Water-Soluble Vitamins in People with Low Glomerular Filtration Rate or On Dialysis: A Review

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ABSTRACT

People with low glomerular filtration rate and people on dialysis are spontaneously at risk for vitamin deficiency because of the potential for problems with decreased appetite and decreased sense of smell and taste, leading to decreased intake, and because decreased energy or decreased cognitive ability results in difficulties in shopping and cooking. Imposed dietary restrictions because of their renal dysfunction and because of comorbidities such as hypertension and diabetes exacerbate this problem. Finally, particularly for water-soluble vitamins, loss may occur into the dialysate. We did not identify any randomized trials of administering daily doses close to the recommended daily allowances of these vitamins. In people who are eating at all, deficiencies of B5 and B7 seem unlikely. It is unclear whether supplements of B2 and B3 are necessary. Because of dialyzability and documented evidence of insufficiency in dialysis patients, B1 supplementation is likely to be helpful. B6, B9, and B12 are implicated in the hyperhomocysteinemia observed in patients on dialysis. These vitamins have been studied in combinations, in high doses, with the hope of reducing cardiovascular outcomes. No reductions in patient-important outcomes were seen in adequately powered randomized trials. Because of their involvement in the homocysteine pathway, however, supplementation with lower doses, close to the recommended daily allowances, may be helpful. Vitamin C deficiency is common in patients on dialysis who are not taking supplements: low-dose supplements are warranted. Vitamins for dialysis patients contain most or all of the B vitamins and low-dose vitamin C. We are not aware of any medical reasons to choose one over another.

There are five main reasons why dialysis patients may have vitamin deficiencies: appetite is reduced, diet is restricted, medications and co-morbidity may interfere with absorption, uremia may alter metabolic pathways, and intradialytic losses may occur (1). Diets restricted in potassium will often be low in vitamin C, and protein-restricted diets are quite likely to be associated with intake of vitamins below the recommended daily allowance (Table 1) (2).

The magnitude of body stores compared with the recommended daily allowance (RDA) varies for different vitamins, and the impact of duration of dietary restriction (whether spontaneous or therapeutically imposed) and of dialysis will depend to some extent on this factor (Table 2) (2).

While frank scurvy, beriberi, and Wernicke's encephalopathy have been reported in dialysis patients, there is concern that subtle vitamin deficiencies, particularly in patients on dialysis, may, in some patients, account for some of the general uremic symptomatology, or for more specific dialysis-associated syndromes such as anemia or peripheral neuropathy (2).

The 2005 KDOQI guidelines do not provide specific recommendations for vitamin supplements to patients on maintenance hemodialysis, but indicate that routine B-vitamin supplementation is needed to replace the losses from dialysis and to prevent rises in serum homecysteine concentrations that result with deficiency in folate, riboflavin, vitamin B6, or B12. Based on DOPPS data, there is a wide variation in vitamin prescription across countries ranging from 3.7% use in the United Kingdom to 71.9% in the United States. A 16% reduced risk of mortality was indentified in individuals taking water-soluble vitamins. In 2007, European Practice Guideline recommended a water-soluble vitamin containing 1.1–1.2 mg of thiamine, 1.1–1.3 mg of riboflavin, 14–16 mg of niacin, 10 mg of pyridoxine and 2.5 μg of vitamin B12, 1 mg of folate, 30 μg of biotin, and

TABLE 1. Relationship between estimated vitamin contents of diets with different protein intake and recommended dietary allowances

Vitamin	Units	Recommended dietary allowance	Daily protein intake g/day		
			40	60	80
Vitamin B1	mg	1.2–1.6	0.6	1.0	1.1
Vitamin B2	mg	1.2–1.8	0.8	1.2	1.8
Vitamin B6	mg	1.6–2.2	1.0	1.2	1.5
Vitamin B7 (Biotin)	mcg	100–200	13.4	17.8	15.8
Vitamin B9 (Folic acid)	mcg	400	260	290	320
Vitamin B12	mcg	3	2.3	3.2	5.1
Vitamin C	mg	40–60	86	87	88

Adapted from (2) with permission.

TABLE 2. Estimated duration of vitamin stores in humans

Vitamin	
Vitamin B1	4–10 days
Vitamin B2	3–4 months
Vitamin B6	3–4 months
Vitamin B9 (Folic acid)	1–1.15 years
Vitamin B12	3–5 years
Vitamin C	3–4 months

Adapted from (2) with permission.

