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EDUCATIONAL REVIEW

Cardiovascular risk factors in children on dialysis: an update

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Abstract

Cardiovascular disease (CVD) is a life-limiting comorbidity in patients with chronic kidney disease (CKD). In childhood, imaging studies have demonstrated early phenotypic characteristics including increases in left ventricular mass, carotid artery intima-media thickness, and pulse wave velocity, which occur even in young children with early stages of CKD. Vascular calcifications are the signature of an advanced phenotype and are mainly found in adolescents and young adults treated with dialysis. Association studies have provided valuable information regarding the significance of a multitude of risk factors in promoting CVD in children with CKD by using intermediate endpoints of measurements of surrogate parameters of CVD. Dialysis aggravates pre-existing risk factors and accelerates the progression of CVD with additional dialysis-related risk factors. Coronary artery calcifications in children and young adults with CKD accumulate in a time-dependent manner on dialysis. Identification of risk factors has led to improved understanding of principal mechanisms of CKD-induced damage to the cardiovascular system. Treatment strategies include assessment and monitoring of individual risk factor load, optimization of treatment of modifiable risk factors, and intensified hemodialysis if early transplantation is not possible.

Keywords Cardiovascular disease · Risk factors · Vascular calcification · Dialysis vintage · Intensified dialysis · Children

Introduction

Chronic kidney disease (CKD) is associated with the development of cardiovascular disease (CVD). Cardiovascular disease is an evolving process starting at early CKD stages, and children with CKD are likely the pediatric population with the highest risk for CVD [1]. In all age groups, but especially in the young, CVD results in excessive morbidity and mortality of dialysis patients, which is attributed to an unparalleled accumulation of risk factors. These include classical CVD risk factors, CKD-related risk factors appearing at early stages of CKD, and dialysis-related risk factors.

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Scope of the problem: pediatric mortality on dialysis

Data from pediatric registries have consistently shown that CVD is the single most important comorbidity preventing long-term survival in pediatric dialysis patients. A recent report by the North American Pediatric Renal Transplant Cooperative Study (NAPRTCS) summarizing data on > 6000 children on dialysis has compared clinical parameters and patient survival in the first 10 years of the registry (1992–2001) with the last decade (2002–2011) [2]. While there was a significant improvement in survival after dialysis initiation in the latter cohort, cardiopulmonary complications remained the leading specified cause of death (21%) in both cohorts. Likewise, population-based registry data from 6473 pediatric patients undergoing chronic renal replacement therapy in 36 European countries in the years 2000–2013 showed CVD as the leading cause of death (18.2%), with cardiac arrest/sudden death (54.4%) as the main contributor [3]. In a study by the Australia and New Zealand Dialysis and Transplant Registry, with data of > 1600 patients receiving renal replacement therapy (study period 1963–2002), CVD was the most common cause of death in the entire cohort; cardiovascular causes accounted for 57% of deaths among

children receiving hemodialysis (HD), 43% among those receiving peritoneal dialysis (PD), and 30% among those with a functioning renal transplant [4]. Mortality rates were 30 times as high as for children without end-stage kidney disease (ESKD). This study showed significantly lower mortality rates in children initiating dialysis during later years of observation (after 1982), similar to a Dutch cohort study observing 381 patients during 1972–1992 [5] and a study of 208 children treated for ESKD during 1973–2012 in Warsaw, Poland [6]. Likewise, an analysis of the large USRDS database on > 23,000 children initiating dialysis treatment in the USA during 1990–2010 found significantly decreasing rates for overall and cardiovascular mortality [7]. Declining mortality rates probably reflect progress in the treatment of risk factors for CVD; however, it should be noted that duration of dialysis treatment (vintage) was a strong independent risk factor for progression of CVD in studies analyzing prevalence and progression of vascular calcifications [8, 9].

Taken together, registry data as well as single center and multicenter studies in children undergoing dialysis treatment have provided solid evidence that CVD is a progressive and life-limiting comorbidity and accelerated by dialysis. In other words, in the individual patient, life expectancy is severely shortened by dialysis and much better with kidney transplantation [10].

Identifying the risk factors: association studies

To understand the effect of dialysis on CVD progression, an increasing body of studies has been devoted to the characterization of the clinical phenotype of CVD and the identification of risk factors associated with the initiation and progression of phenotypic characteristics in young patients with CKD who are usually asymptomatic.

Due to the low incidence of hard CVD endpoints in children with CKD (such as myocardial infarction, stroke, arrhythmia, death), pediatric studies have used surrogate parameters such as the left ventricular mass index (LVMI), the carotid artery intima-media thickness (cIMT), and pulse wave velocity (PWV). Even small increments in measurements of these parameters are highly predictive of future cardiovascular events in the general population and in adults with CKD [11]. Data are compared to normal pediatric values [12–15] and measurements above the 95th percentile for age have been defined as intermediate endpoints for CVD. Thus, the clinical significance of an ever-growing list of risk factors and biomarkers can be investigated by association studies using these intermediate endpoints.

In addition to LVMI, cIMT, and PWV, other noninvasive measurements have been used to characterize the phenotype of CVD in pediatric CKD patients. Endothelial dysfunction, long recognized as the earliest manifestation of vascular disease at the level of the microcirculation, has been detected in children in all stages of CKD using flow-mediated dilation (FMD) of the brachial artery or plethysmographic methods [16, 17]. Recent studies show that microvascular rarefaction, which has been a consistent finding in animal models and in humans with CKD, is associated with tissue hypoxia and dysfunctional angiogenesis [18–20]. Thus, endothelial dysfunction is at least in part due to massive loss of microvessels as part of a CKD-induced systemic microvascular disease.

Dilatation of the aorta measured by echocardiography has recently been described in a high percentage of pediatric CKD patients as a new potential marker of CVD. Aortic dilatation is typically observed in animal models of CKD and vascular calcification and could be an early marker of aneurysm formation [21]. Measurement of the cIMT can be combined with M-mode sonography of the common carotid artery to assess local arterial stiffness, expressed by the distensibility coefficient. Recent studies indicate a decreased distensibility of the carotid artery in children and young adults with CKD [22, 23].

