

Renal transplantation in patients over 60 year old

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Background. There are controversial reports concerning the impact of age – related immune responses in renal transplant recipients. It has been suggested that, older age relates with lower acute and chronic rejection rate, reduced patient and graft survival and less aggressive immunosuppressive therapy is required. More recent reports refer increased recipient age as an independent risk factor for the development of chronic rejection and a higher incidence of acute rejection episodes. **The purpose** of this study was to present the experience of our centre with this particular group of patients, clarify their behavior after transplantation, and discuss possible treatment modalities.

Material. The period 1st Jan 1987 – 31st Dec 2003, among 801 kidney transplants, there were 23 recipients with age > 60 years at time of transplantation (mean age 63.47 ± 3.00 years, range 60.5 – 70.5 years), 16 male and 7 female who received 19 cadaveric (CD) and 4 living related donor (LRD) grafts. Immunosuppression was steroids, MMF / azathioprine, CsA and ATG/basiliximab and mean donor age was 51.61 ± 17.01 years (range 22.3 – 72.8 years). Initial hospital stay, blood pressure, lipid levels, delayed graft function (DGF), acute rejections (AR), patient and graft loss were recorded and cumulative patient and graft survival was calculated.

Results. During the follow up period there were 9 graft losses due to 8 deaths and 1 infection. Deaths were mainly due to cardiovascular and cerebrovascular accidents (75%) and to a lesser degree to infection (12.5%). The mean stay at 1st hospital admission was 32.60 ± 29.16 days. There were 3 AR episodes (13.63%) and 11 cases with DGF (47.82%). The incidence of AR in pts with DGF and age > 60 years was 9.1%. The cumulative patient and graft survival one and five years after kidney transplantation were 82.61% and 74.61% respectively. Abnormal high blood pressure and lipid levels were recorded in these patients.

Conclusions. The main cause of graft loss in patients with age > 60 years was death. There was no graft loss due to AR or chronic allograft nephropathy. The very high rate of DGF is probably due to high incidence of CD transplants, which caused a very prolonged 1st hospital stay. The low incidence of AR with or without DGF suggests deranged immune response. *Hippokratia 2005; 9 (3): 115-118*

Key words: kidney transplantation, elderly recipients, patient survival, graft survival, delayed graft function, acute rejection, blood pressure, lipid disorders

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Tersigni et al reported for the first time ESRD patients above the age of 60 years successfully treated with kidney transplantation¹. Shortly after, Wedel et al reported that the risk of these patients was not graft loss from rejection but rather death with a functioning allograft². On the other hand recently, enhanced cellular immune responsiveness in elderly recipient rats was associated with advanced chronic graft injury³ and increased recipient age in humans was reported as an independent risk factor for the development of chronic allograft nephropathy⁴. So we decided to investigate retrospectively the behaviour of this particular group of patients and to discuss possible future treatment modalities.

Material and methods

Eight hundred and one (801) kidney transplants were performed from 1 Jan 1987 to 31 Dec 2003. The recipients of age ≤ 16 were 86 and were not considered in this study (Table 1). Among the 715 recipients considered,

(3.21%), twenty three were older than 60 years of age.

The elderly patients' and their donors' demographic data are shown in Table 2. The immunosuppression protocols used were steroids, MMF/azathioprine, CsA/tacrolimus and ATG/basiliximab or daclizumab.

One patient was lost to follow up. Initial hospital stay, DGF, AR, patient and graft loss was recorded and cumulative patient and graft survival was calculated. Serum creatinine, total cholesterol, HDL-cholesterol, triglycerides, systolic and diastolic blood pressure, body weight, total serum protein and albumin during time (1st, 3rd, 6th, and 12th month after Rt) were recorded too. Descriptive statistics, repeated measure analysis and Kaplan – Meier were used for statistical analysis (Statistical Package for Social Sciences version 12.0).

Results

The mean time of first hospital stay was 32.60 ± 29.16 days in patients with age > 60 years while it was 21.35 ± 13.48 days in patients with an age ≤ 60 years.

Table 1. Kidney transplants and age (period 1987 – 2003)

Age ≤ 16 year	86	transplants
Age >16 and ≤ 60	692	transplants
Age > 60	23	transplants

Table 2. Recipient – donor demographic data

Recipient age	63.47±3.00 years, range 60.5 – 70.5 years
Recipient sex	men 16 (69.6%) women 7 (30.4%)
Primary renal disease	GN: 7, CPN: 2, PKD: 3, HN: 2, Unknown: 7, missing: 2
Donor Age	51.61±17.01 years (range 22.3 – 72.8 years)
Sex	male 15 female 8
Cadaveric	19 (82.6%) LRD 4 (17.4%)

Eleven of our patients (11/23) presented DGF (47.82 %) possibly due to high percentage of cadaveric transplants (82.6 %) while the incidence of DGF in pts of less than 60 years of age was 16.32 % with a cadaveric transplant incidence 37.13 %.