5 mg of pantothenic acid as well as 75–90 mg of vitamin C daily [2b].

Here, we present a narrative review of a large literature. We conducted literature searches using medical subject headings and synonyms for each vitamin combined with terms for chronic kidney disease or dialysis. We supplemented this with our working knowledge, with reference lists of review articles and textbooks, and with references in articles that we found relevant. For each vitamin, we provide a brief background, discuss deficiency in the general population, and then focus on findings in people with low GFR or on dialysis. Most information was on patients on hemodialysis. Where information was available in patients with nondialyzed chronic kidney disease or peritoneal dialysis, we have included this; however, this information was not always available.

Vitamin B1 (thiamine)

Background

Thiamine is a water-soluble vitamin of the B complex. It is a coenzyme in the metabolism of carbohydrates and branched chain amino acids. In this capacity, it acts as an enzymatic cofactor in oxidative decarboxylation reactions mediated by pyruvate dehydrogenase. It is also involved in the transketolation of the pentose phosphate pathway. Thiamine has functions independent of its coenzyme function in the initiation of nerve impulse propagation.

Thiamine is absorbed in the upper small intestine. Most thiamine in the circulation is within red blood cells and the remaining amount is albumin-bound. Thiamine and its metabolites are excreted principally in urine (3).

Thiamine is found in enriched, fortified, or whole grain products. The RDA for thiamine is 1.2 mg/day in males and 1.1 mg/day in females (4). The tolerable upper intake level (UL) for toxicity is not determined (4).

General Population

Thiamine deficiency manifests clinically as anaerobic metabolism (leading to lactic acidosis), neurologic impairment (peripheral neuropathy), and cardiovascular disease (congestive heart failure). Wernicke's encephalopathy is the most frequently encountered clinical manifestation of thiamine deficiency and occurs in individuals with impaired nutrition from any cause. No adverse effects associated with excess thiamine from food or supplements have been reported.

Thiamine deficiency can be ascertained by its direct measurement in whole blood or serum (normal range: 60–112 nmol/l) or by measuring the activity of the enzyme transketolase in erythrocytes (ETK) before (ETKo) and after an in vitro vitamin supplement is added. This is then expressed as the ratio of enzyme activity after/before vitamin addition (α-ETK). A value of greater than one reflects a large increase in enzyme activity after exogenous addition of the vitamin and reflects intra-cellular deficiency (5).

People with Low Glomerular Filtration Rate & End-Stage Renal Disease

The median thiamine intake in patients with ESRD is insufficient compared with the RDA for the healthy population (6). Studies evaluating circulating plasma concentrations of thiamine report normal levels in dialysis patients (7), whereas those reporting ETKo activity either report normal or low thiamine status (5,8). Two studies have evaluated both simultaneously and demonstrated that most of these patients had normal concentrations of circulating thiamine, but close to 50% of dialysis patients had low or marginal ETKo levels highlighting the controversy in interpreting thiamine status (5,9). The single longitudinal study of thiamine status in a non-supplemented group of 15 dialysis patients demonstrated that nearly all patients maintained normal plasma and erythrocyte thiamine levels over 12 months of observation (7). Cross-sectional studies of dialysis patients identify a very low proportion of patients with thiamine deficiency in patients who receive a postdialysis oral multivitamin containing 100 mg thiamine two or three times per week (5,10).

Thiamine Status and the Dialysis Procedure

Three studies have reported the change in plasma thiamine concentrations before and after a single

dialysis treatment. One study demonstrated that hemodialysis resulted in a small, but potentially clinically significant, lowering of thiamine levels. Although there was a difference between dialyzer types (4% and 9% reduction in thiamine with a low-flux and high-flux dialyzer, respectively), this difference was not statistically significant (11). However, two other studies demonstrated slightly higher concentrations of thiamine after treatment (9,12). Taken together, a consistent effect of dialysis has not been demonstrated.

Thiamine Supplementation

Current recommendations suggest a daily supplement of 1.1–1.2 mg thiamine. We did not identify any comprehensive studies. One study, and a number of case reports, suggests that supplementary thiamine should be particularly considered in dialysis patients with mental status changes (13–16). Baseline thiamine levels pre- and postintravenous thiamine supplementation was assessed in 10 dialysis patients with unexplained encephalopathy and values were compared with those of healthy patients on hemodialysis and healthy controls (16). Dialysis patients with encephalopathy had lower thiamine concentrations (35.3 ± 6.0 nmol/l) than dialysis patients without encephalopathy (85.6 ± 12.2 nmol/l). Healthy control subjects had even higher (96.8 ± 18.6 nmol/l) levels.

