Published in final edited form as:

Prog Pediatr Cardiol. 2016 June ; 41: 33–40. doi:10.1016/j.ppedcard.2015.12.006.

PROGRESSION OF CHRONIC KIDNEY DISEASE AFTER ACUTE KIDNEY INJURY

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Abstract

The incidence of chronic kidney disease (CKD) in children and adults is increasing. Cardiologists have become indispensable members of the care provider team for children with CKD. This is partly due to the high incidence of CKD in children and adults with congenital heart disease, with current estimates of 30–50%. In addition, the high incidence of acute kidney injury (AKI) due to cardiac dysfunction or following pediatric cardiac surgery that may progress to CKD is also well documented. It is now apparent that AKI and CKD are uniquely intertwined as interconnected syndromes. Furthermore, the well-known long-term cardiovascular morbidity and mortality associated with CKD require the joint attention of both nephrologists and cardiologists. Children with both congenital heart disease and CKD are increasingly surviving to adulthood, with synergistically negative medical, financial, and quality of life impact. An improved understanding of the epidemiology, mechanisms, early diagnosis, and preventive measures is of importance to cardiologists, nephrologists, scientists, economists, and policy makers alike. Herein, we report the current definitions, epidemiology, and complications of CKD in children, with an emphasis on children with congenital heart disease. We then focus on the clinical and experimental evidence for the progression of CKD after episodes of AKI commonly encountered in children with heart disease, and explore the role of novel biomarkers for the prediction of CKD progression.

Keywords

Chronic kidney disease; acute kidney injury; congenital heart disease; biomarkers; neutrophil gelatinase-associated lipocalin; kidney injury molecule-1

1. Introduction

The diagnoses of acute kidney injury (AKI) and chronic kidney disease (CKD) are typically approached as two clinical entities with distinct diagnostic and therapeutic pathways.^{1,2} However, these diseases are uniquely intertwined and are increasingly thought of as

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interconnected syndromes.³ CKD has a major impact on health care with an estimated prevalence of 12–14% in the general population.⁴ However, this may under-represent the true prevalence due to limitations in access to care and opportunity for laboratory testing. The prevalence of CKD continues to be a major concern as many of these patients will progress on to end-stage renal disease (ESRD) needing renal replacement therapy and/or kidney transplantation. Approximately 70% of children with CKD from diverse etiologies will progress to ESRD before reaching adulthood. In the current era, the management team for children with CKD has expanded significantly beyond nephrologists. In particular, cardiology has become an integral and consistent stakeholder in this team, due to the high incidence of CKD in children with congenital heart disease, the high incidence of AKI due to cardiac dysfunction or cardiac surgery that may progress to CKD, and the significant long-term cardiovascular morbidity and mortality associated with CKD.^{5–9} Children with both congenital heart disease and CKD are increasingly surviving to adulthood, with enormous and synergistically negative medical, financial, and quality of life impact. Given the potential to institute primary and secondary prevention strategies that minimize CKD progression, an improved understanding of the epidemiology, mechanisms, and early diagnosis is of importance to cardiologists, nephrologists, scientists, economists, and policy makers alike. Herein, we report the current definitions, epidemiology, and complications of CKD in children, with an emphasis on children with congenital heart disease. We then focus on the clinical and experimental evidence for the progression of CKD after episodes of AKI commonly encountered in children with heart disease, and explore the role of novel biomarkers for the prediction of CKD progression.

