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# Chronic Kidney Disease: Treatment of Comorbidities I (Nutrition, Growth, Neurocognitive Function, and Mineral Bone Disease)

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## Abstract

*Purpose of review* This review discusses the complications of nutrition, growth, neurocognitive function, and mineral and bone disorder in pediatric chronic kidney disease. We discuss the most recent evidence-based methods for evaluation and prevention of these complications in addition to treatment strategies to address the complications and mitigate adverse effects.

*Recent findings* Frequent nutritional assessment is important, particularly for infants and young children. Due to anorexia, oral aversion, and dietary restrictions, weight gain may be difficult to achieve. Adequate nutrition is important for growth. Children with CKD tend to be short, which can impact quality of life and social achievements. Once nutrition is optimized, growth hormone is an effective, but underutilized strategy to improving terminal height. Mineral and bone disorder is a difficult but common complication of CKD which may present with and be driven by abnormalities in calcium, phosphorus, and parathyroid hormone levels. Treatment strategies include dietary phosphorus restriction, phosphorus binders, and inactive vitamin D and active vitamin D sterols. Effective treatment may reduce the risk for bone deformities, growth abnormalities, fractures, cardiovascular disease, and mortality. Children with CKD also suffer from cognitive

difficulties. Control of anemia, aggressive childhood nutrition, and decreased exposure to heavy metals (via dialysate and dietary binding agents) has provided substantial improvement to the more profound neurocognitive sequelae observed prior to the 1990s. Current prevention of cognitive sequelae may best be directed at improved blood pressure control and augmented school support.

*Summary* Pediatric CKD has systemic ramifications and can impact all aspects of normal development, including nutrition, growth, bone and mineral metabolism, and neurocognitive function. Regular evaluation for disease complications and prompt treatment can reduce the untoward effects of CKD thereby improving the quality and duration of life.

## Introduction

The diagnosis of chronic kidney disease (CKD) in childhood has potential for profound consequence on growth and nutrition in childhood. In parallel to this, there is risk for cognitive deficit to emerge during the course of advancing CKD. Compared to children with normal renal function, those with CKD may experience significant nutritional restrictions and time away from school—both of which may pose social barriers to somatic and cognitive growth and development. The multidisciplinary care management for these complex patients requires not only an in-depth understanding of the primary renal disease but also an ongoing evaluation to ensure nutritional and developmental needs are being met.

# Nutritional assessment to facilitate growth in pediatric CKD

CKD is stratified into five categories spanning a decline in renal function from early CKD to end-stage renal disease (ESRD). The National Kidney Foundation Kidney Disease Outcomes Quality Initiative (NKF-KDOQI) has published comprehensive consensus nutrition guidelines for the care of children across the spectrum of CKD—these recommendations are more extensive than the space allowable in this review but will be referenced throughout [1]. When renal function declines to an estimated glomerular filtration rate (eGFR) of $< 60$ mL/min/1.73 $m^2$ (stage 3 CKD), systemic laboratory and metabolic abnormalities driven by decreased renal function and uremia may significantly impair nutritional health. These include hyperkalemia, hypocalcemia, hyperphosphatemia, anorexia, and protein-energy wasting.

Nutritional assessment in pediatric CKD should ideally occur in a multidisciplinary setting with input from a physician, nurse, and dietician staff. Pertinent data must encompass longitudinal attention to both objective growth parameters and laboratory measures. Growth data must include weight, height (or length for those under age 2), and head circumference in those children under 3 years of age. All data should be followed serially for trend according to standardized growth tables for age and/or condition.

## Protein energy and calorie needs

Oral aversion and decreased appetite are frequently reported parental concerns in advanced CKD [2•, 3]. Abnormalities in the leptin and ghrelin axis [4, 5], in addition to taste and olfactory disturbances that accompany worsening uremia, may perpetuate oral aversion and poor appetite. Development of oral aversion and subtle decline in appetite can cause a decrease in spontaneous food (energy) intake in parallel to progression of CKD with risk for malnutrition and protein energy wasting to accompany advanced renal disease [6, 7]. To mitigate this risk, nutritional assessment and intervention should be a focus of pediatric CKD cares, particularly in the smallest of patients, when rapid growth and development are occurring and heavily nutrition-dependent [8].

In the non-dialysis CKD population, energy intake should be supplemented to provide approximately 100% of the daily estimated energy expenditure (EER) for chronological age, activity level, and body size [1]. Similarly, protein intake should be a minimum of 100% of the daily recommended intake (DRI) for age and body size in CKD, with some advanced CKD patients on dialysis requiring up to 140% of the DRI for protein [1]. There is no pediatric data to support that restricting protein effectively delays progression of renal disease or time to dialysis initiation [9–11].

For young children and infants, supplemental enteral nutrition may be required to meet nutritional goals if oral intake is insufficient to prevent or correct somatic growth delays [8, 12]. This may necessitate placement of a gastrostomy tube to support the long-term nutritional and fluid requirements of this population, even following transplantation.

Varieties of specialized formulas exist for infants, children, and young adults with renal disease (Table 1). In general, dietary content of renal formulas provide decreased potassium and phosphorus content compared with standard formula. Some also have increased caloric density and are useful in oliguric CKD patients to provide a more concentrated form of nutrition. These should be used with the assistance of an experienced renal dietician to meet the specific caloric, solute, electrolyte, and metabolic needs of pediatric CKD patients. After 1–2 years of age, growth retardation associated with CKD is usually amenable to use of growth hormone therapy (see "Growth" below), but nutrition must be optimized in order to achieve that benefit.

