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Recommended Citation

Anderson CE, Tuokkola J, Qizalbash L, et al. Assessment and management of vitamin status in children with CKD stages 2-5, on dialysis and post-transplantation: clinical practice points from the Pediatric Renal Nutrition Taskforce. *Pediatr Nephrol.* 2024;39(10):3103-3124. doi:10.1007/s00467-024-06303-x

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Assessment and management of vitamin status in children with CKD stages 2–5, on dialysis and post-transplantation: clinical practice points from the Pediatric Renal Nutrition Taskforce

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Received: 4 October 2023 / Revised: 10 January 2024 / Accepted: 10 January 2024 / Published online: 4 April 2024

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Abstract

Children with chronic kidney disease (CKD) are at risk for vitamin deficiency or excess. Vitamin status can be affected by diet, supplements, kidney function, medications, and dialysis. Little is known about vitamin requirements in CKD, leading to practice variation.

The Pediatric Renal Nutrition Taskforce (PRNT), an international team of pediatric kidney dietitians and pediatric nephrologists, was established to develop evidence-based clinical practice points (CPPs) to address challenges and to serve as a resource for nutritional care. Questions were formulated using PICO (Patient, Intervention, Comparator, Outcomes), and literature searches undertaken to explore clinical practice from assessment to management of vitamin status in children with CKD stages 2–5, on dialysis and post-transplantation (CKD2-5D&T). The CPPs were developed and finalized using a Delphi consensus approach. We present six CPPs for vitamin management for children with CKD2-5D&T. We address assessment, intervention, and monitoring. We recommend avoiding supplementation of vitamin A and suggest water-soluble vitamin supplementation for those on dialysis. In the absence of evidence, a consistent structured approach to vitamin management that considers assessment and monitoring from dietary, physical, and biochemical viewpoints is needed. Careful consideration of the impact of accumulation, losses, comorbidities, and medications needs to be explored for the individual child and vitamin before supplementation can be considered. When supplementing, care needs to be taken not to over-prescribe. Research recommendations are suggested.

Keywords Vitamins · Chronic kidney disease · Pediatric Renal Nutrition Taskforce · Clinical practice points · Children

Introduction

Vitamins have essential roles in bodily processes [1, 2]. Deficiencies and excesses may cause adverse clinical consequences, and chronic kidney disease (CKD) increases their risk. Vitamin status can be affected by diet, supplements, kidney function, and dialysis, among other factors.

The most recent pediatric guidelines [3, 4] for vitamin management in CKD were published over 15 years ago and are based on limited evidence. These guidelines made four key points. First, dietary intake should provide 100% of

requirements for healthy children. Second, supplementation should be considered when there is inadequate intake or clinical deficiency is evident. Third, low blood concentrations may be used to confirm deficiency. Fourth, children on dialysis should receive water-soluble vitamin supplementation, if not on enteral or sip feeds (oral nutritional supplements).

Building on prior Kidney Disease Outcomes Quality Initiative recommendations [4], along with information derived from recent literature, we present a comprehensive position paper with six clinical practice points (CPPs) to address vitamin assessment, intervention, and monitoring for children with CKD stages 2–5, those on dialysis and post-kidney transplantation, all henceforth referred to as CKD. These CPPs are based on available evidence, expert opinion, and, where appropriate, extrapolation from adult studies. We

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address fat-soluble vitamins (A (retinol), E (tocopherol), and K (phyloquinone, menaquinone)) and water-soluble vitamins (B1 (thiamin), B2 (riboflavin), B3 (niacin), B5 (pantothenic acid), B6 (pyridoxine), B7 (biotin), B9 (folate), B12 (cobalamin), and C (ascorbic acid)). Vitamin D has been extensively addressed elsewhere and is not included in this review [5].

Methods

The full development process, the purpose, and plans for audit and revision of the recommendations are described in a previous Pediatric Renal Nutrition Taskforce (PRNT) publication [6]. The search criteria are described below (Table S1). The PRNT working group, which included pediatric nephrologists, dietitians, and biochemists, defined the scope, formulated the questions, performed the literature review, developed the CPPs, and conducted the Delphi process. The Delphi group included nephrologists and dietitians from global children's kidney centers.

Development process

PICO (Patient, Intervention, Comparator, and Outcome) questions guided the development of actionable CPPs

A—PICO questions

Population/Patient: children from birth up to 18 years of age with CKD.

Intervention: assessment of vitamin requirements, intake, and clinical evidence of deficiency or excess; use of supplementation and monitoring.

Comparison: vitamin requirements for healthy children and adults with CKD, and biochemical markers, where available (*or no comparator*)

Outcomes: adequate vitamin intake; avoidance of vitamin deficiencies and excesses.

B—Proposed clinical questions for clinical practice points for children with CKD

1. What are the vitamin requirements?
2. Which foods are the main dietary sources?
3. How do dietary modifications affect intake?
4. What are the non-dietary factors which influence vitamin status?
5. How should we approach clinical assessment and monitoring?
6. When is dietary modification or vitamin supplementation indicated?

Literature search

Details of the literature search are described in Table S1. Literature up to and including a publication date of January 2023 was reviewed using PICO and related clinical questions.

Clinical practice points

1. What are the vitamin requirements?
 - 1.1 The vitamin requirements for children with early CKD (stages 2–3a) should approximate those of healthy children of the same chronological age
 - 1.1.1 For children with advanced CKD (stage 3b–5D&T), vitamin requirements may be less or greater than those for healthy children.
 - 1.1.2 We suggest that the intake of vitamin A in CKD, where accumulation may occur, should not exceed the requirements of healthy children.

Evidence and rationale

In order to understand requirements for children with CKD, we first describe the requirements for healthy children as a comparator. A summary of internationally published recommended dietary intakes of vitamins is provided in Table S2 [7–12]. Definitions of requirements can be found in Table S3.

The requirements of vitamins for children and adolescents with CKD have not been determined. Therefore, requirements for healthy children should be used as an initial guide for the assessment of adequate intake. This statement agrees with previous published guidelines. However, additional consideration has been given to advanced CKD, as discussed below, suggesting that requirements may be greater for some vitamins due to the presence of increased oxidative stress and dialysate- and medication-induced losses. Conversely, there is evidence that excess intake of some vitamins causes harm [13–15]. Children with CKD may develop clinical hypervitaminosis A due to decreased urinary excretion and absence of dialytic removal. Hence, high intake of vitamin A in CKD should be avoided [16–26]. These statements, including the restriction of vitamin A intake, are consistent with prior guidelines for children with CKD.

In children with pre-dialysis CKD, we suggest increasing intake, either via diet or supplements, if B vitamins or vitamin C intakes are lower than recommended for healthy children.

Children receiving dialysis may benefit from a higher vitamin C intake. Supplementation may be beneficial for anemia and lipid management in children on dialysis [27, 28]. However, the safe amount to ingest, to avoid the risk of systemic oxalosis, is not known [29, 30]. KDOQI [4] recommends supplementation for dialysis patients, but does not provide a specific supplementation recommendation, though does state that the safe upper limit of total intake of vitamin C is 400–1800 mg per day, depending on age. In one study, supplementation of 250 mg/day of vitamin C did not lead to hyperoxaluria [28]. The UK Scientific Advisory Committee on Nutrition and European Food Safety Authority [7, 15] have not set an upper limit for healthy children. In the absence of dietary or laboratory assessment for B vitamins, it is likely optimal to use a water-soluble multivitamin supplement in children receiving dialysis given the risk of deficiencies and low risk of excess. There are no reports of toxicity using such an approach.

2. Which foods are the main dietary source of vitamins?
 - 2.1 Children with CKD may obtain sufficient vitamin intake through intake of a varied diet and/or a nutritionally complete enteral formula.

Evidence and rationale

The main dietary sources for each vitamin are shown in Table 1; some of these foods may need to be restricted to manage uremia, hyperkalemia, hyperphosphatemia, and hyperlipidemia. A varied diet can help optimize vitamin intake.

3. Dietary modifications and food preparation methods may impact vitamin intake.
 - 3.1 How do dietary modifications affect intake?

Evidence and rationale

Dietary intake of vitamins in children with CKD has been reported to range from below to above estimated requirements for healthy children (Tables S4, S6, S10, S12, S14, S15, S16, S18, S20, S22). Diet modifications for CKD may limit vitamin-rich dietary sources (Table 1) and children with CKD are at increased risk of malnutrition, including a non-optimal vitamin status [31–33]. The risk of malnutrition may be particularly pertinent in children who have advanced CKD, including those on dialysis.

Vitamin intake can also be altered by country-specific food fortification programs and may change with cooking methods designed to reduce potassium intake. For example, boiling in water reduces vitamin content, especially of

water-soluble and heat-labile vitamins [34, 35]. In addition, interactions with other nutrients may affect absorption and metabolism. The vitamin content of enteral formulas is specific at the time of manufacture, but content could change according to storage conditions [36–39].

4. What are the non-dietary factors which influence vitamin intake and status?
 - 4.1 Non-dietary factors, such as CKD stage, dialysis, comorbidities, and medications, should be considered when assessing and monitoring vitamin status and when planning nutritional interventions.

Evidence and rationale

Each vitamin is considered individually below. All children, including patients with CKD, could develop vitamin deficiency due to malabsorption [40, 41]. Table 2 shows the impact of medications and how they can alter vitamin absorption, distribution, metabolism, and excretion. The most commonly prescribed medications for consideration are proton pump inhibitors (B12), furosemide (B6, C), and warfarin (B3, K, E) [42, 43].

Vitamin A is partially excreted by the kidneys and is not removed by dialysis. The kidney tubules have a role in vitamin A catabolism, and thus vitamin A can accumulate in patients with CKD, especially those receiving dialysis [4, 16–26, 44] (Table S27). Transplant patients are considered to have CKD, and elevated levels of vitamin A may be of concern in transplant recipients, especially as kidney function declines [45, 46].

There is limited evidence that blood vitamin E concentrations are elevated in adults and children with CKD [24, 25]. There is conflicting information as to whether vitamin E is lost in hemodialysis (HD) [47–50].

Little is known about vitamin K in children with CKD. There is no evidence for an increased risk of vitamin K deficiency in CKD, though malabsorption due to gastrointestinal disease and poor intake combined with broad-spectrum antibiotics that eliminate gut bacteria producing vitamin K may cause vitamin K deficiency [51–54]. There is no evidence of vitamin K losses in dialysis; however, low serum vitamin K levels are present in patients treated with vitamin K antagonists, a therapy mainly studied in adults with CKD who exhibit side effects such as bleeding and calciphylaxis.