Extended-hours Dialysis

Thiamine levels were lower in patients on extended hours dialysis than in patients on conventional hours (median 211 vs. 439 nmol/l, $p = 0.0005$), but the clinical significance of this is doubtful as no patient was deficient in the extended-hours group and one patient (3.8%) was deficient in the conventional group (Table 3) (17). Patients in this study received a multi-vitamin containing 7.27 mg thiamine daily, six fold more than the RDA.

Summary

The available evidence indicates that there are exceedingly few cases of thiamine deficiency identified in dialysis patients who are routinely exposed to a postdialysis multivitamin supplement containing thiamine. A daily supplement of thiamine hydrochloride (1.1–1.2 mg/day) is recommended by the European Best Practice Guidelines on Nutrition (18). The 2005 recommendations from the National Kidney Foundation Kidney Disease Outcomes Quality Initiative (K/DOQI) for cardiovascular disease do not provide specific recommendation for thiamine supplementation (19). To the best of our knowledge, there is no trial with a clinical endpoint that has evaluated thiamine supplementation in any CKD population. The association between poor thiamine status and unexplained encephalopathy and

its improvement with intravenous thiamine support future studies evaluating thiamine status in a people with low GFR and on dialysis.

Vitamin B2 (Riboflavin)

Background

Riboflavin, or vitamin B2, plays a key role in energy metabolism. It is a central component of the coenzymes flavin mononucleotide and flavin adenine dinucleotide (FAD). Each of these coenzymes is essential for several reduction–oxidation enzymes. Flavins can accept a pair of hydrogen ions, and as such, act as oxidizing agents.

The RDA for riboflavin is 1.3 mg/day in males and 1.1 mg/day in females (4). The upper limit (UL) for toxicity is unknown. Riboflavin is found in organ meats, milk, bread products and fortified cereal.

General Population

Riboflavin deficiency is characterized by angular stomatitis, cheilosis and glossitis and typically occurs in association with other vitamin deficiencies. There is no known riboflavin toxicity.

Riboflavin status is determined by the erythrocyte glutathione reductase activation coefficient (EGRac). This functional assay measures the activity of glutathione reductase before (EGRo) and after in vitro reactivation with FAD. The EGRac is calculated as the ratio of FAD-stimulated to un-stimulated enzyme activity and reflects tissue status (20). An EGRac above 1.3 suggests riboflavin deficiency.

People with Low Glomerular Filtration Rate & End-Stage Renal Disease

Riboflavin status was measured in 43 HD patients who had previously received a low-dose supplement containing folic and ascorbic acid. The EGRac was normal in all patients whilst approximately 10% of patients had insufficient EGRo values (5). In a study of vitamin-supplemented (postdialysis vitamin containing 1.7 mg of riboflavin) dialysis patients, no significant differences in EGRac were noted when patients on standard three-times-weekly hemodialysis or nocturnal dialysis were compared with healthy controls (20). Finally, in a supplemented group of HD patients (postdialysis multivitamin containing 20 mg riboflavin), no case of riboflavin deficiency was identified (10).

The dialyzability of riboflavin has been studied in a group of 30 dialysis patients. There was a 7% reduction in total riboflavin (including FAD, FMN and free riboflavin) postdialysis with no differences between high- and low-flux membranes (11).

Summary

The available evidence suggests that riboflavin deficiency is uncommon in dialysis patients. There

TABLE 3. Vitamin status in plasma of healthy population, patients with CKD, haemodialysis patients and peritoneal dialysis patients

