Pediatric patients with renal disease and cardiovascular complications: A literature review

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Review Article

Abstract

The cardiovascular burden of end stage renal disease (ESRD) in children has recently received more attention, and some authors have recommended that the origins of the increase in cardiovascular morbidity and mortality be found in childhood. In this comprehensive review of the literature, we aim to review the main and most recent studies evaluating cardiovascular risk factors in pediatric kidney disease patients. The literature suggests that ESRD, even in the pediatric population, is associated with a high rate of cardiovascular morbidity and mortality, and needs serious attention. Unfortunately, there is extreme scarcity of data on the efficacy of preventive strategies on cardiovascular morbidity and mortality in pediatric patients with renal disease. Therefore, authors of the current article recommend future studies to be directed to find beneficial and/or potential harmful effects of different interventions conventionally used in this population, including lifestyle modifications and pharmaceutical therapy on cardiovascular indices. Moreover, the effects of these drugs on the renal function of children with minimal kidney disease should be evaluated.

Keywords: Cardiovascular Complication, Children, Kidney Disease, Pediatrics

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Introduction

It is a well-known fact that kidney disease can adversely affect cardiovascular health in the general population.[1] The importance of the issue, however, increases when evidence suggests that the largest share of mortality in renal disease patients is related to cardiovascular insults.[2] Although the issue has been broadly discussed in the adults, there is no mention whether similar connection exists in the pediatric population. In the current literature review, we focus to find potential connections between these two entities in patients of childhood age, and to find the extent of such associations.

The first part of the current review article reviews the existing evidence on potential association between renal disease in children and cardiovascular mortality. In the second part, factors which are potentially connected to cardiovascular mortality in pediatric patients with kidney disease will be evaluated. In the third part, associations between arterial hypertension and kidney disease in children will be reviewed. The forth part discusses functional and anatomical insults to the left ventricle. And in the last part, preventive and therapeutic are described.

Epidemiology of Pediatric Kidney Disease and Cardiovascular Mortality

It is a well-established fact that end stage renal disease (ESRD) induces a high rate of mortality, especially in adult patients compared with that in the general population. Moreover, several studies have suggested that the majority of these patients' mortality is associated with cardiovascular disease that complicates the original renal disease.[2] On the other hand, recent evidence indicates decreasing rates of cardiovascular morbidity and mortality in these patients.[3] Cardiovascular burden of ESRD in children has recently received more attention, and some authors have recommended that the origins of the increase in cardiovascular morbidity and mortality are better to be found in childhood.[4] Cardiovascular disease has been established as the leading cause of morbidity and mortality in adults with childhood-onset ESRD,[5] and the mortality rate of children with ESRD compared to that in the

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general population is 10 times larger than that in their adult counterparts.[6] Table 1 summarizes major data on the cardiovascular causes of death in pediatric patients with ESRD.

Table 1. Major studies evaluating cardiovascular cause of death in pediatric renal disease patients

