Published in final edited form as:
*Am J Kidney Dis*. 2009 August ; 54(2): 345–360. doi:10.1053/j.ajkd.2009.04.027.

# Cardiovascular Disease in CKD in Children: Update on Risk Factors, Risk Assessment, and Management

**Amy C Wilson, M.D., M.S.** and **Mark M Mitsnefes, M.D., M.S.**
Division of Nephrology and Hypertension, Cincinnati Children's Hospital Medical Center, University of Cincinnati, Cincinnati, OH

## Abstract

In young adults with onset of chronic kidney disease in childhood, cardiovascular disease is the most common cause of death. The likely reason for increased cardiovascular disease in these patients is high prevalence of traditional and uremia-related cardiovascular disease risk factors during childhood chronic kidney disease. Early markers of cardiomyopathy, such as left ventricular hypertrophy and left ventricular dysfunction and early markers of atherosclerosis, such as increased carotid artery intima-media thickness, carotid arterial wall stiffness and coronary artery calcification are frequently found in this patient population. The purpose of this review is to provide an update of recent advances in the understanding and management of cardiovascular disease risks in this population.

## Introduction

Despite significant advances in the care of children and adolescents with chronic kidney disease (CKD), long-term survival of children with CKD in the U.S. remains far lower than for the general population. For children on dialysis, anticipated lifespan is reduced by 40–60 years, and for transplant patients by 20–25 years, when compared to an age- and race-matched population[1–3]. Further, the most likely cause of this reduction in survival is an excessive burden of cardiovascular mortality, related to both accelerated ischemic heart disease and premature development of dilated cardiomyopathy in young adult survivors of childhood-onset CKD. The burden of cardiovascular morbidity and mortality in this population has been reviewed in detail previously[4]. The purpose of this review is to provide an update of recent advances in the understanding and management of cardiovascular disease (CVD) risks in this population. Specifically, we have focused on a discussion of traditional CVD risk factors, and their evaluation and management, although those uremia-related risk factors with the most robust evidence for association with CV abnormalities in children with CKD are also reviewed.

## Risk Factors for Cardiovascular Disease

As in adults, the risk factors thought to be responsible for accelerated CVD in children with CKD can be divided into two primary groups: traditional risk factors for atherosclerotic disease (e.g. dyslipidemia, diabetes, hypertension, smoking) and uremia-related risk factors which are unique to or far more prevalent among patients with CKD. A majority of adults who develop

Corresponding author: Mark Mitsnefes, M.D., M.S. Division of Nephrology and Hypertension, Cincinnati Children's Hospital Medical Center, MLC: 7022, 3333 Burnet Avenue, Cincinnati, OH 45229-3039, Telephone: 513-636-4531, Fax: 513-636-7407, E-mail: E-mail: mark.mitsnefes@cchmc.org.

end-stage renal disease (ESRD) do so as a complication of diabetes or generalized atherosclerosis. The frequency of both traditional and uremia-related risk factors for CVD is high, and cardiac disease is already well established at the onset of ESRD in these patients. Although children have neither diabetes nor symptomatic atherosclerosis at the time of starting maintenance dialysis, they unfortunately share similarly high rates of CVD risk factors (Table 1).

## Traditional Risk Factors

The high prevalence of traditional CVD risk factors in children with CKD has been appreciated for over a decade. Little progress has been made in reducing the frequency of these risk factors in the intervening years.

**Hypertension—**Hypertensionis the most common traditional risk factor. North American Pediatric Renal Transplant Cooperative Study (NAPRTCS) data demonstrate uncontrolled hypertension rates of 48% in early CKD, increasing to 50–75% in ESRD[5–8]; unfortunately, this is not improved with transplantation, with reported prevalence of 50–87%[9–13]. Recent data from the Chronic Kidney Disease in Children (CKiD) Study supports that hypertension remains frequent (54%) in patients with early stages of CKD, with up to 25% of study participants having blood pressure in excess of current recommendations[14]. Even more concerning, when examining only those children with hypertension who were on antihypertensive medication, the investigators found that 48% still had elevated blood pressure.

**Dyslipidemia—**Dyslipidemia is also frequent, particularly following kidney transplantation. Reported rates of dyslipidemia range from 50–90%, with elevated total cholesterol and elevated low-density lipoprotein (LDL) cholesterol reported most frequently, and low high-density lipoprotein (HDL) cholesterol reported least often[13,15–23]. The highest rates of dyslipidemia are after renal transplant. However, it is also frequent in CKD stage 2–4: hypertriglyceridemia is most common (31%), followed by high total cholesterol, high LDL cholesterol, and low HDL cholesterol (13%, 13%, and 8%, respectively)[24].

**Obesity—**Obesity in children with CKD has been recognized for some time now; unfortunately, the trends in prevalence are mirroring secular obesity trends, with rates rising from 8% (1995) to 12% (2002) in patients on dialysis (NAPRTCS)[25]. Obesity becomes more common following renal transplant, with both single- and multi-center studies demonstrating doubling of obesity prevalence (from approximately 15% to 30%) in the first year after renal transplant[12,26].

**Abnormalities in Insulin and Glucose Metabolism—**The frequency of abnormalities in insulin and glucose metabolism, particularly following kidney transplantation, is increasingly appreciated. Based on the current American Diabetes Association guidelines[27] for impaired fasting glucose and provisional diagnosis of diabetes mellitus, recent publications examining children receiving kidney transplants demonstrated rates of 16–18% and 7–13%, respectively, with a total of nearly 30% having frank abnormalities in glucose metabolism[23,28]. Small studies in children with CKD stage 2–4 or on dialysis have demonstrated rates of hyperinsulinemia as high as 33%, and rates of abnormal insulin resistance (as measured by elevated homeostasis model assessment for insulin resistance [HOMA-IR]) in up to 16% of patients[29,30], indicating that abnormalities in insulin and glucose metabolism may be present earlier than previously believed.

**Sedentary Lifestyle—**In adults with CKD, sedentary lifestyle and low levels of physical function have been well documented. Painter et al. demonstrated that children with CKD (specifically, those on dialysis and with functioning kidney transplants) are also quite

physically inactive, with less than 10% of non-school time spent participating in physical activity[31]. Furthermore, these study participants had peak oxygen uptake and muscle strength measurements that were uniformly below norms for age and sex; only one out of 40 patients tested achieved a "healthy fitness zone" score on field tests of physical fitness. This corresponds well with data demonstrating that aerobic capacity is already diminished in children and adolescents with early stages of CKD (stage 3), and that it does not (in cross-sectional study) improve in kidney transplant recipients[32]. Given established evidence for the value of regular physical activity and improved fitness in reducing CVD risk in the general population, a reasonable next question is whether similar risk reduction could be achieved in a population with the medical comorbid conditions common in adult survivors of childhood CKD; this remains to be studied.

**Frequency of Traditional Risk Factors—**Also new to the pediatric literature is data on the frequency with which individual traditional risk factors for CVD coexist in children with CKD. Silverstein et al. assessed 45 children who received kidney transplants, all with stage 2–4 CKD at time of study; two-thirds of patients had at least two risk factors for CVD, and one-third had at least 3 risk factors[23]. A multicenter study of over 200 kidney transplant recipients (age 1–21 years) demonstrated that 37% met at least 3 (of a possible 5) diagnostic criteria for the metabolic syndrome at one year post-transplant[12].

## Uremia-Related Risk Factors

In addition to traditional risk factors, there are a host of uremia-related risk factors that uniquely increase risk for atherosclerotic CVD in patients with CKD. These are primarily evident in patients on maintenance dialysis rather than in those with early CKD or following successful transplantation. Although maintenance dialysis is typically a temporary state prior to transplantation in children, the consequences of even relatively short-term dialysis persist well beyond successful transplant into adulthood[3]. We will focus here on those risk factors which are well defined and for which the ability exists to modify those risk factors in the course of routine treatment.

**Volume overload—**Volume overload among patients on maintenance dialysis is frequent. This is primarily related to failure to achieve and maintain a true dry weight, and is a primary mechanism for the development and persistence of hypertension in the maintenance dialysis population, particularly for patients treated with intermittent hemodialysis rather than peritoneal dialysis. Vandevoorde et al. demonstrated that in children on hemodialysis, those who were hypertensive had significantly higher excess weight postdialysis, and increased normalized intradialytic weight gain than did those who were normotensive, with volume overload identified as the main cause of hypertension[33]. This is concordant with previous findings[6] in a European population. Furthermore, long-term volume overload in children is associated with higher rates of cardiac structural and functional abnormalities that will be discussed later in this article[34–37].

**Anemia—**Anemia is another highly-prevalent uremia-related CV risk factor in children and adolescents with advanced CKD; unlike the other major uremia-related risk factors, it appears relatively early in the course of CKD. Despite the wide use of recombinant erythropoeisis stimulating agents (ESAs), it remains common. Recent data from the CKiD cohort demonstrated that below a measured GFR of 43ml/min/1.73m$^2$, hemoglobin decreased by 0.3g/dL for every 5ml/min/1.73m$^2$ drop in GFR[38]. Data from the NAPRTCS Chronic Renal Insufficiency (CRI) registry supports that anemia is common in children with CKD (increasing from 18.5% in stage 2 CKD to 68% in stage 5 predialysis patients); furthermore, patients with anemia were 55% more likely to be hospitalized than those with normal hemoglobin[39]. Anemia remains a significant risk for both morbidity and mortality[39,40]. Until recently, post transplant

anemia has been under-appreciated. However, with introduction of more potent immunosuppression therapy, recently reported anemia rates range from 61% to 86%[41–43].