2. Definition of CKD

CKD is defined as kidney damage for ≥ 3 months with either:

1. structural or functional abnormalities of the kidney, with or without decreased glomerular filtration rate (GFR) as seen by either a) pathological abnormalities or b) markers of kidney damage, including abnormalities in the blood or urine, or abnormalities seen on imaging OR
2. $GFR < 60 \text{ ml/min/1.73 m}^2$, with or without kidney damage.²

It should be noted that even individuals with normal kidney function are included in the CKD definition if they have evidence for persistent renal damage, such as abnormalities in the urine (i.e. persistent proteinuria or hematuria), on kidney biopsy, or imaging tests. On the other hand, patients with a persistently low GFR are also labelled as CKD, even if no abnormalities such as those described above are apparent. CKD is further divided into stages based on estimated GFR (eGFR) with Stage 1 representing those patients having an $eGFR > 90 \text{ ml/min/1.73 m}^2$ and Stage 5 including those patients with an $eGFR < 15 \text{ ml/min/1.73 m}^2$ (Table 1). Children below 2 years of age cannot be staged for CKD using eGFR, because renal development and renal function maturation is still ongoing. However, children younger than 2 years of age can still be classified as moderate or severe CKD if the measured serum creatinine (SCr) is above 2 or 3 standard deviations above the general population, respectively.

3. Measuring or Estimating GFR

Since an assessment of kidney function is essential for the definition and accurate classification of CKD, it is important to consider the commonly used clinical methods for determining GFR. The most commonly used agents for accurate measurement of GFR in clinical practice today include iohexol (a low osmolar, low nephrotoxicity intravenous contrast agent) or radio-isotopes such as ^{99m}Tc -DTPA, ^{51}Cr -EDTA, and ^{125}I othalamate.¹⁰ However, all of these methods are expensive, and require the injection of potentially harmful agents as well as multiple blood draws to determine the clearance of the agent. Therefore, many GFR estimating equations that provide a convenient bedside method to quantify kidney function have been developed. Recently, the Chronic Kidney Disease in Children (CKiD) study¹¹ derived an updated Schwartz formula based on serum creatinine measurements using enzymatic assays:

$$\text{eGFR (ml/min/1.73m}^2\text{)} = [\text{height in cm} \times 0.413] / \text{SCr in mg/dL}$$

This widely used formula is particularly applicable to children 1–16 years of age with a measured GFR between 15–75 ml/min/1.73 m². However, it continues to over-estimate GFR in the CKD population and under-estimate GFR in children with normal kidney function.^{12,13}

As an alternative to SCr-based estimating equations, the use of cystatin C is gaining popularity.¹⁴ Measurement of cystatin C is widely available in most hospitals and laboratories, and has better diagnostic capabilities in CKD.^{15,16} However, some conditions can alter endogenous cystatin C production and may falsely affect GFR estimations. Increased inflammation (including administration of glucocorticoids and other immunosuppressive medications), increased cellular load (as in malignancies), or increased metabolic activity (as in hyperthyroidism) can all elevate plasma cystatin C concentrations without altering GFR.^{17–19} In evaluating children with suspected or confirmed CKD, our current clinical approach is to estimate GFR using both the updated Schwartz as well as a cystatin C-based equation based on a standard immunonephelometric measurement. If the values are within 10% of each other, we use the arithmetic mean. If the values are more than 10% apart from each other, we consider all the confounders that affect serum creatinine and cystatin C, measurements mentioned above that might explain the discrepancy. If accounting for confounders does not provide a rational explanation, we obtain a gold standard GFR measurement (radioisotope GFR).

4. Incidence and Etiology of CKD

CKD has an estimated prevalence of 12–14% in the general population.⁴ However, this is very likely an underestimate of the true prevalence related to limitations in access to care and opportunity for laboratory testing. In adult populations from developed countries, CKD is typically related to systemic hypertension, obesity, diabetes mellitus, and cardiovascular disease.⁸ In particular, it is well known that chronic cardiac dysfunction results in CKD, a relationship that has been termed as cardio-renal syndrome type 2.²⁰ Approximately 25% of adults with chronic heart failure have evidence for CKD, and the degree of CKD is indeed

the strongest predictor of mortality in patients with heart failure.²¹ In addition, numerous recent epidemiologic and experimental studies have revealed that AKI is a major risk factor for CKD, and that CKD is a major risk factor for AKI, thereby identifying these conditions as uniquely intertwined, interconnected syndromes.³