Authors (references)	Cohort follow-up (year)	Main findings	Sample size
Groothoff et al.[7]	Up to 20	Overall 5-, 10-, and 20-year survival after ESRD onset was 87%, 82%, and 78%, respectively with cardiovascular disease accounted for most deaths (41%). In the whole group, LVH, aortic valve calcification, and arterial wall stiffening were highly prevalent. LVH was associated with hypertension at the time of assessment. Aortic valve calcification was strongly associated with a long total duration of peritoneal dialysis	249
Kramer et al.[8]	Up to 10	For young adults starting dialysis in childhood, the average life expectancy was 63 years for those with a functioning graft and 38 years for those remaining on dialysis	1777
Lin et al.[9]	Up to 10	The overall 1-, 5-, and 10-year survival rates for peritoneal dialysis (PD) patients were 98.1%, 88.0%, and 68.4%, respectively, and were 96.9%, 87.3%, and 78.5% for hemodialysis (HD) patients. The death rate was 24.66/1000 dialysis patient-years. Cardiovascular disease (13%) was the second death reason succeeding the infection (23.4%)	475
US Renal Data System[3]	5	In 2005–2009, the 1-year adjusted cardiovascular mortality rate in children age 0–9 was 28.5/1000 patient years, 4.8 and 2.5 times higher, respectively, than for ages 10–14 and 15–19. Children on hemodialysis have higher cardiovascular mortality than those on peritoneal dialysis (23.2 vs. 17.5), while children with a transplant have the greatest survival advantage, with a mortality rate of 2.3	US National data
Parekh et al.[6]	7	Evaluating the risk of cardiac death in children and young adults, of 1380 deaths recorded, 311 (23%) were due to cardiac causes. Percentage of cardiac deaths varied by age and was higher among black patients (0–4 years, 36%; 5–9 years, 18%; 10–14 years, 35%; 15–19 years, 22%; 20–30 years, 32%) than white patients (18%, 12%, 17%, 14%, and 23%, respectively). Among black patients, cardiac deaths occurred in 34% (21.4/1000 patient-years) of dialysis patients, and among white patients 25% (20.5/1000 patient-years)	USRDS
McDonald et al.[10]	Median 9.7	The most common cause of death was cardiovascular disease (45%). Cardiovascular causes accounted for 57 percent of deaths among children receiving hemodialysis, 43% among those receiving peritoneal dialysis, and only 30 percent among those with a functioning renal transplant	1634
Groothoff et al.[11]	Up to 20	Cardiovascular deaths accounted for 41% of the mortality, which was the leading cause of mortality both in patients under dialysis (45% of mortality) and transplant patients with a functioning graft (36%)	251
Chavers et al.[5]	6	Cardiac deaths accounted for 38% (13.7/1000 patient years) of the mortality, representing the leading cause of death in the population. There was no significant difference in cardiac mortality by age or sex. Cardiac deaths were significantly increased among blacks (4.5 vs. 2.1% whites, 1.5% other, P = 0.03)	1454

ESRD: End stage renal disease; LVH: Left ventricular hypertrophy; USRDS: United states renal data system

Risk Factors for Cardiovascular Disease in Pediatric Kidney Disease

While cardiovascular diseases and their unfavorable consequences in the general population generally matters adults and elderly, there is presumptions even among professionals that cardiovascular complications of ESRD in children is minimal. However, speaking based on scientific evidence, the prevalence of cardiovascular disease in pediatric kidney disease is astonishingly high, and is associated with several risk factors. One of the major risk factors associated with a higher cardiovascular disease in ESRD children is patients' gender, with males at higher risk.[7,12] However, there are studies suggesting controversial data with females representing the highest rate of developing cardiovascular complications (including cardiomyopathy, arrhythmia and valvular heart disease.[5] Race is another major playing factor with blacks at highest risk for cardiovascular disorders.[5,6] Obesity has been shown to be highly more prevalent among is proposed as a potential risk factor for cardiovascular complications in childhood, but there is controversy on its role.[4] There are also some other cardiovascular risk factors which are especial to ESRD children, with no evidence for any major effects for them in the general population. The most important of them is impaired calcium-phosphorus metabolism, which is supposed to lead to vascular calcification. ESRD, either in adult individuals or in children, is associated with a secondary hyperparathyroidism that effectively impairs calcium-phosphorus metabolism in this population.[13] However, it is not the end of the story. Treatment of secondary hyperparathyroidism with calcium-containing phosphate binders and vitamin D analogs can result in hypercalcemia as well as increased levels of calcium-phosphorus product, which produce broad calcifications in soft-tissue, with the most clinically dangerous feature in the coronary arteries.[14] It has been suggested that although calcium accumulation begins pre-dialysis, but it is the induction of vascular smooth muscle cell apoptosis in dialysis that is the key event in disabling vascular defense mechanisms and leading to overt calcification.[15] The major studies on the coronary calcification of children with ESRD are listed in table 2.