Vitamin	Healthy	CKD	HD	PD	Dialyzability
Thiamine (B1)	60–112 nmol/l α-ETK <1.18	64.2 ± 24.4 nmol/l (9)	Without supplement: 78.3 ± 60.4 nmol/l (9) 84.6 ± 15.7 nmol/l (5) With supplement: 80 (56–110) nmol/l)(11) 145.9 ± 34.3 (5)	No data	−4% (low-flux dialyzer) and − 9% (high-flux dialyzer)(11) No change in plasma thiamine concentrations pre and postsingle HD treatment(9)
Riboflavin (B2)	α-EGR <1.2 (10) Riboflavin concentration μg/l >40 μg/l (11)		With supplement: 1.02 ± 0.02(10) With supplement 1.00 ± 0.07(10) 163 μg/l (93–324) (11)	Without supplement 1.08 ± 0.08 (164) Without supplement 1.28 ± 0.30 (164)	−7% (low flux dialyzer) – 6% (high flux dialyzer)(10)
Niacin (B3)	14.3–19.0 μg/ml (12)		16.0–19.9 μg/ml (7)		No change postdialysis (n = 5) (7)
B6	5 to 24 ng/ml or 20 to 97 nmol/l (63)	56.9 SD 61.4 nmol/l (130)	Not on supplements: with peripheral neuropathy 5.9 SE 0.8 ng/ml; controls on HD but without peripheral neuropathy 7.2 SE 0.8 (45) Postsupplements 29.7 SE 5.3 ng/ml (45)	On supplements: 150.1 ± 42.2 nmol/l (43)	PD: Low peritoneal clearance: 22.3 ± 3.1 nmol/6 hours (43) PD: Low peritoneal clearance 8.8% of urea clearance (46) PD: Low peritoneal removal of 545 SE 61 nmol/day (42) HD: 7.1 SE 1.0 ng/ml pre-dialysis to 3.7 SE 0.4 ng/ml postdialysis (45)
Pyridoxal-5-phosphate (active B6)	> 7 ng/ml (> 7 mcg/l) or > 30 nmol/l (63)		Not on supplements: 1.6 SD 1.3 mcg/l (2) Not on supplements: 11.1 ± 7.5 nmol/l (predialysis) and 8.0 ± 5.9 nmol/l (postdialysis) (1) On B6 10 mg daily: low-flux HD 53 SD 6.7 ng/ml†; high-flux HD 24 SD 9.7 ng/ml (41)	Not on supplements: 16 SE 3 nmol/l (42) Same patients after supplementation 5–10 mg daily: 65 SE 7 nmol/l in 8 patients after 4 weeks on 5 mg daily; and 45, 55 and 40 nmol/l after 12 – 16 weeks on 10 mg daily in the remaining 3 patients (42) Not on supplements: 1.0 ng/ml to 30 ng/ml (50)	Low-flux HD, average Qb 375 ml/minute: clearance 86 SD 62 ml/minute; high-flux HD, average Qb 375 ml/minute: clearance 173 SD 90 ml/minute (41) HD: with mean duration 3.7 hours and three times weekly dialysis on a high flux substituted cellulose or polyacrilonitrile dialyzer: Percent reduction 27.9% ± 14.2; Kd 54.4 ml/minute ± 38.2 (1) PD: low peritoneal losses of 1.9 SE 0.4 mcg/day (8 SE 2 nmol/day) (42)

Table 3. (Continued)

Vitamin	Healthy	CKD	HD	PD	Dialyzability
Biotin (B7)	> 342 ng/l (> 0.3 ng/ml) (2) 418 SD 368 ng/l (55) Note that plasma levels are not sensitive for biotin deficiency (53)		Unsupplemented patients on HD for at least 3 years: 0.5 to 3.0 ng/ml (60) Unsupplemented patients on HD 1340 SD 577 ng/l (2) Unsupplemented patients on HD 1749 SD 541 ng/l; Supplemented patients on HD 2361 SD 689 ng/l (55) Supplemented patients on HD (10 mg daily for several months): 12.7 to 108.9 ng/ml (60)		HD: In supplemented and unsupplemented patients plasma level decreased by 30 to 33% with each treatment (55)
Folate	2.7 to 17 ng/ml (6.1–38.5 nmol/l) (165) Normal >4.0 ng/ml; indeterminate 3.7 to 3.9 ng/ml; deficient <3.7 ng/ml (166) RBC folate 187 to 645 ng/ml; indeterminate 149 to 186 ng/ml; deficient <149 ng/ml (166)	27.2 SD 11.2 nmol/l (130)	Not on supplements: serum folate 12.4 ± 6.1 nmol/l (predialysis) and 8.6 ± 3.6 (postdialysis) nmol/l (1) Unsupplemented: plasma folate 16.3 SD 8 nmol/l (75) Variable supplementation: conventional hours, RBC folate 504 ng/ml; extended hours, 670 ng/ml (P for the comparison > 0.05) (17)	Not on supplements: RBC folate 850 ± 489 ng/ml; plasma folate 5.8 ± 3.6 ng/ml (both RBC and plasma folate higher in patients on CAPD than patients on HD, $p < 0.0001$) (74) Unsupplemented RBC folate 1333 ± 519 nmol/l; plasma folate 13 ± 8 nmol/l. RBC folate but not plasma folate higher in patients on CAPD than patients on HD, $p < 0.01$ (78)	With mean duration 3.7 hours and three times weekly dialysis on a high flux substituted cellulose or polyacrilonitrile dialyzer: Percent reduction; $26.3 \pm 16.0\%$ Kd 134.7 ± 22.2 ml/minute (1) Estimated losses of 10 – 250 mcg per HD procedure (summarized in (2))
B12	335–345 pmol/l (167)	316.6 SD 146.7 pmol/l (130)	154–932 pmol/l (121) 220–530 pmol/l (122)	453 ± 26 pmol/l (17)	Not dialyzable (17,122)

