Medically Complex Living Kidney Donors: Where Are We Now?

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Selecting living kidney donors has always been controversial.[1] The number of patients reaching end-stage renal disease (ESRD) and potentially benefiting from kidney transplants continues to grow. A major limiting factor in kidney transplantation continues to be the shortage of donor organs. Availability of organs from deceased donors has remained stagnant. The availability and acceptability of kidney donation from deceased donors vary widely across cultures. Some transplant programs, such as those in Japan, do not readily accept deceased donors. One predictable result of these forces has been increased demand to consider a broader array of potential living kidney donors than ever before.

Living kidney donors voluntarily undergo anesthesia and surgical procedures from which they do not directly benefit in a medical sense. These procedures necessarily entail some risk. Although outcomes for living kidney donors

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has been excellent in the near term after nephrectomy, concerns have been raised that donor nephrectomy may place these individuals at slightly higher risk for loss of kidney function and ESRD than they might have had otherwise.[2]

In recent years, selection criteria for living donors have been expanded to include older age groups.[3] This trend has developed in parallel with the advancing age of potential transplant recipients, many of whom receive kidneys from spouses or siblings. Not surprisingly, older age groups are more likely to have identifiable comorbid conditions, such as hypertension, obesity, and glucose intolerance (Figure 1). These individuals regularly have other cardiovascular risk factors, including dyslipidemias. How best to evaluate and manage these disorders over the long-term differ between transplant programs and regions. Categorically excluding such donors obviously risks limiting the benefits of renal transplantation to their recipients. What the impact of these specific conditions, particularly when they appear together, may be regarding the condition of the donated organ and/or subsequent outcomes for

the donor has been controversial. Some programs, including our own, stratify "acceptable" levels of associated medical conditions, such as blood pressure, body weight, and glycemia to different levels by age group. This approach acknowledges the age-related changes in these conditions and reduction in lifetime exposure risk associated with older age.

These issues remain vigorously debated in the transplant world. Major conferences and consensus groups (e.g., Kidney Disease: Improving Global Outcomes) have attempted to unify standards for "acceptable" risk to transplant donors.[1] The overall clinical outcomes for living donors have been remarkably good, with numerous studies identifying minimal added risk for cardiovascular disease or other nonrenal problems. Some studies, but not all, suggest that some kidney donors face a slight, but measurable, risk of ESRD above comparably screened, "normal" populations.[4] The risk of ESRD within donors remains below that of the "general" (unscreened) population.

An important limitation of previous population-based studies has been the absence of data regarding both the support and outcomes of appropriate medical management of these "risk factors," particularly when they appear together. Most of these "medical complexities" can be managed medically, suggesting that perhaps some of the incremental risk can be reduced.

The current report by Hiramitsu et al.[5] addresses several of these questions with data from 802 living kidney donors from Japan observed between 2008 and 2016, with a median follow-up of 56 months.
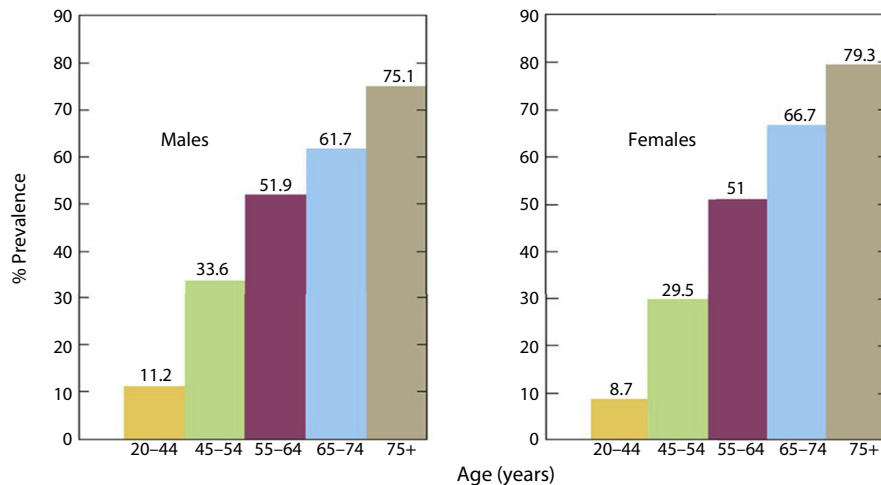
Figure 1. Current prevalence of hypertension in the general U.S. population, based on blood pressure >140/90 mm Hg and/or antihypertensive drug therapy. Figures are undoubtedly higher with the current American Heart Association guidelines that define blood pressure >130/80 mm Hg as hypertensive. These and similar population-based data emphasize the inexorable accumulation of comorbid risks associated with aging. The current study suggests that, when carefully managed, such comorbidities have only minor effects on changes in renal function and/or proteinuria after kidney donation.[7]