## Sodium supplementation

In polyuric renal disease, there may be an inability to conserve sodium, chloride, and/or bicarbonate due to prenatal impairment in nephrogenesis/tubular maturation [13]. Sodium chloride supplementation may be beneficial for somatic and linear growth in this population. Signs of sodium depletion in polyuric renal disease can be subtle and include failure to gain weight despite adequate caloric intake, hyperkalemia, and mild hypochloremia. Animal data support a positive impact of sodium replete dietary status on linear and somatic growth during early life in contrast to sodium depletion [14]. In polyuric children, provision of 2 to 3 mEq/kg/day of sodium chloride may be reasonable with uptitration of sodium chloride potentially necessary to ensure optimal linear and somatic growth. Supplementation should be decreased or stopped if the serum sodium concentration reaches >/= 140 mEq/L, if acidosis develops

**Table 1. Nutrient Content of Commonly Used Enteral Formulas in Pediatric Renal Patients**

| | | *Content per 100 mL* gm/100 mL | | | mg(meq)/100 mL | | | |
|---|---|---|---|---|---|---|---|---|
| | *kcal/mL* | Carbohydrate | Fat | Protein | Sodium | Potassium | Calcium | Phosphorus |
| **Standard formula** | **0.67kcal/mL** | 7.2 | 3.8 | 1.4 | 16 (0.7) | 71 (1.8) | 53 (2.6) | 28 (1.8) |
| **Similac PM 60/40** | **0.67kcal/mL** | 6.9 | 3.8 | 1.5 | 16 (0.7) | 54 (1.4) | 38 (1.9) | 19 (1.2) |
| **Calcilo** | **0.67kcal/mL** | 7.5 | 4.1 | 1.6 | 17.9 (0.78) | 60.2 (1.5) | 2.1 (.11) | 18.3 (1.2) |
| **Renastart** | **1kcal/mL** | 12.6 | 4.8 | 1.6 | 50.4 (2.2) | 23.1 (0.6) | 22.1 (1.1) | 18.9 (1.2) |
| **Suplena*** | **1.8kcal/mL** | 20 | 9.6 | 4.5 | 80 (3.5) | 114 (2.9) | 105 (5.3) | 72 (4.6) |
| **Nepro*** | **1.8kcal/mL** | 16 | 9.6 | 8.1 | 106 (4.6) | 106 (2.7) | 106 (5.3) | 72 (4.6) |

Content value from individual formulas can be compared to percent daily recommended intake needs for patient age and gender as recommended by the World Health Organization
*Denotes a formula often used in adult renal/dialysis populations but can be utilized in the pediatric setting as indicated by nutritional needs

due to excessive chloride supplementation, or if there is any concern for hypertension due to fluid retention from sodium supplementation.

# Growth in pediatric CKD

Growth impairment is a major complication of pediatric CKD and may persist even after renal transplantation. Growth failure in CKD is often multifactorial in nature and can be driven by malnutrition, renal osteodystrophy, metabolic acidosis, and alteration of the growth hormone insulin-like growth factor 1 axis.

## Alterations in growth hormone and insulin-like growth factor 1 axis

Linear growth impairment in pediatric CKD may be augmented by growth hormone (GH) resistance. GH is secreted in a pulsatile manner from the pituitary gland and acts by binding to the GH receptor which results in the production of insulin-like growth factor 1 (IGF-1). GH is freely filtered by the glomerulus; therefore, plasma levels of GH rise as renal function declines in CKD. Despite this elevation in GH in renal failure, IGF-1 blood levels may be normal or low indicating reduced production of IGF-1. Furthermore, there is reduced bioactivity of IGF-1, possibly related to higher levels of IGF-binding proteins which may act as inhibitors to IGF-1 [15]. This pattern of GH and IGF-1 is similar to what is seen in malnutrition. Metabolic acidosis also contributes to decreased secretion and action of GH [16].

## Impact of acidosis

Maintenance of a normal serum bicarbonate concentration is vital for linear growth in pediatric CKD patients. NKF-KDOQI guidelines recommend that serum bicarbonate concentrations be maintained at 22 mmol/L or greater [1]. In the Chronic Kidney Disease in Children Cohort Study (CKiD), children with serum bicarbonate (CO2) level < 18 had height *Z*-scores significantly lower than children with a CO2 between 18 and 22 [17]. Untreated acidosis may have direct deleterious effects on bone and statural growth and may hasten the progression of CKD [18]. In contrast, physiologic bicarbonate supplementation appears to slow the progression of CKD and improves nutritional status [19]. Acidosis should be treated with enteral sodium bicarbonate or sodium citrate solutions.

## Association of renal disease with terminal height

The degree of childhood renal impairment associates with terminal adult height. In pre-ESRD CKD, children with non-glomerular etiology of disease are shorter (– 0.33 vs – 0.62, $p = 0.003$) and height deficits are more pronounced at lower eGFR [17]. In parallel with this, association studies have identified a relationship between anemia and short stature [20] and that erythropoietin therapy associates with improved growth [21]. The CKiD study also identified that for every 10 ml/min/1.73 m2 decline in eGFR, height *Z*-score declines by 0.12 to 0.16 [17]. In infants, short stature is most commonly related to poor energy-based (caloric) nutrition. As discussed above, nutritional intervention is key in early childhood and supplementation to achieve caloric intake of at least 100% of RDA has been shown to result in improved growth rates in infants with

advanced CKD [22]. Furthermore, as previously discussed, sodium chloride supplementation may be required in the polyuric infant and toddler with advanced CKD to maximize linear growth.

Renal transplantation often mitigates the complications associated with severe CKD but catch-up growth after transplantation may be less than ideal, particularly in older children. Children with height deficits prior to transplant often remain short upon reaching final adult height [23]. According to the 2014 North American Pediatric Renal Transplant Cooperative Study (NAPRTCS) Annual Report [24], the mean height *Z*-score at the time of transplantation was – 1.73. This height deficit was greater for males, those aged 2 to 5 years at time of transplant and those with a prior transplant. At the time of attaining final height, the mean *Z*-score was – 1.37, with 25% of transplanted patients having a *Z*-score below – 2.2 and 10% have a *Z*-score below – 3.22.

