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Review

# Kidney transplantation in elderly

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## ABSTRACT

The progressive increase in the elderly population around the world is associated with the increase in the percentage of individuals with chronic diseases such as chronic kidney disease. They constitute new candidates for kidney transplantation as the therapy has been proven to be superior (life quality, survival, cost) compared to dialysis. Some aspects should be considered as elderly individuals present comorbidities (cardiovascular disease, diabetes, hypertension etc.) and changes in the immune system that could impair the success of transplantation at early points of time. Patient death linked to functional kidney allograft occurs in a considerable number of elderly recipients. The decreased immune response has been pointed out as responsible for the lower rates of acute rejection in elderly kidney recipients. However, these patients also present a higher incidence of infections and tumors posttransplantation. Some authors find an increased risk for chronic allograft nephropathy in elderly recipients whereas some authors report similar rates of risk compared to younger recipients. The immunosuppressive regimen is another critical factor for elderly recipients since they already have a diminished immune response. Also, physiological changes in elderly can interfere with the pharmacokinetics and pharmacodynamics of the immunosuppressive drugs causing their increased levels in blood and lower clearance. Long-term studies in elderly recipients are needed in order to establish adequate conditions for kidney transplantation and thus improve quality of life in this population, besides prolonging patient and graft survival.

**KEYWORDS:** aging, chronic kidney disease, kidney transplantation

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## INTRODUCTION

In the past decades there has been an increase in the average life expectancy of the world population [1] and as a consequence the percentage of individuals with chronic diseases has also increased as aging is associated with a higher incidence of chronic diseases [2].

Chronic kidney disease has a higher prevalence in older individuals since estimated glomerular filtration rate (eGFR) declines in parallel with increase in age (Figure 1). The National Health and Nutrition Examination Survey (NHANES 2001-2008) showed that stage 3 chronic kidney disease (CKD) occurs in 26% of patients older than 60 years in the United States [3].

It can be observed in Figure 1 that renal function declines in the studied population with the increase in age and a higher percentage of individuals presented an eGFR lower than 90 mL/min/1.73 $m^2$ [4].

The incidence of older people presenting kidney failure and dependent on dialysis has increased over the last decades. This therapy has provided only a short life expectancy for patients older than 80 years as reported by a USA study [5]. The USA data for 2009 shows that the mortality rate in dialysis patients was 200 per 1,000 and the 5-year

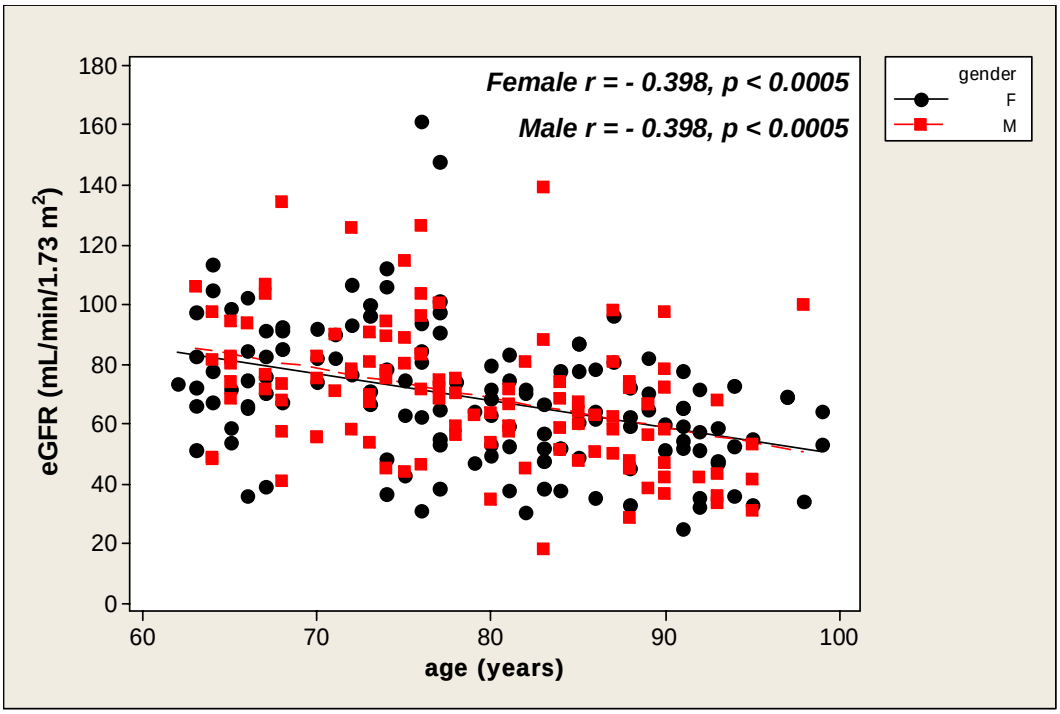


**Figure 1.** Estimated glomerular filtration rate (eGFR) in individuals aged 60 to 101 years living in São Paulo City - Brazil (2011).