Cross-sectional association studies have uniformly shown an increase in surrogate parameters with advancing stages of CKD, suggesting that CVD comorbidity already starts at an early stage of CKD and that progression of CVD parallels the loss of renal function. This has been confirmed by data from a large community-based population of adults showing an independent and graded association between a reduced estimated glomerular filtration rate (eGFR) and the risk of death, cardiovascular events, and hospitalization [24]. However, the effect of different risk factors on progression of CVD can only be answered by prospective cohort studies.

Diagnosing cardiovascular comorbidity in young patients with CKD

The early phenotype

To detect early cardiovascular alterations, prospective cohort studies have included children with predialysis CKD stages. A prospective observational study including > 700 European children with CKD, the Cardiovascular Comorbidity in Children with CKD (4C) study, showed that at baseline (eGFR 10–60 ml/min per 1.73 m^2), left ventricular hypertrophy (LVH) was present in 33.4%, cIMT was elevated in 41.6%, and PWV was increased in 20.1% of patients [25]. Thus, there is extensive myocardial and vascular remodeling and stiffening in many children with predialysis CKD in the absence of symptomatic CVD. Similar results were found in several reports from the CKiD (Chronic Kidney Disease in Children) study, a prospective cohort of 586 US children aged 1–16 years baseline (eGFR 30–90 ml/min per 1.73 m^2) [26]. These large cohort studies are adequately powered for

studying the progression of altered cardiovascular morphology and function and for analyzing the significance of risk factors and biomarkers of this process in children as they advance through successive stages of CKD.

The advanced phenotype: vascular calcifications

Vascular calcifications indicate an advanced stage of vascular damage. Typically located in the arterial media, vascular calcifications are the final result of an active, regulated process of arterial remodeling, which in detail resembles bone formation, mediated by a transition of vascular smooth muscle cells to a chondro-osteoblast phenotype [27]. Simultaneously, a mirror-image impairment of bone remodeling and mineralization has been detected in adult CKD patients, leading to the term chronic kidney disease-mineral bone disorder (CKD-MBD) to characterize the altered mineral, bone, and vascular biology [28].

The presence of coronary artery calcifications (CAC) is strongly predictive of myocardial infarction, heart failure, and stroke in adult predialysis CKD patients [29] and an independent predictor of all-cause mortality, cardiovascular events, and cardiovascular mortality in adult dialysis patients [30]. In the past two decades, several studies using computerized scanning methods for coronary artery calcification, quantified by the Agatston score, have shown a variable prevalence of CAC in young ESKD patients (Table 1). Rapid progression of these lesions during follow-up was first documented in the seminal study by Goodman et al., which described a doubling of calcification scores within 20 months [31]. The only systematic follow-up study showed an increase of the median Agatston score from 101 to 1759 in 48 patients after 2 years; Agatston score decreased in only 3 patients [41].

It should be noted that a differentiation of early and advanced phenotype reflects data of the imaging studies performed in the pediatric CKD population. Significant increases in LVMI, IMT, and PWV have been found in early stages of CKD and even in young children (Table 2). Arterial calcifications may be occasionally seen even in young children with predialysis CKD, but most patients with proven CAC have been adolescents or young adults on dialysis or with a history of dialysis. However, current imaging methods do not necessarily reflect the dynamic changes on a tissue level. Data from arterial biopsies performed in children suggest that CKD induces a calcifying arteriopathy in a continuing process, developing at early stages of CKD with rapid progression on dialysis [51].

Risk factors in dialysis patients identified in association studies

While the prevalence of CAC was quite variable in imaging studies of young patients, the risk factors identified as associated with their presence were remarkably uniform. Moreover, more or less the same risk factors have been universally found in association studies with surrogate CVD endpoints (Table 2), confirming their clinical significance in driving progression of CVD.

Duration of dialysis (dialysis vintage)

Dialysis vintage was a predictor of CAC in 5 of 9 studies evaluating risk factors for CAC in children and young adults (Table 1). Most studies of CAC included not only incident dialysis patients but also adolescents or young adults with childhood-onset ESKD who were transplanted or had returned to dialysis. Dialysis vintage was associated with the presence of calcifications even in patients who had undergone transplantation (in these cases, dialysis vintage is calculated as cumulative time on dialysis). This suggests that calcifications accumulate in a time-dependent manner on dialysis and show little or no regression during the time of a functioning transplant. Figure 1 shows the association of dialysis vintage with Agatson scores across all published studies of CAC in young patients with childhood-onset ESKD. This association shows a strong, albeit insignificant ($p = 0.2$) linear trend, which is remarkable in view of the large age range, relatively small number of subjects investigated, and interindividual variation in the number and severity of risk factors. Given the logarithmic scale of the Agatston score, this linear association suggests an exponential effect of dialysis vintage on the development of vascular calcifications.

Disturbed mineral metabolism/CKD-MBD

Increased serum levels of phosphorus, calcium, and parathyroid hormone (PTH) have been identified as independent predictors of CAC in most imaging studies (Table 1). In retrospect, reported associations with the serum calcium–phosphorus product may be due to the statistical procedures used in multivariate analyses (when significant correlations with calcium and phosphorus are present); since essentially all of the variability of the calcium–phosphorus product is explained by the serum phosphorus levels, the concept has now been abandoned [52]. Moreover, fibroblast growth factor-23 (FGF-23) has not been measured in these studies, which in retrospect is a strong limitation in view of the important role of FGF-23/klotho axis in mineral metabolism and bone and vascular biology [53–55]. In adult dialysis populations, phosphorus, calcium, PTH, and FGF-23 serum levels have been found independently associated with cardiovascular events, and their principal importance regarding survival has been addressed in many excellent reviews. International guidelines for diagnosis and treatment were recently updated [28]. The pathological significance of each of these factors has been shown by a multitude of epidemiological studies, and animal models and