Hypertension in Pediatric Kidney Disease

Hypertension maybe the most common cardiovascular risk factor that develops in young patients with ESRD, which not only accelerates kidney disease course to ESRD, but it induces high cardiovascular burden.[16] The interesting thing about hypertension is that it is, perhaps, the most modifiable risk factor of all; so it is very logical to pay a tremendous amount of attention to control this risk factor. Despite the high relevance of the subject, it has only recently taken attention for research.[17] One of the first major studies surveying the subject was conducted by Mitsnefes et al.[18] who reported from a large cohort of 3743 dialysis children. In this study, authors reported a 77% prevalence of hypertension in their population, and regression analysis showed associated risk factors include: baseline hypertensive status, use of antihypertensive medications, young age, acquired cause of renal failure, black race, initiation of dialysis therapy in 1992 to 1997, and hemodialysis as a mode of renal replacement therapy. In another major study by Flynn et al.[19] reporting from the chronic kidney disease in children (CKiD) prospective cohort study, authors showed that 54% of children with chronic kidney disease (CKD) had hypertension (defined as measured blood pressure (BP) >95th percentile and/or history of antihypertensive medication). Characteristics associated with elevated BP reported by CKiD included black race, shorter duration of CKD, absence of antihypertensive medication use, and elevated serum potassium. Another major study on the subject was conducted by Chavers et al.[20] on 624 American ESRD children revealed an appalling prevalence of hypertension, with 79% having hypertension and 62% under antihypertensive pharmacotherapy. Nevertheless, a more recent study by Halbach et al.[21] showed some improvement in the mentioned factors' epidemiology with 68% of patients representing hypertension, and 58% were prescribed antihypertensive medications. The same study reported that more recent year of dialysis commencement was associated with a higher use of antihypertensive medication and lower systolic BP and diastolic BP z-scores. Other factors associated with higher BP included black race, glomerular disease, younger age, hemodialysis (for systolic BP only), and antihypertensive use. Moreover, patients on hemodialysis or those with glomerular diseases represented the highest percentage of uncontrolled hypertension.[21] In the sole major European study available in the literature, Kramer et al.[22] recently showed that hypertension was present in 69%, 68%, and 67% of hemodialysis, peritoneal dialysis, and

Table 2. Major studies investigating coronary artery and cardiac calcification in children with end stage renal disease (ESRD)

Authors (References)	Diagnosis method	Main findings	Sample size
Goodman et al.[23]	Electron-beam tomography	None of the 23 patients who were younger than 20 years of age had evidence of coronary-artery calcification, but it was present in 14 of the 16 patients who were 20–30 years old	39
Civilibal et al.[24]	Spiral CT scan	CAC was present in 15% of patients (3/15 hemodialysis (HD) patients, 3/24 peritoneal dialysis (PD) patients, and 2/14 kidney transplants). The patients with CAC had longer duration of total dialysis, had higher time-integrated serum phosphorus, calcium-phosphate (CaxP) product, iPTH, vitamin B (12) levels, the amount of cumulative calcium-containing OPBs, and calcitriol intake, and had lower serum hemoglobin level. A stepwise logistic regression analysis revealed that serum phosphorus (P = 0.018) and the cumulative exposure to calcium-containing OPBs (P = 0.016) were the most significant independent predictors in the development of CAC	53
Lumpaopong et al.[25]	Electron-beam tomography	Coronary calcification was observed in 64% patients. The mean daily dose of calcitriol was significantly higher in patients with calcification; but the mean daily dose of total calcium, triglyceride level, and calcium/phosphorus products did not reach a significant level. Using Spearman multivariate correlation, authors found a correlation between the coronary calcium scores and mean daily doses of total calcium and calcitriol (r = 0.750, P =0.008 and r = 0.869, P = 0.001, respectively)	11 renal transplant patients
Shroff et al.[26]	Spiral CT scan	Patients with calcification had lower fetuin-A and higher osteoprotegerin than those without calcification. On multiple linear regression analysis and fetuin-A and osteoprotegerin predicted cardiac calcification (P = 0.02, beta = −0.29 and P = 0.014, ss = 0.33, respectively, model R (2) = 32%)	61 children on dialysis
Gruppen et al.[27]	Echocardiography	110 patients had received a transplant and 30 patients were on dialysis. 27 (19%) had aortic valve calcification. Multiple regression analysis revealed that aortic valve calcification was associated with prolonged peritoneal dialysis (beta = 0.36, P < 0.001)	140 young adults with childhood onset ESRD
Shroff et al.[28]	CT scan	Cardiac calcification score was correlated with iPTH (r = 0.39, P = 0.03), serum PO_4 levels (r = 0.34, P = 0.03) and vitamin D dosage (2.8 fold higher dosage than that in no calcification group; r = 0.28, P = 0.02). Significantly, patients with iPTH levels greater than twice the upper limit of normal had greater cardiac calcification	85 children on at least 6 months dialysis