The true incidence of pediatric CKD is unknown. Data from registries are underestimates because most children with CKD are asymptomatic and may go undiagnosed until kidney disease becomes advanced or until after they have attained adulthood. The ItalKids registry estimated the overall prevalence of CKD in Italian children at 75 cases per million, with 12 new cases per million diagnosed per year.²² The 2014 United States Renal Data System report indicated that 7500 US children are living with ESRD, with a yearly incidence rate of about 1200 children.⁴ The prevalence of ESRD in European children is currently estimated at 90 cases per million with an annual incidence of 15 cases per million. Globally, congenital anomalies of the kidney and urinary tract (including renal dysplasia and obstructive nephropathy) account for 45–50% of all pediatric ESRD.^{23,24} Primary glomerular diseases (such as focal segmental glomerulosclerosis, nephrotic syndromes, and chronic glomerulonephritides) constitute about 25% of pediatric ESRD. Other important causes include cystic kidney disease, nephronophthisis, and AKI.

Of direct pertinence to pediatric cardiologists, there is now mounting evidence for the common occurrence of CKD and ESRD in children with chronic heart disease.^{25–27} This has been substantiated in several studies of children and young adults with congenital heart disease, in whom a decrease in eGFR,²⁸ increased proteinuria,²⁹ or increased urinary excretion of tubular injury biomarkers such as N-acetyl- β -D-glucosaminidase and α 1-microglobulin^{30,31} has been demonstrated in 30–50% of the subjects studied. In children who received a heart transplant for congenital heart disease or dilated cardiomyopathy, more than 50% were found to have a diminished eGFR at a median of 6 years of follow up.²⁷ Importantly, in a large single center study of 1102 adults with congenital heart disease, 50% had CKD based on a decrease in eGFR.³² In comparison with the general population, the prevalence of CKD was 18-fold higher in patients with non-cyanotic heart disease, and 35-fold higher in those with cyanotic heart disease. Furthermore, CKD had a substantial impact on mortality (propensity score-weighted hazard ratio 3.25, 95% CI 1.54 – 6.86, $P=0.002$ for moderately or severely impaired versus normal GFR).³² Several plausible mechanisms contribute to the development of CKD in children with congenital heart disease.^{25, 26} The hyperviscosity due to chronic hypoxia leads to initial glomerular hyperfiltration and subsequent glomerulosclerosis. Chronic renal tissue hypoxia results in a fibrogenic response in the glomeruli, tubules, and interstitium, which contributes to tubule-interstitial fibrosis and worsening CKD.^{25, 26} Several derangements in neurohormonal and autonomic nervous systems that play a key role in the regulation of renal blood flow and GFR have been demonstrated in children with congenital heart disease. Furthermore, children with congenital heart disease are exposed to several factors that lead to AKI, including cardiac surgery (often multiple for step-wise repair of complex anatomic derangements) and nephrotoxin use. Recent reports of AKI using current definitions in large pediatric populations undergoing congenital heart disease surgery have revealed an incidence of 40–50%,^{33–38} with an even higher incidence of 64% among neonates.³⁹ Evidence for, and

mechanisms underlying, the transition from AKI to CKD are discussed in sections 6 and 7 of this review.

5. Complications of CKD and their Management

Children with CKD have a 30 to 150 fold higher mortality rate as compared to age-matched healthy peers.⁴⁰ Cardiovascular disease is the leading cause of death in the pediatric ESRD population. Cardiovascular disease is responsible for 32%, 28% and 22% of deaths seen in US pediatric hemodialysis, peritoneal dialysis, and transplant patients, respectively.⁴¹ Overall, children with ESRD carry a 100–1000 fold increased risk of cardiovascular death as compared to the general pediatric population. Cardiovascular death from arrhythmias, cardiac arrest, valvular disease, or cardiomyopathy occurs amongst all pediatric age groups with CKD, including infants under age one year. Cardiovascular disease, which can be appreciated even in the early stages of CKD, manifests as left ventricular hypertrophy (LVH), diastolic dysfunction, large arterial vessel stiffness, coronary vessel calcification, and systemic hypertension.⁴¹ Thus, a strong focus on reducing both traditional (hypertension, obesity, dyslipidemia and insulin resistance) and uremia-related cardiovascular risk factors (hyperphosphatemia, hypercalcemia, secondary hyperparathyroidism, anemia, inflammation, and hypoalbuminemia) in children with CKD is necessary to reduce mortality and morbidity.⁴²