Table 1 Studies of vascular calcifications in children and young adults with CKD

Author [reference]	Country	Patients *N*, age (years)	CKD stage and method of RRT	Prevalence of VC (AS score, median; range)	Cumulative time on D (years) Mean + SD (range)	Risk factors
Goodman et al. [31]	USA	39 19 ± 7 (7–30)	HD, PD, TX	36% (297; 2–7047)	14 ± 5 Median 13 (0.3–21)	Patients with CAC had longer dialysis vintage, higher BMI, serum P and CaxP, albumin, lower ALP and Chol; higher Ca intake
Eifinger et al. [32]	Germany	16 27.9 + 9.6	HD, PD, TX	38% (526; 1–807)	5.5 ± 4.4 (0–12.8)	Not evaluated
Oh et al. [33]	Germany	28 27.3 + 5.9 (19–39)	HD, PD, TX	92% (226)	5 (0–22)	Independent predictors of CAC: CRP, PTH, cumulative CaxP, homocysteine
Ishitani et al. [34]	USA	19 32.4 (21–48)	TX	47% (100; 24–2200)	0.7 ± 0.7 (preemptive TX)	Not evaluated
Civilibal et al. [35]	Turkey	53 15.7 ± 3.8	HD, PD, TX	15% (101; 9–4332)	6.7 ± 1.9	Independent predictors of CAC: serum P, cumulative intake of Ca-containing P binders
Briese et al. [17]	Germany	40 23.6 ± 5.5	HD, PD, TX	10% (200; 133–2105)	9.5 ± 5.6	Patients with CAC had longer dialysis vintage, higher diastolic BP, higher intake of Ca-containing P binders and cholecalciferol
Shroff et al. [36]	U.K.	85 (5–18) 13.2 ± 4 (5–18)	HD, PD	20% (85; 0–2039)	2.3 ± 1.8	Serum PTH, vitamin D dosage
Shroff et al. [37, 38]	U.K.	61 13.4 ± 4	HD, PD	21% (141; 0–2039)	1.1 (0.25–8.7)	Serum levels of 1,25(OH)2D, hs-CRP; fetuin-A (−), OPG
Srivaths et al. [39]	USA	16 19.1 ± 2.1 (9–21)	HD	31% (CAC) (19; 1–49)	4.1 ± 1.3	Patients with CAC had longer dialysis vintage, higher P, lower Chol
Srivaths et al. [40]	USA	38 15 ± 4	HD, PD	29% (CAC) (20; 2–670)	3.9 ± 1.7	CAC independently associated with HD (vs. PD), age, P, dialysis vintage, residual renal function
Al-Biltagi et al. [9]	Egypt	50 12 ± 3	HD	20% (CAC) 501 ± 483	6.7 + 0.3	Dialysis vintage, PTH*

ALP: alkaline phosphatase; *BMI*: body mass index; *Ca*: serum calcium; *CaxP*: serum calcium–phosphorus product; *Chol*: serum total cholesterol; *EBCT*: electron beam computed tomography; *CAC*: coronary artery calcifications; *FGF-23*: fibroblast growth factor 23; *HD*: hemodialysis; *OPG*: osteoprotegerin; *P*: serum phosphorus; *PD*: peritoneal dialysis; *RRT*: renal replacement therapy; *TX*: transplantation; *VC*: vascular calcifications

*Further predictors of CAC were echocardiographic parameters: the early to late filling velocities across the mitral valve and the left ventricular mass performance index

Table 2 Surrogate markers of CVD in pediatric dialysis patients: associations with risk factors

Author [reference]	Country	Patients (age, years)	LVH	LVMI	cIMT (cIMT-SDS)	PWV	Local stiffness at carotid (Einc)
Mitsnefes et al. [42]	USA	$N = 64$ (1.6–22) 26 HD, 38 PD	Dialysis vintage Hb (−) HD treatment Systolic BP				
Litwin et al. [43]	Poland	37 14.3 ± 3 19 HD, 18 PD			Cumulative phosphate binder intake, past calcium–phosphorus product, young age		
Mitsnefes et al. [23]	USA	$N = 16$ (14.3 + 4.4) 10 HD, 6 PD		PTH Hb (−)	Intake of phosphate binders		Pulse pressure, calcitriol dose
Civilibal et al. [44]	Turkey	$N = 39$ (14.8 ± 3.8) 15 HD, 24 PD		Systolic BP, Hb (−)	Diastolic BP		
Shroff et al. [36]	U.K.	$N = 85$ 21 HD, 64 PD (5–18)			Vitamin D dosage iPTH, PO_4	Vit D dosage	
Shroff et al. [37]	U.K.	$N = 61$ (13.4 ± 4.1) 18 HD, 43 PD				Fetuin-A (−) OPG	
Bakkaloglu et al. [45]	Turkey	$N = 59$ (14.2 ± 4.5) All PD		Hb (−)	Albumin (−) Kt/V urea (−)		
Bircan et al. [46]	Turkey	$N = 47$ (14.7 ± 3.5) All PD	Daytime systolic BP load, hematocrit (−)				
Bakkaloglu et al. [47]	Turkey	$N = 507$ (9.8 + 5.9) All PD	Systolic BP, BMI > 95th PC, PTH > 200 pg/ml, age, urine output (−)				
Chavarria et al. [48]	Mexico	$N = 60$ (12.9 ± 3.4) 29 HD, 31 PD			Time on D Calcitriol dose HD treatment PTH		
Canpolat et al. [49]	Turkey	$N = 33$ (12.9 ± 5.1) 18 PD, 15 HD					
Scavarda et al. [50]	Brazil	$N = 41$ (8.4 ± 4.6) 25 HD, 16 PD	Hypertension				

Only studies providing a multivariate analysis of independent predictors were considered. In studies including different CKD stages, only data of dialysis patients is included; (−) denotes a negative association, all other associations are positive