CAC: Coronary artery calcification; OPBs: Oral phosphate binders; CT: Computed tomography iPTH: Intact parathyroid hormone; ESRD: End stage renal disease

renal transplant patients, respectively. BP values above the 95th percentile were significantly more prevalent in very young patients (under 3 years) compared with 13–17-year olds (odds ratio 2.47), during the 1st year compared to over 5 years of renal replacement therapy (odds ratio 1.80), and in patients on hemodialysis compared to transplant recipients or those on peritoneal dialysis (odds ratios of 2.48 and 1.59, respectively). Over time, mean BPs decreased in both hemodialysis and transplant patients, but not in peritoneal dialysis patients.[22] Besides the prevalence of hypertension among children with kidney disease, maybe the more important issue is the cardiovascular effects of hypertension in this population. In the adult patients, the cardiovascular morbidities of hypertension are well-recognized. However, in the very particular subpopulation of pediatric kidney disease patients, one may rightly think that there might be some substantial differences. Table 3 summarizes data of major studies on the cardiovascular consequences of hypertension in children with kidney diseases.

Structural and/or Functional Abnormalities of the Left Ventricle in Children with Kidney Disease

Structural anomalies have been consistently reported by different studies on pediatric ESRD patients; but the interesting thing is that even when there is minimal renal disease, these abnormalities began to develop and progress through the renal disease advancement.[29,30] A recent report from CKiD study,[31] demonstrated that left ventricular hypertrophy (LVH) has overall prevalence of 17% in pediatric kidney disease patients, while this rate in the International Pediatric Peritoneal Dialysis Network registry,[32] on 507 patients was 48%. Moreover, LVH is more frequently observed in children with clinic measured hypertension, than that defined by ambulatory measures.[33] Although data from CKiD study indicates that children with sustained and masked systolic or diastolic hypertension have higher rates of LVH,[31] Bakkaloglu et al.[32] in a very recent study reported that this is systolic hypertension, and not diastolic that predicts LVH in pediatric kidney disease patients. It has also been proposed elevated parathyroid hormone as a contributing factor in the progression of LVH in higher stages of kidney disease in children.[34]

Data on the ESRD children who undergo renal transplantation also indicates a high rate of LVH. A Midwest Pediatric Nephrology Consortium study,[35] showed that the prevalence of LVH among ESRD children who undergone kidney transplantation was 40% 1-year post-transplant. Most of the studies show the persistence of cardiac hypertrophy and ventricular dysfunction,[36-38] although some evidence also suggest improvement post-transplantation.[39,40]

Impaired left ventricular (LV) filling and compliance early or later in the progression of pediatric kidney disease has been reported overwhelmingly.[41] More the kidney disease progresses, the higher LV dysfunction advances,[42] with the highest prevalence of diastolic dysfunction in patients undergoing maintenance dialysis.[43] There are also several reports documenting subtle alterations in LV wall mechanics in children on maintenance dialysis. The most significant of these alterations are decreased shortening at the myocardial mid-wall,[44,45] diminished contractile reserve during stress,[46] and acute reductions in global and segmental myocardial blood flow simultaneous with an increase in myocardial stunning.[47]

Preventive Strategies to Reduce Cardiovascular Risk

Because risk factors, which contribute in cardiovascular injuries in kidney disease patients are multiple, and they mostly have conjoined contribution in inducing their ominous effects, strategies to risk reduction in this patient population should be complex and perhaps different for each individual patient, based on his/her risk profile. Unfortunately due to the very limited data available in the literature on the treatment and prevention strategies in the pediatric population of kidney disease, herein, we briefly review data on the mentioned strategies in adult kidney disease population.

Lifestyle and nutritional status intervention

Lifestyle modifications, is the most common and probably the most effective intervention in these patients. Although there is data scarcity on the effectiveness of undertaking these strategies in pediatric kidney disease patients, overwhelming data suggests them as effective methods for risk reduction in the general population. Weight loss programs, prevention of smoking, diet modifications, and encouragement to regular exercise are probably the most effective and implementable strategies physicians can prescribe for their patients. Weight loss in obese people has been shown to decrease BP. In 50% or more of individuals, the average decrease in BP is 1–4 mm Hg systolic and 1–2 mm Hg diastolic per kilogram of weight reduction up to the normalization of BP.[48]

Table 3. Data of major studies on the cardiovascular consequences of hypertension in children with kidney diseases