Table 3. (Continued)

Vitamin	Healthy	CKD	HD	PD	Dialyzability
Vitamin C	Usual levels in healthy Europeans 60–90 mcmol/l (168) Acceptable 4 to 15 mg/l (22.8 – 85 mcmol/l) (143) Scorbutic threshold: 2–3 mg/l (11.4-17 mcmol/l) (149); <10 mcmol/l (168)	Patients without diabetes: 6.2 mcg/ml (minimum 1.4; maximum 19.8). Patients with diabetes: 4.5 mcg/ml (minimum 0.6; maximum 13.0) (P for the difference = 0.044) (145) Mean 62 mcmol/l (146)	Unselected 80.3 mcmol/l (146) Not on supplements: 22 ± 6 mcmol/l; on supplements: 34 ± 10 mcmol/l (169) Not on supplements: 10.5 ± 1.7 mcmol/l (170) Overall median 45 mcmol/l (IQR 24 to 75); compliant with supplements of 100 mg/day median 46 (IQR 25 to 75) mcmol/l; non-compliant or partly compliant median 40 (IQR 18 to 76) mcmol/l (135) Unselected, mostly supplemented 59 ± 65 mcmol/l (147) Variable supplementation: conventional hours 1.14 mg/dl; extended hours dialysis 0.3 mg/dl (P for the comparison < 0.001) (17)	Not on supplements: 85.2 ± 16.6 mcmol/l (153) Not on supplements: 2.5 (IQR 1.5 to 4.4) mg/L; on supplements: 7.1 (IQR 4.1 to 17.3) mg/L (149)	In patients on haemodiafiltration diffusive flux of 271 mcg/minute and convective flux of 126 mcg/minute; total loss of vitamin C was 66 mg per session (minimum 8 mg; maximum 230 mg) (150) Mean 40% decrease during 3-hour HD session (169) Mean decrease from 10.5 ± 1.7 mcmol/L to 5.9 ± 1.0 mcmol/L from 3 – 5 hours, mostly low flux membranes (170) In patients on peritoneal dialysis not on vitamin C supplements: vitamin C loss of 175.8 ± 28.8 mcmol/6 hours (153) In patients on peritoneal dialysis: vitamin C loss of 31 mg per 6-hour exchange (148); In patients on peritoneal dialysis receiving 100 mg vitamin C supplement: dialysate removal 0.28 ± 0.03 mmol/day (151)

SD: standard deviation; SE: standard error; CAPD: continuous ambulatory peritoneal dialysis; RBC: red blood cell; IQR: Interquartile range.
We used "±" symbol only when we were unable to determine whether SE or SD was reported.
Units throughout are reported as in the original reports, to reduce the possibility of conversion error. Conversion factors can be found at http://www.amamanualofstyle.com/page/si-conversion-calculator (last accessed January 12, 2013).

are no clinical trials evaluating riboflavin supplementation in dialysis patients and no recommendations for supplementation. No strong evidence exists for supplementation, but studies documenting sufficiency were performed in patients receiving supplements.

Vitamin B3 (Niacin = nicotinic acid; niacinamide = nicotinamide)

Background

Vitamin B3 is crucial in the synthesis of carbohydrates, proteins, and fatty acids and therefore plays key role in energy metabolism.

Niacin and niacinamide are the two physiologically equivalent forms, although niacinamide lacks the pharmacologic effects of niacin (it does not lower cholesterol or cause flushing). Within the mitochondria, niacin, nicotinamide, and tryptophan form nicotinamide adenine dinuceotide (NAD) and NAD phosphate (NADP). These are the active forms of niacin and many enzymatic reactions depend upon them. The niacin component can either accept electrons or donate hydrogen ions and, as such, are crucial in the synthesis of carbohydrates, proteins, and fatty acids.