BP: blood pressure

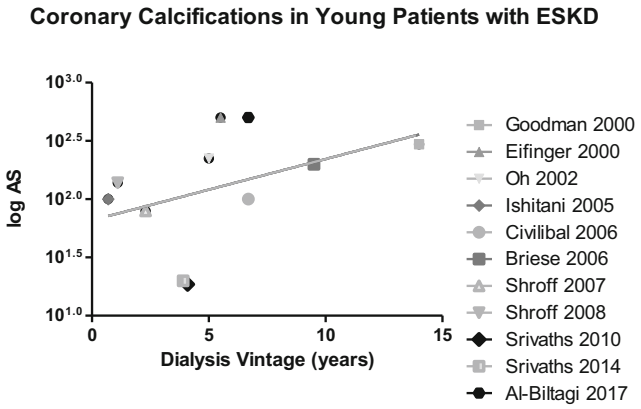

Fig. 1 A plot of the Agatston score (AS, logarithmic scale) of all publications documenting coronary artery calcifications in young patients shows a trend for an increase with time on dialysis ($p = 0.2$). *ESKD* end state kidney disease

in vitro studies have elucidated pathophysiological mechanisms (reviewed in [56]). However, these disturbances are part of a larger system disorder, the CKD-MBD, and should not be viewed and treated individually; they are not regulated independently, their effects on target cells are often interdependent, and treatment of one factor usually influences the others, making treatment of CKD-MBD extremely challenging. Data of > 26,000 adult dialysis patients has shown that 80% of patients were uncontrolled in at least one biochemical variable. In this study employing phenotypes of CKD-MBD to assess differences in clinical outcome, phenotypes with high calcium and PTH > 300 pg/dl were consistently associated with a higher risk [57]. Current guidelines state that hypercalcemia may be harmful in all GFR categories of CKD and call for restriction in the use of calcium-containing phosphate binders [28].

The dramatic effect of dialysis on vascular remodeling was demonstrated in a histological study of arterial biopsies taken from children with CKD; vessels from dialysis patients showed a marked increase in calcium content and induction of apoptosis in vascular smooth muscle cells compared to predialysis vessels, and the arterial calcium content correlated with dialysis vintage, the serum calcium-phosphate product, and the cIMT [51, 58]. Thus, dialysis strongly aggravates CKD-MBD, which may in part be due to difficulties in treating mineral dysregulation (see below). However, it has been suggested that dialysis may disable defense mechanisms protecting from vascular remodeling and calcification. In fact, dialysis treatment was found associated with changes in circulating levels of calcification inhibitors such as fetuin-A and osteoprotegerin (OPG); fetuin-A levels decreased with time on dialysis and were inversely associated with vascular calcification in pediatric patients [37]. In incident adult dialysis patients, OPG and fetuin-A were significantly associated with all-cause and cardiovascular mortality during follow-up [59]. The importance of circulating inhibitors of the calcification process was recently confirmed by several studies using a novel in vitro test (T50 test) for the determination of calcification propensity in blood. This test quantifies the calcification inhibition of serum by treatment with supersaturated calcium and phosphate solutions, which results in the formation of (mainly fetuin-containing) primary calciprotein particles [60]. Calcification propensity was significantly associated with cardiovascular events in predialysis CKD and HD patients [60, 61].

Treatment of mineral dysregulation/CKD-MBD

Surrogate endpoints and vascular calcifications have been found associated with the use of calcium-containing phosphate binders and vitamin D preparations (which enhance intestinal calcium and phosphorus absorption), indicating overtreatment with these medications [38]. Treatment is especially difficult in the pediatric population due to the demands of a growing skeleton. Undertreatment with vitamin D preparations carries the risk of rickets, diminished growth, uncontrolled hyperparathyroidism, and high-turnover bone disease, while oversuppression of PTH may result in adynamic bone disease and—especially in combination with calcium-containing phosphate binders—in vascular calcification, stiffening, and premature aging of arteries [62]. Recent guidelines have therefore argued for a very cautious use of vitamin D preparations and modified recommendations for phosphate binders (see below).

Inflammation

CKD is a state of persistent low-grade inflammation, which is generated by a multitude of disease-related factors and fundamentally involved in many comorbid conditions, as summarized in Fig. 2 [63]. Markers of inflammation such as C-reactive protein and interleukin 6 (IL-6) have been consistently found elevated in CKD patients and are validated predictors of all-cause and cardiovascular mortality [64]. Chronic infections with *Chlamydia pneumoniae*, chronic periodontitis, and other infections may also increase the inflammatory burden. Thus, coronary calcium scores were strongly correlated with C-reactive protein and *C. pneumoniae* seropositivity in one study [33].

Both HD and PD further aggravate inflammation by distinct mechanisms. As extensively reviewed, data collected in adult patients shows that dialysate quality, bioincompatibility of dialysis membranes, accumulation of uremic toxins and oxidation products, and loss of antioxidants are detrimental effects of HD [63, 65]. Data of a recent pediatric study indicates that even a short HD vintage of 3 months increases inflammation and endothelial stress [66]. Peritoneal dialysis adds intraperitoneal inflammation (due to various factors such as peritonitis, bioincompatibility of the dialysis solution, accumulation of glucose degradation products and advanced glycation end products) to the systemic inflammatory burden.

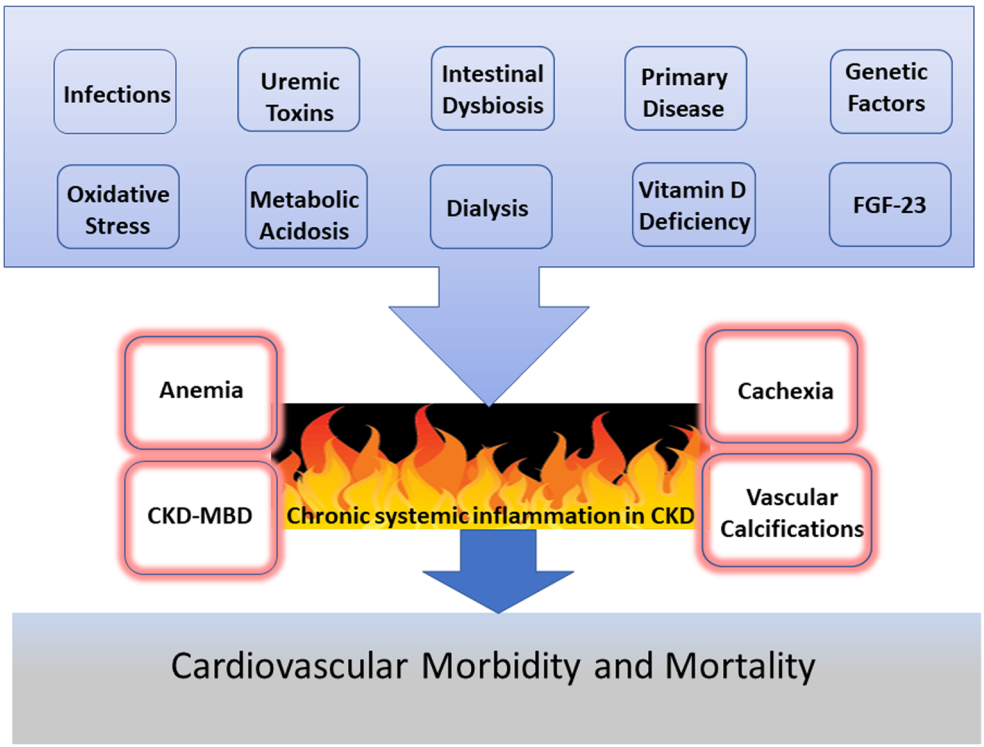

Fig. 2 Causes and consequences of inflammation in chronic kidney disease (CKD)

Recent data from the IPPN network shows that PD promotes inflammation, neoangiogenesis, and further morphologic and functional changes of the peritoneum even with the use of "biocompatible" PD solutions [67].