**Abnormalities in calcium-phosphorous metabolism—**Abnormalities in calcium-phosphorous metabolism are universal among patients with advanced CKD, and they appear to be among the most important drivers of cardiac and vascular disease progression in this population. Hyperparathyroidism affects approximately 30–45% of children with CKD stage 2–4 and nearly 60% of children on dialysis[44]. Among Turkish children with CKD, nearly 30% had a calcium-phosphorus product above target range, and 40% had intact parathyroid hormone >300pg/ml[45]. Associations between abnormal mineral metabolism and changes in vascular structure in children with CKD have also been documented (discussed in detail below).

Although supplementation of $1,25(OH)_2D_3$ in ESRD is an established therapy for control of secondary hyperparathyroidism, there is evidence that$1,25(OH)_2D_3$ has a direct promoter effect on calcium deposition in vascular smooth muscle cells[46]. Nutritional vitamin D deficiency is also quite common in children with CKD, with only 23% of children with CKD stage 2–4 having adequate levels of $25(OH)\text{-}D_3$[47]. Further, nutritional vitamin D deficiency is associated with hyperparathyroidism even among those patients with normal activated vitamin D levels[47].

**Malnutrition and Inflammation—**Finally, the constellation of malnutrition and inflammation appears to be intimately related to the development of vascular disease in adults with CKD. The same inflammatory markers have been identified at high levels in children on maintenance dialysis[48–50]. However, there is no strong evidence to guide inflammation-related risk-modification in children with CKD, although Goldstein et al. did demonstrate reduction in pro-inflammatory cytokine levels with aspirin therapy in children with ESRD[51]. For a more complete review of this subject, the reader is referred to recent reviews by Nurmohamed and Nube[52] and Silverstein[53].

## Spectrum of Cardiovascular Findings in Children With CKD

Clinically evident cardiovascular lesions (symptomatic coronary artery disease, myocardial infarction, cerebrovascular accident) are fortunately rare in children and adolescents with CKD. However, there is increasing evidence demonstrating significant subclinical cardiovascular abnormalities in this population, all of which are independent predictors of CVD morbidity and mortality (both in the general population and in adults with CKD).

### Left ventricular structure and function

As in adults, left ventricular hypertrophy (LVH) develops relatively early in the course of CKD in children, and becomes more common as kidney function declines. Although some small retrospective studies demonstrate regression of LVH with better blood pressure and volume control while on dialysis, others have demonstrated advancement of LVH. Unfortunately, LVH also remains common after pediatric kidney transplant (see Table 2). LVH is also common in adult survivors of ESRD in childhood (47% of male patients and 39% of female patients), as is diastolic dysfunction (13%)[77].

Diastolic dysfunction is thought to be the initial functional LV abnormality evident in children with CKD. Historically, the most widely used method of assessment of impaired LV relaxation has been the use of Doppler measurement of the mitral inflow velocity (E/A ratio). By this method, reduced and/or frankly abnormal E/A ratios have been seen in patients with CKD, ESRD, and renal transplant[54,63,78]. However, left atrial pressure and preload significantly affect the E/A ratio. Given the chronic hypervolemia associated with advanced CKD, E/A ratio may not be an ideal means of assessing diastolic function. More recently, tissue Doppler

imaging (TDI) was introduced as a less load dependent and more accurate means of evaluating diastolic function in CKD. Diastolic dysfunction has also been documented by this method[79–81], thus supporting that the cardiac dysfunction identified in earlier studies was not merely an artifact of the methodology used. Overall, children on maintenance dialysis have worse diastolic dysfunction than those with either CKD stage 2–4 or functioning kidney transplants. Diastolic dysfunction was recently demonstrated to be independently associated with reduced maximal aerobic capacity ($VO_2$max) in children with CKD[82].

Systolic function has classically been thought of as preserved in children with CKD. While that appears to be true of overt systolic function abnormalities (as assessed by LV contractility or endocardial shortening fraction, eSF), recent studies have demonstrated that subclinical systolic dysfunction is common in children with CKD, affecting up to 40% of hemodialysis patients. Further, such abnormalities have been identified relatively early in the course of CKD, albeit at lower frequency[83,84]. These abnormalities have been identified through utilization of midwall shortening fraction (mwSF), which is thought to more accurately estimate systolic function than eSF, particularly in those patients with LVH, as eSF tends to overestimate systolic function in this group.

## Large vessel disease

Large vessel disease occurs at disturbingly early ages among children with CKD. Known abnormalities range from early changes in endothelial function (as assessed by flow mediated dilatation of the brachial artery) to increased carotid intimal media thickness (cIMT), coronary calcifications, and frank atherosclerotic changes. Major risk factors for early vascular disease identified include longer duration of dialysis dependence, higher calcium-phosphorous product, cumulative dose of calcium-based phosphate binders, and cumulative dose of activated vitamin D (specifically calcitriol). Findings of major studies of cIMT and coronary artery calcifications (CAC) in children with CKD published to date are summarized in Tables 3 and 4. Particular attention should be paid to three recently published studies.

First, Krmar et al.[97] concluded, based on their observational study of two groups of kidney transplant recipients (one with strict ambulatory normotension throughout the study, and one with routinely treated hypertension), that blood pressure is not a contributing factor to increased IMT, in that cIMT was not significantly different between the two groups at either baseline or follow-up. However, it should be noted that exceptional blood pressure control was associated with stable cIMT over the 4 year follow-up period despite the fact that population studies have demonstrated a 0.01–0.02mm/yr increase in cIMT among healthy patients[104]. For a more comprehensive review of the use of IMT in children, the reader is referred to a recent review by Litwin and Niemirska[105].

The second study is the recently published longitudinal study of CAC by Civilibal et al[103]. This is the only study to date regarding the natural history of CAC in children with ESRD. Briefly, among a cohort of 48 children studied with multidetector spiral computed tomography at baseline and again 2 years later, 8 were found to have CAC at study inception. None of the 40 patients without CAC at baseline developed CAC in the intervening 2 years. Among the eight with CAC at baseline, the median score increased significantly over the interval, although CAC in one patient did resolve completely. Time averaged mean calcium-phosphorus product was independently associated with final CAC score, and the serum albumin at time of the second scan was the only independent predictor of the change in CAC score over time.

The final study, by Shroff et al. [106], sheds light into the mechanisms responsible for the development of vascular calcification in children with ESRD. In this study, 34 children with CKD (10 predialysis, 24 dialysis) underwent examination of medium-sized muscular arteries. Vessels from both predialysis and dialysis patients had higher calcium load than control vessels.

Dialysis patients had significantly higher calcium load than predialysis patients, despite similar age and kidney function in the two groups; vascular calcification strongly correlated with mean serum calcium-phosphorus product. No predialysis patient (despite increased calcium load) had reduced numbers of vascular smooth muscle cells per unit area. However, among dialysis patients, there was a significant reduction in vascular smooth muscle cell number, even when controlling for vessel calcium load. In summary, it appears that calcium accumulation begins well in advance of initiation of maintenance dialysis, but accelerates and leads to overt changes in vascular structure only following initiation of dialysis. Neither cIMT nor CAC was a sensitive indicator of increased calcium load.

In addition to measuring IMT and CAC, decreased flow-mediated dilation of the brachial artery has been proposed as a marker of vascular dysfunction that may precede frank structural changes. Early work in children indicated promise in this regard, with several small studies demonstrating decreased FMD in patients with advanced CKD (predialyisis, dialysis, and post-transplant)[107–110]. However, a more recent study of children with less severe kidney impairment (CKD stage 2–4) was less promising regarding the promise of FMD as a marker of early vascular changes, with median FMD similar to that of healthy controls[111].

## Evaluation and Management of Cardiovascular Risk in Children With CKD

The most significant change in paradigm regarding management of CV risk in children with CKD came with the 2006 release of the American Heart Association guidelines for CV risk reduction in high-risk pediatric patients[112]. There, for the first time, children with CKD were stratified as “high risk” for the development of CVD, with associated “pathological and/or clinical evidence for manifest coronary disease before 30 years of age.” This group is otherwise limited to patients with homozygous familial hypercholesterolemia, type 1 diabetes, heart transplant recipients, and Kawaski disease patients with current coronary aneurysms. The panel’s treatment recommendations for children with CKD refer the reader to several National Kidney Foundation Kidney Dialysis Outcomes and Quality Initiative (NKF KDOQI) clinical practice guidelines.

Primary among management strategies in childhood CKD/ESRD is the avoidance of long-term dialysis, with preference for preemptive transplantation when feasible, as the strongest evidence for cardiovascular risk reduction is that associated with avoiding dialysis[3]. Although far from perfect with regard to CV risk, successful transplantation can eliminate or significantly improve uremia-related risk factors and increases predicted life expectancy by 20–30 years compared to long-term dialysis. Otherwise, management strategies are specific to the stage of CKD (predialysis, dialysis, or transplant) as each has a unique subset of common risk factors. Current recommendations for management of the most common risk factors are summarized in Table 5, with comments below.

