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Review

Late renal dysfunction after pediatric heart transplantation

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ABSTRACT

Acute as well as chronic renal dysfunctions are a common complication after pediatric heart transplantation and both increase the risk of post transplant morbidity and mortality. The severity of chronic kidney disease after heart transplantation varies from mild dysfunction to end stage renal disease requiring dialysis and/or renal transplantation. Multiple risk factors are involved including preexisting renal disease, peri-transplant hemodynamic renal insults and long-term exposure to calcineurin inhibitors post-transplant. Close monitoring and surveillance of renal function, high blood pressure, and proteinuria are recommended to detect chronic kidney disease at an early stage. Use of calcineurin inhibitor sparing regimens with a close monitoring of drug levels can help slow the progression. In order to prevent further injury, renal protective strategies should be started early in collaboration with a pediatric nephrologist.

1. Introduction

Heart transplantation has shown exponential advances with improved outcomes in children with end-stage heart disease [1]. However, with increasing patient and graft survival rates, chronic kidney disease (CKD) has emerged as an important complication after pediatric heart transplantation with increased risk of post transplant morbidity and mortality in adults as well as children [2–4]. Lee et al. reported a nine fold increased risk of death in children who develop severe renal dysfunction after heart transplantation [5].

The severity of CKD after transplantation may vary from mild renal dysfunction to end-stage renal disease (ESRD) requiring dialysis and/or renal transplantation. The magnitude of the problem is highlighted by the International Society for Heart and Lung Transplantation (ISHLT) registry, which reports 5–13% of pediatric patients needing renal replacement therapy by 13 years after heart transplantation [1].

CKD after heart transplantation is due to multiple factors. These include pre-transplant renal dysfunction due to congenital or acquired causes, peri-transplant hemodynamic renal insults, and long-term post-transplant exposure to calcineurin inhibitors (CNI) [6,7]. In this review, we also discuss the role of close monitoring and pre-emptive management strategies to prevent ongoing renal injury after heart transplantation in children.

2. Definitions

According to the Kidney Disease Outcomes Quality Initiative (K/DOQI) of the National Kidney Foundation (NKF), CKD is defined as kidney damage for at least 3 months, as defined by structural or functional abnormalities of the kidney, with or without decreased glomerular filtration rate (GFR) [8]. CKD is further divided into Stages 1–5, corresponding to the severity of chronic renal dysfunction and nature of complications of CKD (Table 1) [8]. CKD Stage 5 is defined as GFR < 15 ml/min/1.73 m^2 or initiation of renal replacement therapy in the form of dialysis or renal transplantation.

The definitions used in published literature on renal dysfunction after pediatric heart transplantation show a wide variation (Table 2). In the majority of studies CKD is defined as GFR < 60 ml/min/1.73 m^2 for 3 months [4,9]. Di Filippo et al. defined renal dysfunction as GFR < 80 ml/min/1.73 m^2 on two consecutive follow-up visits and severe renal dysfunction as GFR < 50 ml/min/1.73 m^2 [10]. The largest pooled pediatric registry of ISHLT defined severe renal impairment as serum creatinine ≥2.5 mg/dl, dialysis or renal transplant requirement [1]. Such variations in definition lead to conflicting interpretation of the published data.

3. Accurate Measures of Renal Dysfunction

Inulin clearance is the gold standard for GFR measurement, however is rarely used in clinical practice because of a need for a continuous intravenous infusion. Other methods such as creatinine or Iohexol clearance are also not used often in clinical practice in pediatrics because of a need for 24-hour urine collection in former and multiple blood collections in the latter. GFR measurement using nuclear medicine scan (^{99}Tc DTPA or ^{51}Cr EDTA) is a reliable method of assessing renal function

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Table 1
NKF-K/DOQI classification of stages of chronic kidney disease [8].

Stages of CKD	GFR (ml/min/1.73 m^2)	Comment
1	≥90	Kidney damage with normal or increased GFR
2	60–89	Kidney damage with mild reduction in GFR
3	30–59	Moderate reduction in GFR
4	15–29	Severe reduction in GFR
5	<15 or dialysis/transplant	Kidney failure

CKD, chronic kidney disease.
GFR, glomerular filtration rate.
K/DOQI, Kidney Disease Outcomes Quality Initiative.
NKF, National Kidney Foundation.

[11]. However, most isotope clearance tests are time consuming and hence not used for routine monitoring. For day to day patient care, GFR is most commonly estimated (eGFR) using serum creatinine and height in the Schwartz equation [12]. However, in a study in a pediatric heart transplant cohort, the mean eGFR was over estimated by 33 ± 26 ml/min/1.73 m^2 when compared to measured GFR using ^{99}Tc DTPA [13]. Pediatric heart transplant recipients have low serum creatinine due to reduced muscle mass and poor nutritional status from long-standing heart failure. As a result, eGFR may underestimate the severity of CKD. Cystatin C, an endogenous marker independent of muscle mass, provides better estimate of kidney function as compared to creatinine and initial studies have shown promising results in pediatric heart transplant patients [14]. The creatinine–cystatin C based chronic kidney disease in children (CKiD) equation has also been developed to accurately estimate GFR [15].