Inflammation is also linked to cachexia and protein-energy wasting, which has long been recognized as an important risk factor for adverse dialysis outcome in adults. Recently, cachexia was defined as "a complex metabolic syndrome associated with underlying illness and characterized by loss of muscle, with or without loss of fat"; it is associated with low serum albumin and loss of body weight; muscle mass is reduced, whereas fat mass is normal or increased [68]. Thus defined, cachexia is a well-known clinical feature in pediatric dialysis patients, often combined with failure to thrive and stunted growth. Recent research has unraveled a complex pathophysiology underlying the important contribution of cachexia to the multimorbidity of dialysis patients [68].

Dyslipidemia

Dyslipidemia is a classical risk factor for CVD. However, associations with phenotypic characteristics were only found in two studies (showing lower serum total cholesterol (Chol) levels in patients with vascular calcifications, Table 1). Since dialysis patients have an atherogenic lipoprotein profile, this is somewhat surprising. Typically, in nonproteinuric stage 5 CKD and on HD, serum levels of Chol and LDL-C (low-density lipoprotein cholesterol) are within normal limits, while there is accumulation of triglyceride-rich lipoproteins in the circulation; HDL-C levels are typically low. With PD, Chol and LDL-C levels may be increased, which is thought to be due to dialysate protein losses [69]. However, lipoprotein composition is distinctively abnormal, including oxidized lipids within lipoprotein particles, increased levels of the atherogenic lipoprotein (a), and an abnormal high-density lipoprotein (HDL) composition, with altered function of HDL including reduced antioxidant and anti-inflammatory functions [70, 71].

It is obvious that altered lipoprotein composition and function cannot be detected by measurements of lipid levels, which may explain the lack of their significance in many clinical association studies of CKD patients. However, recent large epidemiological studies have even shown "reverse epidemiology": higher blood lipid levels, e.g., Chol, triglyceride/HDL ratio, were associated with better survival of adult HD patients [72]. These studies, and the failure of lipid-lowering medication to improve mortality in adult ESKD patients [73], point to the limitations of simply assessing blood lipid levels as risk factors for ESKD patients and indicate that the pathophysiology of CVD in patients with CKD is different from the general population.

Nevertheless, there is strong evidence that altered lipoprotein composition, especially oxidatively modified lipoproteins, contributes to vascular damage in dialysis patients [74]. HDL isolated from children with stage 2–5 CKD was shown to promote endothelial dysfunction and changes in vascular phenotype [75].

Hypertension

Hypertension is the most prevalent classical risk factor for CVD in pediatric dialysis patients in Europe [76] and the USA [77]. In association studies of pediatric dialysis patients, systolic blood pressure was typically correlated with LVH and LVMI, but not with other vascular measurements or vascular calcification (Tables 1 and 2). This is in contrast to earlier CKD stages, where systolic blood pressure was identified as the single independent factor significantly associated with all surrogate markers of CVD in the 4C study. This suggests that the development of vascular calcifications is mainly driven by other risk factors such as disturbed mineral metabolism. However, hypertension is a strong predictor of survival on dialysis in adult patients. Once established, LVH, mainly reflecting the effects of hypertension, is incrementally associated with adverse CVD outcomes [78].

Anemia

Anemia is a frequent complication on dialysis and associated with inflammation, hyperparathyroidism, hypertension, and morbidity and mortality in pediatric patients [79, 80]. Several pediatric studies (Table 2) have found an association between lower hematocrit/hemoglobin levels and cardiac parameters (LVH/LVMI), which is in line with many large observational studies in adult dialysis patients. It is well known that the development of LVH is a consequence of volume and pressure overload; anemia contributes to LVH, mainly by a chronic increase in cardiac output and chronic volume overload, but also via reduced tissue oxygen delivery by the microcirculation [20]; the combination of increased cardiac workload and reduced oxygen supply may explain the importance of this nontraditional risk factor for cardiac outcomes such as ischemic and congestive heart disease and sudden cardiac death [81].

Hypoalbuminemia

Although hypoalbuminemia in dialysis patients is promoted by, and thus reflects, inflammation and fluid overload, low albumin levels are an independent risk factor for overall and cardiac mortality of dialysis patients, as recently confirmed in a large meta-analysis [82]. It is a prominent feature of cachexia, where muscle atrophy and breakdown of protein stores are mainly attributable to increased proteolysis and not malnutrition [83]. This illustrates the limitations of albumin as a nutritional marker in CKD. In PD patients, peritoneal protein losses may contribute to hypoalbuminemia.

Why is CVD accelerated by dialysis?

Dialysis treatment is the ultimate cardiovascular risk factor for the CKD patient. Several dialysis-related mechanisms have been identified that are responsible for driving progression of CVD in concert (Fig. 3). The identification of these risk factors has uncovered principal mechanisms of CKD-induced damage to the cardiovascular system.

Fluid overload

Fluid overload, mostly due to sodium and water retention of the failing kidney and intradialytic weight gain, is omnipresent in pediatric dialysis units. It is an important cause of death in dialyzed children, contributing 16.1% to the mortality from cardiovascular causes, second only to cardiac arrest/sudden death (54.4%) in European children [3]. Interdialytic weight gain is a strong predictor of LVH in children on HD [84]. Fluid overload further aggravates pre-existing hypertension in CKD and is associated with congestive heart failure and mortality in adults. In a large prospective study of adult HD patients using whole-body bioimpedance spectroscopy for assessment of hydration status, cumulative 1-year fluid overload exposure predicted a significantly higher death risk across all categories of systolic blood pressure [85]. Consequently, residual urine output is associated with better survival of adult patients treated with HD or PD [86].