### Hypertension

Hypertension therapy is determined by CKD stage. Angiotensin-converting enzyme inhibition (ACE-Inhibition) and/or angiotensin-receptor blockade (ARB) is preferred in stage 2–4 CKD. Among patients on maintenance dialysis, meticulous attention to management of volume overload is essential, which may necessitate more frequent or intense dialysis than a standard thrice-weekly regimen. Although data in children is limited[37], it is consistent with evidence in adult hemodialysis patients that significant improvements in volume control, hypertension, and regression in left ventricular hypertrophy can be achieved with either daily in-center dialysis or nocturnal hemodialysis performed 5–7 nights per week[122–124]. Following transplant, in addition to judicious use of antihypertensive agents, minimization/avoidance of iatrogenic causes of hypertension should be considered.

Guidelines suggest that ambulatory blood pressure monitoring "be considered" to assess for nocturnal hypertension, particularly after renal transplant, but stop short of recommending its routine use. However, newer literature suggests that use of annual ambulatory blood pressure monitoring leads to improved rates of achievement of goal blood pressure compared to standard therapy in children with kidney transplants[125]. Recent data from the CKiD cohort demonstrate that masked hypertension (defined as ambulatory hypertension in the presence of casual blood pressure <95$^{th}$ percentile) is present in 25% of patients with stage 2–4 CKD, and that the presence of masked hypertension is associated with a two-fold increase in frequency of LVH at time of initial examination[60]. Therefore, routine use of ambulatory blood pressure monitoring in children with CKD (beginning in early CKD & continuing thereafter) may significantly improve ascertainment and management of hypertension.

## Dyslipidemia

The latest guidelines for lipid screening and treatment in childhood state that for children 8 years and older with diabetes, statin therapy should be considered for those with LDL cholesterol ≥ 130mg/dL[117]. Although these guidelines do not specifically address children with CKD, given that the 2006 guidelines from the American Heart Association clearly place patients with CKD in the same high CV risk group as those with diabetes and heart transplant, it could be argued that statin therapy be standard of care for patients with CKD who are 8 years and older with LDL cholesterol ≥ 130mg/dL, although this is not explicitly stated in any guidelines. There exist no data regarding changes in long-term outcome related to tight lipid control in children with CKD; however, emerging data suggest a survival benefit associated with statin use in adult kidney transplant recipients[126]. Statins are also considered standard of care in all patients >1 year of age following pediatric heart transplantation (with the goal of reducing LDL cholesterol to below 100mg/dL), due to the associated reduction in incidence of transplant vasculopathy. Emerging evidence in adults suggests potential for similar improvements in renal transplant. Serón et al. demonstrated a significant reduction in incidence of renal transplant vasculopathy (33% versus 7%) in the first 6 months after transplant with use of statin therapy compared to placebo[127]. Although it remains unclear what (if any) benefit such treatment would have on long-term graft survival, one might speculate that strategies improving graft survival could improve cardiovascular outcomes over decades.

## Obesity & Physical Inactivity

Evidence from adult maintenance dialysis populations suggests a survival advantage conferred by higher body mass index[128–130]; however, this appears to be limited to those with low body fat and high muscle mass[131]. Per KDOQI, "the safety and efficacy of weight loss in the overweight dialysis patient is unknown… Therefore, weight loss in the dialysis patients should be approached with close monitoring by a registered dietician and physician[121]." However, increased physical activity is encouraged. Whether obesity in children with ESRD confers survival benefits while on maintenance dialysis is unknown. After pediatric kidney transplantation obesity is associated with higher rates of graft loss and graft dysfunction[132, 133]. There is evidence in children that obesity reduces efficacy of antihypertensive therapy[134].

## Hyperinsulinemia/Hyperglycemia

No formal recommendations exist for frequency and type of glucose monitoring or assessment of insulin resistance in children with CKD without preexisting diabetes. For those children with known type I diabetes and CKD of any cause, KDOQI guidelines defer to the American Diabetes Association standards of care for children and adolescents[135]. Following transplantation, serum glucose should be monitored routinely given the high incidence of post-transplantation diabetes. There are no formal guidelines for assessments of insulin resistance

in these patients. However, as abnormal insulin resistance clearly exists prior to the development of frank hyperglycemia (see Risk Factors, above), and given that such data could serve as impetus for more aggressive lifestyle interventions, there may be a role for regular assessments even in patients with earlier stages of CKD.

### Abnormal mineral metabolism

Although there is evidence suggesting that calcium and phosphorous load are associated with significant increase in risk for early CVD, there is little hard evidence supporting improved CV outcomes associated with achievement of these treatment goals. More research is needed regarding optimal clinical management of calcium-phosphorous metabolism, including that regarding the role of non-calcium containing phosphorous binders and calcimimetics in children with ESRD.

### Anemia

Notably, anemia in kidney transplant recipients may be more difficult to treat successfully related to relative ESA-resistance due to multiple factors (immunosuppression-related bone marrow suppression, infections, malignancy, inflammation related to rejection, etc). Also of note, patients in the early pretransplant period are at somewhat higher risk for iron deficiency than at other stages of disease, related to low pretransplant iron stores in the face of increased iron utilization following resumption of erythropoiesis after successful transplant.

### Left Ventricular Hypertrophy

Guidelines recommend screening echocardiography within 3 months of beginning dialysis, with follow-up examinations every six months for those with abnormal studies or annually if normal. As noted previously, meticulous attention to volume control is the treatment strategy most likely to result in improvement of LVH in the maintenance dialysis patient, although there is certainly a role for anti-hypertensive therapy (specifically ACE-Inhibition/ARB) as well. Following transplant, antihypertensive therapy and ACE-Inhibition/ARB become the main therapeutic approach. Given the high frequency of LVH in kidney transplant recipients (Table 2), our center continues with routine echocardiography following transplantation as well, with studies at 1 year post-transplant and then every 2 years thereafter if normal, or annually (at a minimum frequency) if abnormal. There is not enough evidence to recommend a routine evaluation for other intermediate CV outcomes (e.g. IMT or CAC) in children with CKD.

## Conclusions

Morbidity and mortality associated with cardiovascular disease remain a major threat to the long-term survival of children and adolescents with CKD. Cardiovascular risk factors and early cardiovascular changes are common even in very young patients, and much remains to be done to define and achieve optimal management of these patients.

## Acknowledgments

*Support:* None.

*Financial Disclosure:* None.

## References

1. National Kidney Foundation Task Force on Cardiovascular Disease. Controlling the epidemic of cardiovascular disease in chronic renal disease: What do we know? What do we need to know? Special report from the National Kidney Foundation Task Force on Cardiovascular Disease. Am J Kidney Dis 1998;32(Suppl 3):1–121. [PubMed: 9669419]

2. U.S. Renal Data System. USRDS 2003Annual Report. Bethesda: The National Institute of Diabetes and Digestive and Kidney Diseases; [Accessed January 21, 2009]. http://www.usrds.org
3. McDonald SP, Craig JC. Australian and New Zealand Paediatric Nephrology Association. Long-term survival of children with end-stage renal disease. N Engl J Med 2004;350:2637–2639. [PubMed: 15215477]
4. Mitsnefes M. Cardiovascular complications of pediatric chronic kidney disease. Pediatr Nephrol 2008;23:27–39. [PubMed: 17120060]
5. Mitsnefes MM, Ho P-L, McEnery PT. Hypertension and the progression of chronic renal insufficiency in children: a report of the North American Pediatric Renal Transplant Cooperative Study (NAPRTCS). J Am Soc Nephrol 2003;14:2618–2622. [PubMed: 14514740]
6. Loirat C, Ehrich JH, Geerlings W, et al. Report on management of renal failure in children in Europe XXIII, 119. Nephrol Dial Transplant 1994;7 (Suppl 1):26–40. [PubMed: 8008229]
7. Lerner GR, Warady BA, Sullivan EK, Alexander SR. Chronic dialysis in children and adolescents. The 1996 annual report of the North American Pediatric Renal Transplant Cooperative Study. Pediatr Nephrol 1999;13:404–417. [PubMed: 10412861]
8. Mitsnefes MM, Stablein D. Hypertension in pediatric patients on long-term dialysis: a report of the North American Pediatric Renal Transplant Cooperative Study (NAPRTCS). Am J Kidney Dis 2005;45:309–315. [PubMed: 15685509]
9. Smith JM, Ho PL, McDonald RA. Renal transplant outcomes in adolescents: a report of the North American Pediatric Renal Transplant Cooperative Study. Pediatr Transplant 2002;6:493–499. [PubMed: 12453202]
10. Baluarte HJ, Gruskin AB, Ingelfinger JR, Stablein D, Tejani A. Analysis of hypertension in children post renal transplantation – a report of the North American Pediatric Renal Transplant Cooperative Study (NAPRTCS). Pediatr Nephrol 1994;8:570–573. [PubMed: 7819003]
11. Mitsnefes MM, Khoury PR, McEnery PT. Early post transplant hypertension and poor long-term renal allograft survival in pediatric patients. J Pediatr 2003;143:98–103. [PubMed: 12915832]
12. Wilson AC, Greenbaum LA, Barletta GM, et al. High Prevalence of the Metabolic Syndrome and Associated Left Ventricular Hypertrophy in Pediatric Renal Transplant Recipients. Pediatr Transplant. 2009in press
13. Feber J, Wong H, Geier P, Chaudry B, Filler G. Complications of chronic kidney disease in children post-renal transplantation – a single center experience. Pediatr Transplant 2008;12:80–84. [PubMed: 18186892]
14. Flynn JT, Mitsnefes M, Pierce C, et al. Blood pressure in children with chronic kidney disease: a report from the Chronic Kidney Disease in Children Study. Hypertension 2008;52:631–637. [PubMed: 18725579]
15. National Kidney Foundation. K/DOQI Clinical Practice Guidelines for Managing Dyslipidemias in Chronic Kidney Disease. Am J Kidney Dis 2003;41(Suppl 3):S22–S38. [PubMed: 12612946]
16. Querfeld U, Salusky IB, Nelson P, Fine RN. Hyperlipidemia in pediatric patients undergoing peritoneal dialysis. Pediatr Nephrol 1988;2:447–452. [PubMed: 3153058]
17. Querfeld U. Disturbances of lipid metabolism in children with chronic renal failure. Pediatr Nephrol 1993;7:749–757. [PubMed: 8130098]
18. Saland JM, Ginsberg H, Fisher EA. Dyslipidemia in pediatric renal disease: epidemiology, pathophysiology, and management. Curr Opin Pediatr 2002;14:197–204. [PubMed: 11981290]
19. Silverstein DM, Palmer J, Polinsky MS, Braas C, Conley SB, Baluarte HJ. Risk factors for Hyperlipidemia in long-term pediatric renal transplant recipients. Pediatr Nephrol 2000;14:105–110. [PubMed: 10684357]
20. Milliner DS, Morgenstern BZ, Murphy M, Gonyea J, Sterioff S. Lipid levels following renal transplantation in pediatric recipients. Transplant Proc 1994;26:112–114. [PubMed: 8108898]
21. Chavers BM, Hardstedt M, Gillingham KJ. Hyperlipidemia in pediatric kidney transplant recipients treated with cyclosporine. Pediatr Nephrol 2003;18:565–569. [PubMed: 12712377]
22. Sgambat K, He J, McCarter RJ, Moudgil A. Lipoprotein profile changes in children renal transplantation in the modern immunosuppression era. Pediatr Transplant 2008;12:796–803. [PubMed: 18331540]