Many water-soluble vitamins are lost in dialysate due to their small molecular size. Only adult data is available for B complex vitamins. There is evidence for varying degrees of losses in HD for vitamins B1 (Table 3; Table S28) [55–60], B2 [57, 60], B6 [57, 60–62], biotin [63], and folate [57, 60, 62, 64, 65]. There is evidence for varying degrees of

Table 1 Main dietary sources of vitamins and potential impact of dietary modifications

	Meat*†‡ ^A	Nuts, seeds, and meat alternatives	Fish*†‡	Dairy*†‡** and egg	Fruit‡	Vegetables‡	Breads and cereals*†‡	Drinks‡	Processed foods / other*†‡**
Retinol	Liver*†‡ ^A		Eel*†‡	Milk*†‡, egg yolk*†, cheese*†‡**	Yellow‡	Yellow and green leafy‡		Infant and follow-on formula	Butter** , fortified vegetable spreads
E Tocopherol	Liver*†‡ ^A	Almond*†‡	Sardines*†‡	Butter** , egg yolk,		Green and leafy vegetables‡	Wheat germs†‡, whole grains (possibly †‡)	Infant and follow-on formula	Vegetable oil
K1 Phylloquinone				Vegetable/seed fats/oils		Dark green leafy vegetables‡ (e.g., spinach, lettuce), brassica (e.g., cabbage)		Infant and follow-on formula	
K2 Menaquinones and dihydrophyloquinone	Liver*†‡ ^A			Cheese*†‡** , dairy*†‡, egg yolk†‡** , oil, margarine shortenings			Bread (possibly †‡)	Infant and follow-on formula	Chocolate†‡, pie and pie crusts, fast foods, popcorn spices, snacks*†‡** , crackers
B1 Thiamine	Pork*†‡, small amounts in other meats	Quorn nuts*†‡, small amounts in everything	Small amounts in everything	Small amounts in everything	Small amounts in everything	Small amounts in everything	Fortified cereals and bread (possibly †‡)	Infant and follow-on formula	Small amounts in everything
B2 Riboflavin	Organ meat*† ^A (kidney and liver), small amounts in other meats*†‡	Almond*†‡, small amounts in other nuts and seeds*†‡	Small amounts*†‡	Hard cheese*†‡** , small amounts in soft cheese, milk and other milk products*†‡ and eggs*†		Small amounts in green leafy vegetables‡, legumes†	Fortified cereals and bread (possibly †‡)	Fortified milk alternatives infant and follow-on formula	Small amounts
B3 Niacin	Liver*†‡ ^A meat*†‡	Peanuts†	Fish, especially tuna*†‡	Milk*†‡, cheese*†‡** , eggs*†			Whole grains (possibly †‡), Flour		Coffee‡, infant and follow-on formula
B5 Pantothenic acid	Meat*†‡, poultry*†‡ ^A	Nuts†		Eggs*†, Milk*†‡	Avocado‡	Brassic (e.g., cauliflower, cabbage, kale) and vegetables‡	Bread (possibly †‡)	Infant and follow-on formula	
B6 Pyridoxine	Meat, *†‡, poultry*†‡, liver*†‡ ^A	Nuts†	Fish, crayfish*†‡			Water chestnut	Fortified cereals, wheat bran (possibly †‡)	Infant and follow-on formula	
B7 Biotin	Meat (liver ^A) *†‡, fish*†‡, poultry*†‡			Egg yolk*†, some cheeses*†‡**		Some vegetables‡ (mushrooms), soybeans†		Infant and follow-on formula	

Table 1 (continued)

	Meat*†‡ ^A	Nuts, seeds, and meat alternatives	Fish*†‡	Dairy*†‡** and egg	Fruit‡	Vegetables‡	Breads and cereals†‡	Drinks‡	Processed foods / other*†‡**
B9 Folate	Liver*†‡ ^A	Soy†‡		Egg yolk*†‡, egg	Citrus and other fruits‡	Green vegetables‡, (H2O18); pulses†, beetroot	Wheat germ, grains, fortified grain products (possibly †‡)	Infant and follow-on formula	
B12 Cobalamin	Animal products, meat*†‡, fish*†‡, poultry*†‡, liver*†‡ ^A			Dairy products*†‡**, egg yolk*†‡**			Fortified food with B12, e.g., ready-to-eat breakfast cereals (possibly †‡), milk alternatives	Infant and follow-on formula	
C Ascorbic acid					Blackcurrants ‡, guava, kiwi fruit, papaya, orange, strawberries‡	Red and yellow pepper, Brussels sprouts, kale and broccoli, spinach, cauliflower, red cabbage, swede		Infant and follow-on formula, black-currant juice‡, orange juice‡, apple juice (fortified with vitamin C‡), fruit cordials and squashes fortified with vitamin C (values will be country specific), high fruit content cordials and squashes	

These foods may need to be restricted in case of dietary modifications for the management of *uremia, †hyperphosphatemia, ‡hypertlipidemia, **hypertlipidemia, ***hypertlipidemia, ^Ahypervitaminosis A

Table 2 Vitamin interactions with medications [135]

Vitamin	Interactions
Vitamin A/retinol/retinoic acid	Moderate interaction: Etretinate, Tretinoin, Isotretinoin, Bexarotene – risk for retinoid toxicity Tetracycline antibiotics (e.g., doxycycline, minocycline) – increased risk of pseudotumor cerebri Anticoagulants (e.g., heparin, warfarin, dicumarol, bivalirudin, antithrombin III, argatroban, clopidogrel) – increased risk of bleeding Tocofersolan – increased absorption of vitamin A Cholestyramine – decreased absorption Rifampicin – decreased absorption Orlistat – decreased absorption
Vitamin B1/thiamin	Moderate interaction: Fluorouracil – reduced thiamine exposure
Vitamin B2/riboflavin	No moderate or major interactions No contraindications
Vitamin B3/niacin, nicotinamide	Major interaction: Simvastatin, lovastatin, rosuvastatin, cerivastatin, atorvastatin, pitavastatin—increased niacin and statin exposure with risk for myopathy or rhabdomyolysis Methotrexate – increased risk of methotrexate-related severe adverse reactions; reduced active metabolite formation; possibly reduced methotrexate efficacy Moderate interaction: Warfarin – increased risk of bleeding Insulin – decreased blood glucose lowering effect of insulin Fluvastatin, pravastatin – increased risk of myopathy or rhabdomyolysis
Vitamin B5/pantothenic acid	Moderate interaction: Azithromycin, clarithromycin, erythromycin, roxithromycin – decreases level/effect of B5 supplementation
Vitamin B6/pyridoxin, pyridoxal, pyridoxamine	Major interaction: Altretamine – reduced response to altretamine Moderate interaction: Levodopa – decreased levodopa effectiveness Furosemide – significantly increases urinary excretion
Vitamin B7/biotin	No moderate or major interactions No contraindications <i>Long-term use of antiseizure medications may reduce biotin levels</i>
Vitamin B9/folate, folic acid	Major interaction: Capecitabine – concomitant use with folic acid may result in increased fluorouracil exposure and increased risk of fluorouracil-related toxicity Pafolacianine – concurrent use may result in reduced detection of malignant lesions Methotrexate – concurrent use may result in reduced folic acid serum levels and reduced methotrexate efficacy Moderate interaction: Phenytoin – concurrent use may result in decreased folic acid serum levels; decreased phenytoin effectiveness Pyrimethamine – loss of pyrimethamine efficacy Primidone—decreased folic acid serum levels; decreased primidone effectiveness
Vitamin B12/cobalamins, cyanocobalamin methylcobalamin	Moderate interaction: Chloramphenicol – concurrent use may result in decreased efficacy of vitamin B12 when used to treat anemia Mycophenolate mofetil – increased risk of B12 deficiency due to diarrhea Proton pump inhibitors, H2 blockers, and metformin – increased risk of B12 deficiency
Vitamin C/ascorbic acid, ascorbate	Major interaction: Amygdalin – concomitant use with vitamin C may result in increased metabolism of amygdalin leading to increased cyanide levels Deferoxamine – impairment of cardiac function Erythromycin, lincomycin, streptomycin, kanamycin, doxycycline – decreased antibiotic activity Bleomycin – decreased bleomycin efficacy Moderate interaction: Indinavir (protease inhibitor/antiretroviral) – decreased indinavir plasma concentration Amphetamines (dextroamphetamine, lisdexamfetamine, benzphetamine, methamphetamine) – decreased blood levels and effectiveness of amphetamines Furosemide – significantly increases urinary excretion

Table 2 (continued)

Vitamin	Interactions
Vitamin E/tocopherol, tocotrienol	Major interaction: Dicumarol – increased risk of bleeding Moderate interaction: Warfarin – increased risk of bleeding Tocofersolan – increased absorption of vitamin E Cholestyramine – decreased absorption Rifampicin – decreased absorption Orlistat – decreased absorption
Vitamin K/phyloquinone, menaquinone	Moderate interaction: Warfarin – decreased effectiveness of warfarin; reduction in INR Pau D'arco (herbal/medicinal tree bark)—reduced vitamin K effectiveness Tocofersolan – increased absorption of vitamin K Cholestyramine – decreased absorption Rifampicin – decreased absorption Orlistat – decreased absorption

Major – the interaction may be life-threatening and/or require medical intervention to minimize or prevent adverse effects

Moderate – the interaction may result in exacerbation of the patient's condition and/or require an alteration of therapy

losses in peritoneal dialysis (PD) for vitamins B2 (Table 3; Table S28) [66], B6 [57, 60, 62, 66, 67], and folate [66, 68]; losses of B1 are low [66]. There is no information on losses or levels of vitamins B3 or B5 in adults or children receiving dialysis. Losses of folate seem to be higher with high flux HD and lower with PD [64–66, 68–73]. Studies in adults have not demonstrated vitamin B12 losses in dialysis patients [57, 65, 66, 70, 71]. Table 3 summarizes the losses of B vitamins in adults receiving dialysis.

Studies have demonstrated vitamin C losses in dialysate in children on PD [18, 74] and HD [75]. In adults, there is evidence of losses in dialysate in HD [60, 76, 77] and PD [61, 66, 69, 78, 79] as well as reduction in serum vitamin C levels in adults post-HD [60, 76, 77, 80–82] and PD [66, 68, 79, 83] (Table 3). Higher losses have been reported with higher supplementation [76]. In one study, children on HD were more likely to have low blood concentrations compared to children on PD or with CKD2–5 [84]. In adults, there are multiple studies demonstrating low blood concentrations in dialysis patients, with lower levels associated with increasing efficacy and duration of dialysis [60, 68, 69, 73, 76, 77, 79–82, 85] (Table 3). In addition, furosemide increases urinary losses of vitamin C [42].

In the transplant population, there are very limited data, with one small study suggesting no evidence of low status, and perhaps altered B vitamin metabolism with elevated B6 concentrations despite a lack of supplementation [86].

5. How should we approach clinical assessment and monitoring?

5.1 Dietary

- 5.1.1 We suggest that the vitamin intake of children with CKD should be assessed by diet

history/diet records, including food and drink, formulas and nutritional supplements, and a review of medications.

- 5.2.1 We suggest that the frequency of assessment of vitamin intake should be influenced by dietary modifications, child's age, CKD stage, dialysis modality, and intake of medications that interfere with vitamin metabolism.

- 5.1.3 Assessment may need to be more frequent if there are signs or symptoms of deficiency or excess.

Evidence and rationale

Dietary assessment is clinically important given evidence of insufficient dietary intake of vitamins (Tables S4, S6, S10, S12, S14, S15, S16, S18, S20, S22) [18, 25, 28, 31, 31, 87–94]. A complete dietary assessment should include intake from food, formulas, nutritional supplements, and intake from medications [94] with consideration of the effect of food preparation on vitamin content and bioavailability. Assessment of dietary intake has been described in detail in a previous PRNT publication [94], which recommended three 24-h dietary recalls or a 3–4-day diet diary/food record. However, due to potential significant variation in daily intake [95], it is necessary to review adequacy over longer periods of time before taking action [83].