Fluid overload develops easily in PD patients if fluid intake is not adjusted to ultrafiltration volume; data in adult long-term PD patients indicate that overhydration may be the most important cardiovascular risk factor in this population [87]. However, overhydration is not a simple equation problem of fluid and sodium balance; emerging evidence indicates that fluid overload may aggravate inflammation in PD and HD patients via a variety of mechanisms, including proinflammatory effects of tissue sodium [88], and induce microinflammation and markers of endothelial dysfunction [89]. Furthermore, the effects of fluid overload cannot be dissociated from the detrimental effects of high-volume fluid removal, especially with rapid ultrafiltration [90].

Intradialytic hypotension

Intradialytic hypotension (IDH) is a frequent complication during HD. While the prevalence is unknown in pediatric patients, a recent retrospective study using data of almost 40,000 HD patients included in the US Renal Data system found that intradialytic hypotension occurred in 31.1% of patients over a 90-day period [91]. The frequency of IDH was strongly correlated with interdialytic weight gain and IDH showed a significant association with cardiac morbidity and mortality.

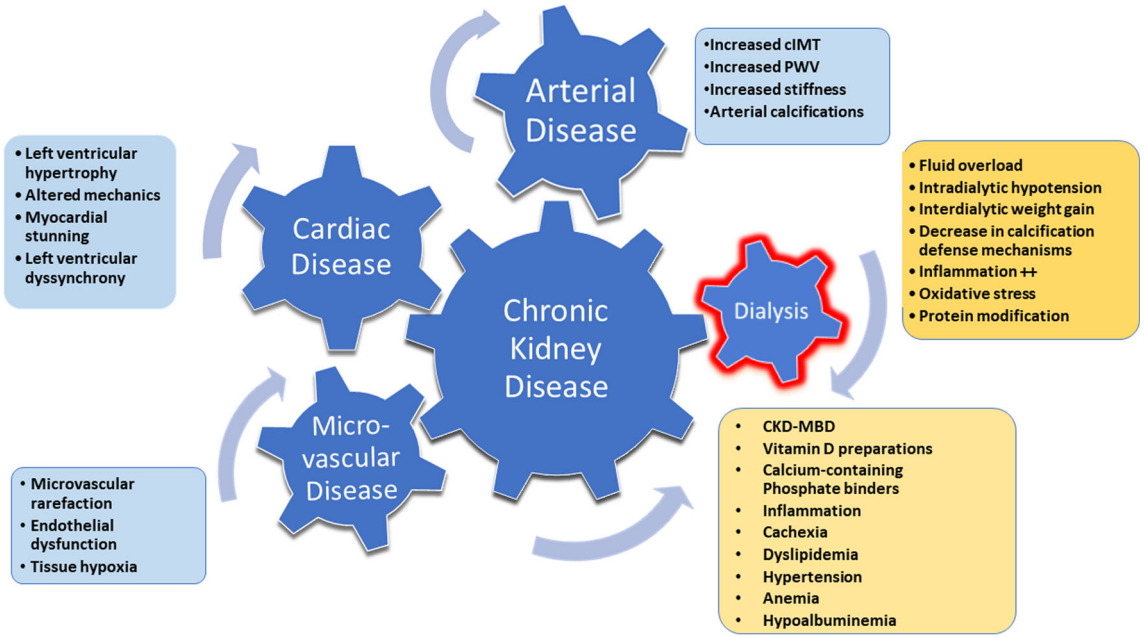

Fig. 3 Cardiovascular phenotype in pediatric dialysis patients: risk factors and mechanisms

Importantly, there is increasing evidence that IDH leads to subclinical myocardial injury. In children and adults, reversible myocardial dysfunction (myocardial stunning) has been demonstrated by serial echocardiography during conventional HD sessions [92]. Stunning within myocardial segments correlates with intradialytic blood pressure changes and ultrafiltration volume and with reductions in myocardial blood flow [93, 94]. Thus, the hemodynamic stress of fluid removal by HD predisposes to clinically significant demand myocardial ischemia, even in children with presumably patent coronary arteries, most likely indicating an insufficient microvascular response [95]. Microvascular rarefaction has been demonstrated in uremic patients including children [18] and in animal models of uremia [20], and a myocyte/capillary mismatch in the myocardium may be the chief contributor to myocardial demand ischemia [96].

Impaired cardiac mechanics

Subclinical systolic dysfunction is a frequent finding in pediatric dialysis patients [97]. Recent advances in diagnostic techniques have further broadened the understanding of subclinical cardiac damage in CKD. Cardiac strain analysis of myocardial deformation by speckle tracking echocardiography has shown that impaired systolic function is already present in children with predialysis CKD, characterized by lower radial strain and mild cardiac dyssynchrony [98]. A longitudinal analysis demonstrated changes in ventricular diastolic function early in the course of CKD and changes in ventricular longitudinal strain in children on dialysis [99], which in adults, are associated with increased mortality [100]. Left ventricular dyssynchrony was detected in children treated with HD and PD and related to volume changes during HD [101]. In adults treated with PD, left ventricular dyssynchrony was associated with dialysis adequacy [102]. Taken together, these data indicate that cardiac mechanics are chronically impaired in patients treated with HD or PD, suggesting underlying effects of dialysis-related factors such as volume overload/removal and possibly insufficient removal of uremic toxins.

Oxidative stress, protein modification

Oxidative stress (OS), defined as an imbalance between oxidative products and antioxidant defense mechanisms, is strongly promoted by dialysis, by both accumulation of oxidation products and removal of antioxidants during dialysis. OS may be more pronounced with HD [65] than with PD treatment [103]. OS causes damage to proteins, organs, and tissues and is a chief contributor to chronic inflammation and anemia. Evidence has accumulated that circulating oxidized proteins are involved in the progression of CVD. Among the lipoproteins, oxidized LDL and oxidized HDL have been found to be associated with cardiovascular events in adult HD patients [104, 105]. Serum levels of lipoprotein (a), a strong, genetically determined risk factor for CKD-associated CVD, are elevated in dialysis patients; recent studies have shown that this lipoprotein transports proinflammatory oxidized phospholipids, which may at least in part explain its atherogenicity [106]. Other proteins generated by OS include oxidized albumin [107], oxidized PTH [108], advanced oxidation protein products (AOPPs), advanced glycation end products (AGEs), and carbonylated proteins (carbonyl stress), all of which have emerged as biomarkers of OS and CKD-associated CVD.