survival rate was lower than 40% whereas in transplantation this rate was 80%. In addition, the cost per patient for hemodialysis ($80,000) and peritoneal dialysis ($60,000) was higher than in transplantation ($30,000) [6].

As a consequence of the increased number in the elderly population, the elevated percentage of individuals with end stage renal disease (ESRD), and transplantation-related benefits, an increase in recipients older than 60 years, waiting for a kidney transplantation is expected.

The active USA waiting list for kidney transplantation increased from 45,290 patients in 2004 to 50,624 patients in 2008, in which 14% and 17%, respectively were patients older than 65 years. On the other hand, the inactive waiting list augmented from 11,851 (2004) to 25,465 (2008) patients with 16% and 18% of them aged 65 years or more in the respective cited years [7].

The advantage in receiving kidney transplantation over dialysis therapy was shown in a longitudinal study by Wolfe *et al*. [8] using data from US Renal Data System (USRDS). Even patients aged from 60 to 74 years at the time of transplantation had improved life expectancy (7.4 deaths/100 patient-year) when compared with patients on the waiting list and treated with dialysis (10 deaths/ 100 patient-year) and long-term dialysis (23.2 deaths/ 100 patient-year). However, as pointed out by Danovitch & Savransky, patients older than 65 years and submitted to dialysis present comorbidities and lower life expectancy and thus only 5% of them would be placed on the kidney transplant waiting list [9]. There is also a tendency to use deceased donors for older recipients given their inherent limited life span, which could contribute for the impaired success in transplantation.

Even with the consideration that only highly selected elderly patients would be placed on the kidney transplant waiting list, complications could occur after transplantation in this population.

## Complications after kidney transplantation performed in elderly patients

In the United States 75% of individuals aged 65 years and older present one chronic illness and

50% have at least two [10]. Common chronic diseases are arthritis, hypertension, heart disease, diabetes, respiratory disease, stroke, and cancer [11]. In the aged population with CKD/ESRD comorbidities such as diabetes, hypertension and cardiovascular disease are greater [12]. Therefore, kidney recipient candidates older than 65 years are more likely to experience posttransplantation hospitalizations and death.

Gill *et al*. [13] evaluated individuals ≥65 years of age presenting cardiovascular risk (low, intermediate, and high) who received kidney transplant from standard criteria deceased donor (SCD), expanded criteria deceased donor (ECD) or living donor (LD) in comparison with dialysis patients in the same conditions. Low, intermediate and high cardiovascular risk was associated with elevated risk of early death after transplantation when donors were SCD and ECD in comparison with wait-listed patients of similar cardiovascular risk. Recipients of LD kidneys presented a lower risk of early death than dialysis treated patients with low and intermediate cardiac risk. The death rate in the first year after transplantation in all patient risk groups was lowest in patients receiving LD kidneys, followed by SCD and ECD. Authors concluded that even though the use of kidneys from deceased donor constitutes an increased risk of early death and remains a barrier to transplantation for elderly patients, transplantation from any donor source presents a reduced long-term risk of death in comparison with dialysis treatment.

Another study conducted by Huang *et al*. [14] showed that 30 days posttransplant the mortality was higher in patients older than 80 years (2.5%) when compared with patients aged 60 to 79 years (1.4% and 1.5% in patients from 60-69 and 70-79, respectively). However, no differences were found among recipients aged 60 to 69, 70 to 79, and 80 years and older, considering the proportion of death from causes such as cardiovascular, infections, tumors, or cerebrovascular.

Nanmoku *et al*. [15] evaluated kidney recipients older than 60 years and even though they presented no significant difference in patient or graft survival in comparison with younger recipients (37.4 ± 13.5 years), the main cause of graft loss in the elderly transplanted population was death due to heart failure.