Vitamin intake should be reviewed whenever there is a major change in diet (e.g., conversion from formula to table food, adoption of a vegan diet), when a patient initiates dialysis, when there is a clinical issue that may affect vitamin balance (e.g., malabsorption, initiation of a medication that may affect vitamin levels), or when there are signs and

Table 3 Losses of water-soluble vitamins in dialysis

Vitamin	Molecular weight	Protein binding	Estimated loss in PD	Estimated loss in HD
Vitamin B1 (thiamin)	337	Albumin	Dialysate: 46 $\mu\text{g} \pm 3$ mcg per session [66]	Serum reduction: 6%—[57] 20% [60] 75–82% (supplemented), 130% (un-supplemented) [56], 43.9% [59] Dialysate: 1.12 \pm 0.88 mg per session [60]
Vitamin B2 (riboflavin)	376	Weak albumin	Dialysate: 832 \pm 145 mcg per session [2]	Serum reduction: 7% [57], 13% [60] Dialysate: 0.28 \pm 0.30 mg per session [60]
Vitamin B3 (niacin)	132	Weak binding in plasma		
Vitamin B5 (pantothenic acid)	219	Not available		
Vitamin B6 (pyridoxin)	169	Albumin Pyridoxal 5'-phosphate	Dialysate: 767 \pm 111mcg per session [66]	Serum reduction: 28% \pm 14% [62], 35% [57], 25.4% [60] Dialysate: 0.33 \pm 0.09 mg per session [60]
Vitamin B7 (biotin)	244	Weak		Serum reduction: 30–33% [63]
Vitamin B9 (folate)	441	No	Dialysate: 107 \pm 5 mcg [66]	Serum reduction: 26% \pm 16% [62], 37% [57], 19% [64], 32.6% [60] Dialysate: 0.3 \pm 0.18 mg [60], 37.3ug (3.6–91.5 μg) [64] per session
Vitamin B12 (cobalamin)	1355	Transcobalamin II	None reported	None reported
Vitamin C	176	No	Dialysate: 32 mg/d [77], 4.476 \pm 0.543–4.659 \pm 0.445 $\mu\text{mol/L}$ [74]; pediatric Dialysate 4.8 \pm 1.2 mg/L (un-supplemented), 10.5 \pm 1.8 mg/L (supplemented) [69], 50 mg/d (un-supplemented), 90 mg/d (supplemented) [79], 56 mg \pm 8 mg per session [66], 40 mg per session [78], 149 μmol per 6 h per session [61]	Dialysate: 0.415 \pm 0.113 $\mu\text{mol/L}$ [75]; pediatric Reduction in serum 52% [76], 50% [77], 51% [81], 33% [80], 60% [82], 66.6% [60] Dialysate: 66 mg [76], 93–334 mg [77], 147.5 \pm 145.5 mg [60] per session

symptoms of deficiency or excess. Dietetic assessment is best carried out by a specialized pediatric kidney dietitian or a suitably trained healthcare professional with the necessary skills and competencies. Vitamin intake based on food records or diet diaries should ideally be calculated using software with a reliable database of foods and nutrients, bearing in mind the differences in vitamin bioavailability and content due to seasonal variation.

5.2 Physical

- 5.2.1 We suggest individualized evaluation for physical signs and clinical symptoms of vitamin deficiency or excess.

Evidence and rationale

Table 4 outlines the clinical manifestations of deficiency and excess, roles of vitamins in the body, and bioavailability of vitamins. The impact of accumulation and losses are described where relevant for each vitamin below (statement 5.3). A clinical examination for signs and symptoms of vitamin deficiency or excess (Table 4) is suggested as part of routine care for children with a variety of chronic conditions [96]. In the absence of evidence, expert opinion suggests the same assessment should be undertaken for children with CKD. The frequency of assessment should be determined by clinical judgment and the outcome of relevant dietary and biochemical assessments. One

challenge is that some of these signs and symptoms overlap with clinical manifestations of CKD (e.g., impaired growth, poor appetite, emesis, diarrhea, and increased fractures). Hence, the clinician must actively consider if vitamin deficiency or excess is a possible explanation for the clinical findings.

5.3 Biochemical

5.3.1 Routine biochemical assessment of vitamin status is not indicated.

5.3.2 We suggest biochemical assessment when there are signs or symptoms of deficiency or excess, and in children with:

- unexplained hypercalcemia or elevated intracranial pressure—assess vitamin A.
- unexplained macrocytic anemia—assess vitamins folate and B12.

5.3.3 Consider biochemical assessment if there are risk factors for deficiencies or excess in children:

- receiving peritoneal dialysis—assess vitamins C, B2, B6, and folate.
- receiving hemodialysis—assess vitamins C, B1, B5, B6, biotin, and folate.
- taking medication that may interfere with vitamin metabolism and/or absorption - assess applicable vitamins

5.3.4 Biochemical assessment should ideally be undertaken when fasted, when not acutely ill, and pre-hemodialysis session.

- measure C-reactive protein (CRP) when assessing vitamin C and B6 levels.

Evidence and rationale

Routine biochemical assessment of vitamin status is not indicated unless there is evidence of malabsorption. Previous guidelines recommended routine biochemical assessment, but there is no evidence in the existing literature that routine monitoring is necessary. This statement differs from previously published guidelines based on current evidence. Vitamin biochemical assessment, as described in Table 4, is, however, appropriate in patients with signs and symptoms compatible with vitamin deficiency or excess. The frequency of monitoring vitamin biochemical status should be determined using clinical judgment. Individual vitamin considerations are discussed below.

Vitamin A

Hypercalcemia secondary to hypervitaminosis A has been reported in pediatric and adult dialysis patients [23, 44, 97–100]. Retinol is a form of vitamin A; elevated retinol levels increase osteoclastic breakdown of bone and decrease osteoblastic bone formation [26]. Vitamin A toxicity may also cause increased intracranial pressure [101]. Hence, biochemical assessment for vitamin A excess, along with evaluation of vitamin intake, should be considered in a patient with advanced CKD and unexplained hypercalcemia or raised intracranial pressure.

Vitamin E

There is no evidence that deficiency or excess from elevated vitamin E levels occurs in CKD. Thus, we do not recommend vitamin E levels be measured.

Vitamin K

Vitamin K-dependent proteins play an important role in coagulation and deficiency can lead to increased bleeding [9, 11, 12]. Hence, assessment for vitamin K deficiency by measuring prothrombin time (PT) (Table 4) is appropriate when there is unexplained bleeding or bruising, especially in a patient with risk factors for deficiency (statement 4.0).

Vitamin B complex

Routine measurement of B complex vitamins is not indicated in children with CKD; suboptimal as well as good biochemical status has been described in the literature [18, 24, 25, 86–89, 92, 102–112], as shown in Tables S5, S7, S11, S13, S17, S19, S21, and S23. The reference normal values for the B complex vitamins are often based on limited data in children and thus must be interpreted with caution.

Measurement of B12 and folate levels in patients with CKD is most recommended as part of the evaluation of unexplained macrocytic anemia. For patients with a borderline B12 level, an elevated methylmalonic acid (MMA) level supports a diagnosis of B12 deficiency; MMA is usually elevated in CKD patients, but high or disproportionately elevated levels of MMA for CKD stage may suggest B12 deficiency [113–115]. Treatment of folic acid deficiency may mask the macrocytic anemia and worsen the neurological manifestations of B12 deficiency, and thus B12 levels should be monitored in patients treated for folic acid deficiency [83].

Noteworthy is recognition that acute inflammation, assessed by the measurement of CRP, lowers the level of vitamin B6 [116]. Hence, CRP should be determined when

Table 4 Clinical manifestations of deficiency and excess, roles of vitamins in the body and their bioavailability (adapted from [136, 137])

Nutrient	Symptoms of deficiency	Symptoms of excess	Diagnostic tests (biomarkers)	Bioavailability (absorption)	Role in the body
Vitamin A	Night blindness, xerophthalmia, keratomalacia, poor bone growth, impaired resistance to infection, follicular hyperkeratosis	Hyperostosis, hepatomegaly, hepatic fibrosis, alopecia, increased cerebrospinal fluid pressure, hypercalcemia, liver damage, bone abnormalities, joint pain, alopecia, headaches, vomiting, skin desquamation	Plasma retinol	Preformed vitamin A (mainly retinol and retinyl esters) is absorbed (70–90%). The absorption of β -carotene is variable (5–65%), depending on food- and diet-related factors, genetic characteristics, and the health status of the subject	Vision; as retinal, which plays a central role in the mechanisms of photo-transduction Systemic maintenance of the growth and integrity of cells in body tissues through the action of retinoic acid, which acts as regulator of genomic expression
Thiamin (B1)	“Wernicke encephalopathy”- peripheral neuropathy, ophthalmoplegia, nystagmus, ataxia, edema, peripheral neuropathy, ataxia, various forms of dysautonomia and nystagmus, lactic acidosis. More advanced symptoms include confabulation, memory loss, psychosis; relation with sudden infant death syndrome and autism	Unknown. Urine is the main route of excretion; however, significant amounts of thiamin are excreted in feces	Thiamine pyrophosphate level, whole blood/red blood cell transketolase activation test	Thiamin absorption declines for an intake higher than 5 mg/day and absorbed thiamin is actively excreted in the urine	Precursor for coenzymes involved in carbohydrate, branched chain amino acid, and energy metabolism
Riboflavin (B2)	Sore throat, hyperaemia and edema of the pharyngeal and oral mucous membranes, cheilosis, glossitis (magenta tongue), and normochromic normocytic anemia characterized by erythroid hypoplasia and reticulocytopenia	Not sufficient clinical evidence for adverse effects of “high” riboflavin intakes; no toxic effects	24-h (preferably) or fasting urinary excretion; urinary excretion curve in relation to riboflavin intake	Absorption efficiency of 95%	Riboflavin is an integral part of the coenzymes; involved in energy metabolism, metabolic pathways, and the formation of some vitamins and coenzymes (involved in the metabolism of niacin and vitamin B6)
Niacin (B3)	Pellagra (photosensitive dermatitis, skin lesions, tongue and mouth soreness, vomiting, diarrhea, depression, and dementia). Early symptoms: weakness, loss of appetite, fatigue, digestive disturbances, abdominal pain, and irritability	Hepatotoxicity and skin flushing	Urinary excretion of niacin metabolites; less sensitive plasma niacin metabolites	The mean absorption of niacin is from about 23% to about 70%; it is lowest from cereals and highest from animal products	Precursor for nicotinamide adenine dinucleotide (NAD) and nicotinamide adenine dinucleotide phosphate (NADP)
Pantothenic acid (B5)	Mood changes, sleep, neurological, cardiac, and gastrointestinal disturbances	No known health risks with excess	Urinary pantothenic acid excretion (cut-off values are absent)	In research in six healthy young men, a mean absorption efficiency of 50% (range 40–61%) was found; further data is lacking; excreted in urine	Component of coenzyme A (CoA) and acyl-carrier proteins

Table 4 (continued)

Nutrient	Symptoms of deficiency	Symptoms of excess	Diagnostic tests (biomarkers)	Bioavailability (absorption)	Role in the body
Pyridoxine (B6)	Facial seborrhea, glossitis, angular stomatitis, cheilosis, mental status changes	Neuropathy, photosensitivity	Pyridoxal 5'-phosphate 4-pyridoxic acid	Absorption mainly is in the proximal small intestine through carrier-mediated, saturable transport process. Absorption efficiency of dietary riboflavin is 95%	As a part of other coenzymes involved in energy metabolism, metabolic pathways, and formation of some vitamins and coenzymes. In particular, involved in the metabolism of niacin and vitamin B6 and required by the homocysteine metabolism
Biotin (B8)	Fine scaly dermatitis, hair loss, conjunctivitis, ataxia, delayed child development	No risk for excess; there is no upper level	In adults: urinary biotin excretion; biomarkers of biotin function (urinary excretion of 3HIA) and 3HIA-carnitine; PCC activity and abundance of biotinylated MCC and PCC in lymphocytes	Free biotin is absorbed nearly completely through a saturable carrier-mediated process (passive diffusion). There is a lack of data on the level of absorption of protein-bound biotin from foods	A co-factor for the enzymes acetyl-CoA carboxylase, propionyl-CoA carboxylase, β -methylcrotonyl-CoA carboxylase and pyruvate carboxylase, which play critical roles in the synthesis of fatty acids, the catabolism of branched-chain. Fecal excretion of biotinamino acids and gluconeogenesis
Folate (B9)	Abdominal cramps, nausea, diarrhea, irritability, poor sleep, seizures, megaloblastic anemia. Neural tube defects	Masking of B12 deficiency symptoms in patients with pernicious anemia not receiving B12 Folic acid regarding sensitive cancers (incl. colorectal cancer)	Acute deficiency – low serum folic acid; chronic deficiency – low red blood cell folic acid	Natural food folate has a lower bioavailability than folic acid; the bioavailability of food folate is around 50%, i.e. half that of folic acid taken on an empty stomach; bioavailability of folic acid from fortified foods or from a supplement ingested with food is about 85%	Cofactors for enzymes involved in one-carbon metabolism. Part of the methionine cycle; producing regulators of important physiological processes
Cobalamin (B12)	Megaloblastic anemia neurological problems, cardiovascular symptoms, methylmalonic aciduria	No adverse effects with excess intake	Blood concentrations of cobalamin, holotranscobalamin, and the metabolites methylmalonic acid and total homocysteine	Absorption of cobalamin is variable, depending on the dietary source, the amount of cobalamin ingested, the ability to release cobalamin from food and the proper functioning of the intrinsic factor system; absorption of 40% (a conservative estimate). The highest losses occur through the feces (in the bile). If the circulating cobalamin exceeds the cobalamin binding capacity of the blood, the excess is excreted in the urine	Coenzyme for metabolic reactions