The incidence of acute rejection in the elderly patients was 13.63% (3/22) while the overall estimated incidence of acute rejection in our centre in patients over the age of 16 is 24.67% (period 1987-2001). The incidence of AR in pts with DGF and age > 60 years was only 9.1 % while the incidence of AR in pts with DGF and age < 60 years was 29.5 %. The cause of death was cardiovascular accident in 50.0% of cases, infection in 12.5%, and cerebrovascular accident in 25.0% and unknown in 12.5% of cases. The one and five year cumulative patient and graft survival was 82.61% and 74.35% respectively (Figure 1 and 2).

Serum creatinine, total cholesterol, diastolic blood pressure, total protein, albumin serum levels during the 1st post-transplant year was not significantly different between pts of > 60 year old and < 60 year old. Systolic blood pressure proved to be significantly higher in patients > 60 year old (Figure 3). The elderly patients presented high levels of total cholesterol, triglycerides and low levels of HDL-cholesterol. (Table 3).

Discussion

Until today, many centres are reluctant to accept patients > 60 years old onto the waiting list, as these patients are frail, have more comorbid conditions⁵ and their overall life expectancy is lower than the younger population.

There are reports showing that immunosuppression protocols with CsA are safe and effective in elderly ESRD patients⁶, survival with a kidney graft exceeds survival on dialysis even in elderly patients⁷⁻⁹ and age per se does not constitute a contraindication to transplantation.

At the same time, it has been supported that elderly

Table 3. Total cholesterol, triglycerides and HDL – cholesterol levels during the first post-transplant year.

	Total cholesterol	Triglycerides	HDL-cholesterol
1 st pst month	258.14±56.05	172.60±65.61	48.50±28.17
3 rd pst month	254.71±69.07	276.40±118.33	46.66±18.47
6 th pst month	241.00±44.72	139.42±72.21	39.00±10.12
1 st pst year	260.00±3305	174.40±56.53	38.00±4.96

transplanted patients have a degree of immune incompetence¹⁰, an increased tendency for serious infections² and require less aggressive immunosuppressive therapy¹¹. That theory was supported by the continuing observation of lower rejection rates, lower incidence of chronic rejection but higher risk of infections noted in elderly transplant recipients¹⁰⁻¹³. Our observation of only 13.63 % (3/22) incidence of AR in elderly patients while the overall estimated incidence of acute rejection in our centre in patients over the age of 16 is 24.67% (period 1987-2001)¹⁴, is in agreement with these reports.

In our material the main cause of graft loss (75%) was death in agreement with Webel et al². Recently Ojo et al have shown that the increased age at the time of transplantation has a major influence on long term graft survival and death with a functioning allograft accounts for almost 40% of the grafts lost in long term follow up¹⁵. This higher post-transplant mortality must be considered against a significant survival advantage of transplantation over dialysis patients who are suitable for transplantation and a continuous improvement in the outcome of transplantation in the elderly over time^{9,16}. We have shown in a previous work that the frequency of acute rejection is significantly higher among patients with DGF¹⁴. The low incidence (9.1%) of AR found in the elderly patients with DGF in our centre is another clue favouring a deranged immune function in these patients.

The incidence of cadaveric transplants in the elderly recipients was above the average recorded in our centre and is compatible with their age. Possibly the higher incidence of DGF in this cohort of patients is related to the prolonged cold ischemia time in cadaveric transplants and to the tendency of older patients to hemodynamically induced ARF¹⁷. The observed increased first hospital stay is relevant to DGF noticed in these patients.

It has been shown that there is significantly greater survival probability in ESRD patients over the age of 60 who underwent transplantation as opposed to matched controls that remained on dialysis⁸. Our cumulative patient and graft survival one and five years after kidney transplantation were 82.61% and 74.61% (Figure 1 and 2) is in accordance of recent data demonstrating very similar 5-year graft (54% - 74%) and patient survival (52% - 74%) rates, confirming the improvement made but also the concept that most patients in this high-risk group die with functioning grafts¹².