23. Silverstein DM, Mitchell M, LeBlanc P, Boudreaux JP. Assessment of risk factors for cardiovascular disease in pediatric renal transplant patients. Pediatr Transplant 2007;11:721–729. [PubMed: 17910648]
24. Saland, JM.; Pierce, CB.; Flynn, JT., et al. Dyslipidemia in Children with CKD: A Report of The Chronic Kidney Disease in Children (CKiD) Study. Poster presented at: American Society of Nephrology Renal Week 2008; November 4–9; Philadelphia, PA. 2008.
25. Hanevold CD, Ho PL, Talley L, Mitsnefes MM. Obesity and renal transplant outcome: a report of the North American Pediatric Renal Transplant Cooperative Study . Pediatrics 2005;115:352–356. [PubMed: 15687444]
26. Mitsnefes MM, Khoury P, McEnery PT. Body mass index and allograft function in pediatric renal transplantation. Pediatr Nephrol 2002;12:535–539. [PubMed: 12172770]
27. American Diabetes Association. Diagnosis and classification of diabetes mellitus. Diabetes Care 2004;27:S5–S10. [PubMed: 14693921]
28. Prokai A, Fekete A, Kis E, et al. Post-transplant diabetes mellitus in children following renal transplantation. Pediatr Transplant 2008;12:643–649. [PubMed: 18093088]
29. Lai HL, Kartal J, Mitsnefes M. Hyperinsulinemia in pediatric patients with chronic kidney disease: the role of tumor necrosis factor-alpha. Pediatr Nephrol 2007;22:1751–1756. [PubMed: 17541791]
30. Lindblad YT, Axelsson J, Bárány P, et al. Hyperinsulinemia and insulin resistance, early cardiovascular risk factors in children with chronic kidney disease. Blood Purif 2008;26:518–525. [PubMed: 18987465]
31. Painter P, Krasnoff J, Mathias R. Exercise capacity and physical fitness in pediatric dialysis and kidney transplant patients. Pediatr Nephrol 2007;22:1030–1039. [PubMed: 17372771]
32. Weaver DJ Jr, Kimball TR, Knilans T, et al. Decreased maximal aerobic capacity in pediatric chronic kidney disease. J Am Soc Nephrol 2008;19:624–630. [PubMed: 18184856]
33. Vandevoorde RG, Barletta GM, Chand DH, et al. Blood pressure control in pediatric hemodialysis: the Midwest Pediatric Nephrology Consortium study. Pediatr Nephrol 2007;22:547–553. [PubMed: 17115195]
34. Ulinski T, Genty J, Viau C, Tillous–Borde I, Deschênes G. Reduction of left ventricular hypertrophy in children undergoing hemodialysis. Pediatr Nephrol 2006;21:1171–1178. [PubMed: 16850307]
35. Mitstnefes MM, Barletta GM, Dresner IG, et al. Severe cardiac hypertrophy and long-term dialysis: the Midwest Pediatric Nephrology Consortium Study. Pediatr Nephrol 2006;21:1167–1170. [PubMed: 16807760]
36. Fischbach M, Terzic J, Laugel V, et al. Daily on-line haemodiafiltration: a pilot trial in children. Nephrol Dial Transplant 2004;19:2360–2367. [PubMed: 15266034]
37. Fischbach M, Dheu C, Seuge L, Menouer S, Terzic J. In-center daily on-line hemodiafiltration: a 4-year experience in children. Clin Nephrol 2008;69:279–284. [PubMed: 18397702]
38. Fadrowski JJ, Pierce CB, Cole SR, Moxey-Mims M, Warady BA, Furth SL. Hemoglobin decline in children with chronic kidney disease: baseline results from the chronic kidney disease in children prospective cohort study. Clin J Am Soc Nephrol 2008;3:457–462. [PubMed: 18235140]
39. Staples AO, Wong CS, Smith JM, et al. Anemia and risk of hospitalization in pediatric chronic kidney disease. Clin J Am Soc Nephrol 2009;4:48–56. [PubMed: 19056614]
40. Warady BA, Ho M. Morbidity and mortality in children with anemia at initiation of dialysis. Pediatr Nephrol 2003;18:1055–1062. [PubMed: 12883982]
41. Feber J, Wong H, Geier P, Chaudry B, Filler G. Complications of chronic kidney disease in children post renal-transplantation – a single center experience. Pediatr Transplant 2008;12:80–84. [PubMed: 18186892]
42. El-Husseini AA, Sobh MA, Ghonheim MA. Complications of pediatric live-donor kidney transplantation: a single center's experience in Egypt. Pediatr Nephrol 2008;23:2067–2073. [PubMed: 18071759]
43. White CT, Schisler T, Er L, Djurdjev O, Matsuda-Abedini M. CKD following kidney transplantation in children and adolescents. Am J Kidney Dis 2008;51:996–1004. [PubMed: 18455846]
44. NAPRTCS. The NAPRTCS 2005 Annual Report. [Accessed February 10, 2009]. http://spitfire.emmes.com/study/ped/annlrept/annlrept2005.pdf