Other complications of CKD include growth failure,^{43–45} and progression of CKD with resultant hypertension, proteinuria, anemia, and acidosis. Irrespective of the etiology, approximately 70% of children with CKD will progress to ESRD before reaching adulthood, with a median GFR change over time of $-4.3 \text{ ml/min/1.73 m}^2$ per year and $-1.5 \text{ ml/min/1.73 m}^2$ per year in glomerular and non-glomerular etiologies, respectively.⁴⁶ Non-modifiable risk factors associated with faster CKD progression include older age, glomerular cause, and more advanced CKD.⁴⁷ Modifiable risk factors associated with CKD progression include hypertension, proteinuria, anemia, and acidosis. Both hypertension and proteinuria have been independently associated with more rapid CKD progression in various pediatric CKD observational studies.^{48, 49} In children with CKD from any etiology, strict blood pressure control has been shown to slow the progression of kidney disease and reduce the risk of cardiovascular disease. In particular, both angiotensin converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs) have been proven effective in controlling blood pressure, reducing proteinuria, and slowing progression of CKD in these patients.^{50–52} Anemia in pediatric CKD and ESRD patients is associated with significant mortality and morbidity, including a decreased quality of life, left ventricular hypertrophy (LVH), and increased hospitalization.^{53–55}

6. AKI to CKD – Clinical Evidence

The previous assumption that patients who survive an AKI episode would completely recover kidney function has now been debunked by over a decade of retrospective observational studies of large administrative databases as well as prospective follow up studies in adult populations.^{56–60} A meta-analysis of published cohort studies in over 1

million adult participants showed that adults with AKI are at a 9-fold higher risk of developing CKD, and a 3-fold increased risk of developing ESRD.⁶¹

Similar data is now accumulating in the pediatric population.^{62–65} Large cohort studies have also suggested a link between pediatric AKI and CKD. In a meta-analysis of 49 studies reporting on the long-term follow up of 3,476 children with AKI due to hemolytic uremic syndrome, 16% developed CKD when defined as an eGFR of $< 80 \text{ ml/min/1.73m}^2$ and 25% showed evidence for CKD based on proteinuria and hypertension.⁶⁶ A second meta-analysis examining 32 manuscripts that included 46,249 infants revealed that low birth weight imparted a significant risk for later CKD development (81% greater risk of albuminuria and 79% greater risk of eGFR $< 60 \text{ ml/min/1.73m}^2$) compared to normal birth weight infants.⁶⁷ Premature neonates with low birth weight are commonly exposed to several risk factors for AKI (including hypoxia, ischemia, nephrotoxins, sepsis, and congenital diseases including heart disease) before nephrogenesis is completed. Several small recent studies have explored the direct relationship between pediatric AKI and the development of CKD, and have been the subject of a recent systemic review that included 10 publications and 346 children with AKI from diverse etiologies who were followed for a mean period of 6.5 years.⁶⁸ The pooled incidences of reduced eGFR, proteinuria, hypertension, and mortality were reported to be 28% (95% CI 23.3–32.7%), 13.2% (CI 8.9–17.5%), 6.6% (CI 3.8–9.4%), and 17.6% (CI 13.6–21.6%) respectively. The incidence of clinically apparent CKD was particularly high in critically ill hospitalized children with AKI, in the range of 30–60% of patients at follow up.^{69–74} While these incidences of adverse outcomes after pediatric AKI are obviously quite high compared to the general population, none of these studies included a control group of children with the same exposure who did not develop AKI. It is therefore difficult to determine the attributable risk of these adverse outcomes specifically to AKI versus the underlying illness. Ongoing prospective long-term follow-up studies of children undergoing cardiac surgery, such as the TRIBE-AKI⁷⁵ and ASSESS-AKI⁷⁶ studies, have therefore been designed to include control groups. In addition, the incidence of CKD reported in the meta-analysis of adult AKI studies⁶¹ is significantly greater than that reported in children.⁶⁸ The comparable rates for CKD based on an abnormal eGFR were 25.8 per 100 patient-years (CI 3.4–72.2) and 6.3 per 100 patient years (CI 5.1–7.5) in adults and children respectively. This is likely attributable to the fact that adults encounter known comorbid risk factors for CKD (such as older age, hypertension, obesity, diabetes mellitus, cardiovascular disease, and medications) much more commonly than children. It is also likely that the relatively pristine pediatric kidney is more resilient and better capable of recovery after AKI.

