PCI or vascular surgery is performed before the patient is accepted for transplantation. In addition, all patients are screened for malignancy, haematological, pulmonary and gastro-intestinal disease following EDTA guidelines. As a consequence, the patients listed for transplantation are a selected group of the healthiest ESRD patients. This positive selection is important to take into account when our results are interpreted. In the absence of European survival data of elderly dialysis patients listed for transplantation, our results indicate that age per se should not be a contraindication to kidney transplantation as long as the patient fulfils the established selection criteria. To address this further we are currently initiating a study to compare the survival of elderly patients starting dialysis with those who receive a transplant.

**Conclusion**

Our data show no difference in graft survival between the elderly, senior and control patients when censored for death with functioning graft. As expected, elderly and old recipients have inferior survival compared to the control group. Knowing the poor prognosis of these patients in dialysis we consider our 5-year patient survival rate of 55% in the elderly group as acceptable. The acceptable results depend upon several factors, including a pre-transplant screening used to identify the elderly patients most likely to benefit from kidney transplantation. The local availability of donor organs must also be considered, but in our opinion age per se should not be a limiting factor. Our findings are especially important in the face of the growing number of elderly patients with ESRD evaluated for kidney transplantation.

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