Authors (references)	Main findings	Population size
Johnstone et al.[49]	No correlation was found between BP and LVH in children on dialysis	32 CRF, 10 peritoneal dialysis, 30 renal transplants (age < 27 year)
Mitsnefes et al.[50]	Multiple logistic regression analysis revealed hemodialysis versus peritoneal dialysis as a significant independent predictor for severe LVH, while higher systolic BP remained in the final model was found to be an independent predictor with lower significance level	64 (< 22 year)
Chinali et al.[44]	Systolic dysfunction was most common (48%) in patients with concentric hypertrophy and associated with lower hemoglobin levels	130 pre-dialysis children (< 18 year)
Mitsnefes et al.[51]	Multiple regression analysis showed that baseline LVMI (P = 0.005) and interval change in indexed systolic BP (P = 0.027) were independent predictors for LVMI changes	29 children at the initiation of dialysis (age < 18 year)
Chavers et al.[5]	The most common cardiovascular "events" were arrhythmias, valvular disease, and cardiomyopathy; cardiac deaths accounted for just 9% of all reported events	1454
Mitsnefes et al.[34]	Lower initial LVMI and hemoglobin level and interval increase in iPTH and nighttime systolic BP load during a follow-up independently predicted interval increase in LVMI	31
Sinha et al.[33]	Patients with LVH had consistently higher BP values than those without. Multiple linear regression demonstrated a strong relationship between systolic BP and LVMI. Clinic measured systolic BP showed a stronger relationship than ambulatory measures	49 non-hypertensive children (all below 95th percentile)
Matteucci et al.[52]	After restrict control of hypertension for at least 1 year, LVH prevalence decreased significantly from 38% to 25%. Changes in LVMI were restricted to patients with LVH at baseline (−7.9 g/m$^{2.7}$; P < 0.02). In multivariate analysis, improvement in myocardial function was associated with reduction in BP (r = −0.4; P < 0.05), independently of LVMI reduction	84
Shamszad et al.[53]	Post-dialysis hypertension was associated with elevated LVMI (OR = 2.9, 95% CI = 1.5–5.5)	63 (mean age: 14.1 year)
Bakkaloglu et al.[32]	Systolic (but not diastolic) hypertension (OR = 1.93, 95% CI = 1.25–2.98), high body mass index, use of continuous ambulatory peritoneal dialysis, renal disease other than hypo/dysplasia, and hyperparathyroidism were identified as independent predictors of LVH	507 peritoneal dialysis patients (age < 19 year)

CRF: Chronic renal failure; OR: Odds ratio; CI: Confidence interval; BP: Blood pressure; LVH: Left ventricular hypertrophy; LVMI: Left ventricular mass index; iPTH: Intact parathyroid hormone

In a recent and very extensive meta-analysis of 13 studies on the effects of weight loss in kidney disease patients, Navaneethan et al.[54] reported that a decrease in body mass index (BMI) with nonsurgical interventions was associated with a significant decrease in proteinuria [Weighted mean difference (WMD) −1.31 g/24 h; 95% confidence interval (CI) −2.11 to −0.51] and systolic BP with no further decrease in glomerular filtration rate (GFR) during a mean follow-up of 7.4 months. In morbidly obese individuals (BMI >40 kg/m^2) with glomerular hyperfiltration (GFR >125 ml/min), surgical

interventions for weight loss resulted in a decrease in GFR (WMD −25.56 ml/min; 95% CI −36.23 to −14.89), albuminuria, and systolic BP.[54] Diet modification is probably the most efficient intervention method in CKD patients, due to overwhelming data on the survival effects of malnutrition in this patient population. In a 2-year cohort of an American hemodialysis population of as large as 53,933 patients, Shinaberger et al.[55] have reported that a decrease in protein intake during the first 6 months in patients was associated incrementally with greater death risks in the subsequent 18 months, whereas an increase in protein-nitrogen appearance tended to correlate with reduced death risk. In contrary, Kalantar-Zadeh et al.[56] in a prospective cohort of 122 hemodialysis patients reported an increase in hospitalization rate and mortality in patients undergoing protein-nitrogen appearance and/or albumin level normalizations. On the other hand, in a more recent study, Shinaberger et al.[57] in a 3-year trial showed that restricting protein intake in order to control hyperphosphatemia may lead to greater mortality. They reported that a simultaneous decrease in phosphatemia and protein nitrogen appearance is associated with the worse survival rate compared to other combinations of the two factors. Hemoglobin is also an important marker for nutritional status. Regidor et al.[58] in their study have reported that having hemoglobin levels within the range of the recommended Kidney Disease Quality Outcomes Initiative hemoglobin target (11–11.5 g/dl) for hemodialysis patients was associated with a higher death risk compared with the 11.5–12-g/dl range. A decrease or increase in hemoglobin over time was also associated with higher or lower death risk, respectively, independent of baseline hemoglobin. Moreover, use of erythropoiesis stimulating agents in these patients was associated with better survival.[58] Although there are controversies on the survival advantage of effects of erythropoiesis stimulating agents in dialysis patients.[59,60] However, similar findings to Fort et al. have also been reported from other societies.[61]

