



Are older adults safe and suitable candidate donors or recipients for kidney transplantation?

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Because the prevalence of end-stage renal disease (ESRD) is increasing worldwide, the number of elderly dialysis patients has been consistently increasing. According to the Korean Renal Data System (KORDS), the mean age of patients on prevalent dialysis was 65.0 years, and patients aged ≥ 65 years represented more than half of dialysis patients in 2019 in Korea [1]. This trend is paralleled by an increasing rate of kidney transplant (KT) in the elderly population. Due to the shortage of kidney donors and both the increase in age and life expectancy of dialysis patients, many elderly ESRD patients are dying while waiting for KT. Based on the Korean Network for Organ Sharing (KONOS) 2019 annual report, the mean wait time for KT in elderly dialysis patients aged ≥ 75 years (2,706 days) and aged 65 to 74 years (1,944 days) was longer than for all dialysis patients (1,737 days). Although eligible older recipients reported longer survival than dialysis patients who remained on the waiting list [2], older dialysis patients often experience difficulties in undergoing KT due to high comorbidity and increased risk of early postoperative complications and immunosuppression. To date, there is no definitive

upper age limit for KT, but it is still debated whether elderly patients should be placed on the waiting list for KT or remain on dialysis.

In addition, elderly donors have been gradually increasing over the past decades to expand the donor pool and reduce waiting times for KT. Historically, the discard rates of kidneys from elderly deceased donors (DDs) were high; however, longevity matching to provide kidneys of elderly DDs to elderly recipients or patients with a shorter life expectancy recently allowed better allocation of kidneys in current clinical practice. In living donor (LD) KT, selection and allocation of suitable elderly individuals as living KT donors are more difficult and complex. Lower baseline kidney function and high comorbidities of elderly donors can shift the balance of benefit and risk, with poorer graft function for the recipient and increased perioperative complications and longer-term risks for the donor. Therefore, acceptance of older adults as kidney donors remains controversial.

In the present issue of *Kidney Research and Clinical Practice*, Lim et al. [3] investigated the clinical effects of donor or recipient age on patient survival and graft outcomes of KT recipients over 20 years. A total of 1,023 KT recipients was divided into four groups of donors and recipients

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based on 60 years of age: old-to-old, young-to-old, old-to-young, and young-to-young groups. Among participants, 129 recipients (12.6%) were >60 years of age at the time of KT, and 154 patients (15.1%) received a kidney from older donors aged ≥ 60 years. During the follow-up period of 69.2 months, elderly recipients experienced significantly higher mortality, especially infection-related mortality, than younger recipients; however, the incidence of cardiovascular and cancer-related mortality did not differ between elderly and younger recipients. Elderly individuals receiving a kidney from elderly and younger donors were associated with 3.06- and 2.89-fold higher risk of all-cause mortality, respectively, compared with younger individuals receiving a kidney from younger donors. However, significant differences were not found regarding the incidence of delayed graft function, graft failure, acute and late rejection, and infection-related hospitalization between elderly and younger recipients.

Several researchers reported that increased recipient age has a critical effect on the clinical outcomes of KT. Elderly recipients experience more infection-related complications and are at increased risk of death due to infections [4]. In contrast, the incidence of acute rejection is generally thought to decline with increased recipient age [4]. The higher infectious complications and lower acute rejection in elderly recipients might be due to the combined effects of immunosenescence and immunosuppressive medications. Immunosenescence, defined as dysregulation of the immune system caused by aging, is associated with weaker immune responses and increases disease susceptibility such as tumors and infections in elderly transplant recipients [5]. Immunosenescence affects both the innate and adaptive immune systems, with the most notable changes observed in the adaptive T cell immune system in transplant recipients [6]. Aging-related thymic involution reduces the T cell thymic output and results in reduced numbers of naïve T cells and T regulatory cells. Aging also leads to accumulation of memory T cells associated with increase in cytokine production and defective CD4⁺ and CD8⁺ memory T cell function. Furthermore, commonly used immunosuppressive agents for KT have age-specific effects. Aging decreases total body clearance of calcineurin inhibitors and increases intracellular lymphocyte calcineurin inhibitor concentrations in transplant recipients [7]. Therefore, higher drug levels after similar dosing of

immunosuppressive agents can induce greater immune compromise in elderly recipients. Because the classical immunosuppressive protocols have been established in clinical trials, from which elderly patients are often excluded, the optimal immunosuppressive regimens and use of microbial prophylaxis have not been established in elderly recipients [4]. The effects of aging on the immune system should be further investigated to assist with tailored immunosuppressive regimens and appropriate infection prophylaxis for elderly recipients.

