Chronic kidney disease is a major public health problem in the United States. Recent observations indicate that nearly 20 million adult Americans have some degree of chronic kidney disease and that the majority are not those with end-stage disease but have various stages of milder degrees of kidney damage. However, for those with kidney disease not on dialysis (or transplanted), the risk for progression of kidney disease to end stage is markedly increased; moreover, these individuals are at very high risk for nonrenal cardiovascular events, such as myocardial infarction, stroke, heart failure, and sudden death. Several recent studies indicate that chronic kidney disease is an independent risk factor for cardiovascular morbidity and mortality, and this relationship is graded, continuous, and inversely related to the level of estimated glomerular filtration rate. Still, it is not yet known whether chronic kidney disease is simply a marker of underlying serious cardiovascular disease or whether the kidney disease itself contributes the risk, perhaps through accumulation of unwanted (detrimental) metabolites, the presence of a uremic milieu, or through known risk factors, such as hypertension. Both hypertension and diabetes are major risk factors for the development and progression of kidney disease; other factors related to cardiovascular health have also been implicated, including homocysteine, abnormal calcium phosphorus metabolism, chronic inflammation, anemia, and oxidative stress.

Renal transplantation is currently the optimal treatment for end-stage kidney disease and is associated with improved quality of life, as well as survival advantage, as compared with any chronic dialysis modality. Living donor kidney transplantation has increased dramatically in the past several years as the shortage of organs, especially from cadaver donors, has sharply limited the ability to fulfill the needs of those on transplant waiting lists. Living donor transplants, whether or not from related individuals (eg, parent or sibling), provide superior results as compared with cadaveric kidney transplant overall. Although transplanted individuals have a better outcome than those on dialysis, these individuals remain at high risk for cardiovascular disease because of continuing risks from persistent hypertension, dyslipidemia, long-term corticosteroid and immunosuppressive drugs, and secondary hyperparathyroidism. Consequently, cardiovascular disease is the main cause of mortality among those who have undergone successful kidney transplantation. Therefore, identifying and treating cardiovascular risk in this population remains an important unmet need.

Detection of risk factors for the development of kidney disease among donors, as well as development and progression of kidney damage among transplant recipients, are important clinical issues. The National Kidney Foundation is developing guidelines for living transplant donors in order to address these issues. Aortic stiffness has been identified as a marker for cardiovascular risk independent of age, atherosclerosis, blood pressure, drug treatment, and presence of native kidneys in kidney transplant patients. Pulse wave velocity (PWV) is a measure of aortic stiffness, and higher PWV correlates with cardiovascular events in dialysis patients. In this issue of Hypertension, Bahous et al sought to do the following: (1) discover whether there is a consistent difference in the factors influencing aortic stiffness in kidney donors and their matched controls; and (2) determine whether the determinants of aortic PWV include not only the renal immunologic conflict because of transplantation, but also other unidentified factors related to donor arterial structure and function. The authors studied renal transplant recipients, their respective living donors (90% were living related), and a control group of nondonors without kidney disease in a longitudinal analysis to evaluate the relationships between PWV and kidney function. They found that aortic PWV was significantly higher in donors as compared with nondonors at follow-up and that this increase was independent of blood pressure, age, and gender. They also found a higher aortic PWV in transplant recipients as compared with age and gender-matched nondonor controls. As expected age, mean arterial pressure, smoking status, and time since donation were factors associated with increased aortic PWV in the living donor group. Interestingly, factors influencing donor pulse pressure (PP) evaluated at end of follow-up PWV included proteinuria and/or microalbuminuria. On the other hand, analysis of proteinuria and/or microalbuminuria as dependent variables revealed that their presence was influenced, not only by end of follow-up PP, but also by time since donation, yet mean arterial pressure had no influence in this regard.