45. Bek K, Akman S, Bilge I, et al. Chronic kidney disease in children in Turkey. Pediatr Nephrol. 200810.1007/s00467-008-0998-4
46. Jono S, Nishizawa Y, Shioi A, Morii H. 1,25-Dihidroxy-vitamin $D_3$ increases in vitro vascular calcification by modulating secretion of endogenous parathyroid hormone-related peptide. Circulation 1998;98:1302–1306. [PubMed: 9751679]
47. Menon S, Valentini RP, Hidalgo G, Peschansky L, Mattoo TK. Vitamin D insufficiency and hyperparathyroidism in children with chronic kidney disease. Pediatr Nephrol 2008;23:1831–1836. [PubMed: 18575896]
48. Goldstein SL, Currier H, Watters L, Hempe JM, Sheth RD, Silverstein D. Acute and chronic inflammation in pediatric patients receiving hemodialysis. J Pediatr 2003;143:653–657. [PubMed: 14615740]
49. Cengiz N, Baskin E, Agras PI, Sezgin N, Saatci U. Relationship between chronic inflammation and cardiovascular risk factors in children on maintenance hemodialysis. Transplant Proc 2005;37:2915–2917. [PubMed: 16213260]
50. Sylvestre LC, Fonseca KP, Stinghen EA, Pereira AM, Meneses RP, Pecoits-Filho R. The malnutrition and inflammation axis in pediatric patients with chronic kidney disease. Pediatr Nephrol 2007;22:864–873. [PubMed: 17340148]
51. Goldstein SL, Leung JC, Silverstein DM. Pro- and anti-inflammatory cytokines in chronic pediatric dialysis patients: effect of aspirin. Clin J Am Soc Nephrol 2006;1:979–986. [PubMed: 17699316]
52. Nurmohamed SA, Nube MJ. Reverse epidemiology: paradoxical observations in haemodialysis patients. Neth J Med 2005;63:376–381. [PubMed: 16301758]
53. Silverstein DM. Inflammation in chronic kidney disease: role in the progression of renal and cardiovascular disease. Pediatr Nephrol. 200810.1007/s00467-008-1046-0
54. Johnstone LM, Jones CL, Grigg LE, Wilkinson JL, Walker RG, Powell HR. Left ventricular abnormalities in children, adolescents and young adults with renal disease. Kidney Int 1996;50:998–1006. [PubMed: 8872976]
55. Mitsnefes MM, Kimball TR, Witt SA, Glascock BJ, Khoury PR, Daniels SR. Left ventricular mass and systolic performance in pediatric patients with chronic renal failure. Circulation 2003;107:864–8. [PubMed: 12591757]
56. Poyrazoglu HM, Düsünsel R, Narin F, et al. Homocysteine and left ventricular hypertrophy in children with chronic renal failure. Pediatr Nephrol 2004;19:193–198. [PubMed: 14658062]
57. Malikènas A, Cerniauskiene V, Jakutovic M, Jankauskiene A. Left ventricular geometry in children with chronic renal failure. Medicina 2005;41(Suppl 1):5–11. [PubMed: 15901968]
58. Matteucci MC, Wühl E, Picca S, et al. Left ventricular geometry in children with mild to moderate renal insufficiency. J Am Soc Nephrol 2006;17:218–226. [PubMed: 16280471]
59. Mitsnefes MM, Kimball TR, Kartal J, et al. Progression of left ventricular hypertrophy in children with early chronic kidney disease: 2-year follow-up study. J Pediatr 2006;149:671–675. [PubMed: 17095341]
60. Mitsnefes, M.; Flynn, J.; Cohn, S., et al. Left ventricular hypertrophy and masked hypertension: a report from the Chronic Kidney Disease in Children (CKiD) cohort. Poster presented at: American Society of Nephrology Renal Week 2008; November 4–9; Philadelphia, PA. 2008.
61. Weaver DJ, Kimball TR, Koury PR, Mitsnefes MM. Cardiac output and associated left ventricular hypertrophy in pediatric chronic kidney disease. Pediatr Nephrol 2009;24:565–567. [PubMed: 19048301]
62. Drukker A, Urbach J, Glaser J. Hypertrophic cardiomyopathy in children with end-stage renal disease and hypertension. Proc Eur Dial Transplant Assoc 1981;18:542–547. [PubMed: 7199148]
63. Morris KP, Skinner JR, Wren C, Hunter S, Coulthard MG. Cardiac abnormalities in end stage renal failure and anaemia. Arch Dis Child 1993;68:637–643. [PubMed: 8323332]
64. Loirat C, Ehrich JH, Geerlings W, et al. Report on management of renal failure in children in Europe, XXIII, 1992. Nephrol Dial Transplant 1994;9(Suppl 1):26–40. [PubMed: 8008229]
65. Mitsnefes MM, Daniels SR, Schwartz SM, Meyer RA, Khoury P, Strife CF. Severe left ventricular hypertrophy in pediatric dialysis: prevalence and predictors. Pediatr Nephrol 2000;14:898–902. [PubMed: 10975295]

66. Mitsnefes MM, Schwartz SM, Daniels SR, Kimball TR, Khoury P, Strife CF. Changes in left ventricular mass index in children and adolescents after renal transplantation. Pediatr Transplant 2001;5:279–284. [PubMed: 11472607]

67. Lumpaopong A, Tuntrakool C, Thirakhupt P, Chulamokha Y. Left ventricular hypertrophy and LV geometry in chronic dialysis children and adolescents. J Med Assoc Thai 2005;88(Suppl 3):S202–205. [PubMed: 16858959]

68. Uçar T, Tutar E, Yalçinkaya F, et al. Global left-ventricular function by tissue Doppler imaging in pediatric dialysis patients. Pediatr Nephrol 2008;23:779–785. [PubMed: 18231814]

69. Mitsnefes MM, Schwartz SM, Daniels SR, Kimball TR, Khoury P, Strife CF. Changes in left ventricular mass index in children and adolescents after renal transplantation. Pediatr Transplant 2001;5:279–284. [PubMed: 11472607]

70. Becker-Cohen R, Nir A, Ben-Shalom E, Rinat C, Feinstein S, Farber B, Frishberg Y. Improved left ventricular mass index in children after renal transplantation. Pediatr Nephrol 2008;23:1545–1550. [PubMed: 18548286]

71. Guízar-Mendoza JM, Amador-Licona N, Lozada EE, et al. Left ventricular mass and heart sympathetic activity after renal transplantation in children and young adults. Pediatr Nephrol 2006;21:1413–1418. [PubMed: 16909241]

72. Matteucci MC, Giordano U, Calzolari A, Turchetta A, Santilli A, Rizzoni G. Left ventricular hypertrophy, treadmill tests, and 24-hour blood pressure in pediatric transplant patients. Kidney Int 1999;56:1566–1570. [PubMed: 10504509]

73. El-Husseini AA, Sheashaa HA, Hassan NA, El-Demerdash FM, Sobh MA, Ghoneim MA. Echocardiographic changes and risk factors for left ventricular hypertrophy in children and adolescents after renal transplantation. Pediatr Transplant 2004;8:249–254. [PubMed: 15176962]

74. Kitzmueller E, Véscei A, Pichler J, et al. Changes of blood pressure and left ventricular mass in pediatric renal transplantation. Pediatr Nephrol 2004;19:1385–1389. [PubMed: 15517413]

75. Bullington N, Kartal J, Khoury P, Mitsnefes M. Left ventricular hypertrophy in pediatric kidney transplant recipients: long-term follow-up study. Pediatr Transplant 2006;10:811–815. [PubMed: 17032427]

76. Muscheites J, Meyer AA, Drueckler E, et al. Assessment of the cardiovascular system in pediatric chronic kidney disease: a pilot study. Pediatr Nephrol 2008;23:2233–2239. [PubMed: 18597123]

77. Gruppen MP, Groothoff JW, Prins M, et al. Cardiac disease in young adult patients with end-stage renal disease since childhood: a Dutch cohort study. Kidney Int 2003;63:1058–1063. [PubMed: 12631088]

78. Goren A, Glaser J, Drukker A. Diastolic function in children and adolescents on dialysis and after kidney transplantation: an echocardiographic assessement. Pediatr Nephrol 1993;7:725–728. [PubMed: 8130091]

79. Mitsnefes MM, Kimball TR, Border WL, et al. Impaired left ventricular diastolic function in children with chronic renal failure. Kidney Int 2004;65:1461–1466. [PubMed: 15086489]

80. Mitsnefes MM, Kimball TR, Border WL, et al. Abnormal cardiac function in children after renal transplantation. Am J Kidney Dis 2004;43:721–726. [PubMed: 15042550]

81. Saygili A, Yildirim SV, Cengiz N, Uslu Y, Tokel K, Saatçi U. Assessment of left ventricular diastolic function by Doppler tissue imaging in children with end-stage renal disease. Acta Paediatr 2005;94:1055–1059. [PubMed: 16188849]

82. Weaver DJ Jr, Kimball TR, Knilans T, et al. Decreased maximal aerobic capacity in pediatric chronic kidney disease. J Am Soc Nephrol 2008;19:624–630. [PubMed: 18184856]

83. Chinali M, deSimone G, Matteucci MC, et al. Reduced systolic myocardial function in children with chronic renal insufficiency. J Am Soc Nephrol 2007;18:593–598. [PubMed: 17215443]

84. Weaver DJ Jr, Kimball T, Witt SA, et al. Subclinical systolic dysfunction in pediatric patients with chronic kidney disease. J Pediatr 2008;153:565–569. [PubMed: 18534216]

85. Groothoff JW, Gruppen MP, Offringa M, et al. Increased arterial stiffness in young adults with end-stage renal disease since childhood. J Am Soc Nephrol 2002;13:2953–2961. [PubMed: 12444214]

86. Oh J, Wunsch R, Turzer M, et al. Advanced coronary and carotid arteriopathy in young adults with childhood-onset chronic renal failure. Circulation 2002;106:100–110. [PubMed: 12093777]

87. Mitsnefes MM, Kimball TR, Witt SA, Glascock BJ, Khoury PR, Daniels SR. Abnormal carotid artery structure and function in children and adolescents with successful renal transplantation. Circulation 2004;110:97–101. [PubMed: 15210594]

88. Litwin M, Wühl E, Jourdan C, et al. Altered morphologic properties of large arteries in children with chronic renal failure and after renal transplantation. J Am Soc Nephrol 2005;16:1494–1500. [PubMed: 15772249]

89. Mitsnefes MM, Kimball TR, Kartal J, et al. Cardiac and vascular adaptation in pediatric patients with chronic renal disease: role of calcium-phosphorus metabolism. J Am Soc Nephrol 2005;16:2799–2803.