Three small single center studies have examined the AKI-to-CKD transition in children following cardiac surgery. Shaw et al followed 11 pediatric cardiac surgery patients who developed AKI requiring dialysis, and found that 3 children displayed abnormalities in GFR when measured 1–5 years after the AKI episode, but none had proteinuria.⁷⁷ A study reported by Mel et al of 25 children who required peritoneal dialysis for cardiac surgery-associated AKI showed that only one patient had a reduction in eGFR at a mean follow up of 5 years, and none developed proteinuria.⁷⁸ A recent study by Cooper et al followed 51 children who underwent cardiopulmonary bypass (33 with AKI defined as a $> 50\%$ increase in serum creatinine from baseline and 18 without AKI) for a mean duration of 7 years.⁷⁹

Children in both groups displayed normal eGFR, normal blood pressures, and normal levels of proteinuria and microalbuminuria. However, at long-term follow up, patients in the AKI group demonstrated significantly increased levels of the established tubule injury biomarkers interleukin-18 (IL-18), kidney injury molecule-1 (KIM-1) and liver-type fatty acid-binding protein (L-FABP) when compared to the age-matched AKI-negative group or to a group of healthy children.⁷⁹ Collectively, these preliminary studies in children with AKI following cardiac surgery suggest the ongoing evolution of subtle sub-clinical kidney injury, and support the need for long-term follow up into and throughout adulthood.

7. AKI to CKD – Experimental Evidence

Long before the recent human studies implicating the strong relationship between AKI and CKD were completed, direct evidence for this link has existed in experimental animal models, as illustrated in several recent reviews.^{80–86} The kidney does possess a remarkable capacity for repair and regeneration after AKI.^{87–89} This requires regeneration of tubules and the endothelium, and resolution of the inflammatory infiltrate. Elegant genetic fate mapping studies have now established that surviving tubule cells have the ability to undergo dedifferentiation and replace lost neighboring tubular epithelial cells. Endothelial repair requires angiogenesis and pericyte support. Recent studies have identified persistent renal hypoxia as a key player in the pathogenesis of the AKI to CKD transition.^{81,82} AKI has been shown to result in decreased expression of critical angiogenesis factors such as vascular endothelial growth factor (VEGF), as well as the detachment of supportive pericyte cells, leading to failure of endothelial cells to regenerate and to profound peritubular capillary rarefaction. This further exacerbates tissue hypoxia, and has three major downstream effects that promote tubulointerstitial fibrosis: (a) failure of tubule epithelial cells to regenerate and repair, (b) recruitment of inflammatory cells that secrete profibrotic cytokines, and (c) activation of fibroblasts. The role of cell cycle regulation has also gained considerable attention. In the early phases of AKI, proximal tubule cells become arrested in the G2/M stage, thereby limiting proliferation of damaged cells. However, prolonged cell cycle arrest leads to a maladaptive response, including activation of pro-inflammatory and pro-fibrotic pathways leading to tubulointerstitial fibrosis. Mechanisms underlying the normal reparative pathways, as well as the maladaptive pathways that drive the AKI to CKD transition, are areas of intense current investigation, and targeting these pathways holds promise for improving the outcomes of AKI in the clinical setting.⁹⁰