In kidney recipients, PWV was also increased as compared with age- and gender-matched nondonor controls. They also found that the most powerful predictor of aortic PWV in transplant recipients was age followed by blood pressure.
However, transplant rejection and smoking played minor roles in explaining the higher PWV. Interestingly, among control groups, family members of donors as compared with unrelated historic controls were more likely to be female, heavier, and with higher diastolic blood pressure and lower pulse pressure at follow-up. The authors conclude that, “This study is the first to show that increased pulse wave velocity, a marker of cardiovascular risk, may be elevated along the life of donors by comparison with healthy controls.” But they properly note that additional studies are needed to confirm that this is in fact the case. The study did not provide longituidal comparisons of the normal controls and the donor controls. In addition, information on albuminuria or proteinuria (note that proteinuria was not an exclusion criterion for a kidney donor in this study) over time in the donors, including before donation, is not provided. Moreover, the authors could not find a consistent difference in the factors determining PWV in the donors and their recipients.

It is not surprising that the regression models identify different factors that contribute to PWV in donors and recipients, including kidney rejection. But the transplant recipients also have higher residual hypertension, dyslipidemia, vascular calcification, cardiac hypertrophy, and other factors. In addition, comparisons between donors and control populations should be interpreted with caution. For example, the statement that the PWV was increased in the donor as compared with the control population is misleading. Because a change was not measured, it is impossible to know whether the PWV is increased compared with the nondonor controls. The PWV is, on average, higher in the donors than in the nondonor control group, but this difference does not reflect an increase in anything, because a single measurement was used for the comparisons. Thus, the difference could easily be because of chance variation among donor and nondonor controls. This study had no measures or markers of genetics, yet the authors imply, based on noninvasive physiological surrogate markers, that some genetic determinants of the donor kidney influenced the aortic stiffness in the transplant recipients. Although this is possible, there are no data to support this suggestion. The authors appropriately caution us that additional studies, including genetic studies, would be needed to confirm or refute this possibility.

Many confounding variables cannot be accounted for in this analysis, including the fact that transplant patient behaviors and clinical management could have changed dramatically over the 14-year period during which the cases of kidney transplant were cumulated. In this regard, it is possible that the donor population changed its behaviors as well, and the accuracy and reproducibility of PWV notwithstanding, a single measurement is not likely to provide much predictive power for future events among donors.

The most important aspect of this study is the ability to achieve a high follow-up observation rate among donors. The authors are positioned to conduct long-term follow-up of both donors and recipients, which may provide new insights into the relationships among PWV, aortic stiffness, and renal and cardiovascular outcomes.

What can we conclude about the two main issues studied by the authors? First, the authors did not find significant differences among factors that account for PWV in transplant recipients and their donors, and, second, they did not find any contribution of donor arterial structure (there were no measures of structure) or function [PWV of the donor (see Table 5 in Bahous et al) was not significant in the regression model of the recipient] as a contributing factor to PWV in recipients. Thus, the authors were able to exclude these two issues as important contributing factors in this patient population under the circumstances of this analysis.

What can one conclude about long-term consequences of kidney donation on donor kidney function from this study? Because there is no information on change in kidney function or cardiovascular events among donors, we cannot conclude anything about these important outcomes. However, the data indicating that albuminuria, hypertension, dyslipidemia, and smoking are prevalent in the donor population studied over 14 years at this center would suggest that these donors should be monitored closely and managed properly for risk. In the absence of measurement of creatinine clearance at baseline (eg, within a few months after donation), it is not possible to determine whether or not there was any decline in remnant kidney function among donors. Still, it is reassuring that kidney function of the remaining kidney remained, on average, normal for the donor population at the follow-up time point. This provocative observation should provide fodder for close and long-term follow-up of donors and recipients with regard to renal and cardiovascular outcomes. This study tells us that larger scale and long-term follow-up of donors and kidney transplant recipients is needed to identify important clinical variables that can predict outcomes and, thus, provide new insights into the diagnosis and management of kidney and cardiovascular disease.

References


Pressure, Waves, and Kidney Outcomes in Kidney Transplant Donors and Recipients
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