Table 4 (continued)

Nutrient	Symptoms of deficiency	Symptoms of excess	Diagnostic tests (biomarkers)	Bioavailability (absorption)	Role in the body
Vitamin C (ascorbic acid)	“Scurvy”- osmotic diarrhea, gingival bleeding, perifollicular hemorrhage, long bone changes (arthropathy) Decreased immunity, impaired wound healing, localized pain, and CVD	Massive doses predispose to kidney stones; nausea, abdominal pain; rebound scurvy when massive doses stopped	White blood cell ascorbate concentration, radiographic evidence of long bone widening	About 80% for an intake of about 100 mg/day	Enzyme cofactor for biochemical reactions catalyzed oxygenases. A role in the biosynthesis of collagen. Essential for the synthesis of carnitine and catecholamines. Involved in the metabolism of cholesterol to bile acids antioxidant Important antioxidant protecting lipid cell walls from oxidative damage and resulting dysfunction, particularly in erythrocytes and nerve cells. Role in platelet aggregation Enhances cell-mediated and humoral immunity
Vitamin E	Hemolytic anemia in premature infants; fat malabsorption causes deficiency; hyporeflexia and spinocerebellar and retinal degeneration	Bleeding, impaired leukocyte function	Plasma alpha-tocopherol	In presence of fat 75%	
Vitamin K	Bleeding tendency	No adverse effects on high prophylactic doses	Deficiency can be demonstrated by a vitamin K-responsive increase in prothrombin time or partial thromboplastin time	Absorption and transport in the body is complex; absorption is dependent on the kind of meal; fat has a positive effect on the absorption; it is not possible to estimate precisely an average absorption from the diet	Cofactor of γ -glutamyl carboxylase that catalyzes the carboxylation of glutamic acid residues into γ -carboxyglutamic acid residues in vitamin K-dependent proteins, which convert them into their active forms. These Gla-proteins are involved in different physiological processes, including blood coagulation or bone mineralization

measuring B6 and the level of B6 should be repeated if it is initially low in the setting of an elevated CRP level.

Vitamin C

Routine measurement of vitamin C is not indicated in children with CKD [25, 28, 74, 75, 84, 89]. Plasma vitamin C can be measured if there is clinical suspicion of deficiency or excess (Table 4). Since oxalate is a byproduct of vitamin C metabolism (statement 6.2), plasma or urine oxalate can also be measured if vitamin C excess is suspected [29, 117]. Plasma vitamin C should be measured in a fasting state, and before dialysis in HD patients. Moreover, acute inflammation lowers the level of vitamin C [116]. Thus, CRP should be measured when measuring vitamin C. If the CRP is elevated, the vitamin C concentration should be repeated once the CRP level has normalized.

6. When is dietary modification or supplementation indicated?

6.1 Intervention is indicated:

- if dietary assessment suggests a risk of deficiency or excess.
- if clinical and/or biochemical evidence suggests a risk of deficiency or excess.

6.2 Fat-soluble vitamins

- 6.2.1 Dietary sources rich in vitamin A should be limited in children with CKD.
- 6.2.2 If nutritional supplements and formulas are indicated, consider one with a lower vitamin A content.
- 6.2.3 If a multivitamin supplement is indicated, consider one with a low or zero vitamin A content.
- 6.2.4 Avoid routine vitamin E and K supplementation unless a comorbidity predisposing to deficiency is present.

6.3 Water-soluble vitamins

- 6.3.1 In the case of low water-soluble vitamin intake, consider dietary modification and/or vitamin supplementation.
- 6.3.2 Water-soluble vitamin supplementation (particularly vitamins C, B6, and folate) may be needed in children on dialysis because of dialysate losses.
- 6.3.3 Water-soluble vitamin supplementation may be needed in children while taking

medications that interfere with vitamin metabolism.

6.3.4 We suggest folate and vitamin B12 supplementation may be required in children with macrocytic anemia and biochemical evidence of deficiency.

6.3.5 Consider the benefits versus risks of vitamin C supplementation due to its metabolism to oxalate.

Evidence and rationale

There are limited studies describing the dietary intake and serum concentrations of vitamins in children with CKD, and results vary with CKD stage. Reported intakes range from lower to higher than the estimated requirements for healthy children, with higher intakes in children receiving vitamin supplements [18, 18, 23, 25, 28, 31, 31, 87–89, 89–93]. Similarly, serum concentrations range from below normal to above normal [16, 18, 18, 20–26, 74, 75, 84, 87, 89, 92, 102, 104, 105, 107, 109, 111, 118, 119]. Risk of excess intake for those vitamins that accumulate with declining kidney function is greatest when patients receive vitamin supplements (Tables S4, S6, S10, S12, S14, S15, S16, S18, S20, S22). These practice points are consistent with previous guidelines but include additional guidance on when and how to adjust dietary intake and prescribe vitamin supplements.

Fat-soluble vitamins

Supplementation of fat-soluble vitamins is not recommended.

Vitamin A

There is a high risk of vitamin A toxicity, due to decreased excretion. A diet with high amounts of vitamin A-rich foods can far exceed the recommended intake for healthy children. Hence, the nutritional evaluation in children with CKD should include assessment for high intake of vitamin A from dietary sources (e.g., consumption of liver). Formulas, nutritional supplements, and vitamin supplements may also lead to excessive intake of vitamin A [18, 22, 23, 89]. Consequently, it has been proposed that children with CKD be prescribed no or the lowest vitamin A content possible when using nutritional or vitamin supplements, with the goal to limit intake to the recommended intake for healthy children, or lower [3].

Vitamin E

There are no studies of vitamin E supplementation in children with CKD. Supplementation studies in adult patients are limited with inconclusive results. Supplementation is

not recommended, and excess intake should be avoided [83]. A meta-analysis of supplementation trials suggested a dose-dependent relationship of increased all-cause mortality (0.4%) with high-dose vitamin E supplementation [120].

Vitamin K

There is no evidence to support the routine supplementation of vitamin K in patients with CKD [121]. It is important to avoid vitamin K supplementation in patients receiving warfarin for anticoagulation [83]. Children receiving frequent antibiotic therapy should be carefully monitored for risk of deficiency.

Water-soluble vitamins

Water-soluble vitamins are commonly lost in dialysate. Sufficient dietary intake may not occur due to overall poor intake, selective eating, and dietary modifications due to CKD. Eating a varied diet rich in water-soluble vitamins, with due regard for necessary dietary modifications, is encouraged. Given the cost and limits of biochemical assessment, use of a balanced water-soluble multivitamin supplement is a practical option in children with poor dietary intake for sustained periods of time, increased losses due to dialysis, or chronic furosemide therapy (Table 2). Since commercial vitamin supplements may provide a far higher intake than requirements, it is recommended that children with CKD are monitored for clinical evidence of vitamin excess. Children receiving enteral or oral formulas will likely not need a multivitamin supplement.

Vitamin B complex

There are no trials looking at the effects of vitamin B complex intake on serum levels in children with CKD. Study results in adults vary, with patients receiving dialysis having low or adequate blood concentrations with and without supplementation (Table S28) [56, 61, 66, 68, 69, 73, 79, 122–125]. Hyperhomocysteinemia, which may be secondary to folate or B12 deficiency, is common in children with CKD, including post-transplant [107, 108]. Although there are reports of improved hematologic parameters [126], homocysteine levels [127], and oxidative stress indices [128] with folate supplementation in children with CKD, there is no evidence for empirical supplementation with pharmacological doses of folate in the absence of biochemical-proven deficiency.

When folate supplementation is initiated, consider vitamin B12 supplementation if biochemical measurements of B12 are not available [83].

Vitamin C

There are no body stores of vitamin C and thus blood concentrations decrease quickly after stopping supplementation [66]. Supplementation may increase levels, although the evidence of clinical benefit is limited [83]. Supplementation of children may not be sufficient to normalize blood vitamin C concentration in those who receive dialysis [25, 28, 75]. In adults, there are multiple studies demonstrating improvement in vitamin C blood concentrations with supplementation [68, 69, 77, 79–82].

In one pediatric study, intravenous supplementation with 250 mg vitamin C post-HD decreased total and LDL cholesterol [27]. In adult kidney transplant recipients, lower vitamin C concentrations were associated with a higher risk of graft failure [129].

Functional iron deficiency is an important cause of anemia in CKD patients, and vitamin C may increase iron bioavailability [130]. Studies have demonstrated a benefit of oral vitamin C supplementation on anemia indices in children with CKD 4–5D [28] and adults on PD [78]; anemia indices have also improved with intravenous vitamin C supplementation in adult HD patients [131, 132]. Excess supplementation and intake of vitamin C may, however, lead to elevated blood oxalate concentrations. Due to decreased oxalate excretion in the urine, plasma oxalate levels increase in children and adults receiving dialysis, but the effect on tissue levels of oxalate is uncertain. There are case reports of systemic oxalosis in children and adults [29, 30]. Most studies did not see an elevation in serum oxalate levels with a maximum vitamin C supplementation of 250 mg per day [28, 131, 133, 134], while some did with supplementation of 500 mg per day [82]. Thus, supplementation should be provided with caution and total intake of vitamin C from diet and formulas should not exceed 250 mg per day [28, 30].

Results of the Delphi survey

Thirty-one responses were received via an electronic Delphi survey, comprising 18 dietitians and 13 pediatric nephrologists across 16 countries. Delphi respondents are listed under Acknowledgements as “Participants in Delphi survey.”