Programs from Japan have accepted more liberal criteria to expand availability of transplantation within the context of government-ensured medical management for donors in follow-up. These authors defined subgroups of accepted living donors with a cumulative range of preoperative comorbidities (PCs) (between 0 and 3). They broke them into groups considered healthy (0 comorbidities, $n = 214$), medically complex with 1 abnormality (PC1, $n = 302$), 2 abnormalities (PC2, $n = 196$), or 3 abnormalities (PC3, $n = 90$). It should be emphasized that these "abnormalities" were relatively minor (blood pressure above 140/90 or antihypertensive drug treatment; glucose intolerance: elevated glucose with or without treatment, but HbA1c <6.5% and normal albumin/creatinine ratio; dyslipidemia: high-density lipoprotein <40, low-density lipoprotein >140, or triglycerides >150 mg/dl, or treatment; obesity: body mass index >30 kg/m^2). Importantly, the Japanese health system supports treatment of these conditions, so

insurance and follow-up care did not pose a barrier to management of these abnormalities, either before or after kidney donation. Most of these individuals indeed were treated effectively throughout the follow-up periods up to 8 years. Not surprisingly, mean ages rose progressively with accumulated abnormalities from a mean of 52.3 years in the zero comorbidity group to 65.3 years in the PC3 group. Medical abnormalities were more prevalent in men for each of the groups with defined comorbidities. Preoperative conditions were generally well-managed, with average levels within the most complex group (PC3) of a mean preoperative blood pressure 132/76 mm Hg, low-density lipoprotein cholesterol 123 mg/dl, fasting glucose 105 mg/dl, and body mass index 24.4 kg/m^2. Dyslipidemia was common in all cohorts, and obesity was rare. Hence, these groups of abnormalities mainly differed based on the increasing prevalence of hypertension (rose from 15.2% [PC1] to 98% [PC3]) and glucose intolerance (rose from 18.5% [PC1]

to 100% [PC3]). An important finding from this study indicated that the degree of interstitial fibrosis, glomerulosclerosis, and arteriolosclerosis on the implantation biopsy routinely obtained was correlated with the presence of multiple comorbidities (PC3). These data are consistent with data from implantation biopsies in other cohorts.[6] The effect of single or double abnormalities was no longer evident when adjusted for age and sex. Follow-up measurements of the changes in kidney function over time were compared for all of these groups. Importantly, changes in estimated glomerular filtration rate (GFR) were approximately 30 ml/min per 1.73 m^2 for all subjects and did not differ based on the presence or absence of these comorbidities. Proteinuria was low, but rose slightly in subjects with combined hypertension and glucose intolerance to levels above baseline, although it remained within the normal range. No identifiable difference in mortality was observed up to 120 months after kidney donation after stratification for ages younger than or older than 60 years.

These observations are reassuring in several respects. They support the effective practices in Japanese transplant centers regarding close follow-up and treatment of individuals with hypertension, glucose intolerance, and other risk factors in potential and actual kidney donors. Importantly, the observation that initial reductions in estimated GFR after donor nephrectomy were not associated with worsening proteinuria or progressive loss of GFR over long-term follow-up argues against labeling kidney donors as having a chronic kidney disease (stage 2–3 chronic kidney disease). Furthermore, these results again highlight structural changes within the kidney associated with aging and comorbidities, including glucose

intolerance and hypertension. Remarkably, these changes on the implantation biopsy had little effect on kidney function in the donors over the follow-up period.

One must recognize the limitations of these data, of course. The authors themselves acknowledge that follow-up remains relatively short-term. Most importantly for Western readers, however, one must acknowledge that the degrees of obesity and glucose intolerance among American and European populations are more substantial than in Japan. Although hypertension and lipid disorders lend themselves to straightforward management, glucose intolerance and obesity become more complex and are not easily reversed. In many Western societies, they tend to be relentlessly progressive. The degree to which donor nephrectomy in individuals outside of Japan magnifies the risk to long-term kidney function likely will remain controversial. Taken together, these data nonetheless support the limited adverse effect of comorbid conditions associated with aging on long-term outcomes of kidney donation, particularly when they are carefully managed.

DISCLOSURE

The author declared no completing interests.

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