90. Briese S, Wiesner S, Will JC, et al. Arterial and cardiac disease in young adults with childhood-onset end-stage renal disease: impact of calcium and vitamin D therapy. Nephrol Dial Transplant 2006;21:1906–1914. [PubMed: 16554325]

91. Poyrazo÷lu HM, Düuünsel R, Yikilmaz A, et al. Carotid artery thickness in children and young adults with end stage renal disease. Pediatr Nephrol 2007;22:109–116. [PubMed: 16944211]

92. Shroff RC, Donald AE, Hiorns MP, et al. Mineral metabolism and vascular damage in children on dialysis. J Am Soc Nephrol 2007;18:2996–3003. [PubMed: 17942964]

93. Bilginer Y, Ozaltin F, Basaran CA, et al. Carotid intima-media thickness in children and young adults with renal transplant: internal carotid artery vs. common carotid artery. Pediatr Transplant 2007;11:888–894. [PubMed: 17976124]

94. Van Summeren MJH, Hameleers JM, Schurgers LJ, et al. Circulating calcification inhibitors and vascular properties in children after renal transplantation. Pediatr Nephrol 2008;23:985–993. [PubMed: 18286307]

95. Litwin M, Wühl E, Jourdan C, et al. Evolution of large-vessel arteriopathy in paediatric patients with chronic kidney disease. Nephrol Dial Transplant 2008;23:2552–2557. [PubMed: 18344239]

96. Ziolkowska H, Brzewski M, Roszkowska-Blaim M. Determinants of the intima-media thickness in children and adolescents with chronic kidney disease. Pediatr Nephrol 2008;23:805–811. [PubMed: 18228041]

97. Krmar RT, Balzano R, Jogestrand T, Cedazo-Minguez A, Englund MS, Berg UB. Prospective analysis of carotid arterial wall structure in pediatric renal transplants with ambulatory normotension and in treated hypertensive recipients. Pediatr Transplantation 2008;12:412–419.

98. Delucchi A, Dinamarca H, Gainza H, Whittle C, Torrealba I, Iñiguez G. Carotid intima-media thickness as a cardiovascular risk marker in pediatric end-stage renal disease patients on dialysis and in renal transplantation. Transplant Proc 2008;40:3244–3246. [PubMed: 19010244]

99. Milliner DS, Zinsmeister AR, Lieberman E, Landing B. Soft-tissue calcification in pediatric patients with end-stage renal disease. Kidney Int 1990;38:931–936. [PubMed: 2266678]

100. Goodman WG, Goldin J, Kuizon BD, et al. Coronary-artery calcification in young adults with end-stage renal disease who are undergoing dialysis. N Engl J Med 2000;342:1478–1483. [PubMed: 10816185]

101. Ishitani MB, Milliner DS, Kim DY, et al. Early subclinical coronary artery calcification in young adults who were pediatric kidney transplant recipients. Am J Transplant 2005;5:1689–1693. [PubMed: 15943627]

102. Civilibal M, Caliskan S, Adaletli I, et al. Coronary artery calcifications in children with end-stage renal disease. Pediatr Nephrol 2006;21:1426–1433. [PubMed: 16821026]

103. Civilibal M, Caliskan S, Kurugoglu S, et al. Progression of coronary calcification in pediatric chronic kidney disease stage 5. Pediatr Nephrol 2009;24:555–563. [PubMed: 18982357]

104. Johnson HM, Douglas PS, Srinivasan SR, et al. Predictors of carotid intima-media thickness progression in young adults: The Bogalusa Heart Study. Stroke 2007;38:900–905. [PubMed: 17272779]

105. Litwin M, Niemirska A. Intima-media thickness measurements in children with cardiovascular risk factors. Pediatr Nephrol. 200810.1007/s00467-008-0962-3

106. Shroff RC, McNair R, Figg N, et al. Dialysis accelerates medial vascular calcification in part by triggering smooth muscle cell apoptosis. Circulation 2008;118:1748–1757. [PubMed: 18838561]

107. Kari J, Donald AE, Vallance DT, et al. Physiology and biochemistry of endothelial function in children with chronic renal failure. Kidney Int 1997;52:468–72. [PubMed: 9264003]

108. Lilien MR, Schröder CH, Levtchenko EN, Koomans HA. Growth hormone therapy influences endothelial function in children with renal failure. Pediatr Nephrol 2004;19:785–9. [PubMed: 15173937]
109. Lilien MR, Stroes ES, Op't Roodt J, de Jongh S, Schröder CH, Koomans HA. Vascular function in children after renal transplantation. Am J Kidney Dis 2003;41:684–91. [PubMed: 12612994]
110. Lilien MR, Koomans HA, Schröder CH. Hemodialysis acutely impairs endothelial function in children. Pediatr Nephrol 2005;20:200–4. [PubMed: 15627169]
111. Wilson AC, Urbina E, Witt SA, Glascock BJ, Kimball TR, Mitsnefes M. Flow-mediated vasodilatation of brachial artery in children with chronic kidney disease. Pediatr Nephrol 2008;23:1297–1302. [PubMed: 18458956]
112. Kavey RW, Allada V, Daniels SR, et al. Cardiovascular risk reduction in high-risk pediatric patients: a scientific statement from the American Heart Association Expert Panel on Population and Prevention Science: the Councils on Cardiovascular Disease in the Young, Epidemiology and Prevention, Nutrition, Physical Activity and Metabolism, High Blood Pressure Research, Cardiovascular Nursing, and the Kidney in Heart Disease; and the Interdisciplinary Working Group on Quality of Care and Outcomes Research: endorsed by the American Academy of Pediatrics. Circulation 2006;114:2710–2738. [PubMed: 17130340]
113. National Kidney Foundation. K/DOQI Clinical Practice Guidelines on Hypertension and Antihypertensive Agents in Chronic Kidney Disease. Am J Kidney Dis 2004;43(suppl 1):S223–S229.
114. National High Blood Pressure Education Program Working Group on High Blood Pressure in Children and Adolescents. The fourth report on the diagnosis, evaluation, and treatment of high blood pressure in children and adolescents. Pediatrics 2004;114(2 Suppl 4th Report):555–576. [PubMed: 15286277]
115. National Kidney Foundation. K/DOQI Clinical Practice Guidelines for Managing Dyslipidemias in Chronic Kidney Disease. Am J Kidney Dis 2003;41(Suppl 3):S61–S70. [PubMed: 12612955]
116. Kasiske B, Cosio FG, Beto J, et al. Clinical practice guidelines for managing dyslipidemias in kidney transplant patients: a report from the Managing Dyslipidemias in Chronic Kidney Disease Work Group of the National Kidney Foundation Kidney Disease Outcomes Quality Initiative. Am J Transplant 2004;4 (Suppl 7):13–53. [PubMed: 15027968]
117. Daniels SR, Greer FR. the Committee on Nutrition. Lipid Screening and Cardiovascular Health in Childhood. Pediatrics 2008;122:198–208. [PubMed: 18596007]
118. National Kidney Foundation. K/DOQI Clinical Practice Guidelines for Nutrition in Chronic Renal Failure. Am J Kidney Dis 2000;35(suppl 2):S1–S140. [PubMed: 10895784]
119. National Kidney Foundation. K/DOQI Clinical Practice Guidelines for Bone Metabolism and Disease in Chronic Kidney Disease. Am J Kidney Dis 2003;42(suppl 3):S1–S202. [PubMed: 14520607]
120. National Kidney Foundation. KDOQI Clinical Practice Guidelines and Clinical Practice Recommendations for Anemia in Chronic Kidney Disease. Am J Kidney Dis 2006;47(suppl 3):S1–S146.
121. National Kidney Foundation. Section III. State of the science: novel and controversial topics in cardiovascular diseasesin K/DOQI Clinical Practice Guidelines for Cardiovascular Disease in Dialysis Patients. Am J Kidney Dis 2005;45(suppl 3):S76–S114.
122. Nesrallah G, Suri R, Moist L, Kortas C, Lindsay RM. Volume control and blood pressure management in patients undergoing quotidian hemodialysis. Am J Kidney Dis 2003;42:13–17. [PubMed: 12830438]
123. Fagugli RM, Palumbo B, Ricciardi D, et al. Association between extracellular water, left ventricular mass and hypertension in haemodialysis patients. Nephron Clin Pract 2003;95:2322–2338.
124. Chan CT, Floras JS, Miller JA, Richardson RM, Pierratos A. Regression of left ventricular hypertrophy after conversion to nocturnal hemodialysis. Kidney Int 2002;61:2235–2239. [PubMed: 12028465]
125. Krmar RT, Berg UB. Blood pressure control in hypertensive pediatric renal transplants: role of repeated ABPM following transplantation. Am J Hypertens 2008;21:1093–1099. [PubMed: 18704114]

126. Wiesbauer F, Heinze G, Mitterbauer C, Harnoncourt F, Hörl WH, Oberbauer R. Statin use is associated with prolonged survival of renal transplant recipients. J Am Soc Nephrol 2008;19:2211–2218. [PubMed: 18650477]

127. Serón D, Oppenheimer F, Pallardó LM, et al. Fluvastatin in the prevention of renal transplant vasculopathy: results of a prospective, randomized, double-blind, placebo-controlled trial. Transplantation 2008;15:82–87.

128. Hakim RM, Lowrie E. Obesity and mortality in ESRD: is it good to be fat? Kidney Int 1999;55:1580–1581. [PubMed: 10201027]

129. Cheung AK, Sarnak MJ, Yan G, et al. Atherosclerotic cardiovascular disease risks in chronic hemodialysis patients. Kidney Int 2000;58:535–362.