Donor age has also been a crucial factor for reduced graft function and lower graft and patient survival [8]. Lim et al. [3] found that the proportion of transplant recipients with serum creatinine levels of ≥ 1.5 mg/dL at 1 year after KT was higher in recipients from elderly donors than in recipients from younger donors. Elderly individuals who received a kidney from elderly donors had lower kidney function than recipients who received a kidney from younger donors during the five years after KT. In addition, young individuals receiving a kidney from elderly donors were associated with 2.41-fold higher risk of death-censored graft failure compared with young individuals receiving a kidney from young donors. However, significant differences were not found in the incidence of delayed graft function and graft failure between recipients from elderly and younger donors.

The pathophysiologic mechanism for negative outcomes of increased donor age in KT can be explained by immunosenescence. When transplanting the kidney, activation of innate immune responses occurs in the donor organ, particularly in response to organs donated after brain death and graft ischemia. Aging affects the co-stimulation of dendritic cell precursors and dendritic cells and hinders the function of neutrophils and natural killer cells. These age-associated effects result in impaired function of the innate immune system [9]. Substantial number of passenger dendritic cells deriving from the transplanted kidney have been shown to disseminate into the recipient. The immunogenicity in an older transplanted kidney affects transplant recipients through passenger dendritic cells. In addition, aging can influence the detrimental consequences of renal ischemia/reperfusion injury (IR) during KT by increasing immunogenicity in the allograft [6]. Aging also enhances the development of atherosclerosis, which in an allograft, contributes to the risk of allograft vasculopathy by activating the production of monocyte- and T cell-attracting chemo-

Table 1. Effects of aging on donor kidney and transplant recipients after kidney transplantation

	Kidney from older donor	Older recipient
Effects	Increased immunogenicity	Reduced numbers of naïve T cells and T regulatory cells
	Increased susceptibility to renal ischemia/reperfusion injury	CD4 ⁺ and CD8 ⁺ memory T cell dysfunction
	Functional impairment of repair system	Increased cytokine production
	Increased graft atherosclerosis	Increased levels of immunosuppressive agents
	Decreased nephron number	Multiple comorbidity conditions
Results	Increased incidence of acute rejection	Increased patient death
	Increased risk of graft failure	Increased infection-related complications
	Increased risk of delayed graft function	Lower incidence of acute rejection
	Increased transplant vasculopathy	Increased risk of graft failure

kines [6]. Last, the major characteristics of aging kidney are a decrease in glomerular filtration rate, loss of functioning nephrons, and increase of glomerulosclerosis and tubular atrophy. These features can contribute to decreasing the functional reserve of kidneys received from elderly donors, which might increase their susceptibility to IR injury and decrease transplant kidney function. Table 1 summarizes the effects of aging on donor kidney and transplant recipients after KT.

Although acceptance of older adults as living kidney donors appears appropriate, the decline in kidney function after donation in elderly donors requires precise pretransplant donor workup. Because most LD have reduced kidney function after donation, all older LD candidates should continue to be assessed and carefully selected to minimize the risk of post-donation adverse outcomes [10]. Thus, a living kidney donation from elderly donors who have been thoroughly screened and continuously followed up can be safe. In cases of DDs, the Kidney Donor Risk Index and Kidney Donor Profile Index scoring systems are widely used to predict posttransplant graft function. The use of these indicators can aid in selecting suitable elderly DDs. Taken together, these findings suggest that elderly kidney donors can be acceptable for KT with active preoperative surveillance and careful perioperative management.

Currently, elderly recipients and donors are no longer a contraindication of KT. Transplant programs should consider older patients with ESRD as acceptable KT candidates if any contraindications do not exist during the evaluation process. The decision regarding eligibility for KT in elderly recipients must be made in the best interest of recipients based on objective medical and surgical criteria. The use of selected kidneys from elderly donors can result in favorable

patient and graft outcomes and expand the donor pool. Further research and public debate on patient selection and appropriate management of older donors and recipients are needed to improve patient and graft survival after receiving or donating a kidney.

Conflicts of interest

The author has no conflicts of interest to declare.

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