In our patients, the main reason of death was cardiovascular and cerebrovascular accidents (75% of

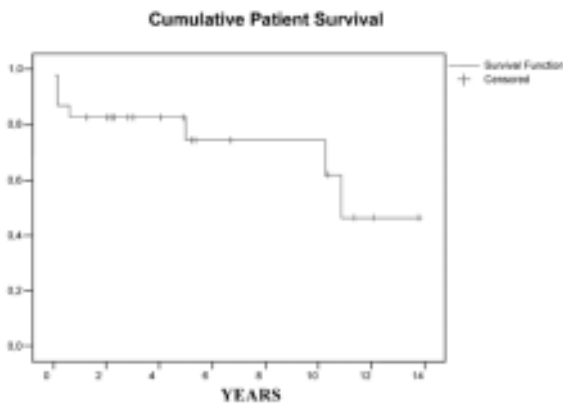


Figure 1. Cumulative patient survival

cases). Post-transplant morbidity has been attributed mainly to infectious complications and an increased prevalence of malignancy¹². Immunosuppression seems to correlate with an increased incidence of infectious adverse events¹⁰. In our material infection was responsible for only 12.5% of deaths and serious malignancies were not noticed in discordance with other reports². According to our results systolic blood pressure was significantly higher in the aged recipients, a significant risk factor for cardiovascular disease.

Donor age has been identified as a risk factor for poor graft outcome¹⁸. In recent studies grafts from donors older than 60 years of age demonstrated significantly reduced function in young recipients¹⁹ and had reduced survival rates in recipients aged 60 years old or older compared with those from donors aged 60 years or younger²⁰. Analysis of the United Network of Organ Sharing registry data revealed an improved renal allograft function when both donors and recipients were older than 60 years²¹.

The information relevant to the impact of mycophenolate mofetil (MMF) or azathioprine (AZA) on patients' survival is contradictory and needs further investigation^{22,23}. It has been proposed that in elderly patients with a Rt, MMF is associated with lower early and late rates of acute rejection compared to AZA²² and that the scheme MMF, CsA and Pred seems to be correlated with an increased incidence of infectious adverse events as compared with AZA, CsA, Pred in elderly patients¹⁰.

Currently, in our centre, there is no age limit for access to transplantation but only 3.5 % of transplant recipients were > 60 years old on day of transplantation, a rate much lower than that reported by others⁹. Fifty per cent of our elderly transplants were accomplished the last 4 years. In the present situation of organ shortage there is a bias against elderly patients²⁴. Eurotransplant (ET) to oppose this problem established the Eurotransplant Senior Program (ESP). According to ESP grafts > 65 year old are allocated locally to elderly recipients to reduce the cold ischemia time. HLA matching is not applied and the percentage of elderly

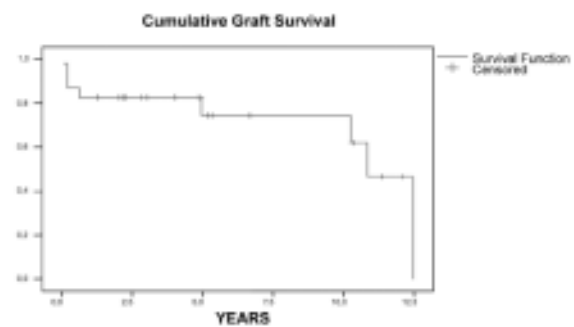


Figure 2. Cumulative graft survival

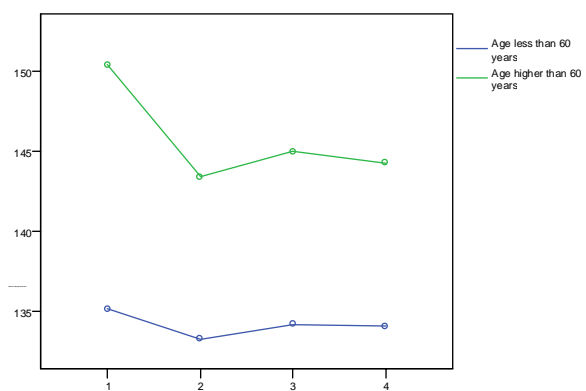


Figure 3. Systolic blood pressure during time. Green line: recipients > 60 year old, Blue line: recipients < 60 year old ($p = 0.013$ repeated measures analysis) 1= 1st month, 2= 3rd month, 3= 6th month, 4= 12th month after Rt

recipients has increased from 6.2% in 1995 to 10.8% in 2002²⁵.

According to United States Renal Data System the elderly recipient with an imminent LRT should never offered of cadaveric renal transplantation²⁶. On the other hand, elderly patients without a LRD and a prolonged waiting list time as it happens in Greece, will benefit if they accept an extended criteria donor²⁷.

Selection of elderly patients for transplantation must be based on estimation of the medical risk. The patient's motivation is important but only if the medical risk is acceptable as judged by the doctor. Special tests must be performed in older patients in addition to those required for the routine recipient work-up²⁸. The major reason for renal allograft loss is not rejection but patient death due to cardiovascular and infection reasons. Attention to prevention of infection and worsening of cardiovascular disease is as critical as prevention of rejection in these patients. The avoidance of agents toxic on the myocardium or the vessel wall must be taken into account. Hypertension and lipid abnormalities must be treated aggressively.

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