130. Kopple JD. Nutritional status as a predictor of morbidity and mortality in maintenance dialysis patients. ASAIOJ 1997;43:246–250.Review

131. Nishizawa Y, Shoji T, Ishimura E. Body composition and cardiovascular risk in hemodialysis patients. J Ren Nutr 2006;16:241–244. [PubMed: 16825028]

132. Hanevold CD, Ho PL, Talley L, Mitsnefes MM. Obesity and renal transplant outcome: a report of the North American Pediatric Renal Transplant Cooperative Study. Pediatrics 2005;115:352–356. [PubMed: 15687444]

133. Mitsnsefes MM, Khoury P, McEnery PT. Body mass index and allograft function in pediatric renal transplantation. Pediatr Nephrol 2002;17:535–539. [PubMed: 12172770]

134. Hanafy S, Pinsk M, Jamali F. Effect of obesity on response to cardiovascular drugs in pediatric patients with renal disease. Pediatr Nephrol. 200810.1007/s00467-008-1064-y

135. American Diabetes Assocation. Standards of Medical Care in Diabetes. Diabetes Care 2005;28:S4–S36. [PubMed: 15618112]

**Table 1**

Key Risk Factors for CVD in Children With CKD & Relevance after Kidney Transplant

| Risk Factor | Prevalence | Impact of Kidney Transplant |
|---|---|---|
| Hypertension | 48–87% | Prevalence increases significantly after kidney transplant, to ~80–90% at 1 year |
| Dyslipidemia | 50–90% | Highest rates occur after kidney transplant, largely iatrogenic |
| Obesity | 10–30% | Rates double in 1st year after kidney transplant |
| Abnormal glucose metabolism | Up to 30% | Studied almost exclusively in kidney transplant ; minimal data in children with CKD or end-stage renal disease |
| Sedentary lifestyle/poor overall fitness | Near 100% | Contrary to expectations, does not improve significantly after kidney transplant |
| Coexistence of multiple Risk factors | Up to 66% | Emerging data indicates prevalence rises sharply after kidney transplant |
| Anemia | 18–86% | Previously thought less common after kidney transplant; new data shows prevalence up to 86% after kidney transplant |
| Hyperparathyroidism | 30–60% | Improves with kidney transplant |

Abbreviations: CKD, chronic kidney disease; CVD, cardiovascular disease.

**Table 2**

LVH in children with CKD

| Study | Type | Population | Frequency of LVH | Geometry* | LVH associations |
|---|---|---|---|---|---|
| | | **Studies in patients with CKD Stage 2–4** | | | |
| Johnstone et al, 1996 (54) | Cross-sectional | Mean eGFR not reported. | 22% (n=32) | All concentric | |
| Mitsnefes et al. 2003 (55) | Cross-sectional | Mean GFR 39 ml/min/1.73m$^2$ | 24% (n=25) | Not reported | Contractile reserve during exercise similar to control group. |
| Poyrazoglu et al. 2004 (56) | Cross-sectional | eGFR 17–48 ml/min/1.73m$^2$) | 50%(n=10) | Not reported | Lower hemoglobin |
| Malikenas et al. 2005 (57) | Cross-sectional | Mean eGFR 34 ml/min/1.73m$^2$ | 36% (n=56) | 23%E, 13%C | More common at lower eGFR |
| Matteucci et al. 2006 (58) | Cross-sectional | Mean eGFR 49 ml/min/1.73m$^2$ | 33%(n=156) | 12%C, 21%E | Males, anemia, obesity; BP not. |
| Mitsnefes et al. 2006 (59) | Prospective cohort, followed 2 yrs | Mean measured GFR 49 ml/min/ 1.73m$^2$ at echo 1, 43ml/min/ 1.73m$^2$ at echo 2 | 19% at echo 1; 39% at echo 2 (n=31) | Echo 1: 13%E, 6%C; Echo 2: 23%E, 16%C | Initial LVMI, lower hemoglobin, rise in iPTH, night SBP load all associated w/change in LVMI |
| Mitsnefes et al. 2008 (60) | Cross-sectional | Stage 2–4 CKD; mean GFR 42ml/ min/1.73m$^2$ | 19% (n=293) | 13%E/6%C | Both confirmed & masked HTN |
| Weaver et al. 2008 (61) | Cross-sectional | Stage 2–4 CKD; mean GFR 46ml/ min/1.73m$^2$ | 17% (n=45) | Not reported | Higher cardiac output |
| | | **Studies in patients on maintenance dialysis** | | | |
| Drukker et al, 1981 (62) | Cross-sectional | HD | 40% (n=10) | Not reported | “moderate to severe” HTN |
| Morris et al, 1993 (63) | Cross-sectional | Dialysis (12 PD, 1 HD) | 92% (n=13) | Not reported | 50% also had diastolic dysfunction |
| Loirat et al, 1994 (64) | Cross-sectional | PD and HD | 59% HD (n=85); 29% PD (n=198) | | |
| Johnstone et al, 1996 (54) | Cross-sectional | PD | 30% (n=10) | All concentric | |
| Mitsnefes et al, 2000 (65) | Cross-sectional | PD and HD | 85% HD (n=26); 68% PD (n=38) | Of 48 w/LVH, 25E, 23C. | |
| Mitsnefes et al, 2001 (66) | Retrospective cohort | 13 HD, 16PD | 69% at initiation & at follow-up | Of 20 w/LVH, 11E, 9C | Change in LVMI over time correlated w/change in SBP index |
| Poyrazoglu et al. 2004 (56) | Cross-sectional | 9 PD, 8 HD | 88% (n=17) | Not reported | Lower hemoglobin |
| Lumpaopong et al. 2005 (67) | Retrospective | 11 HD, 3PD | 57% (n=14) | 7E, 1C | Higher BP |

| Study | Type | Population | Frequency of LVH | Geometry* | LVH associations |
|---|---|---|---|---|---|
| Ulinski et al, 2006 (34) | Prospective cohort | HD | Start dialysis: 82%; 41% at 16mof/u (n=17) | Not reported | Higher BP is only independent predictor |
| Mitsnefes et al. 2006 (35) | Retrospective cohort | HD at least 2 years' duration (n=17) | Initiation: 82% 2 years: 82% | Initial: 3C/11E 2yr: 5C/9E | |
| Ucar et al. 2008 (68) | Cross-sectional | Maintenance PD | 76% (n=25) | 14C/5E | Higher LVMI associated with increased global LV dysfunction |
| **Longitudinal studies of patients prior to (on dialysis) and following rena) transplantation** | | | | | |
| Mitsnefes et al, 2001 (69) | Prospective cohort | 16 PD; 7HD w/subsequent RT | 52% while on dialysis vs 56% after transplant | Not reported | Mean LVMI decreased but not significant |
| Becker-Cohen et al. 2008 (70) | Prospective cohort | PD and HD, then RT | D: 50% (n=12); RT: 54%–>8% (n=13) | Not reported | Reduction in LVMI after RT; no change if stayed on dialysis |
| Guizar-Mendoza et al. 2006 (71) | Prospective cohort, ages 8–35 yrs | PD and HD, then RT (n=40) | Pre-RT: 82.5%; Post-RT57.5% | Not reported | No patient with increase in LVM after RT: mean LVMI pre-RT 73g/m$^2$,[7] |
| **Studies in patients with successful renal transplantation** | | | | | |
| Johnstone et al, 1996 (54) | Cross-sectional | | 63% (n=30) | All concentric | |
| Matteucci et al, 1999 (72) | Cross-sectional | | 82% (n=28) | Not reported | Higher mean 24hr SBP |
| El-Husseini et al, 2004 (73) | Cross-sectional | | 48% (n=73); median of 4.6 yrs post-RT | Not reported | Also showed 14% prevalence of LV systolic dysfunction |
| Kitzmueller et al, 2004 (74) | Retrospective cohort | | 48% (n=39); 20 w/2 yr repeat | Not reported | Subgroup of 20: 60% w/ LVH at initial echo; 70% w/ LVH on f/u |
| Bullington et al. 2006 (75) | Retrospective cohort | Up to 3 echos per pt. | 54% in echo 1 (n=47) | 59%E/41%C | 14 pts w/3 echos: LVH in 57% at echo 1 vs 64% at echo 3. |
| Silverstein et al. 2008 (23) | Cross-sectional | Mean GFR 88ml/min/1.73m$^2$ | 18.2% (n=45) | Not reported | |
| Wilson et al. 2009 (12) | Cross-sectional | | 40% (n=113) | 53%C, 47%E. | Metabolic syndrome |
| Muscheites et al. 2008 (76) | Cross-sectional | CKD 2–4, ESRD, & RT | 50% (n=26); 8 w/severe LVH | Not reported | |

C, concentric; E, eccentric; eGFR, estimated glomerular filtration rate; ESRD, end-stage renal disease; HD, hemodialysis; HTN, hypertension; iPTH, intact parathyroid hormone; LVMI, left ventricular mass index; RT, renal transplant; PD, peritoneal dialysis.

To convert GFR in mL/min/1.73m$^2$ to mL/s/1.73m$^2$, x0.01667.