8. Biomarkers for AKI to CKD Progression

There is a paucity of sensitive and specific biomarkers for the early prediction of progression from AKI to CKD.^{62,91} Estimations of GFR reflect late functional changes, and not early structural alterations in the kidney that would identify subtle damage. Functional changes are inherently delayed due to the well-known concept of “renal reserve” – irrespective of the underlying disease, with progressive destruction of nephrons, the kidney has an innate ability to maintain GFR by hyperfiltration and compensatory hypertrophy of the remaining healthy nephrons. This nephron adaptability allows for continued clearance of plasma solutes, so that the plasma markers used in calculating eGFR (SCr and cystatin C) show significant increases only after about 50% of the GFR has been lost. In addition, these

plasma markers are confounded by a large number of variables, as already reviewed in section 3. Proteinuria (or more specifically, albuminuria and microalbuminuria) has also been used as a marker of CKD progression. However, a large number of glomerular, tubular, and interstitial pathophysiologic mechanisms can lead to proteinuria, and significant structural damage has typically already occurred before proteinuria is measurable, and progressive renal function decline has usually already commenced at the onset of microalbuminuria. Thus, improved biomarkers are clearly needed to stratify subjects who are at greatest risk for CKD progression, who might maximally benefit from increased surveillance, early prevention, and specific interventions. Given the well documented progression from AKI to CKD in human and animal models, novel AKI biomarkers such as neutrophil gelatinase-associated lipocalin (NGAL), kidney injury molecule-1 (KIM-1), liver-type fatty acid binding protein (L-FABP), and interleukin-18 (IL-18) have recently been examined as markers of recovery after AKI or progression of CKD.

8.1 NGAL

The most extensively studied novel AKI biomarker is NGAL, especially in the setting of pediatric cardiac surgery.^{92–98} Animal models of AKI and the AKI-to-CKD transition have identified NGAL and KIM-1 as two of the most upregulated genes and proteins in the kidney, suggesting a biologic plausibility for these proteins as biomarkers of the chronically injured kidney.^{99–102} NGAL protein expression was first noted to be markedly increased in kidney biopsy samples from humans with a variety of chronic glomerular and tubular diseases.^{103,104} Cross-sectional studies revealed that CKD is also associated with increased concentrations of NGAL in both urine and plasma when compared to normal individuals, although not to the same extent as in AKI.¹⁰³ Several subsequent publications have documented the relationship between incident CKD and NGAL levels. Plasma and urine NGAL were shown to correlate well with measured or estimated GFR in children with CKD from various etiologies.^{105,106} In a study of subjects with CKD due to autosomal dominant polycystic kidney disease, both urine and plasma NGAL were found to be elevated and inversely correlated with GFR, and a sub-set of patients with higher cystic growth displayed the highest concentrations of urine and plasma NGAL, indicating a correlation with disease severity and progression.¹⁰⁷ Urinary NGAL is elevated in patients with HIV-associated nephropathy (HIVAN), and abundant NGAL mRNA expression in dilated microcystic tubules in a transgenic mouse model of HIVAN, suggesting the utility of urine NGAL for the early diagnosis of CKD due to HIVAN.¹⁰⁸ Elevated levels of NGAL, as well as an inverse correlation with GFR, have now been documented in a number of publications examining patients with CKD due to membranous nephropathy, primary focal segmental glomerulosclerosis, type-2 diabetic nephropathy, and in a mixed population with CKD stages 2–4.^{109–112} Both serum and urinary NGAL levels are significantly elevated in type-1 diabetes mellitus despite normal urinary albumin excretion, suggesting NGAL as a more sensitive and predictive biomarker of CKD than microalbuminuria in this population.¹¹³ Both serum and urine NGAL concentrations increased in subjects chronically treated with cyclosporine, with a positive correlation between biomarker levels and serum cyclosporine levels despite absence of changes in eGFR, suggesting the use of NGAL for the early detection of CKD in chronic nephrotoxicity.¹¹⁴ A number of studies have documented NGAL as a useful measure of CKD in chronic lupus nephritis in children and adults.^{115–120}

