Kidney Transplantation in the Elderly: It's Not All Gloom and Doom

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In the United States, the number of end stage renal disease (ESRD) patients on maintenance dialysis has increased 20 percent in the last decade to 1700 per million, and 100,000 new cases are added every year. The largest increase in both incident and prevalent cases of ESRD has been in individuals ≥65, with rates three- to fourfold higher compared with younger individuals (Figure 1). Nearly 50 percent of all patients on dialysis are ≥65. This increase in the older patient population is likely due to the increasing prevalence of diabetes and hypertension that has contributed to a rise in ESRD. In addition, the average life expectancy of patients on dialysis has improved in the last two decades. Nevertheless, the rate of death is six times higher for patients on dialysis compared with the general population, with mortality being highest in the elderly population (1).

Do elderly patients benefit from kidney transplantation?

Although the rate of kidney transplantation among older patients is 5 to 15 times lower than that among patients <65, this rate has increased by 54 percent in the last decade (2). This increase indicates that kidney transplantation offers better survival and quality of life, even among elderly patients. Most of the earlier studies showing survival benefit among patients undergoing kidney transplantation were criticized for including healthy patients in large cohorts of dialysis patients. This selection bias was overcome in a large U.S. study involving 228,552 dialysis patients in whom outcomes were compared only between patients on the waiting list for kidney transplantation and patients who received a kidney transplant (3). Of the 88,500 patients who were ≥60, only 6925 (8 percent) were wait-listed for transplantation, around half of whom eventually underwent deceased donor transplantation. On comparing outcomes among patients 60 to 70 and those who remained wait-listed on dialysis, the risk of death among transplanted patients was highest within the first two weeks and remained high until 148 days after transplantation. Long-term mortality risk was 61 percent lower among patients who underwent kidney transplantation. This translated into an average increase in life span of 4.3 and 2.8 years for patients 60 to 64 and 64 to 69 years of age, respectively. Similarly, in a Scandinavian study involving 325 patients 60 to 70, the 1-, 5-, and 7-year survival rates were 93, 70, and 46 percent in the transplanted group compared with 81, 30, and 15 percent in the wait-listed group, with an average increase in life expectancy of 3 years (4).

Rao et al. (5) performed a large retrospective analysis to determine outcomes in 5567 patients ≥70 who underwent kidney transplantation in the United States from 1990 to 2003. One in five patients was ≥75. Although the survival rate was equal among the transplanted and wait-listed patients in the first 2 years, the long-term mortality risk was 56 percent lower for kidney transplant recipients (Figure 2). At 4 years, the adjusted survival for transplant recipients was 66 percent compared with 51 percent in the wait-listed patients. This survival benefit was most notable in ESRD patients with diabetes and hypertension. Even elderly patients ≥75 had a 33 percent reduction in mortality after kidney transplantation. The 1- and 3-year graft survival rates among transplant recipients were 93.1 and 89.1 percent, respectively.

In a recent study of a highly selected group of patients with a median age of 81, death-censored graft survival was reported to be similar to that of patients 60 to 69 (6), although perioperative mortality was higher (2.5 percent versus 1.5 percent). Based on these data, it is obvious that there is no age limit for kidney transplantation. Carefully selected elderly patients clearly benefit from transplantation. In addition to the survival benefit and improved quality of life, kidney transplantation may be an economically viable option in older individuals, particularly if the waiting period is less than 2 years. Beyond this, the financial benefits tend to be variable. Live donor kidney transplantation is therefore an attractive option for these patients.

How can we meet the growing demand for kidney transplantation in the elderly?

The benefits of transplantation noted in these studies have resulted in a growing demand for kidney transplantation in the elderly population, who now constitute the fastest growing segment of the waiting list population (Figure 3). Currently, in six patients wait-listed for kidney transplantation ≥65, and the waiting time has increased to 3.6 years in the last 2 years. It is projected that without transplantation, 46 percent of these patients are likely to die while on the waiting list (7).

The number of kidney transplantations performed annually has not matched this increasing demand, especially in the elderly population. This is largely due to organ shortage, a paucity of live donors, changes in organ allocation policies that favor young recipients, lack of referrals for transplantation evaluation due to physician attitudes toward the elderly, and ethical concerns about offering a kidney to an older patient versus a younger patient. It has been argued that although kidney transplantation offers improved survival in the elderly as opposed to remaining on dialysis, the magnitude of benefit is not the same as in younger groups. The average life expectancy increases by 11 years in patients 40 to 59 versus only 4 years in patients 60 to 70 in the absence of comorbidities such as vascular disease or diabetes. However, death-censored allograft survival is similar in older and younger patients and is independent of age. Therefore, it has been suggested that through preferential transplantation of organs from the older donor to the older recipient, overall graft survival may be optimized.

To meet this growing demand for kidney transplantation in the elderly and to overcome the organ shortage, several kidney transplant centers have used the strategy of increasing the donor pool by accepting expanded criteria kidneys, defined as donor age ≥60 or ≥50 with any two of the following conditions: history of hypertension, serum creatinine level ≥1.5 mg/dL, or death due to cerebro-
Bethesda, MD, National Institutes of Health, National Institute of Diabetes and Chronic Kidney Disease and End-Stage Renal Disease in the United States, Adapted from U.S. Renal Data System.

because the addition of older live donors and comparable outcomes with young compared with standard criteria donors with transplantation from old live donors favorable patient and graft survival outcomes.