**Table 3**

Intima-media thickness (IMT) in children with CKD

| Study | Type | Population | Findings | IMT Associations | Notes |
|---|---|---|---|---|---|
| Groothoff et al. 2002 (85) | Cross-sectional | 130 adult survivors of childhood ESRD | IMT similar to controls but higher stiffness & lower distensibility | | |
| Oh et al. 2002 (86) | Cross-sectional | 19–39 yr old survivors of childhood CKD | IMT significantly higher than controls | Dialysis time; Ca X P | |
| Mitsnefes et al. 2004 (87) | Cross-sectional | 31 pediatric RT vs. healthy matched control | Higher carotid IMT, lower distensibility | SBP load, number of BP meds | eGFR 44–128 ml/min/1.73m$^2$ |
| Litwin et al. 2005 (88) | Cross-sectional | 55 CKD 2–4; 37 on dialysis; 34 post-RT; 270 healthy control | cIMT, femoral artery IMT increased in all pt groups | Mean past Ca x P, young age, dialysis at time of study | Dialysis patients significantly worse than CKD or RT |
| Mitsnefes et al. 2005 (89) | Cross-sectional | 44 CKD 2–4; 16 on dialysis; 35 healthy control | cIMT & stiffness higher in both CKD & ESRD | Increased Ca x P and dialysis; | Arterial compliance similar in CKD 2–4 and controls; worse in dialysis |
| Briese et al. 2006 (90) | Cross-sectional | 40 young adults with childhood ESRD | IMT similar to healthy controls | n/a | Relatively low Ca intake & Vit. D compared to other study populations |
| Poyrazoglu et al. 2007 (91) | Cross-sectional | 34 children & young adults with ESRD; 20 controls | Higher IMT in ESRD than control | Increased BP, LVMI negative correlation w/iPTH | |
| Shroff et al. 2007 (92) | Cross-sectional | 85 children on dialysis >6 months | Higher IMT in ESRD than control | Increased iPTH & Ca x P | If iPTH < 2x upper limit of normal, vasculature comparable to controls |
| Bilginer et al. 2007 (93) | Cross-sectional | 24 children & young adults with RT; 20 controls | Carotid IMT higher in RT than control | Duration of renal failure, duration of dialysis, mean past Ca x P | |
| van Summeren et al. 2008 (94) | Cross-sectional | 29 children with RT; 54 healthy controls | IMT& elasticity of carotid significantly higher than in controls | No association with calcification inhibitors (MGP & fetuin-A) | Fetuin-A decreased in RT vs. control; no differences in MGP levels |
| Muscheites et al. 2008 (76) | Cross-sectional | 26 children with CKD 2–4, ESRD, or RT; 24 controls | IMT SDS score significantly higher than controls | Impaired FMD | |
| Litwin et al. 2008 (95) | Observational cohort (12 months f/u) | 24 CKD 2–4; 32 ESRD (19 had RT between 1 & 2 evaluation) | Mean IMT-SDS above norms in all group | Total dialysis vintage, BP, phosphate | Patients with RT showed stabilization/ partial regression of IMT |
| Ziolkowska et al. 2008 (96) | Cross-sectional | 32 CKD 2–4; 28 ESRD; 43 controls | 37 patients w/abnl IMT (18 CKD, 19 CSRD) | Negative correlation with fetuin-A | 15 patients also w/abnormal vessel wall echogenicity & 2 with calcifications |
| Krmar et al. 2008 (97) | Observational cohort (mean 4.1 year f/u interval) | 31 RT; 21 controls | Baseline & f/u IMT both higher than controls | No significant associations between BP& IMT | Controls only studied at baseline; IMT in RT patients was stable over time |
| Delucchi et al. 2008 (98) | Cross-sectional | 8 children on dialysis; 12 RT; 30 controls | Both pt groups with IMT higher than control | Duration of dialysis | |

*Am J Kidney Dis*. Author manuscript; available in PMC 2010 August 1.

BP, blood pressure; CKD, chronic kidney disease; Ca X P, calcium-phosphorous product; eGFR, estimated glomerular filtration rate; ESRD, end-stage renal disease; FMD, flow-mediated vasodilatation; IMT, intima-media thickness; iPTH, intact parathyroid hormone; LVMI, left ventricular mass index; MGP, matrix Gla protein; RT, renal transplant.

**Table 4**

Calcification in children with CKD

| Study | Type | Population | Findings | CAC Associations | Notes |
|---|---|---|---|---|---|
| Milliner et al. 1990 (99) | Retrospective autopsy series | 120 pediatric CKD, dialysis, RT | 10% w/CAC; soft tissue calcification in 60% | Vitamin D, age at onset of ESRD, Ca x P, male sex | Autopsy study; 4 patients w/ evidence of MI or calcification of myocardium |
| Goodman et al. 2000 (100) | Cross- sectional | 39 dialysis pts (age 7–30); 60 controls | No CAC in pts <20 yrs; 14/16 pts>20 years w/ CAC | Age, serum P, duration of dialysis, Ca intake, Ca x P | 10 patients w/CAC had f/u scan at mean 20 mos; calcification score nearly doubled |
| Oh et al. 2002 (86) | Cross- sectional | 19–39 yr old childhood CKD survivors (n=37) | 92% w/CAC | Current dialysis, dialysis duration, iPTH, CRP, Ca x P, *C pneumoniae* seropositivity, homocysteine | 34% also w/cardiac valve calcification; 32% w/aortic calcification |
| Ishitani et al. 2005 (101) | Cross- sectional | 21–48 yr old pediatric RT recipients (n=19) | 47% w/CAC, all in pts >30 yrs old | None identified as significant | 12 pts never dialyzed; 6 w/ ≤6 months total dialysis time; 1 w/24 months total dialysis |
| Briese et al. 2006 (90) | Cross- sectional | 40 young adults w/ childhood ESRD | 10% w/moderate to severe CAC. | Age, ESRD duration; time on dialysis; BP; cIMT; total Ca dose, Vit. D intake | Relatively low Ca intake & Vit D compared to other study populations |
| Civilibal et al. 2006 (102) | Cross- sectional | Children w/ESRD (15 HD, 24 PD, 14 RT) | 15% w/CAC (20% HD, 12.5% PD, 14% RT) | Dialysis duration, serum P, Ca x P, iPTH, & vit$B_{12}$; Hgb; total Ca & Vit D doses | 3 patients w/severe (high probability of stenosis) lesions. |
| Shroff et al. 2007 (92) | Cross-sectional | 85 children on dialysis>6 mos | 20% w/CAC (27% among those w/iPTH ≥ 2x upper limit of normal) | Time integrated iPTH, serum phosphorous | 2 w/severe CAC; only high iPTH group had moderate/ severe CAC |
| Civilibal et al. 2009 (103) | Prospective cohort | 48 children w/ ESRD; 8 w/baseline CAC | 0% CAC incidence. Among those with baseline CAC, median score increased | Final Ca x P; inverse association w/ serum albumin | 1 CAC resolution; 3 w/mild decrease; 3 w/moderate increase; 1 w/large increase |

BP, blood pressure; Ca X P, calcium-phosphorous product; CAC, coronary artery calcification; cIMT, carotid intima media thickness; CKD, chronic kidney disease; CRP, c-reactive protein; ESRD, end-stage renal disease; HD, hemodialysis; Hgb, hemoglobin; PD, peritoneal dialysis; Hgb, hemoglobin; RT, renal transplant.

**Table 5**

Summary of Treatment Goals for CVD Risk Factors in Children With CKD

| Risk factor | Goal | Reference |
|---|---|---|
| Hypertension | Blood pressure <90$^{th}$ percentile for age, sex, and height, or <120/80mmHg, whichever is lower. | NKF KDOQI Clinical Practice Guidelines on Hypertension and Antihypertensive Agents in Chronic Kidney Disease[113] and the Fourth report on blood pressure in children[114]. |
| Dyslipidemia | Maintenance of total cholesterol, LDL cholesterol, HDL cholesterol, and triglycerides in age-appropriate ranges for high cardiovascular disease risk patients. | NKF KDOQI Clinical Practice Guidelines for Managing Dyslipidemias in Chronic Kidney Disease[115] & for Managing Dyslipidemias in Kidney Transplant Patients[116] (note: these guidelines contain recommendations only for patients older than 13 years, with end-stage renal disease & transplant, respectively). For patients with stage 2–4 CKD, and those younger than 13 years, see clinical report by Daniels et al.[117] for age-appropriate guidelines in high-risk patients. |
| Obesity & Physical Inactivity | Maintenance of normal body habitus (Body mass index between 5$^{th}$ and 85$^{th}$ percentile for age, sex). | NKF KDOQI Clinical Practice Guidelines for Nutrition in Chronic Renal Failure[118]. |
| Hyperinsulinemia/Hyperglycemia | Maintenance of normoglycemia and normal insulin sensitivity. | No pediatric-specific guidelines exist. |
| Abnormal mineral metabolism | Phosphorous, Ca x P, and intact parathyroid hormone goals vary by age and CKD stage. | NKF KDOQI Clinical Practice Guidelines for Bone Metabolism and Disease in Children with Chronic Kidney Disease[119]. |
| Anemia | Maintenance of hemoglobin in the range of 11.0 to 12.0gm/dL in patients receiving erythropoeisis stimulating agent (ESA) therapy, along with maintenance of adequate iron stores. | KDOQI Clinical Practice Guidelines and Clinical Practice Recommendations for Anemia in Chronic Kidney Disease[120]. |
| LVH | Maintenance of normal left ventricular mass and function; in those patients with pre-existing left ventricular hypertension, normalization of echocardiographic findings. | KDOQI Clinical Practice Guidelines for Cardiovascular Disease in Dialysis Patients[121]. |

Abbreviations: NKF, National Kidney Foundation; KDOQI, Kidney Disease Outcomes Quality Initiative; LDL, low-density lipoprotein; HDL, high-density lipoprotein; CKD, chronic kidney disease; Ca x P, calcium-phosphorus product.