Several additional studies have established the relationship between NGAL and incident CKD in diverse clinical settings, including pediatric heart transplants,¹²¹ adolescents in Nicaragua,¹²² and large cohorts of normal subjects including the Multi-Ethnic Study of Atherosclerosis (MESA) cohort¹²³ and the Atherosclerosis Risk in Communities (ARIC) study.¹²⁴ Finally, in the large Chronic Renal Insufficiency Cohort (CRIC) study, urine NGAL levels were independently associated with ischemic atherosclerotic events.¹²⁵ The fact that the increased NGAL levels in CKD derive from the chronically injured kidney was substantiated in recent unbiased gene expression profiling studies on kidney biopsy specimens from 48 patients with CKD.¹²⁶ NGAL and KIM-1 were among the most highly upregulated genes, and their expression levels correlated with the extent of tubulointerstitial fibrosis and tubular cell injury in human biopsy samples.¹²⁶

Several studies have examined NGAL as a discriminatory marker of CKD progression. In one of the first studies reported, 96 subjects with CKD stages 2–4 due to a variety of causes were followed for a median of 18.5 months, during which 32% reached the composite end-point for CKD progression (doubling of baseline serum creatinine and/or onset of end-stage renal disease).¹¹² Both urine and plasma NGAL at baseline predicted CKD progression, independent of other factors such as eGFR and age. High baseline values for both serum and urine NGAL were associated with a significantly faster evolution to the composite end-point. In a subsequent prospective observational cohort study of 158 patients with CKD stage 3 or 4, 25% reached a composite endpoint of death or dialysis requirement.¹²⁷ The baseline urine NGAL was independently associated with the endpoint, and improved risk prediction over the clinical model. These findings were confirmed in the CRIC cohort of 3386 patients with CKD, in whom 689 cases developed CKD progression (defined as 50% reduction in eGFR or dialysis requirement).¹²⁸ Baseline urine NGAL was an independent risk factor for progression (hazard ratio 1.7 comparing highest to lowest quartile). Adding urine NGAL to a model that included other CKD progression risk factors led to net reclassification improvement of 25%, but did not significantly improve the C-statistic.¹²⁸

Since AKI can lead to CKD and ESRD, recent studies have focused on whether biomarkers such as NGAL can predict recovery or non-recovery from an episode of severe AKI. In one multicenter cohort of patients with community-acquired pneumonia who developed dialysis-requiring AKI, elevated plasma NGAL alone moderately predicted non-recovery, and improved the prediction upon reclassification when combined with the clinical model.¹²⁹ In another multicenter cohort of critically ill patients with dialysis-requiring AKI who had urine NGAL levels measured on days 1, 7, and 14, serially decreasing levels of urine NGAL were associated with greater odds of renal recovery.¹³⁰

Collectively, the studies reported herein indicate that NGAL is emerging as a promising biomarker for the early detection and staging of CKD, and for predicting recovery from AKI or progression of CKD.

8.2 KIM-1

Pre-clinical transcriptomic profiling studies in animal models of AKI-to-CKD as well as humans with CKD have revealed KIM-1 expression to be markedly upregulated.^{101,126} Several studies have reported on the utility of KIM-1 as a biomarker of AKI in the setting of

pediatric cardiac surgery.^{95,131,132} Reports on the potential utility of KIM-1 as a CKD biomarker have also been published. In a kidney biopsy study of 74 patients with CKD from various etiologies, KIM-1 was primarily expressed at the luminal side of dedifferentiated proximal tubules in areas with fibrosis and inflammation, and correlated positively with morphological damage and negatively with renal function.¹³³ Urinary KIM-1 levels measured in a subset of these patients were also negatively correlated with eGFR. In a prospective study of 145 kidney transplant patients followed for an average of 4 years, elevated urinary KIM-1 levels were independently associated with a 5-fold increased risk of graft loss.¹³⁴ Recent studies have confirmed the relationship between KIM-1 and incident CKD in diverse clinical settings, including normal subjects in the Multi-Ethnic Study of Atherosclerosis (MESA) cohort¹²³ and the Atherosclerosis Risk in Communities (ARIC) study,^{124,135} and in patients with IgA Nephropathy.¹³⁶ KIM-1 is also emerging as a promising marker of CKD progression in a variety of cohorts, including adults with chronic heart failure,¹³⁷ HIV infection,¹³⁸ and type I diabetes.^{139,140} Thus, KIM-1 should be added as a promising biomarker for the early detection of incident CKD, and for predicting CKD progression.