Several factors may influence growth improvement following kidney transplantation. Younger age at transplant, lower doses of prednisone and eGFR > 50 ml/min/1.73m$^2$ are associated with improved height velocity after renal transplant [23–25]. Living donor recipients and those not requiring antihypertensive medications also exhibit better 2-year standardized height changes (0.25 vs 0.13 and 0.37 vs 0.15, respectively) [24]. Although pre-pubertal transplanted children undergo an impressive increase in height velocity after transplant, even surpassing that of normal children, final height is still reduced in at least a third of patients. Children older than 9 years at time of transplant or with a GFR < 50 ml/min/1.73m$^2$ are less likely to show a positive change in standardized height with the use of recombinant growth hormone (rhGH) post-transplant [23]. Despite this, significant improvements in terminal height have been observed in the most recent NAPRTCS cohort when compared with the first cohort, with average final height from the years 1987–1991 of – 1.93 and average final height of – 0.89 of the most recent cohort [24].

## Association of growth on quality of life

Optimal height attainment is important for both medical and psychosocial aspects of care. In children initiating dialysis, short stature is associated with an increased risk of hospitalizations and death [23, 26]. In pre-ESRD, short stature associates with poorer health-related quality of life (HRQoL) in the physical functioning domains [27]. In ESRD, short adult height is associated with deficits in social and work life including education, employment, and marriage [28]. Additionally, use of rhGH and increase in height *Z*-score are associated with better HRQoL scores in physical and social functioning by parent proxy [29].

Due to the many untoward effects of short stature, incorporating treatment options into the care of the pediatric CKD patient is vital. Although improvement in management of metabolic acidosis and anemia facilitates augmented growth in children with CKD, use of rhGH is the most important contributor to improved terminal height status. Children treated with rhGH experience significant improvements in growth velocity and final adult height [30]. Age of initial use, use prior to the onset of the pubertal growth spurt, and ideal weight at the start of rhGH are the most important predictors of positive response [30, 31] .

Despite its effectiveness, recombinant growth hormone remains underutilized. The CKiD study identified that only 23% of the children with severe short stature were prescribed rhGH [17]. A recent publication

investigated the reasons for poor utilization of growth hormone by surveying 73 pediatric nephrologists. The most common reason identified for not prescribing rhGH was family refusal. Other reasons identified included medical contraindications, insurance limitation, and impending transplantation [32]. Aside from medical contraindications, these barriers should be surmountable in order to prescribe rhGH and afford children with CKD the best opportunity to avoid the complications associated with short stature.

Despite gains in terminal height over the past two decades, children with CKD remain at risk for short stature. The etiology of growth failure is multifactorial; however, administration of rhGH is an effective intervention to improve final adult height.

# CKD mineral and bone disorder

Mineral and bone disorder (MBD) is a common complication of chronic kidney disease and in children is particularly onerous given a dynamic, growing skeleton. MBD is accelerated by disorders of phosphate, calcium, parathyroid hormone, vitamin D, and fibroblast growth hormone regulation. These changes manifest as abnormalities in bone and mineral metabolism as well as extraskeletal calcification which may accelerate cardiovascular disease. In the pediatric patient with CKD, MBD manifests as poor linear growth, renal osteodystrophy, fractures—occurring at two-to threefold higher rates than the general pediatric population—and bone deformities [33]. Table 2 outlines the treatment recommendations from the Kidney Disease: Improving Global Outcomes (KDIGO) 2017 evidence-based clinical practice guideline for MBD [34••].

## Bone mineral regulation

One of the earliest markers of CKD MBD is a rise in FGF23 to provide a compensatory increase in urinary phosphorus excretion [35]. Elevated FGF23, in turns, suppresses renal 1-alpha-hydroxylase, leading to decreased calcitriol and increased PTH in an attempt to further decrease systemic hyperphosphatemia. In addition to its impact on bone mineral regulation, FGF23 exerts key systemic effects. Several studies have identified associations between elevated FGF23 levels and kidney disease progression and in both the CKD and general population with cardiovascular disease and mortality [36–39].

.Secondary hyperparathyroidism is a key feature of CKD progression. Secondary hyperparathyroidism is common in children with CKD, and active vitamin D sterols such as calcitriol are effective in decreasing PTH levels in those with moderate to advanced CKD. With disease progression, there is reduced activity of 1-alpha hydroxylase within the proximal convoluted tubule that limits the conversion of inactive (25OH) to active vitamin D (1-25OH). Thus, further emphasis may be needed on active vitamin D (calcitriol) sterols to achieve control of secondary hyperparathyroidism in order to prevent development of severe hypocalcemia, hyperphosphatemia, and hyperparathyroidism. Notably, the 2017 KDIGO MBD Guidelines for pediatric patients do slightly contrast for those in adults, whereby the use of vitamin D analogs can

**Table 2. Summary of KDIGO CKD-MBD Recommendations[15]**

Kidney Disease: Improving Global Outcomes (KDIGO) is the global nonprofit organization developing and implementing evidence-based clinical practice guidelines in kidney disease. The KDIGO CKD-MBD recommendations were updated in 2017 and are outlined here.

Laboratory surveillance

1) Stage 2 CKD: monitor calcium, phosphate, pth and alkaline phosphatase activity

2) Stage 3 CKD: continue monitoring for stage 2CKD in addition to 25OH vitamin D and replete if insufficient (< 20 ng/mL)

Recommendations for diagnosis of CKD MBD

1) Recommend bone mineral density testing to assess fracture risk ***if*** results will impact treatment decisions

2) Consider biopsy ***if*** knowledge of the type of renal osteodystrophy will impact treatment decisions

3) Measurements of PTH or bone specific alkaline phosphatase can be used to evaluate bone disease given that markedly high or low values predict underlying bone turnover rates.

4) Do not routinely measure bone-derived turnover markers of collagen synthesis (e.g., procollagen type I C-terminal propeptide) and/or breakdown (e.g., type I collagen cross-lined telopeptide).