Considering that older patients present an impaired immune response, it is important to evaluate their mortality due to infections and malignancy caused by the addition of continuous immunosuppressive regimen. Meier-Kriesche *et al.* [16] compared patients in waiting list and after a renal transplantation for the risk of infection-related mortality and malignancy using the USRDS database. The annual adjusted death rate per 1000 patients due to infection was 10.9 and 3.0 for waiting list (WL) and renal transplantation (Tx), respectively in individuals aged 18 to 29 years whereas it was 20.0 and 16.7 in individuals older than 65 years. The study shows an exponential growth of infection-related death in Tx patients ($R^2 = 0.99$) and a linear growth ($R^2 = 0.96$) in the WL patients associated with the increase in age. For malignancy the annual adjusted death rates per 1000 patients was 0.2 and 0.6 for WL and Tx, respectively in individuals aged 18 to 29 years while it was 5.3 for WL and 7.1 for Tx in individuals older than 65 years. There was a linear growth of malignancy-related death in association with aging but a higher rate was observed for the transplanted group. Trouillhet *et al.* [17] transplanted kidneys from the same donor (matched, living or cadaveric) in recipients older than 65 years (n = 40) and in younger recipients (n = 40) in order to compare these two groups for infection episodes. In a median follow-up of 18 months 80% and 32% of infection was observed in older recipients and younger recipients, respectively. Bacterial infections were the most frequent etiologies in both groups and sites by the frequency were urinary, pulmonary and gastrointestinal. Viral and fungal infections were also more frequent in older recipients. The analysis of 73,707 patients (age > 18 years) registered in the USRDS and UNOS showed that recipients ≥65 years presented a higher rate of graft loss censored for patient death (15%), death due to all reasons (18.6%), death due to infection (4.8%), and death due to opportunistic infection (0.52%) in the first 2 years of follow-up. On the other hand, the relative risk of acute rejection decreased progressively and significantly with aging. The study showed 6-fold increase in death due to infection in older recipients whereas

the acute rejection was almost half in these patients when compared with recipients aged 18-29 years [18].

A study in England (2001 to 2012) evaluating individuals below 50, 50 to 59, 60 to 69, 70 to 79 and above 80 years old showed that mortality risk increased with aging and the most common causes for death in recipients 70 years old and over were cardiac (21.2%), infection (21.2%), and malignancy (20.2%) [19].

**Kidney allograft survival**

Another factor to be considered when transplanting in older recipients is graft survival. Both ESRD and aging have been associated with T-cell dysfunction due to T-cell lymphopenia, loss of naïve T cells, and increased number of terminally differentiated memory T cells. Considering that T cells have an essential role in acute rejection lower rates of this event could be expected in elderly patients with ESRD [20-22]. An additional advantage is that sensitization reduces with aging as confirmed by Palomar *et al.* [23] who reported higher panel reactive antibodies in younger recipients (4.3%) than older (2.07%) through a study involving 363 kidney transplanted patients.

**Acute rejection**

It is not fully understood how donor and recipient age affects rejection. Some authors consider that donor age rather than recipient age is a limitation for success in kidney transplantation.

The 2-year follow-up study of Huang *et al.* [14] using OPTN/UNOS database showed that graft survival was 85% for recipients aged 60 to 69 years, 81% for recipients aged 70 to 79 years, and 69% for recipients 80 years old. In addition, 2-year death-censored graft survival for 60 to 69 years was 93%, for 70 to 79 years was 92%, and for 80 years and older was 91%.

Gallinati *et al.* [24] evaluated 85 recipients (65 to 83 years old) of kidney from SCD and observed 34.1% of delayed graft function (DGF), 16.5% of acute rejection, and 81% 1-year graft survival. In immediate graft function, 1-year graft survival was 98% whereas in DGF cases the 1-year graft survival was 48%. Mezrich *et al.* [25] studied the evolution of kidney transplantation using ECD and SCD in recipients aged 40 to 59 years and ≥60 years old. Patient and graft survival (5-year actuarial rate) were diminished in ≥60 years old receiving ECD kidney in comparison with older recipients from SCD donors. The combination of older recipients and ECD donors also presented a worse outcome than younger recipients and ECD donors. Multivariate analysis showed that ECD kidneys represent an independent predictor of worse outcome in older recipients. Lim *et al.* [26] studied 1037 recipients older than 60 years who received kidneys from donors older than 60 years (n = 221) or younger than 60 years. Older donors were associated with a higher incidence of delayed graft function and death-censored graft failure. In addition, recipients of older donors presented a significant decrease in the eGFR after 1 year and 5 years of follow-up.