Of the six clinical practice recommendation statements, overall, a 91.1% consensus was achieved with a “strongly agree” or “agree” response, 6.6% had a “neutral” response, 1.7% “disagree,” and 0.5% “strongly disagree” response. All but one statement met the stipulated 70% or higher level of consensus. The one statement received a response rate of 65% agreement (statement 5.3.1). The respondents queried the need for vitamin D biochemical assessment and suggested routine biochemical assessment in chronic disease. Vitamin D has been extensively reviewed in previous

Table 5 Summary of clinical practice point statements

	Statements
1.0 What are the vitamin requirements?	<p>1.1 The vitamin requirements for children with early CKD (stages 2–3a) should approximate those of healthy children of the same chronological age</p> <p>1.1.1 For children with advanced CKD (stage 3b–5D&T), vitamin requirements may be less or greater than those for healthy children</p> <p>1.1.2 We suggest that the intake of vitamin A in CKD, where accumulation may occur, should not exceed the requirements of healthy children</p>
2.0 What are the main dietary sources?	2.1 Children with CKD may obtain sufficient vitamin intake through intake of a varied diet and/or a nutritionally complete enteral formula
3.0 How do dietary modifications affect intake?	3.0 Dietary modifications and food preparation methods may impact vitamin intake
4.0 What are the non-dietary factors which influence vitamin intake and status?	4.1 Non-dietary factors, such as CKD stage, dialysis, comorbidities, and medications should be considered when assessing and monitoring vitamin status and when planning nutritional interventions
5.0 How should we approach clinical assessment and monitoring?	<p>5.1—Dietary</p> <p>5.1.1 We suggest that the vitamin intake of children with CKD should be assessed by diet history/diet records, including food and drink, formulas and nutritional supplements, and a review of medications</p> <p>5.2.1 We suggest that the frequency of assessment of vitamin intake should be influenced by dietary modifications, child's age, CKD stage, dialysis modality, and intake of medications that interfere with vitamin metabolism</p> <p>5.1.3 Assessment may need to be more frequent if there are signs or symptoms of deficiency or excess</p> <p>5.2—Physical</p> <p>5.2.1 We suggest individualized evaluation for physical signs and clinical symptoms of vitamin deficiency or excess</p> <p>5.3—Biochemical</p> <p>5.3.1 Routine biochemical assessment of vitamin status is not indicated</p> <p>5.3.2 We suggest biochemical assessment when there are signs or symptoms of deficiency or excess, and in children with:</p> <ul style="list-style-type: none"> - unexplained hypercalcemia or elevated intracranial pressure—assess vitamin A - unexplained macrocytic anemia—assess folic acid and vitamin and B12 <p>5.3.3 Consider biochemical assessment if there are risk factors for deficiencies or excess in children:</p> <ul style="list-style-type: none"> - receiving peritoneal dialysis—assess vitamins C, B2, B6, and folic acid - receiving hemodialysis—assess vitamins C, B1, B5, B6, biotin, and folic acid - taking medication that may interfere with vitamin metabolism and/or absorption—assess applicable vitamins <p>5.3.4 Biochemical assessment should ideally be undertaken when fasted, when not acutely ill, and pre-hemodialysis session</p> <ul style="list-style-type: none"> - measure C-reactive protein (CRP) when assessing vitamin C and B6 levels
6.0 When is dietary modification or supplementation indicated?	<p>6.1 Intervention is indicated:</p> <ul style="list-style-type: none"> - if dietary assessment suggests a risk of deficiency or excess - if clinical and/or biochemical evidence suggests a risk of deficiency or excess <p>6.2 Fat-soluble vitamins</p> <p>6.2.1 Dietary sources rich in vitamin A should be limited in children with CKD</p> <p>6.2.2 If nutritional supplements and formulas are indicated, consider one with a lower vitamin A content</p> <p>6.2.3 If a multivitamin supplement is indicated, consider one with a low or zero vitamin A content</p> <p>6.2.4 Avoid routine vitamin E and K supplementation unless a comorbidity predisposing to deficiency is present</p> <p>6.3 Water-soluble vitamins</p> <p>6.3.1 In the case of low water-soluble vitamin intake consider dietary modification and/or vitamin supplementation</p> <p>6.3.2 Water-soluble vitamin supplementation (particularly vitamins C, B6, and folic acid) may be needed in children on dialysis as a result of dialysate losses</p> <p>6.3.3 Water-soluble vitamin supplementation may be needed in children while taking medications that interfere with vitamin metabolism</p> <p>6.3.4 We suggest folic acid and vitamin B12 supplementation may be required in children with macrocytic anemia and biochemical evidence of deficiency</p> <p>6.3.5 Consider the benefits versus risks of vitamin C supplementation due to its metabolism to oxalate</p>

publications and was not in scope for this review. The most recent vitamin D review reference is noted in the paper. Evidence covered in the rationale does not currently support routine biochemical vitamin assessment and a research recommendation has been made to explore criteria for biochemical assessment. The taskforce team carefully reviewed all of the statements in light of these responses; none required significant change.

Summary of statements

A summary of statements is provided in Table 5.

Research recommendations

There is a need for well-designed longitudinal observational studies of the dietary intake of vitamins and the serum status of vitamins over time, accompanied by randomized controlled studies designed to help determine the vitamin requirements for children with CKD. The most pressing topics to explore are:

Intake/requirements

- Determination of the requirements for optimal health, specifically:
 - vitamin K—the potential for improved vascular and bone health.
 - vitamin A—benefits and risks of limiting intake below reference requirements.
 - vitamin C—safe upper level regarding oxalate accumulation, kidney stone formation, and nausea
 - vitamin C and B complex—losses on dialysis, effects of diuretics, and urine losses.
 - impact of transplantation on vitamin status.
 - development of dietary intake assessment methods that reflect true intake and/or dietary risk.
 - exploration of the relationship between outcome measures such as improved cognition, growth, and quality of life, with improved vitamin status.

Biochemical status

- Assessment methods for vitamin biochemical status.
- Determination of the safe serum concentrations of:
 - vitamin A
 - vitamin C with respect to oxalate
- Assessment of status in children not receiving vitamin supplements.

Supplementation

- Development of optimal age-based multivitamin supplement.
- Determination of the amount of supplementation needed to achieve normal serum concentrations, body stores, and functions.
- Exploration of the benefit and long-term safety of:
 - vitamin E supplementation and other antioxidant vitamins in improving clinical outcomes such as cardiovascular risk, disease progression, and mortality.
 - vitamin K supplementation with long-term use of antibiotics and for bone health.
 - vitamin C supplementation on oxalosis, cardiovascular risk and/or erythrocyte lifespan, lipid levels, and anemia management.
 - vitamin B3 supplementation on lipid levels and phosphate management.
 - folate supplementation on anemia management.

Conclusions

Vitamins have essential roles in body processes. CKD can alter vitamin intake and biochemical status and thus requirements may differ in children with CKD compared with their healthy peers. We present clinical practice points designed to address clinical issues pertaining to vitamin status in children with CKD as a key aspect of their nutritional management. Ensuring sufficient vitamin intake and status is essential not only to prevent deficiencies and excess, but also to help ensure long-term health. Consuming rich dietary sources of most vitamins should be promoted. Dietary modifications necessary for urea, phosphate, potassium, and lipid management may reduce vitamin intake, but should not compromise vitamin status.

Supplementary Information The online version contains supplementary material available at <https://doi.org/10.1007/s00467-024-06303-x>.

Acknowledgements Vitaflo International Ltd. is a nutrition company which produces specialized clinical nutrition products for metabolic disorders, nutrition support, and specific conditions such as kidney disease. Vitaflo International Ltd. has funded the meetings held by the Pediatric Renal Nutrition Taskforce. RS is funded by a National Institute for Health Research (NIHR), CDF-2016-09-038, Career Development Fellowship. This publication presents independent research funded by the NIHR.

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Declarations

Conflict of interest The authors declare no competing interests.

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References

- Bender D (2003) Nutritional biochemistry of the vitamins, 2nd edn. Cambridge University Press, Cambridge
- World Health Organization (2004) Vitamin and mineral requirements in Human Nutrition, 2nd edn. World Health Organization, Geneva
- Coleman J, Edefonti A, Watson AR (2001) Guidelines by an ad hoc European committee on the assessment of growth and nutritional status in children on chronic peritoneal dialysis. *Perit Dial Int* 21:1–9. <https://doi.org/10.1177/089686080102100321>
- KDOQI Work Group (2009) KDQOI clinical practice guideline for nutrition in children with CKD: 2008 update. Executive summary *Am J Kidney Dis* 53:S11–S104. <https://doi.org/10.1053/j.ajkd.2008.11.017>
- Shroff R, Wan M, Nagler E, Bakkaloglu S, Cozoliina M, Bacchetta J, Edefonti A, Stefanidis C, Vande Walle J, Ariceta G, Klaus G, Haffner D, Schmitt C (2017) Clinical practice recommendations for treatment with active vitamin D analogues in children with chronic kidney disease Stages 2–5 and on dialysis. *Nephrol Dial Transplant* 32:1114–1127. <https://doi.org/10.1093/ndt/gfx080>
- McAlister L, Pugh P, Greenbaum L, Haffner D, Rees L, Anderson C, Desloovere A, Nelms C, Oosterveld M, Paglialonga F, Polderman N, Qizalbash L, Renken-Terhaerd J, Tuokkola J, Warady B, Walle JV, Shaw V, Shroff R (2020) The dietary management of calcium and phosphate in children with CKD stages 2–5 and on dialysis-clinical practice recommendation from the Pediatric Renal Nutrition Taskforce. *Pediatr Nephrol* 35:501–518. <https://link.springer.com/article/10.1007/s00467-019-04370-z>
- Department of Health (1991) Dietary reference values for food energy and nutrients for the United Kingdom. Report of the Panel on Dietary Reference Values of the Committee on Medical Aspects of Food Policy. Report on Health and Social Subjects. https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/743786/Dietary_Reference_Values_for_Food_Energy_and_Nutrients_for_the_United_Kingdom_1991_.pdf. Accessed 30 May 2023
- Food and Nutrition Division. FAO Rome (2001) Human vitamin and mineral requirements. Report of a joint FAO/WHO expert consultation. Bangkok, Thailand. https://www.fao.org/3/y2809e/y2809e.pdf?from=article_link
- Institute of Medicine (US) Panel on Micronutrients (2001) Dietary reference intakes for vitamin A, vitamin K, arsenic, boron, chromium, copper, iodine, iron, manganese, molybdenum, nickel, silicon, vanadium, and zinc. 5, Vitamin K. National Academies Press, Washington, DC. https://www.ncbi.nlm.nih.gov/books/NBK22299/#_ncbi_dlg_citbx_NBK222299. Accessed 30 May 2023
- National Health and Medical Research Council (2006) Nutrient reference values for Australia and New Zealand including recommended dietary intakes. <https://www.nhmrc.gov.au/about-us/publications/nutrient-reference-values-australia-and-new-zealand-including-recommended-dietary-intakes>. Accessed 30 May 2023
- Nordic Council of Ministers and the Nordic Council (2012) Nordic Nutrition Recommendations 2012. Integrating nutrition and physical activity. <https://www.norden.org/en/publication/nordic-nutrition-recommendations-2012>. Accessed 30 May 2023
- European Food Safety Authority (2013) Scientific Opinion on nutrient requirements and dietary intakes of infants and young children in the European Union. <https://efsa.onlinelibrary.wiley.com/doi/epdf/10.2903/j.efsa.2013.3408>. Accessed 30 May 2023
- Institute of Medicine (US) Subcommittee on interpretation and uses of dietary reference intakes; Institute of Medicine (US) Standing Committee on the Scientific Evaluation of Dietary Reference Intakes (2000) Dietary Reference Intakes: Applications in Dietary Assessment. 6, Using the Tolerable Upper Intake Level for Nutrient Assessment of Groups. <https://www.ncbi.nlm.nih.gov/books/NBK222879/>. Accessed 30 May 2023
- Expert Group on Vitamins and Minerals. Food Standards Agency (2003) Safe upper levels of vitamins and minerals. <https://cot.food.gov.uk/sites/default/files/vitmin2003.pdf>. Accessed 30 May 2003
- Scientific Committee on Food. European Food Safety Authority (2006) Tolerable Upper Intakes Levels for Vitamins and Minerals. https://www.efsa.europa.eu/sites/default/files/efsa_rep/blobserver_assets/ndatolerableuil.pdf. Accessed 30 May 2023
- Casey CE, Moser MC, Hambidge KM, Lum GM (1981) Zinc, copper, and vitamin A in pediatric dialysis. *J Pediatr* 98:434–435. [https://doi.org/10.1016/s0022-3476\(81\)80715-9](https://doi.org/10.1016/s0022-3476(81)80715-9)
- Gentile M, Fellin G, Manna G, D'Amico G, Testolin G, Porrini M, Simonetti P (1988) Vitamin A and retinol binding protein in chronic renal insufficiency. *Int J Artif Organs* 11:403–404
- Kriley M, Warady BA (1991) Vitamin status of pediatric patients receiving long-term peritoneal dialysis. *Am J Clin Nutr* 53:1476–1479. <https://doi.org/10.1093/ajcn/53.6.1476>
- Vannucchi M, Vannucchi H, Humphreys M (1992) Serum levels of vitamin A and retinol binding protein in chronic renal patients treated by continuous ambulatory peritoneal dialysis. *Int J Vitam Nutr Res* 62:107–112
- Lipkin AC, Lenssen P (2008) Hypervitaminosis A in pediatric hematopoietic stem cell patients requiring renal replacement therapy. *Nutr Clin Pract* 23:621–629. <https://doi.org/10.1177/0884533608327082>
- Lughetti L, Perugini C, Predieri B, Madeo S, Bellomo G, Bernasconi S, Balli F (2008) Low-density lipoprotein oxidizability in children with chronic renal failure. *Pediatr Int* 50:447–453. <https://doi.org/10.1111/j.1442-200X.2008.02614.x>
- Fassinger N, Imam A, Klurfeld DM (2010) Serum retinol, retinol-binding protein, and transthyretin in children receiving dialysis. *J Ren Nutr* 20:17–22. <https://doi.org/10.1053/j.jrn.2009.05.005>
- Manickavasagar B, McArdle AJ, Yadav P, Shaw V, Dixon M, Blomhoff R, Connor GO, Rees L, Ledermann S, Van't Hoff W, Shroff R, (2015) Hypervitaminosis A is prevalent in children