Recommendations for Treatment of CKD-MBD-phosphorus and calcium

1) Treatment in CKD stages 3-5 should be based on serial assessments of phosphate, calcium, PTH and considered together

2) In children CKD 3-5, target phosphate levels toward the normal range

3) In children CKD 3-5, maintain serum calcium in normal range

4) CKD stage 5d: use dialysate low-calcium concentration 1.25-1.50 mmol/l (2.5-3.0 meq/L)

5) Base decisions about phosphate lowering treatment on progressively or persistently elevated serum phosphate

6) In children with CKD stage 3-5, base the choice of phosphate lowering treatment on calcium and minimize the dose of calcium-based phosphate binders

7) Avoid long term use of aluminum containing binders

8) Limit dietary phosphate intake in treatment of hyperphosphatemia and consider phosphate source when making restrictions

9) CKD stage 5d consider increasing dialytic phosphate removal in treatment of persistent hyperphosphatemia

Recommendations for Treatment of abnormal PTH

1) Optimal PTH levels are unknown in CKD stage 3-5 (non-dialysis). Persistently elevated or progressively rising levels should be evaluated for modifiable factors

2) For the non-dialysis CKD patient, minimize vitamin D analogues to avoid hypercalcemia unless needed otherwise to maintain serum calcium levels in age-appropriate normal range.

3) For dialysis patients, maintain PTH levels in the range of approximately 2 to 9 times the upper normal limit for local lab assay. Marked changes in either direction within this range should be addressed promptly.

4) Patients with CKD 5d requiring PTH-lowering therapy may require a combination of calcimimetics with vitamin D analogues.

5) Those with severe hyperparathyroidism who fail to respond to medical therapy may require parathyroidectomy.

Recommendations for Evaluation and treatment of kidney transplant bone disease

1) In the immediate post-kidney transplant period, measure serum calcium and phosphorus at least weekly until stable

2) It is reasonable to manage calcium, phosphorus and PTH abnormalities as for patients with CKD stages 3-5 until graft function stabilizes.

3) Vitamin D deficiency should be treated using treatment strategies recommended for the general population until advanced CKD develops in the transplant kidney.

be considered to maintain serum calcium in age-appropriate ranges [34••]. In patients on hemodialysis, the use of calcitriol has been found to provide a survival benefit [40]. When using calcitriol, side effects of hypercalcemia and hyperphosphatemia must be monitored since both can contribute to soft tissue calcification.

Calcium balance is altered in CKD, and hypocalcemia or hypercalcemia may be observed. Hypocalcemia is a primary feature of untreated, late CKD secondary to poor hydroxylation of 25(OH)D to active 1,25(OH)D within the

proximal renal tubular cells, as noted previously. Hypocalcemia can be directly treated using both active 1,25(OH)D and inactive 25(OH)D vitamin D supplementation. Hypercalcemia may be observed in the setting of calcium supplementation; CKD stages 3–4 patients receiving 2 g/day or more of calcium-based binders are in positive calcium balance and risk development of hypercalcemia [41].

Current data suggest that nearly 30% of children with mild to moderate CKD have baseline 25(OH)D deficiency associated with potentially modifiable dietary risk factors and low nutritional vitamin D supplementation [42]. Vitamin D levels should be maintained in the normal range (> 20 ng/mL) by supplementation with vitamin $D_2$ or vitamin $D_3$. Most patients with stage 3–5 CKD will achieve optimal bone health with supplementation of enteral calcitriol either alone or in combination with 25(OH)D supplementation.

Phosphorus homeostasis is dependent on renal excretion via native GFR and tubular function. As such, urinary phosphorus excretion decreases with progressive CKD. In clinical practice, patients with CKD stages 4–5 may require both dietary phosphorus restriction and an enteral phosphorus-binding agent to decrease the total amount of dietary phosphorus absorbed and prevent hyperphosphatemia. A variety of phosphate-binding agents exist including calcium carbonate, calcium acetate, and the non-calcium-containing binder sevelamer hydrochloride. Lanthanum carbonate is a non-calcium-containing binder used for adults, but there is not any pediatric data available to support its use. Ferric citrate is another non-calcium-containing phosphorus binder and is approved for use for adults on hemodialysis, but again there are no pediatric data available yet. Calcium-containing binders may pose problems by causing hypercalcemia, especially in those treated with vitamin D or those with adynamic bone disease. Use of calcium-containing binders over non-calcium-containing binders is associated with vascular calcification, cardiovascular disease and mortality [43]. Effective treatment for hyperphosphatemia is likely important, since poor control of serum calcium and phosphorus concentrations is associated with secondary and/or tertiary hyperparathyroidism, the development of metabolic bone disease, an increased risk of systemic cardiovascular calcifications even after the patient is transplanted [44, 45], and in adults with ESRD, hyperphosphatemia serves as an independent risk factor for death [46–48].

## Renal osteodystrophy

Renal osteodystrophy (ROD) is defined as an alteration of bone quality in patients with CKD and is classified based on bone biopsy histological descriptors relating to bone turnover, mineralization, and volume [49]. Renal osteodystrophy encompasses a spectrum of abnormal bone metabolism, ranging from states of elevated PTH and high bone turnover (osteitis fibrosis cystica) to low turnover and suppressed PTH levels (adynamic bone disease). Since bone biopsy is infrequently performed, PTH, calcium, phosphorus, and alkaline phosphatase levels are often used together as surrogate indicators of bone turnover in order to guide the diagnosis and treatment of renal osteodystrophy. The pathological correlates of ROD range from osteitis fibrosis cystica

(increased bone turnover) to osteoid (low bone turnover/adynamic bone). One study evaluating ROD by histological examination in a peritoneal dialysis population found that 57% have high bone turnover, 39% have normal bone turnover, and 4% have low bone turnover. Interestingly, 48% of all subjects demonstrated abnormal bone mineralization [50].

