Defined by the Company One Keeps: The Importance of Cardiac Comorbidities after Kidney Transplant Cardiac Remodeling and Outcomes

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Aesop –
“A man is known by the company he keeps”

Patients with chronic kidney disease (CKD) have an increased risk of cardiovascular disease (CVD) compared with the general population [1]. Especially in those with advanced CKD or on hemodialysis (HD), CV mortality is 10-fold higher [2]. Many factors account for this, including a high prevalence of risk factors for coronary artery disease (CAD) such as diabetes mellitus (DM), hypertension (HTN), hyperlipidemia, but also other, less appreciated factors such as hemodynamic stressors as volume and pressure overload, anemia, uremic toxins, endothelin, parathormone, alterations in calcium and phosphorus metabolism, and homocysteine [3]. This constellation of cardiac pathology is sometimes termed uremic cardiomyopathy and often includes progressive left ventricular hypertrophy (LVH) and/or systolic dysfunction [4].

Even though kidney transplantation (KT) improves survival rates compared to the patients on HD, the risk of CV events remains higher in transplant recipients compared with the general population, and 60% of all deaths are from CV causes [5]. In addition, death from CVD is

also the most common cause of graft loss, accounting for 30% of graft loss overall [6].

There is a strong two-way interplay between CKD and CVD. CV mortality is increased in patients along the entire spectrum of severity of their CKD – in those who are not yet on HD, in those who are on HD, as well as in those who redevelop CKD after successful KT. Similarly, poorer cardiac function worsens renal function and leads to more rapid progression of CKD, which is often clinically recognized as the cardiorenal syndrome [7]. Cardiac adverse remodeling that occurs in both the structural and functional dimensions is an important determinant of this CV mortality, and as such, study of the alterations of LV structure and function prior to and after KT allows longitudinal tracking of those patients who improve and those who remain at high risk for CV complications [8]. LV structural remodeling such as diffuse interstitial fibrosis occurs early in CKD and is associated with myocardial dysfunction [9]. Such changes can be tracked using cardiac MRI (CMR) T1 mapping that can quantify interstitial fibrosis, and also by measuring strain using echocardiography [9, 10]. Additionally, the development of LVH either by echocardiography or more accurately by

CMR increases as renal function deteriorates and predicts future cardiovascular events [11]. Several studies have now shown that cardiac structure and function can also improve after KT – in particular, regression of LVH has been well studied. In a large South Korean study of 767 patients undergoing KT, LVH by transthoracic echocardiography was seen in 71% and declined to 66% at 1 year and to 57% at 5 years after KT. LV geometry also normalized from 20% at baseline to 22% at 1 year and to 27% at 5 years after KT [12]. Longstanding HTN and diabetes are the usual causes of LVH in such patients. LVH is related not only with worse cardiac but also with worse renal outcomes in this population. Although HD reduces uremic symptoms and improves the quality of life, it may paradoxically exacerbate LVH due to repetitive hemodynamic stresses. In the Frequent Hemodialysis Network Daily Trial, CMR showed less LVH in the group being dialyzed six times per week as compared with the conventional, three-times-per-week group [13]. Reasons for this may include better uremic toxin clearance and better intravascular volume and blood pressure control. In a study of 105 KT recipients [14], LV mass index (LVMI) by echocardiography decreased 13.0 g/m² after KT. In another study, An et al. [12] reported similar results showing LVMI improvement of 9.2 g/m² at 1 year and 19.1 g/m² at 5 years after KT. Along the lines of cardio-renal interaction alluded to above, LVH that does not regress after KT is associated with renal graft failure. Three pretransplant clinical factors have been identified with lack of LVH regression – these include time on HD, high blood pressure, and anemia.

Aside from these morphological alterations such as LVH discussed above, LV systolic function also plays an important role in cardiorenal outcomes in these patients. In a study that examined the impact of pretransplant LV function on graft survival, an LVEF of <50% was associated with poorer graft survival [15]. In another large retrospective echocardiography study of 232 patients, LVEF overall improved from 53 to 56% [16], and in particular in the 66 patients who had baseline LV systolic dysfunction, it improved from 41 to 50% ($p < 0.001$). These patients had better CV outcomes than those in whom it did not improve.

Kobayashi et al. [17] demonstrate that the presence of CV comorbidities prevents reverse cardiac remodeling after KT. In their single-center substudy of the prospective DIVAT (computerized and VAlidated data in Transplantation) French database of transplanted patients, they included 56 patients who had echocardiographic data prior to and a median of 24 months after KT. The

mean age of the study participants was 48 ± 15 years, 73% were male, and 98% had HTN at baseline. The mean LVEF improved from 63.9% prior to KT to 69.6% after kidney transplantation, whereas there was no significant change in LVMI or in diastolic parameters. In multivariate analysis, valvular heart disease, CAD, heart failure, and DM were associated with no significant or smaller improvement in cardiac structure and function following KT. The limitations of this study are that it is a retrospective non-randomized, small study and is subject to bias and also unable to define causality. Furthermore, the follow up was short. Nonetheless, the premise that the higher the burden of pre-existing CV comorbidities, the lesser the cardiac recovery that follows KT makes intuitive sense, and can likely be explained by the degree of myocyte dysfunction that precedes the KT. If cardiac dysfunction has already progressed substantially pre-KT, it may not recover fully and/or take longer time to show recovery than the short time duration that the present study lasted.

The authors should be congratulated for their well-designed and conducted analysis, which adds to the extant literature on this topic. The main message of the present study is that patients with cardiovascular co-morbidities that frequently coexist in such patients, such as CAD, DM, heart failure, or valvular heart disease, had limited favorable cardiac reverse remodeling after KT. This is not unexpected and likely has to do with more extensive cardiomyocyte pathology at baseline when such conditions that cannot be fully captured by metrics, such as LV mass or ejection fraction, coexist. More sensitive imaging techniques to look at myocyte structure and function such as echocardiography and CMR tissue characterization, elastography, diffusion tensor imaging, and multiparametric strain may need to be employed to pick up these changes. As such, this study adds to the literature in confirming the strong interplay that occurs in the cardiorenal axis wherein disease progression in one organ fuels progressive pathology in the other organ and vice versa. Ultimately, for optimal outcomes, we would need to arrest disease progression simultaneously in both organs before this companionship turns sour.

Disclosure Statement

The authors declare that they have no conflicts of interest to disclose.

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