- with CKD and contributes to hypercalcemia. *Pediatr Nephrol* 30:317–325. <https://doi.org/10.1007/s00467-014-2916-2>
24. Joyce T, Court Brown F, Wallace D, Reid CJD, Sinha MD (2018) Trace element and vitamin concentrations in paediatric dialysis patients. *Pediatr Nephrol* 33:159–165. <https://doi.org/10.1007/s00467-017-3773-6>
 25. Tuokkola J, Kiviharju E, Jahnukainen T, Hölttä T (2021) Differences in dietary intake and vitamin and mineral status of infants and children on dialysis receiving feeds or eating normal food. *J Ren Nutr* 31:144–154. <https://doi.org/10.1053/j.jrn.2020.07.003>
 26. Harris M, Varnell C, Taylor V, Nehus ST, Zhang B, Erkan E (2022) Hypervitaminosis A in pediatric patients with advanced chronic kidney disease. *J Ren Nutr* 32:275–281. <https://doi.org/10.1053/j.jrn.2021.03.010>
 27. El Mashad GM, El Sayed HM, Nosair NA (2016) Effect of vitamin C supplementation on lipid profile, serum uric acid, and ascorbic acid in children on hemodialysis. *Saudi J Kidney Dis Transpl* 27:1148–1154. <https://doi.org/10.4103/1319-2442.194602>
 28. Hongsawong N, Chawprang N, Kittisakmontri K, Vittayananan P, Srisuwan K, Chartapisak W (2021) Vitamin C deficiency and impact of vitamin C administration among pediatric patients with advanced chronic kidney disease. *Pediatr Nephrol* 36:397–408. <https://doi.org/10.1007/s00467-020-04662-9>
 29. D'Costa MR, Winkler NS, Milliner DS, Norby SM, Hickson LJ, Lieske JC (2019) Oxalosis associated with high-dose vitamin C ingestion in a peritoneal dialysis patient. *Am J Kidney Dis* 74:417–420. <https://doi.org/10.1053/j.ajkd.2019.01.022>
 30. Kennedy SS, Perilloux A, Pereira RC, Handelman G, Wesseling-Perry K, Salusky IB (2021) Vitamin C overload may contribute to systemic oxalosis in children receiving dialysis. *Pediatr Nephrol* 36:435–441. <https://doi.org/10.1007/s00467-020-04702-4>
 31. My Thuc LT, Dung NQ, Ha VN, Tam ND, Hang Nga NT (2019) Actual diet and nutritional deficiencies status in children on peritoneal dialysis at the Vietnam National Hospital of Pediatrics. *Saudi J Kidney Dis Transpl* 30:924–931. <https://doi.org/10.4103/1319-2442.265470>
 32. Sgambat K, Cheng YI, Charnaya O, Moudgil A (2019) The prevalence and outcome of children with failure to thrive after pediatric kidney transplantation. *Pediatr Transplant* 23:e13321. <https://doi.org/10.1111/ptr.13321>
 33. Karava V, Dotis J, Kondou A, Printza N (2023) Malnutrition patterns in children with chronic kidney disease. *Life (Basel)* 13:713. <https://doi.org/10.3390/life13030713>
 34. Maharaj PPP, Prasad S, Devi R, Gopalan R (2015) Folate content and retention in commonly consumed vegetables in the South Pacific. *Food Chem* 182:327–332. <https://doi.org/10.1016/j.foodchem.2015.02.096>
 35. Lee S, Choi Y, Jeong HS, Lee J, Sung J (2018) Effect of different cooking methods on the content of vitamins and true retention in selected vegetables. *Food Sci Biotechnol* 27:333–342. <https://doi.org/10.1007/s10068-017-0281-1>
 36. Frias J, Vidal-Valverde C (2001) Stability of thiamine and vitamins E and A during storage of enteral feeding formula. *J Agric Food Chem* 49:2313–2317. <https://doi.org/10.1021/jf001243d>
 37. Frias J, Peñas E, Vidal-Valverde C (2009) Changes in vitamin content of powder enteral formulas as a consequence of storage. *Food Chem* 115:1411–1416. <https://doi.org/10.1016/j.foodchem.2009.01.070>
 38. Baéz R, Rojas G, Sandoval-Guillén J, Valdivia-López AM (2012) Effect of storage temperature on the chemical stability of enteral formula. *Adv J Food Sci Tech* 4:235–242
 39. Yang H, Xu L, Hou L, Xu TC, Ye SH (2022) Stability of vitamin A, E, C and thiamine during storage of different powdered enteral formulas. *Heliyon* 8:e11460. <https://doi.org/10.1016/j.heliyon.2022.e11460>
 40. Sathe MN, Patel AS (2010) Update in pediatrics: focus on fat-soluble vitamins. *Nutr Clin Pract* 25:340–346. <https://doi.org/10.1177/0884533610374198>
 41. Kiani AK, Dhuli K, Donato K, Aquilanti B, Velluti V, Matera G, Iaconelli A, Connelly ST, Bellinato F, Gisoni P, Bertelli M (2022) Main nutritional deficiencies. *J Prev Med Hyg* 63:E93–E101. <https://doi.org/10.15167/2421-4248/jpmh2022.63.2S3.2752>
 42. Mydlík M, Derzsiová K, Zemberová E (1999) Influence of water and sodium diuresis and furosemide on urinary excretion of vitamin B(6), oxalic acid and vitamin C in chronic renal failure. *Miner Electrolyte Metab* 25:352–356. <https://doi.org/10.1159/000057474>
 43. Langan RC, Goodbred AJ (2017) Vitamin B12 deficiency: recognition and management. *Am Fam Physician* 96:384–389
 44. Werb R, Clark WF, Lindsay RM, Jones EO, Linton AL (1979) Serum vitamin A levels and associated abnormalities in patients on regular dialysis treatment. *Clin Nephrol* 12:63–68
 45. Yatzidis H, Digenis P, Koutsicos D (1976) Hypervitaminosis A in chronic renal failure after transplantation. *Br Med J* 2:1075. <https://doi.org/10.1136/bmj.2.6043.1075-a>
 46. Jeon HJ, Shin DH, Oh J, Kee YK, Park JY, Ko K, Lee S (2022) Urinary retinol-binding protein 4 is associated with renal function and rapid renal function decline in kidney transplant recipients. *Transplant Proc* 54:362–366. <https://doi.org/10.1016/j.transproceed.2021.10.028>
 47. De Bevere V, Nelis H, Leenheer A, De Paepe M, Ringoir S (1982) Vitamin E in hemodialysis patients. *JAMA* 247:2371. <https://doi.org/10.1001/jama.247.17.2371b>
 48. Koca T, Berber A, Koca H, Demir T, Kohen T (2010) Effects of hemodialysis period on levels of blood trace elements and oxidative stress. *Clin Exp Nephrol* 14:463–468. <https://doi.org/10.1007/s10157-010-0310-3>
 49. Yang S, Xiao L, Xu B, Xu X, Lui F, Sun L (2014) Effects of Vitamin E-coated dialyser on oxidative stress and inflammation status in hemodialysis patients: a systematic review and meta-analysis. *Ren Fail* 36:722–731. <https://doi.org/10.3109/0886022x.2014.890858>
 50. Hulqvist M, Hegbrant J, Nilsson-Thorell C, Lindholm T, Nilsson P, Linden T, Hultqvist-Bengtsson U (1997) Plasma concentrations of vitamin C, vitamin E and/or malondialdehyde as markers of oxygen free radical production during hemodialysis. *Clin Nephrol* 47:37–46
 51. Haden, (1957) Vitamin K deficiency associated with prolonged antibiotic administration. *AMA Arch Intern Med* 100:986–988. <https://doi.org/10.1001/archinte.1957.00260120130015>
 52. Shevchuk Y, Conly J (1990) Antibiotic-associated hypoprothrombinemia: a review of prospective studies, 1966–1988. *Rev Infect Dis* 12:1009–1026
 53. Bhat R, Deshmukh C (2003) A study of vitamin K status in children on prolonged antibiotic therapy. *Indian Pediatr* 40:36–40
 54. Elalfy M, Ebeid F, Elagouza I, Ibrahim F, Hassan N, Botros B (2018) Negative impact of prolonged antibiotics or persistent diarrhea on vitamin K1 levels in 2–24 weeks aged Egyptian infants. *Mediterr J Hematol Infect Dis* 10:e2018010
 55. Marumo F, Kamata K, Okubo M (1986) Deranged concentrations of water-soluble vitamins in the blood of undialyzed and dialyzed patients with chronic renal failure. *Int J Artif Organs* 9:17–24
 56. Frank T, Czeche K, Bitsch R, Stein G (2000) Assessment of thiamin status in chronic renal failure patients, transplant recipients and hemodialysis patients receiving a multivitamin supplementation. *Int J Vitam Nutr Res* 70:159–166. <https://doi.org/10.1024/0300-9831.70.4.159>
 57. Heinz J, Domröse U, Westphal S, Luley C, Neumann KH, Dierkes J (2008) Washout of water-soluble vitamins and of homocysteine during haemodialysis: effect of high-flux and