8.3. L-FABP

The utility of urinary L-FABP to predict AKI in children undergoing cardiac surgery is well established.^{95,141} The urinary excretion of L-FABP is also increased in the setting of CKD.¹⁴² In a large health screening study, urinary excretion of L-FABP was found to be increased in subjects with hypertension and diabetes mellitus, even in the absence of overt kidney damage.¹⁴³ In patients with type-2 diabetes, urinary L-FABP levels were associated with degree of proteinuria, and independently predicted the progression of diabetic nephropathy, regardless of disease stage.^{144–146} In a clinical trial of patients with nondiabetic CKD, urine L-FABP levels correlated with urine protein and serum creatinine levels. Notably, L-FABP levels were significantly higher in the group of patients with mild CKD who progressed to more severe disease.¹⁴⁷ In a prospective, observational, multicenter study of outpatients with CKD, high urinary L-FABP was independently associated with the development of ESRD.¹⁴⁸ However, in a large multicenter case-control study of 135 patients with ESRD and 186 controls who were matched on sex, race, kidney function, and diabetes status at baseline (Atherosclerosis Risk in Communities Study), no association between urinary L-FABP and ESRD was observed.¹³⁵ Thus, additional studies are required to further establish the role of L-FABP as a CKD biomarker.

8.4 IL-18

Urinary IL-18 levels have diagnostic and prognostic value in children who develop AKI after cardiac surgery.^{75,95,148} A potential relationship between urinary IL-18 and incident CKD has been shown in adolescents and adults in Nicaragua.^{122,149} In HIV-infected women, the highest tertile of urinary IL-18 was independently associated with faster CKD progression.¹³⁸ However, urine IL-18 levels did not predict kidney scarring and reflux nephropathy in children with vesicoureteral reflux.¹⁵⁰ Currently available data are insufficient to recommend IL-18 as a biomarker of CKD progression.

9. Conclusions

Chronic kidney disease is an increasingly significant burden on health care systems world-wide, and is particularly prevalent in patients with congenital and acquired heart disease. The diagnosis of CKD is associated with a substantial amount of morbidity and mortality. Mechanistic explanations of CKD are beginning to be reported including changes in biomarker expression, genotyping, and epigenetic phenomenon which offer insight into the causation and open a window of opportunity for further understanding of this process. AKI is recognized to play a major role in the development of CKD and links between duration, severity, and frequency of AKI episodes and development of CKD have been established. AKI and CKD should be approached as a continuum of kidney disease. In children with heart disease, opportunities to diagnose and manage AKI in an effort to avoid progression to CKD should be acted upon in a collaborative fashion between nephrologists and cardiologists. Long term follow up of children with AKI up into and throughout adulthood is required to detect subclinical and clinical progression to CKD and especially for the management of the cardiovascular sequelae of CKD progression. Further investigation is needed to better delineate the causes and impact of CKD in children with congenital or acquired cardiac disease. Novel biomarkers such as NGAL and KIM-1 hold promise in identifying CKD patients who are most likely to progress, and therefore most likely to benefit from available primary and secondary prevention strategies.

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Table 1

Stages of CKD in children ≥ 2 years of age [3]

Stage	eGFR (ml/min/1.73 m ²)
1	90
2	60–89
3	30–59
4	15–29
5	15

Estimated glomerular filtration rate (eGFR) most commonly employs the modified bedside Schwartz formula.