In a study evaluating ROD in pediatric pre-ESRD CKD, abnormalities in high bone turnover became increasingly common with worsening of CKD: none in CKD stage 2, 13% with CKD stage 3, and 29% with CKD stages 4/5. Within the cohort, 8% had evidence of decreased bone turnover. Abnormal mineralization was seen in 29% with CKD stage 2, 42% CKD stage 3, and 79% with CKD stages 4/5 [51]. ROD clinically manifests as slipped epiphyses of the femur, humerus, radius, and ulna lead to pain, difficulty in walking, and skeletal deformities. Skeletal deformities include genu valum, genu varum, and pes varus. Imaging is a valuable tool to provide information regarding bone deformities, extraskeletal calcification, and bone mineral density. Significant bone deformities may be resistant to active vitamin D sterol treatment. Treatment typically involves treating hyperparathyroidism and bone disease in this setting with vitamin D analogs, although patients with refractory disease may in rare cases require parathyroidectomy.

## Cognitive changes in pediatric CKD

There is a solid base of pediatric literature to support the presence of cognitive difficulties in pediatric CKD patients. These difficulties, ranging from mild to pervasive, may emerge in infancy and persist through the adult transition of care. Arguably, better anemia control, aggressive childhood nutrition, and decreased exposure to heavy metals (via dialysate and dietary binding agents) have provided substantial improvement to the more profound neurocognitive sequelae observed prior to the 1990s. This section will provide a general overview to the cognitive concerns documented in the pediatric CKD population.

### *Intelligence*

In general, data support an overall normal to low-normal range intelligence (IQ) for the pediatric CKD population—with a trend toward lower IQ associated with more severe renal disease [52, 53]. Data from the CKiD study provides the most robust sample to date for children with mild to moderate CKD. Hooper et al. [53], published data on neurocognition in children from the CKiD cohort having mild to moderate CKD. This demonstrated generally average range cognitive functioning for the CKD sample, but it was noted that nearly one-third of participants scored at least one standard deviation below the mean on IQ.

### *Executive function and attention*

Executive function represents the cognitive processes required for planning, organization, and goal-directed behavior. The Conners' Continuous Performance Test-II (CPT-II) is often utilized to assess both attention and

executive function. Data from the CKiD sample suggests that longer duration of CKD may be associated with increased odds for poor performance on the CPT-II, particularly in the domain "errors of commission"—a measure of attention regulation and inhibition control (executive function) [54]. Patients with higher blood pressure variability, assessed by ambulatory blood pressure monitoring, may also evidence poorer performance on tests of executive function [55]. Single-center data also support the presence of executive function difficulties in pediatric CKD and ESRD patients with difficulties potentially driven by attention-predominant tasks [56, 57].

### *Academic achievement*

Despite recognition of neurocognitive weaknesses in the pediatric CKD population, there are few studies addressing academic achievement. Single-center data suggest a trend for lower single-test achievement scores, particularly in the domains of mathematics and reading and that lower achievement could be accentuated by worsened renal function [52]. Evaluation of academic achievement data from the CKiD study supports that low academic achievement may be found in approximately one-third of children with CKD, with most difficulty observed in the content domain of mathematics; however, no effect of CKD-related medical variables was noted on academic achievement [58].

### *Development and behavior*

Early studies examining neurodevelopmental and adaptive functioning in preschool children with CKD suggested risk for potentially pervasive developmental sequelae with progressive disease [59, 60]. More recent data suggest that preschool children with mild to moderate CKD generally perform within the average range of cognitive functioning; however, a sizeable number of preschoolers with CKD may be at risk for lower IQ/developmental delay and adaptive behavior problems [61•]. Limited data exist on the behavioral functioning of children with CKD. Using the Behavior Assessment System for Children (BASC), Hooper et al. [62], showed support for parental-specific concerns related to the child on individual clinical scales of anxiety, depression, and somatization. Conversely, there were no differences observed on any BASC clinical scales from the self-report of children with CKD and healthy controls.

### *Association of cognition with CKD progression*

Numerous CKD-related variables have been investigated in parallel to cognition to establish a mechanistic link between observed cognitive deficits and CKD decline; thus far, there remains only modest ability to discriminate risk for cognitive decline using these clinical variables. In particular, reduction in renal function, proteinuria, duration of renal disease, and/or hypertensive status appears to confer the most risk for observable cognitive deficits in children with mild to moderate CKD [53, 54, 57, 63]. For example, Lande et al. [63]

demonstrated that hypertensive children with mild to moderate CKD have lower IQ scores, and interestingly, it was noted that the systolic blood pressure index correlated inversely with non-verbal IQ, even when controlling for disease-related and social variables.

## Conclusion

Chronic kidney disease in childhood has far-reaching, systemic ramifications including risk for inadequate nutrition and growth, disordered bone and mineral metabolism, and neurocognitive dysfunction. The care of the pediatric CKD patient is certainly complex; however, detailed monitoring can provide opportunity for reductions in morbidity and mortality to lend greater longevity and quality of life.

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## Compliance with Ethics Guidelines

**Conflict Of Interest**
Amy J. Kogon and Lyndsay A. Harshman declare no conflict of interest.

**Human and animal rights and informed consent**
This article does not contain any studies with human or animal subjects performed by any of the authors.

## References and Recommended Reading

Papers of particular interest, published recently, have been highlighted as:
- • Of importance
- •• Of major importance

1. National Kidney Fountation. KDOQI clinical practice guideline for nutrition in children with CKD: 2008 update. Am J Kidney Dis. 2009;53(3):S1–123.
2.• Ayestaran FW, Schneider MF, Kaskel FJ, Srivaths PR, Seo-Mayer PW, Moxey-Mims M, et al. Perceived appetite and clinical outcomes in children with chronic kidney disease. Pediatr Nephrol. 2016;31(7):1121–7. https://doi.org/10.1007/s00467-016-3321-9
This paper utilized data from the Chronic Kidney Disease in Children (CKiD) study and highlights the importance of self-reported appetite in the pediatric CKD population. Lower appetite is directly related to diminishing renal function and poorer clinical outcomes, including more hospitalizations and lower quality of life.
3. Warady BA, Kriley M, Belden B, Hellerstein S, Alan U. Nutritional and behavioral-aspects of nasogastric tube-feeding in infants receiving chronic peritoneal-dialysis. Adv Perit D. 1990;6:265–8.
4. Cheung W, Yu PX, Little BM, Cone RD, Marks DL, Mak RH. Role of leptin and melanocortin signaling in uremia-associated cachexia. J Clin Invest. 2005;115(6:1659–65. https://doi.org/10.1172/JCI22521.