Fijter & Persijn [27] reviewed the most recent findings about kidney transplantation in elderly and concluded that donor age is a limiting factor for transplant success both in younger and older recipients.

Pratschke *et al*. [28] observed for 6 months, older kidney recipients (67.9 ± 2.5 years) who received kidneys from aged donors (≥65 years) and compared them with younger patients (45.6 ± 11.3 years) who received kidneys from adult donors (<65 years). Recipient survival was 100% in the older group and 98.7% in the younger group whereas kidney survival was 88.5% in the elderly and 93.2% in the younger population. In 6 months of evaluation both groups presented similar incidence of delayed graft function, acute rejection episodes and mean serum creatinine.

In kidney recipients from a Scottish regional transplant unit (2001-2010) it was found that the use of elderly donors in elderly recipients was associated with DGF, organ failure in the first year after transplantation, and increased serum creatinine at 1 year. However, biopsy proven acute rejection (BPAR) was less common in older recipients [29].

The evaluation of younger and older kidney recipients of living donors showed that acute rejection 1 year after transplantation was more frequent in the younger recipients (41%) than in the older ones (21.7%) whereas cytomegalovirus (CMV) infection was more common in the elderly recipients. After a mean patient observation

period of 7 years it was possible to observe that the poorest patient survival occurred in the older group whereas both the death uncensored and censored graft survival rates were similar when youngest and oldest groups were compared [30].

### Chronic graft failure

Meier-Kriesche *et al.* [31] analyzed 59,509 kidney transplanted patients using USRDS database (1988-1997). Recipients aged 18-49 years, 50-64 years, and ≥65 years presented progressive increasing rates of death censored graft loss (3.9%, 5.0%, and 8.6% per 100 patients/yr) and graft loss to chronic allograft failure (CAF) (2.2%, 2.9%, and 3.9% per 100 patients/yr). Recipients ≥65 years conferred a higher relative risk (1.67) for CAF whereas recipients from 18-49 and 50-64 years presented 1.0 and 1.29 as relative risk, respectively. Authors also analyzed Caucasian recipients (n = 11,009) who were transplanted with kidney from living donors and presented no acute rejection episode within the first 6 months posttransplant and found that recipient age was an independent risk for CAF development.

Roodnat *et al*. [32] analyzed 509 cadaveric renal transplants using cyclosporine (CsA) as primary immunosuppressive regimen from 1983 to 1990 and found that patient survival decreases with increasing age but no statistical difference was observed when recipients from <44 years, 44-55 years, and older than 56 years were compared for the chronic rejection (14%, 19%, and 12%, respectively, p = 0.64). However, the occurrence of infection as the cause of graft failure was higher in older recipients (5%, 0%, and 12%, respectively). In addition, Cox proportional hazards analysis showed that recipient age was an independent variable influencing patient survival, graft survival censored for death, and overall graft survival.

Keith *et al*. [33] analyzed patients from UNOS database (1995 to 2000) transplanted with organs from deceased donors and observed a decreased incidence of chronic graft failure with increase in age. Chronic allograft nephropathy (CAN) in recipients aged 10 to 19 years and older than 60 years was 3.91% and 1.52% (events per 100 patients/yr), respectively. Decreased incidence of CAN was found even when authors evaluated recipients by race, except that African-Americans presented a higher rate of CAN in all age groups studied when compared with Caucasians.

### Immunosuppressive regimen and older recipients

Older recipients present lower rates of acute rejection episodes whereas higher rates of death and allograft loss censored for death are also observed. Considering that death by infection [16, 17] and risk of malignancy [34, 35] are significantly increased in this population it would be beneficial to have different immunosuppressive regimens for older recipients.

It is not fully understood how the physiologic changes related to aging affect the pharmacokinetics and pharmacodynamics of immunosuppressive drugs. However, it is known that elderly population presents changes in drug disposition and susceptibility to adverse drug reactions [36]. In addition, elderly present a greater risk for drug-drug interactions secondary to polypharmacy.