Plasma proteins, by exposure to urea and its dissociation by-product, isocyanic acid, or by an enzymatic reaction involving myeloperoxidase, may undergo carbamylation, resulting in a change in structure and function. The accumulation of carbamylated proteins parallels increases in urea in the circulation, which has renewed scientific interest in urea as a uremic toxin [109]. Recent studies have shown that serum carbamylated albumin, as a systemic marker of carbamylation burden, has a high predictive value for mortality in adult HD patients [110, 111]. In addition, carbamylation may affect LDL, HDL, and other circulating proteins involved in atherosclerosis and arteriosclerosis [112].

Reducing the risk factor load in dialyzed children

Since preemptive or at least early kidney transplantation is often not possible, a concerted effort for risk factor load reduction should be made in every young patient. Of course, patient cooperation is essential. Individual medical and psychosocial strategies are warranted for the child and adolescent on dialysis, and the need for a comprehensive approach involving caregivers, nursing staff, renal dieticians and psychosocial counseling cannot be overemphasized [113, 114].

General preventive measures include encouraging physical exercise and measures to lower smoking exposure if present; smoking should not be tolerated. Exercise training is feasible during dialysis [115]. Physical activity might be stimulated by the use of activity-tracking devices [116].

Although malnutrition has been reported in dialyzed children [49], recent combined data from pediatric registries (including dialyzed and transplanted patients) show a low prevalence of underweight (3.5%), whereas 20.8% of the patients were overweight and 12.5% obese [117]. Nutritional management should therefore focus on prevention of both malnutrition and obesity. In patients with low serum albumin and loss of dry weight, cachexia may be present; currently developed diagnostic measures may help to better define the cachexia phenotype in ESKD to provide individualized treatment and nutritional support [118].

Prevention of fluid overload demands estimation of dry weight, which is notoriously inaccurate with clinical methods. Unfortunately, currently available techniques for exact estimation of dry weight have limitations, including bioimpedance measurements [119, 120]. Emerging evidence indicates that lung ultrasound may be useful in the assessment of dry weight, but this method needs larger validation studies in children [119]. Given the well-known problems with management of interdialytic weight gain (especially in adolescents) and the inaccuracies in dry weight estimation, management of fluid overload remains one of the most challenging aspects of care for pediatric dialysis patients. However, residual urine output is a protective factor [45] and care should be taken to avoid loss of residual renal function. Data from the IPPN network has shown that diuretic therapy significantly reduced the risk for oligoanuria, whereas renin–angiotensin system antagonists significantly increased the risk [121].

Fluid overload frequently associates with inflammation, amplifying the cardiovascular risk, as shown in a recent international cohort study of adult HD patients [122]. Intestinal dysbiosis and barrier dysfunction with accumulation of gut-derived uremic toxins may also contribute to inflammation [123]. Accordingly, current studies are focusing on intestinal toxin binding by absorbents such as sevelamer [124] and preventive therapies with probiotics [125].

To improve treatment of mineral dysregulation/CKD-MBD, a working group has recently issued recommendations for native vitamin D therapy and active vitamin D preparations in pediatric patients [126, 127]. While calcium-containing phosphate binders are the cheapest and still most frequently used phosphate binders, they carry the risk of calcium overload and are associated with CAC. A single randomized trial comparing sevelamer hydrochloride and calcium carbonate in pediatric dialysis patients found similar control of serum phosphorus levels, a lower incidence of hypercalcemia with calcium carbonate, and a higher incidence of metabolic acidosis with sevelamer treatment [128]. A recent review of 23 randomized trials in adult patients comparing sevelamer with calcium-based binders concluded that sevelamer attenuated progression of coronary and aortic calcification but was not associated with a significant difference in all-cause or cardiovascular mortality [129]. Several other calcium-free phosphate binders have been used in adult patients; however, a recent meta-analysis evaluating all currently available phosphate binders found no evidence that phosphate binder treatment reduces all-cause mortality compared to placebo in adults with CKD [130]. These findings illustrate the multimorbidity of CKD patients and the complex pathophysiology of CVD; still there is consensus that phosphate lowering with phosphate binders and maintaining the phosphorus level in its normal range is beneficial to prevent progression of CVD in CKD patients. Sevelamer carbonate (as opposed to sevelamer hydrochloride) does not cause metabolic acidosis; safety and efficacy were recently confirmed in a first multicenter study of hyperphosphatemic pediatric patients with CKD [131]. Since hypercalcemia is frequent with calcium-containing binders, more studies in pediatric patients are needed to evaluate calcium-free preparations. Calcimimetic drugs have been successfully used to control severe secondary or tertiary hyperparathyroidism, but experience in children is still limited [132]. In children undergoing PD, phosphate removal may potentially be improved by monitoring phosphate clearance and adapting PD prescription [133].

Anemia (Hb < 10 g/dl) is found in a high prevalence in children on HD and PD, as shown by data from pediatric

registries [2, 80, 134]. A recent retrospective cohort study in children on HD has shown that, in contrast to adult patients, Hb levels of 12 g/dl and above are not associated with increased cardiovascular comorbidity [135]. These data indicate that therapy with erythropoiesis-stimulating agents (ESAs) and iron supplementation can be augmented in many patients to avoid this treatable risk factor.

Data from registry studies in the USA and Europe show that hypertension is uncontrolled in about half of the PD patients and in the majority of HD patients [76, 77]. To improve hypertension control, aggressive therapeutic measures are warranted, including better management of dry weight and fluid intake, dietary sodium intake, antihypertensive medications, and optimization of dialysis [136]. In addition, newer diagnostic methods (tissue Doppler, speckle tracking echocardiography) should be considered for monitoring of cardiac strain.