General Population

The RDA for niacin is 16 mg/day in males and 14 mg/day in females. The UL of toxicity of niacin is 35 mg/day (4). Niacin is readily found in meat, fish, poultry, and enriched whole grain products. Niacin is an accepted treatment for the reduction of total and LDL-cholesterol in the general population (21,22). The main side effect of supplementation with niacin is the flushing reaction associated with nicotinic acid, a symptom that can be reduced with sustained release preparations (23).

Deficiency and toxicity of vitamin B3: Deficiency of niacin results in a photosensitive pigmented dermatitis called pellagra. Although common in the 1800s, this now only exists in developed countries as a complication of alcoholism, anorexia, or malabsorptive disease. In the general population, niacin toxicity has included GI symptoms as well as elevated transaminases and myopathy.

People with Low Glomerular Filtration Rate & End-Stage Renal Disease

There are very few measures of niacin status in people with low glomerular filtration rate or ESRD. Whole blood niacin and erythrocyte niacin concentrations were measured monthly in 15 dialysis patients who were not taking a postdialysis multivitamin (7). The niacin concentration in the whole blood was in the low-normal range and remained so for the duration of the 12-month follow-up. The erythrocyte niacin concentration was normal in the majority of these patients throughout the period of observation.

In a rodent model of CKD, nicotinamide was demonstrated to inhibit the NaPi-2b sodium-dependent phosphate cotransporter within the GI tract (24). It has therefore been studied as a phosphorus-lowering agent in people with low GFR because of its potential to impair absorption of dietary phosphate (25,26). As attractive as such a drug may appear, the metabolism of niacin and nicotinamide in individuals with low GFR has not been well studied; there is preliminary evidence that a metabolite of nicotinamide, N-methyl-2-pyridine-5-carboxamide, may in fact accumulate and be a uremic toxin (27–29).

Niacin levels do not change pre- and post a single hemodialysis treatment (12). Whether niacin is present in the dialysate has not been studied. As it does not circulate as a free compound, it is plausible that it is not dialyzable.

Summary

There are no trials utilizing niacin that have studied a clinical endpoint. The available evidence suggests that niacin could potentially accumulate in dialysis patients, and long-term safety in this population is unclear. Given the potential for modifying phosphorus absorption with simultaneous lipid lowering, studies of both short- and long-term tolerability and toxicity are required. There is no recommendation for niacin prescription for individuals with low GFR or ESRD.

Vitamin B5 (Pantothenic acid)

Background

Pantothenic acid is essential to the synthesis of coenzyme-A as well as in the synthesis and metabolism of proteins, carbohydrates, and fats.

General Population

Pantothenic acid is found in nearly all food sources and thus deficiency states are poorly defined and exceedingly rare. Toxicity is presumed to be unlikely and there is no UL of intake defined for this vitamin (4).

People with Low Glomerular Filtration Rate & End-Stage Renal Disease

Pantothenic acid levels were measured in the 1960s in hemodialysis and peritoneal dialysis patients and were reported as normal (30).

Summary

There is no recommendation to supplement patients with low GFR or ESRD with this vitamin and, based on the available evidence, it is likely not indicated.

Vitamin B6 (pyridoxine, pyridoxal, or pyridoxamine, or pyridoxine hydrochloride)

Background

Vitamin B6 is a water-soluble vitamin named by Szent-György in 1934, who discovered a substance that prevented dermatitis acrodynia in rats (31). The human deficiency syndrome is characterized by seborrhoeic skin lesions, microcytic and hypochromic anemia, weakness, irritability, nervousness, and insomnia (32). The vitamin exists in several different forms (pyridoxine, pyridoxal and pyridoxamine); the supplementary form most often given is pyridoxine. All are converted to the active form pyridoxal 5-phosphate (PLP). Vitamin B6 is a cofactor for reactions such as transamination, decarboxylation, dehydratase, and side chain cleavage reactions for at least 140 distinct enzymes, and is implicated in pathways as diverse as red blood cell synthesis, homocysteine metabolism, macronutrient metabolism, histamine synthesis, and gene expression (32). Some forms of vitamin B6 also appear to protect against glycation or carbonylation reactions (33,34).