Another strategy of increasing the donor pool to improving chances of transplantation in the elderly has been to offer an older donor kidney to the elderly recipient to optimize survival. This hypothesis was tested as a part of the European Senior Transplant Program in which 18 “very old” donor kidneys (mean age, 78) were transplanted into older individuals (mean age, 68 years) and compared with the two control groups who received age-matched kidneys (mean age, 68 for donor and recipient) and HLA-matched kidneys (mean age of donor, 48; mean age of recipient, 68), respectively (10). The 1-, 3-, and 5-year survival rates were 93, 83, and 80 percent, respectively, in the study group and did not differ significantly with the control group. In this study, however, the average cold ischemia time was ≤10 hours, a critical factor that favored good graft outcomes.

Recent studies have also reported favorable patient and graft survival outcomes with transplantation from old live donors compared with standard criteria donors and comparable outcomes with young live donors. This is encouraging news, because the addition of older live donors to the pool may help reduce the waiting times for transplantation, which is so crucial for survival in this elderly population. Transplanting two marginal kidneys instead of one and paired living donor match programs are also other options and have met with reasonable success at several transplant centers in the United States and abroad (11).

How should we determine the suitability of the elderly patient for transplantation?

Patient selection is crucial, because not all elderly patients benefit from kidney transplantation. In the Minnesota study that examined the risk factors for graft loss among the elderly, the 10-year graft survival was 39 percent versus 53 percent among younger recipients. Although graft loss due to death was the predominant cause, the major risk factors identified were nonskin malignancies, vascular disease, smoking, and donor age (12). The risk of malignancy after transplantation was five times higher in elderly patients and inversely correlated with the time of remission of the cancer. Infection episodes were also fivefold higher, particularly with the presence of comorbidities such as diabetes, diverticulitis, and urinary tract infections. Cardiovascular disease, infectious complications, and malignancies account for most deaths in elderly patients after transplantation (Figure 4). It is therefore important that older patients be screened extensively for any risk of vascular disease, infections, and occult malignancy before undergoing kidney transplantation.

In addition to screening the patient for suitability for transplantation, it is vital to prognosticate the risk on an individual basis so that a decision about live donation and staying on the waiting list for deceased donors can be made. In a large retrospective analysis on the scientific registry database, it was noted that patients with diabetes, blood group O and K, high plasma renin activity (≥30 percent), and African American race and patients on dialysis at listing were more likely to die while on the waiting list and were therefore more likely to benefit from live donor kidney transplantation (7). In addition, the considerable variation in mortality that exists in dialysis patients on the waiting list depending upon the United Network Organ Sharing region, is also critical to decision making about live donation versus staying on the waiting list.

How should we manage immunosuppression in the elderly?

Immunosuppressive therapy modification is particularly important in elderly patients, because aging has been associated with a higher risk of infectious complications and a lower risk of acute rejection episodes. In a retrospective analysis of 73,707 kidney transplant recipients from 1988 to 1997, the incidence of death due to infection was six times higher and the incidence of graft loss was 1.5 times lower in elderly patients (Figure 5) (13).

In a retrospective cohort study performed at the University of Maryland, elderly patients who received standard immunosuppression (tacrolimus target level 10–12 ng/mL; mycophenolate mofetil 2 g/d) had a threefold higher risk of allograft loss and death compared with elderly patients who received less intense immunosuppression (tacrolimus target level 8–10 ng/mL; mycophenolate mofetil 1 g/d). The acute rejection rates were similar in the 2 years of follow-up (14). Several factors could account for this difference. First, the pharmacokinetics and pharmacodynamics of the immunosuppressive agents change with age, notably a reduction in activity of the cytochrome P450 family of isoenzymes that increases the bioavailability of calcineurin inhibitors. Second, older age leads to a gen-
eralized decrease in T cell proliferative responses, impaired IL-2 synthesis and expression on T cells, and increased IL-6 activity, all of which decrease immunogenicity and may be an explanation for fewer incidences of allograft rejection episodes in the elderly. Third, despite lower risk of acute rejection, chronic allograft fibrosis accounts for most cases of death-censored graft loss in the elderly. Although speculative, it is believed that older graft results in a senescence-related reduction in the reparative processes, worsens chronic changes such as fibrosis and vascular damage after transplantation, and eventually promotes allograft failure.

It is therefore imperative that immunosuppression be selected carefully in elderly patients, because both over- and underimmunosuppression are harmful. Consequently, IL-2 receptor antagonists are preferred over lymphocyte-depleting agents for the induction of immunosuppression in patients ≥60. Decreased target levels of tacrolimus and mycophenolate mofetil dose are recommended in the elderly to balance the risk of infection and acute rejection (14). Rapid steroid withdrawal is also recommended in the elderly, particularly in low-risk recipients. Because calcineurin inhibitors aggravate chronic changes, targeting lower levels of calcineurin inhibitors may increase allograft survival in elderly recipients.

Kidney transplantation can be considered the renal replacement therapy of choice in the older patient, provided that patient selection is appropriate. Because transplantation is associated with increased morbidity and mortality within the first 2 years, only patients with a life expectancy ≥2 years and good functional and cognitive status should be considered for kidney transplantation. Extensive pretransplantation screening for malignancies, infections, and vascular disease is mandatory, because death with a functioning allograft accounts for most cases of allograft loss in the elderly patient. It is also vital to tailor the immunosuppression in older patients to carefully balance the risk of infection and chronic allograft loss.

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References