5. Rodriguez Ayala E, Pecoits-Filho R, Heimburger O, Lindholm B, Nordfors L, Stenvinkel P. Associations between plasma ghrelin levels and body composition in end-stage renal disease: a longitudinal study. Nephrol Dial Transplant. 2004;19(2):421–6.
6. Foreman JW, Abitbol CL, Trachtman H, Garin EH, Feld LG, Strife CF, et al. Nutritional intake in children with renal insufficiency: a report of the growth failure in children with renal diseases study. J Am Coll Nutr. 1996;15(6):579–85.
7. Rees L, Mak RH. Nutrition and growth in children with chronic kidney disease. Nat Rev Nephrol. 2011;7(11):615–23. https://doi.org/10.1038/nrneph.2011.137.
8. Rees L, Jones H. Nutritional management and growth in children with chronic kidney disease. Pediatr Nephrol. 2013;28(4):527–36. https://doi.org/10.1007/s00467-012-2258-x.
9. Wingen AM, Fabian-Bach C, Schaefer F, Mehls O. Randomised multicentre study of a low-protein diet on the progression of chronic renal failure in children. European Study Group of Nutritional Treatment of Chronic Renal Failure in Childhood. Lancet. 1997;349(9059):1117–23.
10. Kopple JD, Levey AS, Greene T, Chumlea WC, Gassman JJ, Hollinger DL, et al. Effect of dietary protein restriction on nutritional status in the modification of diet in renal disease study. Kidney Int. 1997;52(3):778–91.
11. Chaturvedi S, Jones C. Protein restriction for children with chronic renal failure. Cochrane Database Syst Rev. 2007;4:CD006863. https://doi.org/10.1002/14651858.CD006863.
12. Rees L, Shaw V. Nutrition in children with CRF and on dialysis. Pediatr Nephrol. 2007;22(10):1689–702. https://doi.org/10.1007/s00467-006-0279-z.
13. Parekh RS, Flynn JT, Smoyer WE, Milne JL, Kershaw DB, Bunchman TE, et al. Improved growth in young children with severe chronic renal insufficiency who use specified nutritional therapy. J Am Soc Nephrol. 2001;12(11):2418–26.
14. Wassner SJ. The effect of sodium repletion on growth and protein turnover in sodium-depleted rats. Pediatr Nephrol. 1991;5(4):501–4.
15. Kiepe D, Tonshoff B. Insulin-like growth factors in normal and diseased kidney. Endocrinol Metab Clin N Am. 2012;41(2):351–74vii. https://doi.org/10.1016/j.ecl.2012.04.015.
16. Maniar S, Kleinknecht C, Zhou X, Motel V, Yvert JP, Dechaux M. Growth hormone action is blunted by acidosis in experimental uremia or acid load. Clin Nephrol. 1996;46(1):72–6.
17. Rodig NM, McDermott KC, Schneider MF, Hotchkiss HM, Yadin O, Seikaly MG, et al. Growth in children with chronic kidney disease: a report from the chronic kidney disease in children study. Pediatr Nephrol. 2014;29(10):1987–95. https://doi.org/10.1007/s00467-014-2812-9.
18. Mitch WE. Influence of metabolic acidosis on nutrition. Am J Kidney Dis. 1997;29(5):R46–R8. https://doi.org/10.1016/S0272-6386(97)90115-3.
19. de Brito-Ashurst I, Varagunam M, Raftery MJ, Yaqoob MM. Bicarbonate supplementation slows progression of CKD and improves nutritional status. J Am Soc Nephrol. 2009;20(9):2075–84. https://doi.org/10.1681/Asn.2008111205.
20. Kausman JY, Powell HR, Jones CL. Anemia in pediatric renal transplant recipients. Pediatr Nephrol. 2004;19(5):526–30. https://doi.org/10.1007/s00467-004-1427-y.
21. Boehm M, Riesenhuber A, Winkelmayer WC, Arbeiter K, Mueller T, Aufricht C. Early erythropoietin therapy is associated with improved growth in children with chronic kidney disease. Pediatr Nephrol. 2007;22(8):1189–93. https://doi.org/10.1007/s00467-007-0472-8.
22. Kari JA, Gonzalez C, Ledermann SE, Shaw V, Rees L. Outcome and growth of infants with severe chronic renal failure. Kidney Int. 2000;57(4):1681–7. https://doi.org/10.1046/j.1523-1755.2000.00013.x.
23. Nissel R, Brazda I, Feneberg R, Wigger M, Greiner C, Querfeld U, et al. Effect of renal transplantation in childhood on longitudinal growth and adult height. Kidney Int. 2004;66(2):792–800. https://doi.org/10.1111/j.1523-1755.2004.00805.x.
24. North American Pediatric Renal Transplant Cooperative Study Annual Report. 2014. https://web.emmes.com/study/ped/annlrept/annualrept2014.pdf. Accessed 25 Jan 2019
25. Nissel R, Lindberg A, Mehls O, Haffner D, Pfizer international growth database international B. Factors predicting the near-final height in growth hormone-treated children and adolescents with chronic kidney disease. J Clin Endocrinol Metab. 2008;93(4):1359–65. https://doi.org/10.1210/jc.2007-2302.
26. Fine RN, Ho M, Tejani A, North American Pediatric Renal Trasplant Cooperative S. The contribution of renal transplantation to final adult height: a report of the North American pediatric renal transplant cooperative study (NAPRTCS). Pediatr Nephrol. 2001;16(12):951–6. https://doi.org/10.1007/s004670100002.
27. Gerson AC, Wentz A, Abraham AG, Mendley SR, Hooper SR, Butler RW, et al. Health-related quality of life of children with mild to moderate chronic kidney disease. Pediatrics. 2010;125(2):e349–57. https://doi.org/10.1542/peds.2009-0085.
28. Broyer M, Le Bihan C, Charbit M, Guest G, Tete MJ, Gagnadoux MF, et al. Long-term social outcome of children after kidney transplantation. Transplantation. 2004;77(7):1033–7.
29. Al-Uzri A, Matheson M, Gipson DS, Mendley SR, Hooper SR, Yadin O, et al. The impact of short stature on health-related quality of life in children with chronic kidney disease. J Pediatr. 2013;163(3):736–41 e1. https://doi.org/10.1016/j.jpeds.2013.03.016.

