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Heterogeneous Cardiovascular Profiles in CKD: ADPKD Versus non-ADPKD

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Chronic kidney disease (CKD) is defined as kidney damage or a sustained decrease in glomerular filtration rate, irrespective of the cause.[1] For simplicity, we often lump all kidney diseases into a single entity of "chronic kidney disease" and describe the level of kidney function with estimated glomerular filtration rate and degree of albuminuria. In reality, the term CKD encompasses heterogeneous pathologies with unique renal and extrarenal manifestations as well as prognosis. One such example is autosomal dominant polycystic kidney disease (ADPKD). The renal pathology, natural history, and extrarenal manifestations in ADPKD differ from the more common causes of CKD, such as diabetes mellitus and hypertension. Thus comes an important question-what is the cardiac outcome of ADPKD patients post-transplant? Is the cardiac risk profile in ADPKD patients similar to patients with end stage kidney disease (ESKD) from other causes?

ADPKD is the most common inherited kidney disease. Whereas ADPKD makes up approximately 5% of patients who commence dialysis every year in the United States, cystic diseases, of which ADPKD forms the major proportion, make up almost 10% of all kidney transplants.[2] Patients with ADPKD have a better chance of being listed for kidney transplant. Once listed, they also have a better chance of receiving a kidney transplant, and a lower waitlist mortality compared to patients with ESKD secondary to diabetes. These observational data reflect a survival advantage for patients with ADPKD. Whether this survival advantage is due to a lower risk of cardiovascular disease remains controversial. Cardiovascular disease is a major cause of mortality in CKD, accounting for almost 50% of all deaths in CKD stages 4 to 5 and patients on dialysis. Even after a successful kidney transplant, cardiovascular disease remains a major risk for mortality post-transplant. CKD itself is 1 of the strongest risk factors for cardiovascular disease. In fact, the risk for developing cardiovascular disease in patients with CKD surpasses the risk of reaching ESKD. CKD results in cardiovascular disease in multiple ways. It is associated with characteristic changes in blood vessels and the heart from hemodynamic changes as well as high circulating inflammatory mediators, and other enzymes and hormones. Both cardiovascular disease and CKD share common risk factors, such as hypertension, dyslipidemia, smoking, and hyperglycemia. In addition, CKD increases the risk of vascular and valvular calcification. The subsequent changes in hemodynamics, including increase in pulse wave velocity, increased cardiac afterload, and left ventricular hypertrophy then leads to decreased cardiovascular perfusion. Low vitamin K and serum magnesium levels exacerbate calcification. Vitamin K repletion retards valvular calcification.[3] Similarly, magnesium interferes with hydroxyapatite crystal formation and halts vascular calcification in advanced CKD.[4]

The evaluation for kidney transplantation is a complex process where cardiac evaluation is 1 of the key components. Echocardiograms and/or cardiac stress tests are requested from a majority of potential candidates to assess risks of both short-term and long-term cardiac events. Though ADPKD itself may not affect the blood vessels in the way that diabetes does, resultant CKD, stimulation of the renin-angiotensin-

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aldosterone system from compression of the renal vasculature from cyst growth causing local ischemia, and associated hypertension can lead to left ventricular hypertrophy and vascular endothelial damage.[5] Indeed, components of the renin-angiotensin-aldosterone system, such as renin, angiotensinogen, angiotensin-converting enzyme, angiotensin II receptor, and angiotensin II peptide have been detected in renal cysts in ADPKD.[6] In addition, polycystin products PC1 and PC2 are found in vascular muscle cells, endothelial cells, and cardiomyocytes with alterations in cell function. Insulin resistance, endothelial dysfunction, inflammation and mineral metabolism disorders, valvular abnormalities, especially affecting the mitral valve, and vascular aneurysms are more common in ADPKD than in the general population.[7] Despite a lower cardiac risk profile than some other causes of ESKD, cardiovascular issues remain a major cause of morbidity and mortality in patients with ADPKD.

In the study by Chedid *et al.*,[8] the authors evaluated cardiac profile pretransplant and assessed cardiovascular outcomes post-transplant in patients with ADPKD in comparison to patients with ESKD from other causes. The authors assessed a large cohort of over 2700 kidney transplant patients with pretransplant echocardiograms at a single large academic center. Comparisons between patients with ADPKD, patients with diabetic nephropathy, and those with a cause of ESKD that is not ADPKD or diabetes were made using propensity score matching based on age and sex at kidney transplantation. Not unexpectedly, patients with ADPKD were found to have lower rates of left ventricular hypertrophy and less left ventricular systolic and diastolic dysfunction at the time of transplantation. Patients with ADPKD also had the best post-transplant survival, as would be expected given their pretransplant cardiovascular profile. Nevertheless, patients with ADPKD experienced worsening in valvular function on repeat echocardiogram and an increase in the sinus of Valsalva diameter post transplantation. Interestingly, patients with ADPKD in this study had lower rates of mitral regurgitation and tricuspid regurgitation at the time of transplantation compared to patients without ADPKD, despite known associations between ADPKD and mitral and tricuspid valve dysfunction.

This study is unique because it sought data from echocardiograms, genetic analysis for patients with ADPKD, and detailed clinical data from electronic medical records which are not available in large registries and databases such as the United States Renal Data System and the Scientific Registry of Transplant Recipients. The comparison of patients with ADPKD with propensity score matched controls is also a strength of this study. In addition, the availability of post-transplant echocardiograms allowed the evaluation of changes in cardiac status after transplantation. Nevertheless, this comparison was somewhat limited by the reduced numbers of patients who received echocardiograms compared to pretransplant, and the potential for indication bias in the patients who received these examinations post-transplant because the reasons for patients receiving these post-transplant echocardiograms were not reported. It is also important to note that the cohort of patients selected for kidney transplantation is a highly selected cohort of patients with ESKD who have undergone extensive pretransplant evaluation. Therefore, the cardiovascular findings in this study reflect this highly selected cohort and not the cardiac status of patients with ESKD in general. This may explain the lower rates of mitral and tricuspid regurgitation at the time of transplantation seen in patients with ADPKD in this study, because patients with ADPKD with significant valvular disease found during pretransplant evaluation would likely have been excluded from transplantation.

Overall, the study adds important insights into the cardiovascular profile of patients with ADPKD who received a kidney transplant, in comparison to patients with diabetes and those with other causes of ESKD. Further research into the prevalence and progression of valvular heart disease in patients with ADPKD post-transplant may help guide the cardiovascular care these patients.

DISCLOSURE

All the authors declared no competing interests.

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