- low-flux dialyser membranes. *Nephrology* (Carlton) 13:384–389. <https://doi.org/10.1111/j.1440-1797.2008.00946.x>
58. Ubukata M, Amemiya N, Nitta K, Takei T (2015) Serum thiamine values in end-stage renal disease patients under maintenance hemodialysis. *Int J Vitam Nutr Res* 85:348–355. <https://doi.org/10.1024/0300-9831/a000242>
 59. Jankowska M, Rudnicki-Velasquez P, Storoniak H, Rutkowski P, Rutkowski B, Krzysiński K, Dębska-Ślizień A (2017) Thiamine diphosphate status and dialysis-related losses in end-stage kidney disease patients treated with hemodialysis. *Blood Purif* 44:294–300. <https://doi.org/10.1159/000480651>
 60. Bévier A, Novel-Catin E, Blond E, Pelletier S, Parant F, Koppe L, Fouque D (2022) Water-soluble vitamins and trace elements losses during on-line hemodiafiltration. *Nutrients* 14:3454. <https://doi.org/10.3390/nu14173454>
 61. Mydlík M, Derzsiová K, Válek A, Szabó T, Dandár V, Takác M (1985) Vitamins and continuous ambulatory peritoneal dialysis (CAPD). *Int Urol Nephrol* 17:281–286. <https://doi.org/10.1007/BF02085415>
 62. Leblanc M, Pichette V, Geadah D, Ouimet D (2000) Folic acid and pyridoxal-5'-phosphate losses during high-efficiency hemodialysis in patients without hydrosoluble vitamin supplementation. *J Ren Nutr* 10:196–201. <https://doi.org/10.1053/jren.2000.16327>
 63. Jung U, Helbich-Endermann M, Bitsch R, Schneider S, Stein G (1998) Are patients with chronic renal failure (CRF) deficient in Biotin and is regular Biotin supplementation required? *Z Ernährungswiss* 37:363–367. <https://doi.org/10.1007/s003940050038>
 64. Cunningham J, Sharman VL, Goodwin FJ, Marsh FP (1981) Do patients receiving haemodialysis need folic acid supplements? *Br Med J (Clin Res Ed)* 282:1582. <https://doi.org/10.1136/bmj.282.6276.1582>
 65. Lee EY, Kim JS, Lee HJ, Yoon DS, Han BG, Shim YH, Choi SO (1999) Do dialysis patients need extra folate supplementation? *Adv Perit Dial* 15:247–250
 66. Boeschoten EW, Schrijver J, Krediet RT, Schreurs WH, Arisz L (1988) Deficiencies of vitamins in CAPD patients: the effect of supplementation. *Nephrol Dial Transplant* 3:187–193
 67. Mydlík M, Derzsiová K, Zemberová E (1997) Metabolism of vitamin B6 and its requirement in chronic renal failure. *Kidney Int Suppl* 62:S56–S59
 68. Henderson LS, Leung ACT, Shenkin A (1984) Vitamin status in continuous ambulatory peritoneal dialysis. *Perit Dial Int* 4:143–145. <https://doi.org/10.1177/089686088400400307>
 69. Blumberg A, Hanck A, Sander G (1983) Vitamin nutrition in patients on continuous ambulatory peritoneal dialysis (CAPD). *Clin Nephrol* 20:244–250
 70. House AA, Wells GA, Donnelly JG, Nadler SP, Hébert PC (2000) Randomized trial of high-flux vs low-flux haemodialysis: effects on homocysteine and lipids. *Nephrol Dial Transplant* 15:1029–1034. <https://doi.org/10.1093/ndt/15.7.1029>
 71. Lasseur C, Parrot F, Delmas Y, Level C, Ged C, Redonnet-Vernhet I, Montaudon D, Combe C, Chauveau P (2001) Impact of high-flux/high-efficiency dialysis on folate and homocysteine metabolism. *J Nephrol* 14:32–35
 72. Mudge DW, Rogers R, Hollett P, Law B, Reiger K, Petrie JJB, Price L, Johnson DW, Campbell SB, Isbel NM, Sullivan M, Hawley CM (2005) Randomized trial of FX high flux vs standard high flux dialysis for homocysteine clearance. *Nephrol Dial Transplant* 20:2178–2185. <https://doi.org/10.1093/ndt/gfh987>
 73. Coveney N, Polkinghorne KR, Linehan L, Corradini A, Kerr PG (2011) Water-soluble vitamin levels in extended hours hemodialysis. *Hemodial Int* 15:30–38. <https://doi.org/10.1111/j.1542-4758.2010.00505.x>
 74. Zwolińska D, Grzeszczak W, Szczepanska M, Makulska I, Kiliś-Pstrusińska K, Szprynger K (2009) Oxidative stress in children on peritoneal dialysis. *Perit Dial Int* 29:171–177
 75. Zwolińska D, Grzeszczak W, Szczepańska M, Kiliś-Pstrusińska K, Szprynger K (2006) Vitamins A, E and C as non-enzymatic antioxidants and their relation to lipid peroxidation in children with chronic renal failure. *Nephron Clin Pract* 103:c12–c18. <https://doi.org/10.1159/000090506>
 76. Morena M, Cristol J-P, Bosc J-Y, Tetta C, Forret G, Leger C-L, Delcourt C, Papoz L, Descomps B, Canaud B (2002) Convective and diffusive losses of vitamin C during haemodiafiltration session: a contributive factor to oxidative stress in haemodialysis patients. *Nephrol Dial Transplant* 17:422–427. <https://doi.org/10.1093/ndt/17.3.422>
 77. Böhm V, Tiroke K, Schneider S, Sperschneider H, Stein G, Bitsch R (1997) Vitamin C status of patients with chronic renal failure, dialysis patients and patients after renal transplantation. *Int J Vitam Nutr Res* 67:262–266
 78. Finkelstein FO, Juergensen P, Wang S, Santacrose S, Levine M, Kotanko P, Levin NW, Handelman GJ (2011) Hemoglobin and plasma vitamin C levels in patients on peritoneal dialysis. *Perit Dial Int* 31:74–79. <https://doi.org/10.3747/pdi.2009.00154>
 79. Shah GM, Ross EA, Sabo A, Pichon M, Bhagavan H, Reynolds RD (1991) Ascorbic acid supplements in patients receiving chronic peritoneal dialysis. *Am J Kidney Dis* 18:84–90. [https://doi.org/10.1016/s0272-6386\(12\)80295-2](https://doi.org/10.1016/s0272-6386(12)80295-2)
 80. Wang S, Eide TC, Sogn EM, Berg KJ, Sund RB (1999) Plasma ascorbic acid in patients undergoing chronic haemodialysis. *Eur J Clin Pharmacol* 55:527–532. <https://doi.org/10.1007/s002280050668>
 81. Fehrman-Ekholm I, Lotsander A, Logan K, Dunge D, Odar-Cederlöf I, Kallner A (2008) Concentrations of vitamin C, vitamin B12 and folic acid in patients treated with hemodialysis and on-line hemodiafiltration or hemofiltration. *Scand J Urol Nephrol* 42:74–80. <https://doi.org/10.1080/00365590701514266>
 82. Sirover WD, Liu Y, Logan A, Hunter K, Benz RL, Prasad D, Avila J, Venkatchalam T, Weisberg LS, Handelman GJ (2015) Plasma ascorbic acid concentrations in prevalent patients with end-stage renal disease on hemodialysis. *J Ren Nutr* 25:292–300. <https://doi.org/10.1053/j.jrn.2014.09.007>
 83. Ikizler TA, Burrowes JD, Byham-Gray LD, Campbell KL, Carrero J-J, Chan W, Fouque D, Friedman AN, Ghaddar S, Goldstein-Fuchs DJ, Kaysen GA, Kopple JD, Tetra D, Yee-Moon Wang A, Cuppari L (2020) KDQOI clinical practice guideline for nutrition in CKD: 2020 update. *Am J Kidney Dis* 76:S1–S107. <https://doi.org/10.1053/j.ajkd.2020.05.006>
 84. Naseri M, Shahri HMM, Horri M, Rasoli Z, Salemian F, Jahan-shahi S, Moeenloayaa G, Pourhasan M (2015) Antioxidant vitamins status in children and young adults undergoing dialysis: a single center study. *Indian J Nephrol* 25:206–212. <https://doi.org/10.4103/0971-4065.140717>
 85. Raimann JG, Abbas SR, Liu L, Larive B, Beck G, Kotanko P, Levin NW, Handelman G; Frequent Hemodialysis Network Trial (2019) The effect of increased frequency of hemodialysis on vitamin C concentrations: an ancillary study of the randomized Frequent Hemodialysis Network (FHN) daily trial. *BMC Nephrol* 20:179. <https://doi.org/10.1186/s12882-019-1311-4>
 86. Harmer M, Wootton S, Gilbert R, Anderson C (2019) Vitamin B6 in pediatric renal transplant recipients. *J Ren Nutr* 29:205–208. <https://doi.org/10.1053/j.jrn.2018.09.003>
 87. Stockberger RA, Parrott KA, Alexander SR, Miller LT, Leklem JE, Jenkins RD (1987) Vitamin B-6 status of children undergoing continuous ambulatory peritoneal dialysis. *Nutr Res* 7:1021–1030. [https://doi.org/10.1016/S0271-5317\(87\)80173-2](https://doi.org/10.1016/S0271-5317(87)80173-2)
 88. Coleman JE, Watson AR (1992) Micronutrient supplementation in children on continuous cycling peritoneal dialysis (CCPD). *Adv Perit Dial* 8:396–401
 89. Warady BA, Kriley M, Alon U, Hellerstein S (1994) Vitamin status of infants receiving long-term peritoneal dialysis. *Pediatr Nephrol* 8:354–356. <https://doi.org/10.1007/BF00866365>