30. Haffner D, Schaefer F, Nissel R, Wuhl E, Tonshoff B, Mehls O. Effect of growth hormone treatment on the adult height of children with chronic renal failure. German study Group for Growth Hormone Treatment in chronic renal failure. N Engl J Med. 2000;343(13):923–30. https://doi.org/10.1056/NEJM200009283431304.
31. Mehls O, Lindberg A, Nissel R, Haffner D, Hokken-Koelega A, Ranke MB. Predicting the response to growth hormone treatment in short children with chronic kidney disease. J Clin Endocrinol Metab. 2010;95(2):686–92. https://doi.org/10.1210/jc.2009-1114.
32. Akchurin OM, Kogon AJ, Kumar J, Sethna CB, Hammad HT, Christos PJ, et al. Approach to growth hormone therapy in children with chronic kidney disease varies across North America: the Midwest Pediatric Nephrology Consortium report. BMC Nephrol. 2017;18(1):181. https://doi.org/10.1186/s12882-017-0599-1.
33. Denburg MR, Kumar J, Jemielita T, Brooks ER, Skversky A, Portale AA, et al. Fracture Burden and Risk Factors in Childhood CKD: Results from the CKiD Cohort Study. J Am Soc Nephrol. 2016;27(2):543–50. https://doi.org/10.1681/ASN.2015020152.
34.•• Ketteler M, Block GA, Evenepoel P, Fukagawa M, Herzog CA, McCann L, et al. Executive summary of the 2017 KDIGO Chronic Kidney Disease-Mineral and Bone Disorder (CKD-MBD) Guideline Update: what's changed and why it matters. Kidney Int. 2017;92(1):26–36. https://doi.org/10.1016/j.kint.2017.04.006
The KDIGO 2017 Clinical Practice Guideline Update is a selective update to the 2009 KDIGO mineral bone disease guidelines. The guidelines are adult- and pediatric-specific and cover the spectrum of non-dialysis CKD to transplant. Pertinent to this update is the diagnosis of bone abnormalities and treatment of CKD-MBD by phosphate lowering and calcium maintenance.
35. Portale AA, Wolf M, Juppner H, Messinger S, Kumar J, Wesseling-Perry K, et al. Disordered FGF23 and mineral metabolism in children with CKD. Clin J Am Soc Nephrol. 2014;9(2):344–53. https://doi.org/10.2215/CJN.05840513.
36. Arnlov J, Carlsson AC, Sundstrom J, Ingelsson E, Larsson A, Lind L, et al. Higher fibroblast growth factor-23 increases the risk of all-cause and cardiovascular mortality in the community. Kidney Int. 2013;83(1):160–6. https://doi.org/10.1038/ki.2012.327.
37. Gutierrez OM, Januzzi JL, Isakova T, Laliberte K, Smith K, Collerone G, et al. Fibroblast growth factor 23 and left ventricular hypertrophy in chronic kidney disease. Circulation. 2009;119(19):2545–52. https://doi.org/10.1161/CIRCULATIONAHA.108.844506.
38. Gutierrez OM, Mannstadt M, Isakova T, Rauh-Hain JA, Tamez H, Shah A, et al. Fibroblast growth factor 23 and mortality among patients undergoing hemodialysis. N Engl J Med. 2008;359(6):584–92. https://doi.org/10.1056/NEJMoa0706130.
39. Seeherunvong W, Abitbol CL, Chandar J, Rusconi P, Zilleruelo GE, Freundlich M. Fibroblast growth factor 23 and left ventricular hypertrophy in children on dialysis. Pediatr Nephrol. 2012;27(11):2129–36. https://doi.org/10.1007/s00467-012-2224-7.
40. Teng M, Wolf M, Lowrie E, Ofsthun N, Lazarus JM, Thadhani R. Survival of patients undergoing hemodialysis with paricalcitol or calcitriol therapy. N Engl J Med. 2003;349(5):446–56. https://doi.org/10.1056/NEJMoa022536.
41. Hill KM, Martin BR, Wastney ME, McCabe GP, Moe SM, Weaver CM, et al. Oral calcium carbonate affects calcium but not phosphorus balance in stage 3-4 chronic kidney disease. Kidney Int. 2013;83(5):959–66. https://doi.org/10.1038/ki.2012.403.
42. Kumar J, McDermott K, Abraham AG, Friedman LA, Johnson VL, Kaskel FJ, et al. Prevalence and correlates of 25-hydroxyvitamin D deficiency in the chronic kidney disease in children (CKiD) cohort. Pediatr Nephrol. 2016;31(1):121–9. https://doi.org/10.1007/s00467-015-3190-7.
43. Jamal SA, Vandermeer B, Raggi P, Mendelssohn DC, Chatterley T, Dorgan M, et al. Effect of calcium-based versus non-calcium-based phosphate binders on mortality in patients with chronic kidney disease: an updated systematic review and meta-analysis. Lancet. 2013;382(9900):1268–77. https://doi.org/10.1016/S0140-6736(13)60897-1.
44. Cozzolino M, Gallieni M, Brancaccio D. The mechanisms of hyperphosphatemia-induced vascular calcification. Int J Artif Organs. 2008;31(12):1002–3.
45. Hruska KA, Choi ET, Memon I, Davis TK, Mathew S. Cardiovascular risk in chronic kidney disease (CKD): the CKD-mineral bone disorder (CKD-MBD). Pediatr Nephrol. 2010;25(4):769–78. https://doi.org/10.1007/s00467-009-1337-0.
46. Block GA, Hulbert-Shearon TE, Levin NW, Port FK. Association of serum phosphorus and calcium x phosphate product with mortality risk in chronic hemodialysis patients: a national study. Am J Kidney Dis. 1998;31(4):607–17.
47. Kestenbaum B, Sampson JN, Rudser KD, Patterson DJ, Seliger SL, Young B, et al. Serum phosphate levels and mortality risk among people with chronic kidney disease. J Am Soc Nephrol. 2005;16(2):520–8. https://doi.org/10.1681/ASN.2004070602.
48. Tentori F, Blayney MJ, Albert JM, Gillespie BW, Kerr PG, Bommer J, et al. Mortality risk for dialysis patients with different levels of serum calcium, phosphorus, and PTH: the dialysis outcomes and practice patterns study (DOPPS). Am J Kidney Dis. 2008;52(3):519–30. https://doi.org/10.1053/j.ajkd.2008.03.020.
49. Moe S, Drueke T, Cunningham J, Goodman W, Martin K, Olgaard K, et al. Definition, evaluation, and classification of renal osteodystrophy: a position statement from kidney disease: improving global outcomes