4. Prevalence of CKD

A wide variability in prevalence of CKD after pediatric heart transplant is noted in literature. This is a result of difference in definitions of CKD and its severity, and differences in methods used for measuring GFR. The inclusion and exclusion criteria and the follow-up duration post transplant are varied, and contribute to inter-study difference. Most studies are single center with relatively small number of patients. Pooled data from ISHLT registry has to be interpreted with caution to account for the differences in immunosuppression protocols at various centers. Thus, defining prevalence of CKD after heart transplantation is challenging. A comparison of key pediatric studies and their reported prevalence is shown in Table 2.

Feingold et al. [4] utilized a large, multi-institutional Pediatric Heart Transplant Study (PHTS) database to determine renal function in children after heart transplants. Authors focused on late renal dysfunction (eGFR < 60 ml/min/1.73 m^2 at >1 year post transplant) in children who had relatively preserved renal function (eGFR ≥ 60 ml/min/1.73 m^2) at one-year post transplant. Late renal dysfunction (Stages 3–5 CKD) was noted in 29% of patients at 5 years, and 43% of patients at 10 years [4]. Gijsen et al. conducted a systematic review of literature in children after heart and/or lung transplant who were on tacrolimus-based regimen. They reported a prevalence of mild CKD (Stages 1–2) one-year post transplant in 22.7% to 40% of patients and severe CKD (Stages 3–5) in 6.8%–46% of patients [9].

The burden of ESRD (dialysis or renal transplant) in pediatric heart transplant and other solid organ transplant patients can also be evaluated from Scientific Registry of Transplant Recipients (SRTR) data. Of 5569 children who underwent heart transplant in this 20-year national cohort, 3% were diagnosed with ESRD during a median follow-up period

Table 2
Summary of studies on prevalence and progression of CKD after pediatric heart transplantation.

Author (Reference)	Year	N	Study design	CKD definition	Follow-up	Prevalence/progression
Dipchand et al. [1]	2014	>11,000	ISHLT registry (2000–2012)	Creatinine >2.5 mg/dl, dialysis or renal transplant	13 yrs	Renal replacement therapy (dialysis or transplant): 5–13%
Ruebner et al. [16]	2013	5569	SRTR registry (1999–2010)	ESRD: chronic dialysis or renal transplant	5.6 yrs. (median)	ESRD: 3%; incidence rate of ESRD 4.4/1000 person–years, median time to ESRD 10.2 yrs
Tang et al. [21]	2011	3598	UNOS database (1993–2008)	Creatinine >2.5 mg/dl, chronic dialysis/transplant	7 yrs renal function data	Severe renal dysfunction: 1% at 1 & 5 yrs
Feingold et al. [4]	2011	812	PHTS database (1993–2006)	eGFR < 60 at >1 year	4.1 yrs (median)	Late renal dysfunction: 5 yrs: 29%, 10 yrs: 43%
Bharat et al. [13]	2009	91	Retrospective (Single-center)	mGFR and eGFR	5 yrs (median)	Mild CKD (GFR 60–90): 1 yrs: 16%, 5 yrs: 67%, severe (GFR < 30): 7 yrs: 8%
Simmonds et al. [27]	2009	100	Retrospective (Single-center)	eGFR (NKF-K/DOQI)	5.3 yrs (mean)	Tacrolimus group: mild CKD 40%, moderate CKD 14%. Cyclosporine switch group: mild CKD 52%, moderate CKD 10%
Sachdeva et al. [19]	2007	77	Retrospective (Single-center)	eGFR < 75	5 yrs (median)	Pre-transplant: 33%, 1 yrs: 17%, 3 yrs: 21%, 5 yrs: 26%
Lee et al. [5]	2007	2032	SRTR registry (1990–1999)	Creatinine >2.5 mg/dl, ESRD	7 yrs (mean)	10 yrs actuarial risk for CKD: 11.8%, ESRD: 4.3%
Di Filippo et al. [10]	2005	88	Retrospective (Single-center)	eGFR < 80: dysfunction, eGFR < 50: severe	7 yrs	Renal dysfunction (eGFR < 80): 21%, severe renal dysfunction (eGFR < 50): 6.8%
English et al. [18]	2002	123	Retrospective (Two-center)	eGFR & mGFR	7 yrs	Steady decline in GFR over time. Tacrolimus group GFR: 1 month: 98, 5 yrs: 90 Cyclosporine group GFR:1 month:110, 5 yrs: 81
Pradhan et al. [17]	2002	46	Retrospective (Single-center)	eGFR % normal for age	9 yrs	eGFR < 75% at transplant: 22%, 1 yrs: 55%, 5 yrs: 85%. eGFR < 50% at 5 yrs: 15%
Hornung et al. [29]	2001	54	Retrospective (Single-center)	Mean eGFR	5 yrs (median)	Mean eGFR At transplant: 79, 1 yr: 72, 2 yrs: 65, 4 yrs: 60 (n = 35), 8 yrs: 57 (n = 14)

CKD, chronic kidney disease.
ESRD, end stage renal disease (need for dialysis or transplant).
eGFR, estimated glomerular filtration rate using Schwartz formula.
GFR, glomerular filtration rate in ml/min/1.73 m^2.
ISHLT, International Society of Heart and Lung Transplantation.
K/DOQI, Kidney Disease Outcomes Quality Initiative.
mGFR, measured GFR.
NKF, National Kidney Foundation.
N, number of study subjects.
PHTS, Pediatric Heart Transplant Study.
SRTR, Scientific Registry of Transplant Recipients.
UNOS, United Network for Organ Sharing.