90. Foreman JW, Abitbol CL, Trachtman H, Garin EH, Feld LG, Strife CF, Massie MD, Boyle RM, Chan JC (1996) Nutritional intake in children with renal insufficiency: a report of the growth failure in children with renal diseases study. *J Am Coll Nutr* 15:579–585. <https://doi.org/10.1080/07315724.1996.10718633>
91. Pereira AM, Hamani N, Nogueira PC, Carvalhaes JT (2000) Oral vitamin intake in children receiving long-term dialysis. *J Ren Nutr* 10:24–29. [https://doi.org/10.1016/s1051-2276\(00\)90019-0](https://doi.org/10.1016/s1051-2276(00)90019-0)
92. Don T, Friedlander S, Wong W (2010) Dietary intakes and biochemical status of B vitamins in a group of children receiving dialysis. *J Ren Nutr* 20:23–28. <https://doi.org/10.1053/j.jrn.2009.04.008>
93. Kim H, Lim H, Choue R (2014) Compromised diet quality is associated with decreased renal function in children with chronic kidney disease. *Clin Nutr Res* 3:142–149. <https://doi.org/10.7762/cnr.2014.3.2.142>
94. Nelms CL, Shaw V, Greenbaum LA, Anderson C, Desloovere A, Haffner D, Oosterveld MJS, Paglialonga F, Polderman N, Qizalbash L, Rees L, Renken-Terhaerd J, Tuokkola J, Vande Walle J, Shroff R, Warady BA (2021) Assessment of nutritional status in children with kidney diseases-clinical practice recommendations from the Pediatric Renal Nutrition Taskforce. *Pediatr Nephrol* 36:995–1010. <https://doi.org/10.1007/s00467-020-04852-5>
95. Erkkola M, Kyttälä P, Takkinen H-M, Kronberg-Kippilä C, Nevalainen J, Simell O, Ilonen J, Veijola R, Knip M, Virtanen SM (2011) Nutrient intake variability and number of days needed to assess intake in preschool children. *Br J Nutr* 106:130–140. <https://doi.org/10.1017/S0007114510005167>
96. Berger MM, Shenkin A, Schweinlin A, Amrein K, Augsburger M, Biesalski H-K, Bischoff SC, Casaer MP, Gundogan K, Lepp H-L, de Man AME, Muscogiuri G, Pietka M, Pironi L, Rezzi S, Cuerda C (2022) ESPEN micronutrient guideline. *Clin Nutr* 41:1357–1424. <https://doi.org/10.1016/j.clnu.2022.02.015>
97. Farrington K, Miller P, Varghese Z, Baillod RA, Moorhead JF (1981) Vitamin A toxicity and hypercalcaemia in chronic renal failure. *Br Med J (Clin Res Ed)* 282:1999–2002. <https://doi.org/10.1136/bmj.282.6281.1999>
98. Praga M, Diaz Rubio P, Morales JM, Cañizares F, Ruilope LM, Gutierrez-Millet V, Nieto J, Rodicio JL (1987) Implications of hypervitaminosis A on the calcium-phosphate metabolism and on blood lipids in hemodialysis. *Am J Nephrol* 7:281–286. <https://doi.org/10.1159/000167486>
99. Fishbane S, Frei GL, Finger M, Dressler R, Silbiger S (1995) Hypervitaminosis A in two hemodialysis patients. *Am J Kidney Dis* 25:346–349. [https://doi.org/10.1016/0272-6386\(95\)90020-9](https://doi.org/10.1016/0272-6386(95)90020-9)
100. Bhalla K, Ennis D, Ennis E (2005) Hypercalcemia caused by iatrogenic hypervitaminosis A. *J Am Diet Assoc* 105:119–121. <https://doi.org/10.1016/j.jada.2004.10.006>
101. Hathcock J, Hattan D, Jenkins J, McDonald J, Sundaresan P, Wilkening V (1990) Evaluation of vitamin A toxicity. *Am J Clin Nutr* 52:183–202
102. Litwin M, Abuauba M, Wawer ZT, Grenda R, Kuryt T, Pietraszek E (2001) Folate, vitamin B12, and sulfur amino acid levels in patients with renal failure. *Pediatr Nephrol* 16:127–132. <https://doi.org/10.1007/s004670000524>
103. Aldámiz-Echevarría L, Sanjurjo P, Vallo A, Aquino L, Pérez-Nanclares G, Gimeno P, Rueda M, Ruiz I, Urreiziti R, Rodríguez-Soriano J (2002) Hyperhomocysteinemia in children with renal transplants. *Pediatr Nephrol* 17:718–723. <https://doi.org/10.1007/s00467-002-0894-2>
104. Coleman JE, Watson AR, Chowdhury S, Thurlby D, Wardell J (2002) Comparison of two micronutrient supplements in children with chronic renal failure. *J Ren Nutr* 12:244–247. <https://doi.org/10.1053/jren.2002.35317>
105. Feinstein S, Sela B-A, Drukker A, Becker-Cohen R, Raveh D, Gavendo S, Frishberg Y (2002) Hyperhomocysteinemia in children on renal replacement therapy. *Pediatr Nephrol* 17:515–519. <https://doi.org/10.1007/s00467-002-0901-7>
106. Merouani A, Delvin EE, Genest J, Rozen R, Lambert M (2002) Plasma homocysteine concentration changes after renal transplantation in children. *Pediatr Nephrol* 17:520–523. <https://doi.org/10.1007/s00467-002-0868-4>
107. Canepa A, Carrea A, Caridi G, Dertenois L, Minniti G, Cerone R, Canini S, Calevo MG, Perfumo F (2003) Homocysteine, folate, vitamin B12 levels, and C677T MTHFR mutation in children with renal failure. *Pediatr Nephrol* 18:225–229. <https://doi.org/10.1007/s00467-002-1058-0>
108. Hamatani R, Otsu M, Chikamoto H, Akioka Y, Hattori M (2014) Plasma homocysteine and folate levels and dietary folate intake in adolescents and young adults who underwent kidney transplantation during childhood. *Clin Exp Nephrol* 18:151–156. <https://doi.org/10.1007/s10157-013-0819-3>
109. Joyce T, Brown FC, Adalat S, Reid CJD, Sinha MD (2018) Vitamin B6 blood concentrations in paediatric dialysis patients. *Pediatr Nephrol* 33:2161–2165. <https://doi.org/10.1007/s00467-018-4053-9>
110. Pontes KSDS, Klein MRST, da Costa MS, Rosina KTC, Barreto APMM, Silva MIB, Rioja SDS (2019) Vitamin B12 status in kidney transplant recipients: association with dietary intake, body adiposity and immunosuppression. *Br J Nutr* 122:450–458. <https://doi.org/10.1017/S0007114519001417>
111. Joyce T, Rasmussen P, Melhem N, Clothier J, Booth C, Sinha MD (2020) Vitamin and trace element concentrations in infants and children with chronic kidney disease. *Pediatr Nephrol* 35:1463–1470. <https://doi.org/10.1007/s00467-020-04536-0>
112. Harshman LA, Lee-Son K, Jetton JG (2018) Vitamin and trace element deficiencies in the pediatric dialysis patient. *Pediatr Nephrol* 33:1133–1143. <https://doi.org/10.1007/s00467-017-3751-z>
113. Herrmann W, Schorr H, Geisel J, Riegel W (2001) Homocysteine, cystathionine, methylmalonic acid and B-vitamins in patients with renal disease. *Clin Chem Lab Med* 39:739–746. <https://doi.org/10.1515/CCLM.2001.123>
114. Oberley MJ, Yang DT (2013) Laboratory testing for cobalamin deficiency in megaloblastic anemia. *Am J Hematol* 88:522–526. <https://doi.org/10.1002/ajh.23421>
115. Stabler SP (2013) Clinical practice. Vitamin B12 deficiency. *N Engl J Med* 368:149–160. <https://doi.org/10.1056/NEJMcp1113996>
116. Gerasimidis K, Bronsky J, Catchpole A, Embleton N, Fewtrell M, Hojsak I, Indrio F, Hulst J, Koglsmeier J, de Koning B, Lapilonne A, Molgaard C, Moltu SJ, Norsa L, Verduci E, Domellof M; ESPGHAN Committee on Nutrition (2020) Assessment and interpretation of vitamin and trace element status in sick children. A Position Paper from the ESPGHAN Committee in Nutrition. *J Pediatr Gastroenterol Nutr* 70:873–881. <https://doi.org/10.1097/MPG.0000000000002688>
117. Assimos DG (2004) Vitamin C supplementation and urinary oxalate excretion. *Rev Urol* 6:167
118. Drukker A, Itai T, Stankiewicz H, Goldstein R (1988) Plasma vitamin E levels in uremic children and adolescents. *Child Nephrol Urol* 9:208–210
119. Becker-Cohen R, Rinat C, Ben-Shalom E, Feinstein S, Ivgi H, Frishberg Y (2012) Vitamin A deficiency associated with urinary retinol binding protein wasting in Dent's disease. *Pediatr Nephrol* 27:1097–1102. <https://doi.org/10.1007/s00467-012-2121-0>
120. Miller ER 3rd, Pastor-Barriuso R, Dalal D, Riemersma RA, Appel LJ, Guallar E (2005) Meta-analysis: high-dosage vitamin E supplementation may increase all-cause mortality. *Ann Intern Med* 142:37–46. <https://doi.org/10.7326/0003-4819-142-1-200501040-00110>
121. Witham M, Lees J, White M, Band M, Bell S, Chantler D, Ford I, Fulton R, Kennedy G, Littleford R, McCrea I, McGlynn D,

- Panarelli M, Ralston M, Rutherford E, Severn A, Thomson N, Traynor J, Struthers A, Wetherall K, Mark P (2020) Vitamin K supplementation to improve vascular stiffness in CKD: the K4Kidneys randomized controlled trial. *J Am Soc Nephrol* 31:2434–2445. <https://doi.org/10.1681/ASN.2020020225>
122. Kopple JD, Mercurio K, Blumenkrantz MJ, Jones MR, Tallos J, Roberts C, Card B, Saltzman R, Casciato DA, Swendseid ME (1981) Daily requirement for pyridoxine supplements in chronic renal failure. *Kidney Int* 19:694–704. <https://doi.org/10.1038/ki.1981.69>
 123. Ramirez G, Chen M, Boyce HW, Fuller SM, Butcher DE, Brueggemeyer CD, Newton JL (1986) The plasma and red cell vitamin B levels of chronic hemodialysis patients: a longitudinal study. *Nephron* 42:41–46. <https://doi.org/10.1159/000183631>
 124. Descombes E, Hanck AB, Fellay G (1993) Water soluble vitamins in chronic hemodialysis patients and need for supplementation. *Kidney Int* 43:1319–1328. <https://doi.org/10.1038/ki.1993.185>
 125. Moriwaki K, Kanno Y, Nakamoto H, Okada H, Suzuki H (2000) Vitamin B6 deficiency in elderly patients on chronic peritoneal dialysis. *Adv Perit Dial* 16:308–312
 126. Bamgbola OF, Kaskel F (2005) Role of folate deficiency on erythropoietin resistance in pediatric and adolescent patients on chronic dialysis. *Pediatr Nephrol* 20:1622–1629. <https://doi.org/10.1007/s00467-005-2021-7>
 127. Schröder CH, de Boer AW, Giesen AM, Monnens LA, Blom H (1999) Treatment of hyperhomocysteinemia in children on dialysis by folic acid. *Pediatr Nephrol* 13:583–585. <https://doi.org/10.1007/s004670050748>
 128. Bennett-Richards K, Kattenhorn M, Donald A, Oakley G, Varghese Z, Rees L, Deanfield JE (2002) Does oral folic acid lower total homocysteine levels and improve endothelial function in children with chronic renal failure? *Circulation* 105:1810–1815. <https://doi.org/10.1161/01.cir.0000014417.95833.1d>
 129. Sotomayor CG, Bustos NI, Yepes-Calderon M, Arauna D, de Borst MH, Berger SP, Rodrigo R, Dullaart RPF, Navis GJ, Bakker SJL (2021) Plasma vitamin C and risk of late graft failure in kidney transplant recipients: results of the transplantlines biobank and cohort study. *Antioxidants (Basel)* 10:631. <https://doi.org/10.3390/antiox10050631>
 130. Deved V, Poyah P, James MT, Tonelli M, Manns BJ, Walsh M, Hemmelgarn BR; Alberta Kidney Disease Network (2009) Ascorbic acid for anemia management in hemodialysis patients: a systematic review and meta-analysis. *Am J Kidney Dis* 54:1089–1097. <https://doi.org/10.1053/j.ajkd.2009.06.040>
 131. Tarnag DC, Wei YH, Huang TP, Kuo BI, Yang WC (1999) Intravenous ascorbic acid as an adjuvant therapy for recombinant erythropoietin in hemodialysis patients with hyperferritinemia. *Kidney Int* 55:2477–2486. <https://doi.org/10.1046/j.1523-1755.1999.00479.x>
 132. Shahrbanoo K, Taziki O (2008) Effect of intravenous ascorbic acid in hemodialysis patients with anemia and hyperferritinemia. *Saudi J Kidney Dis Transpl* 19:933–936
 133. Canavese C, Petrarulo M, Massarenti P, Berutti S, Fenoglio R, Palletto D, Lanfranco G, Bergamo D, Sandri L, Marangella M (2005) Long-term, low-dose, intravenous vitamin C leads to plasma calcium oxalate supersaturation in hemodialysis patients. *Am J Kidney Dis* 45:540–549. <https://doi.org/10.1053/j.ajkd.2004.10.025>
 134. Liu Y, Weisberg LS, Langman CB, Logan A, Hunter K, Prasad D, Avila J, Venkatchalam T, Berns JS, Handelman GJ, Sirover WD (2016) Plasma oxalate levels in prevalent hemodialysis patients and potential implications for ascorbic acid supplementation. *Clin Biochem* 49:1133–1139. <https://doi.org/10.1016/j.clinbiochem.2016.05.025>
 135. Greenwood Village, CO:Truven Health Analytics. Vitamin A, Vitamin B1, Vitamin B2, Vitamin B3, Vitamin B5, Vitamin B6, Vitamin B7, Vitamin B9, Vitamin B12, Vitamin C, Vitamin E, Vitamin K. In: Micromedex: drug interactions (University of Iowa ed.) [Electronic version]. Retrieved April 24, 2023, from <http://www.micromedexsolutions.com/>
 136. EFSA (2013) EFSA NDA Panel (EFSA Panel on Dietetic Products, Nutrition and Allergies), 2013. Scientific Opinion on nutrient requirements and dietary intakes of infants and young children in the European Union. In: European Food Standards Authority. <https://efsa.onlinelibrary.wiley.com/doi/epdf/10.2903/j.efsa.2013.3408>. Accessed 30 May 2023
 137. Vega MRW, Cerminara D, Desloovere A, Paglialonga F, Renken-Terhaerd J, Walle JV, Shaw V, Stabouli S, Anderson CE, Haffner D, Nelms CL, Polderman N, Qizalbash L, Tuokkola J, Warady BA, Shroff R, Greenbaum LA (2023) Nutritional management of children with acute kidney injury-clinical practice recommendations from the Pediatric Renal Nutrition Taskforce. *Pediatr Nephrol* 38:3559–3580. <https://doi.org/10.1007/s00467-023-05884-3>

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