Pharmacological intervention

Due to the multifactorial nature of the kidney disease and its associations with cardiovascular morbidities, pharmacological interventions to address them are very extent and efficacy of several of them has already been confirmed. Hence, here, we focus on the most recent major studies evaluating pharmacological intervention, especially controversial ones, to reduce cardiovascular risk factors in kidney disease patients.

Rosuvastatin is a statin whose effectiveness in reducing cardiovascular events has been proved in the general population; however in the kidney disease, patient's data has only been published recently. Fellstrom et al.[62] conducted an international, multicenter, randomized, double-blind, prospective trial involving 2776 patients, 50–80 years of age, who were undergoing maintenance hemodialysis, and after 3 months of initiation of rosuvastatin, the mean reduction in low-density lipoprotein (LDL) cholesterol levels was 43%. However, rosuvastatin had no effect on individual components of the cardiovascular end point. There was also no significant effect on mortality.[62] Ezetimib is a Niemann–Pick C1-like 2 protein blocker that potently prevents the absorption of cholesterol from the gastrointestinal tract.[63] Simvastatin is also a potent statin that has the same effect on lipid profile. In the Study of Heart and Renal Protection trial,[64] Baigent et al., for the first time evaluated the effects of simvastatin and ezetimib on the cardiovascular outcome of kidney disease patients on 9438 (3023 on dialysis) kidney disease patients. During a median follow-up of 4.9 years patients treating with simvastatin plus ezetimibe experienced a 17% proportional reduction in major atherosclerotic events than patients taking placebo (11.3% vs. 13.4%; rate ratio: 0.83, 95% CI: 0.74–0.94; log-rank P = 0.0021).[64] However, the second United Kingdom Heart and Renal Protection study[65] revealed that there is no statistically significant effect for the addition of ezetimibe to simvastatin on triglyceride or high-density lipoprotein cholesterol levels in kidney disease patients. Potential effects of oral 1α-hydroxy vitamin D3 has also been examined on the cardiovascular mortality of hemodialysis patients, and has been shown to be associated with reduced risk for cardiovascular death in this cohort of ESRD patients.[66]

The power of renal protective effects of angiotensin-converting enzyme inhibitors (ACEI) or angiotensin II receptor blockers (ARB) is also controversial. A comprehensive meta-analysis of 49 studies showed that the effects of ACEI and ARB in reducing proteinuria was similar to each other, but combination therapy by both of the agents induced a higher effect.[66,67] In the very recent and large Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial, Rahman et al.[68] reported no difference in cardiovascular mortality, coronary heart disease, cardiovascular disease, stroke, or ESRD in participants with an estimated GFR <60,

between using chlorthalidone and amlodipine, or chlorthalidone and lisinopril. Because there are several valuable review articles in the literature on the subject, we refer interested readers to them.[69]

Conclusion

Evidence suggests that ESRD even in the pediatric population is associated with a high rate of cardiovascular morbidity and mortality, and needs high levels of attention. Unfortunately, there is scarcity of data on the efficacy of preventive strategies on cardiovascular morbidity and mortality in pediatric patients with renal disease. This limitation of data exists both in pharmacological and non-pharmacological interventions in childhood kidney disease population. We recommend future studies to be directed to find therapeutic effects of different agents on various cardiovascular indices, including structural and functional measures, as well as adverse effects associated with those drugs. Moreover, the effects of these drugs on the renal function of children with minimal kidney disease should be evaluated.

Conflict of Interests

Authors have no conflict of interests.

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