Jacobson *et al*. [37] observed for 6 months, kidney transplant recipients (18-34, 35-64, and 65-84 years) treated with tacrolimus (TAC) or CsA and found a decline in calcineurin inhibitor (CNI) clearance with increase in age. Older subjects received a median of 1 and 2 mg/day lower TAC dose than middle and young aged adults and achieved higher median drug troughs. CsA was administered at 100 mg/day lower dose in older subjects who reached higher troughs than younger adults. Authors concluded that further studies are needed since CNI lower doses could be used in older recipients, reducing drug-related toxicities in this population.

Falck *et al*. [38] evaluated recipients of kidney transplantation according to CsA pharmacokinetics. Recipients older than 65 years achieved $C_2$ levels with lower doses of CsA than the younger recipients. A lower drug clearance was observed in older recipients. Also, a significant increase in intracellular-to-whole blood CsA ratio was observed in this population.

Sommerer *et al*. [39] studied stable older (≥65 years) kidney recipients receiving median daily CsA dosage of 150 mg (50-250). In 12 months of follow-up the levels of CsA in the blood of recipients presented a significant variability for

$C_0$ (102 mcg/L, range 33-157) and $C_2$ (551 mcg/L, range 254-1228) whereas no acute rejection episode was reported. NFAT-regulated gene expression (RGE) was assayed in order to indirectly evaluate T-cell activation. Patients with opportunistic and herpes viral infections presented lower residual NFAT-RGE. In addition, there was a tendency of lower residual NFAT-RGE in patients with malignancy. Authors found that higher levels of immunosuppression were associated with infections and malignancy in a considerable proportion of elderly recipients of kidney allografts. They suggest that pharmacodynamic monitoring and individualized immunosuppression could reduce these complications in senior recipients.

Induction agents commonly used in transplantation could be an additional risk for infection and malignancy in elderly recipients. Cherikh *et al*. [40] analyzed 38,519 primary kidney transplants from UNOS-OPTN database and observed that immunosuppressive induction was administered in 38% of cases. In recipients older than 55 years (n = 10,197) the posttransplant lymphoproliferative disorder (PTLD) incidence was 0.26%. Considering all recipients, IL-2RA was associated with lower PTLD incidence (0.50%) whereas anti-thymocyte globulin presented higher rates (monoclonal = 0.85%, and polyclonal = 0.81%). In a follow-up of 5 years González-Roncero *et al.* [41] showed that induction with 2 doses of daclizumab (anti-IL-2RA) in combination with MMF, TC and steroids provided long-term survival results, adequate renal function (1.61 ± 0.6 mg/dL), and acceptable safety profile in patients (61.3 ± 6.2 years old) transplanted with kidneys from ageing donors (64.4 ± 5.3). Authors report that the primary cause of graft loss was patient death mainly due to cancer. Of all cases, skin cancer was the most common (50%) followed by PTLD (11%) and other solid tumors (39%). Other analyses using UNOS-based database have found that alemtuzumab administered to kidney recipients older than 60 years was associated with a higher risk of acute rejection, death, and graft loss [42, 43].

Immunosuppressive regimens based on MMF/CsA/prednisolone and azathioprine/CsA/prednisolone were compared in recipients ≥55 years [44] and ≥65 years [45], with MMF protocol presenting improved graft and patient survival at the follow-up period (3 and 4 years posttransplantation, respectively). However, a single-center evaluation of recipients over 55 years showed graft survival of 96% in azathioprine protocol and 87% in MMF protocol after two years follow-up. Patient survival for the azathioprine and MMF protocols at 2 years was 100% and 87%, respectively [46].

Calcineurin-inhibitor-free or withdrawal protocols have been proposed for older recipients. A protocol with induction (antithymocyte globulin) followed by MMF and corticosteroids was used by Arbogast *et al*. [47] in patients with mean age of 64 years. Cumulative 5-year patient survival (88%), allograft survival (70%), and graft function (mean serum creatinine 1.5mg/dL) were excellent considering that deceased donors with mean age of 67 years were used. Others obtained similar results using antilymphocitic or basiliximab induction followed by MMF and steroids [48, 49, 50].

## CONCLUSIONS

Kidney transplantation is superior to dialysis for patients with chronic kidney disease, even for individuals older than 60 years. However, elderly recipient death with functioning graft can occur at early points of time due to cardiovascular disease/infection/malignancy. In order to prolong patient and graft survival in elderly an extensive pretransplant evaluation of the recipient and adequate immunosuppressive regimen should be considered.

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## CONFLICT OF INTEREST STATEMENT

None.

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