(KDIGO). Kidney Int. 2006;69(11):1945–53. https://doi.org/10.1038/sj.ki.5000414.
50. Bakkaloglu SA, Wesseling-Perry K, Pereira RC, Gales B, Wang HJ, Elashoff RM, et al. Value of the new bone classification system in pediatric renal osteodystrophy. Clin J Am Soc Nephrol. 2010;5(10):1860–6. https://doi.org/10.2215/CJN.01330210.
51. Wesseling-Perry K, Pereira RC, Tseng CH, Elashoff R, Zaritsky JJ, Yadin O, et al. Early skeletal and biochemical alterations in pediatric chronic kidney disease. Clin J Am Soc Nephrol. 2012;7(1):146–52. https://doi.org/10.2215/CJN.05940611.
52. Duquette PJ, Hooper SR, Wetherington CE, Icard PF, Gipson DS. Brief report: intellectual and academic functioning in pediatric chronic kidney disease. J Pediatr Psychol. 2007;32(8):1011–7. https://doi.org/10.1093/jpepsy/jsm036.
53. Hooper SR, Gerson AC, Butler RW, Gipson DS, Mendley SR, Lande MB, et al. Neurocognitive functioning of children and adolescents with mild-to-moderate chronic kidney disease. Clin J Am Soc Nephrol. 2011;6(8):1824–30. https://doi.org/10.2215/CJN.09751110.
54. Mendley SR, Matheson MB, Shinnar S, Lande MB, Gerson AC, Butler RW, et al. Duration of chronic kidney disease reduces attention and executive function in pediatric patients. Kidney Int. 2015;87(4):800–6. https://doi.org/10.1038/ki.2014.323.
55. Lande MB, Mendley SR, Matheson MB, Shinnar S, Gerson AC, Samuels JA, et al. Association of blood pressure variability and neurocognition in children with chronic kidney disease. Pediatr Nephrol. 2016;31(11):2137–44. https://doi.org/10.1007/s00467-016-3425-2.
56. Gipson DS, Hooper SR, Duquette PJ, Wetherington CE, Stellwagen KK, Jenkins TL, et al. Memory and executive functions in pediatric chronic kidney disease. Child Neuropsychol. 2006;12(6):391–405. https://doi.org/10.1080/09297040600876311.
57. Ruebner RL, Laney N, Kim JY, Hartung EA, Hooper SR, Radcliffe J, et al. Neurocognitive dysfunction in children, adolescents, and young adults with CKD. Am J Kidney Dis. 2016;67(4):567–75. https://doi.org/10.1053/j.ajkd.2015.08.025.
58. Harshman LA, Johnson RJ, Matheson MB, Kogon AJ, Shinnar S, Gerson AC, et al. Academic achievement in children with chronic kidney disease: a report from the CKiD cohort. Pediatr Nephrol. 2018;34:689–96. https://doi.org/10.1007/s00467-018-4144-7.
59. Qvist E, Pihko H, Fagerudd P, Valanne L, Lamminranta S, Karikoski J, et al. Neurodevelopmental outcome in high-risk patients after renal transplantation in early childhood. Pediatr Transplant. 2002;6(1):53–62.
60. Warady BA, Belden B, Kohaut E. Neurodevelopmental outcome of children initiating peritoneal dialysis in early infancy. Pediatr Nephrol. 1999;13(9):759–65. https://doi.org/10.1007/s004670050694.
61.• Hooper SR, Gerson AC, Johnson RJ, Mendley SR, Shinnar S, Lande MB, et al. Neurocognitive, social-behavioral, and adaptive functioning in preschool children with mild to moderate kidney disease. J Dev Behav Pediatr. 2016;37(3):231–8. https://doi.org/10.1097/DBP.0000000000000267
The impact of CKD in early development has been widely documented in advanced CKD/ESRD. This paper utilized data from the Chronic Kidney Disease in Children (CKiD) study to detail neurocognitive outcomes for pediatric patients with more mild to moderate CKD. Findings suggest relatively intact functioning for preschool children. Higher eGFR and lack of anemia were associated with more intact developmental level/IQ.
62. Hooper SR, Duquette PJ, Icard P, Wetherington CE, Harrell W, Gipson DS. Social-behavioural functioning in paediatric chronic kidney disease. Child Care Health Dev. 2009;35(6):832–40. https://doi.org/10.1111/j.1365-2214.2009.00992.x.
63. Lande MB, Gerson AC, Hooper SR, Cox C, Matheson M, Mendley SR, et al. Casual blood pressure and neurocognitive function in children with chronic kidney disease: a report of the children with chronic kidney disease cohort study. Clin J Am Soc Nephrol. 2011;6(8):1831–7. https://doi.org/10.2215/CJN.00810111.

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