Altogether, current evidence indicates that treatment of modifiable cardiovascular risk factors is insufficient. These include foremost mineral dysregulation, especially phosphorus levels, anemia, and hypertension. Since even short periods of dialysis are associated with detrimental effects on the cardiovascular system, these risk factors especially demand aggressive management and careful monitoring. However, the additional effect of dialysis-related risk factors requires modifications of standard dialysis therapy for optimization of cardiovascular prevention.

To overcome the limitations of conventional HD, intensified HD programs in the form of short daily (SDHD), nocturnal intermittent (NIHD, in center), daily home (DHHD), or daily nocturnal home HD (NHHD) have been developed in various pediatric centers [137]. First, an SDHD program was initiated in Strassburg, France, in 2004 combining in-center high-efficiency online hemodiafiltration (HDF) with growth hormone therapy and reporting impressive catch-up growth with this modality [138]. Patients participating in a program of NHHD founded in Toronto, Canada, in 2005 were shown to have improvement in quality of life and school attendance [139]. Also in 2005, a program for in-center NIHD was established in Berlin, Germany [140], reporting further improvement of dialysis efficacy with HDF compared to HD in a crossover study of NIHD patients; this dialysis modality may be especially attractive for adolescents [141]. Improved growth was also reported in patients undergoing NHHD in Sao Paolo, Brazil, during 2008–2010 [142]. In short, patients with all forms of intensified HD were free of fluid or dietary restrictions; medications (including phosphate binders, erythropoietin, and antihypertensive agents) could be reduced; and control of blood pressure, phosphate levels, and anemia was improved. While data from these programs clearly show the feasibility and unmatched advantages of intensified HD, published experience is limited to less than 100 children and adolescents, indicating obstacles to a wider implementation of intensified dialysis. A recent online survey among pediatric nephrologists identified lack of adequate funding and shortage of staff, and to a lesser degree, lack of expertise and motivation as barriers [143].

In contrast, HDF can be implemented in dialysis units without major logistical changes if machines with HDF capability and ultra-pure dialysis fluid are available [144]. A pooled analysis of four randomized trials in adult patients comparing HDF with conventional HD demonstrated a reduction in mortality risk [145]. Recent pediatric experience with HDF showing significant improvements in blood pressure, phosphorus and PTH levels [141], cardiovascular function, and inflammatory status, respectively [146, 147], have renewed interest in HDF for children. In a substudy of the ongoing Hemodiafiltration, Heart and Height (3H) study [148], a switch from conventional HD to HDF resulted in significant improvement in inflammation, antioxidant capacity, and endothelial risk profile after 3 months [66]. Thus, HDF holds promise for improvements in cardiovascular status for pediatric HD patients, but final results of the 3H study must be awaited.

In summary, the cardiovascular risk factor load determines the long-term prognosis of most CKD patients. The individual risk factor load should be assessed and monitored in every patient and treatment of modifiable risk factors optimized. For dialysis patients, the high burden of risk factors, the strong association between vascular changes and dialysis vintage, evidence of early calcification in arterial biopsy samples, and rapid progression of calcifications in imaging studies clearly favor treatment with intensified HD if at all possible. Intensified HD should at least be provided for high-risk patients if early transplantation is not feasible. Preliminary data in children and studies in adult patients also indicate that HDF should be considered for all HD patients if suitable equipment is available.

Key summary points

- In children with CKD, cardiovascular comorbidity is recognized in early stages of the disease. It is progressive, accelerated by dialysis, and limits the life expectancy of young patients.
- Imaging studies have demonstrated increases in left ventricular mass, carotid artery intima-media thickness, and pulse wave velocity as early phenotypic characteristics. Vascular calcifications are the signature of an advanced phenotype.
- Major risk factors significantly associated with phenotypic characteristics in cross-sectional studies of dialysis patients include dialysis vintage, dysregulated mineral metabolism and its treatment, hypertension, inflammation, dyslipidemia, anemia, and hypoalbuminemia.

- Dialysis treatment aggravates pre-existing risk factors and accelerates CVD. Salt and fluid overload, intradialytic hypotension, impaired cardiac mechanics, oxidative stress, and protein modification have been identified as important dialysis-related additional risk factors.
- Even short periods of dialysis are associated with detrimental effects on the cardiovascular system, and dialysis vintage is strongly associated with coronary artery calcifications, which can progress rapidly. Modifiable risk factors, especially mineral dysregulation, hypertension, and anemia, demand aggressive management and careful monitoring.
- The additional effect of dialysis-related risk factors requires modifications of standard dialysis therapy for optimization of cardiovascular prevention. Intensified HD, especially when combined with HDF, provides unmatched benefits and should be considered if early transplantation is not possible, especially for high-risk patients.

Multiple choice questions (up to 3 correct answers can be selected) [answers are provided following the reference list]

1. Coronary artery calcifications in children:
   a) Are usually asymptomatic
   b) Are associated with time on dialysis treatment (dialysis vintage)
   c) Disappear rapidly after transplantation
   d) Can be excluded by electrocardiography
   e) Are part of the CKD-MBD spectrum
2. Intradialytic hypotension on hemodialysis
   a) Is associated with interdialytic weight gain
   b) Indicates hypoglycemia
   c) Is associated with reversible myocardial dysfunction (myocardial stunning)
   d) Is rarely seen in pediatric patients
   e) Can be prevented by additional i.v. fluid at the start of the HD session
3. Hypercalcemia in dialysis patients
   a) Is usually a sign of volume contraction (dehydration)
   b) Could indicate overdosing of vitamin D preparations
   c) Can be tolerated as long as PTH and phosphate levels are controlled
   d) Is a typical side effect of calcimimetic drugs
4. Intensified dialysis
   a) Should not be considered for adolescents because of time commitments
   b) Was found associated with improved growth and well-being in some studies
   c) Relieves dietary and fluid restrictions and decreases medication burden
   d) Can be combined with HDF for higher dialysis efficacy
   e) Cannot be performed in children because of the high volume of substitution fluid
5. Left ventricular hypertrophy
   a) Results from volume and pressure overload
   b) Is usually not found in PD patients treated with biocompatible dialysis fluids
   c) Is incrementally associated with adverse CVD outcomes
   d) Is associated with hypertension, but not with anemia
   e) Is only reversible by transplantation

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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Answers

1. a, b, e; 2. a, c; 3. b; 4. b, c, d; 5. a, c