PLP is also a component of two enzymes that metabolize homocysteine, by transulfuration, to cysteine (35): deficiency of B6 leads to hyperhomocysteinemia (36), which is associated with thrombosis and atherosclerosis.

Dietary sources of B6 include fortified cereals, organ meats, fortified soy-based meat substitutes, yeast, nuts, beans, avocados, and bananas (31,37).

Most reports of toxicity, in the form of peripheral neuropathy, have occurred in the context of intakes of >600 mg daily, although reports of toxicity in people taking 300–500 mg have appeared (38).

General Population

Because B6, B12, and folate intersect at the homocysteine pathway (35), and homocysteinemia is a graded risk factor for atherosclerosis (39), trials of combinations of these vitamins have been conducted in the general population in the hope of reducing the risk of cardiovascular disease. In general, these trials have been negative: we summarize them in the section on B12 use in the general population, below.

Cognition

A Cochrane review of a limited number of studies found no evidence that B6 has beneficial effects on mood or on cognition (40).

People with low glomerular filtration rate & end-stage renal disease

Dietary Intake and Levels

In 36 unsupplemented patients on high-flux thrice weekly hemodialysis, PLP levels were low in 56% and in the low normal range in a further 38%, with clinically important dialytic losses documented (Table 3) (1). PLP levels fell when patients who were receiving B6 10 mg daily were changed from low-flux to high-flux dialysis, but were still judged to be sufficient by the investigators (Table 3) (41). From their primary data and a review of previous literature of supplemented and unsupplemented patients, the authors concluded that 10 mg/day supplementation was likely adequate, even for patients undergoing high-flux hemodialysis (41). In patients on high-flux hemodialysis who had not previously received supplementation, mean values were grossly deficient at $1.6 \pm SD$ 1.3 mcg/l (2). B6 12–17 mg/day normalized PLP and one of two measures of PLP-sufficiency at the red cell level: the other measure required the much higher dose of 43–64 mg/day for normalization (2).

In a study of 11 unsupplemented patients on peritoneal dialysis, mean dietary intake was 50% and 59% on the RDA on two separate occasions, and were correlated with protein intake (42). In this study, despite normal plasma B6 levels in all patients, PLP levels were low (<40 nmol/l) in all patients. PLP was not correlated with dietary intake. In another study of patients on PD who received B6 5–20 mg daily supplementation, B6 levels were in the normal range and higher than those of controls; losses in dialysate were small (Table 3) (43). PLP was not measured in this study.

In unselected prevalent patients on PD, who had not been receiving supplements, all of whom had been found to be PLP-deficient (levels <40 nmol/l) at baseline, supplementation of 5 mg daily normalized PLP levels in 8 of 11 patients, and the remaining 3 normalized during a more prolonged period of supplementation at a dose of 10 mg (42).

In contrast to their levels of other water-soluble vitamins, patients on extended hours dialysis had higher levels of PLP than patients on conventional dialysis (23 vs. 11 mg/ml, $p = 0.03$), perhaps because dialysis losses were offset by higher dietary intake of this nutrient (17). In this study, none of the patients on extended-hours dialysis, but 35% of patients on conventional dialysis, had levels considered deficient. Patients were taking a multivitamin containing 0.7 mg pyridoxine daily.

Higher levels of supplementation of B6 may be required at times of erythropoietin-driven red cell synthesis. Erythrocyte B6 levels fell after the initiation of erythropoietin despite supplements of 5 mg of pyridoxine daily, but were normalized by 3 months of further treatment with pyridoxine 20 mg daily (44).

Dissociation between B6 and PLP Levels

Because most studies have measured either B6 (43,45,46) or PLP (1,2,41,17), but not both, we do not know if the finding of marked discrepancy

between PLP and B6 levels observed in one small study of patients on peritoneal dialysis is reproducible. In this study, none of 11 patients were deficient by B6 and all were found deficient by PLP (42). The investigators speculated that uremic patients might have specific problems with synthesis or PLP from B6 or with excess degradation, perhaps by circulating alkaline phosphatase (42).

Biochemical and Surrogate Outcomes

Vitamin B6 is a cofactor for the production of glycine from glyoxalate, reducing the availability of glyoxalate as a substrate for degradation into oxalate (47). Vitamin B6 supplementation lowered oxalate levels in a small study of patients on peritoneal dialysis who were receiving ascorbate supplementation (48). The clinical utility of this approach has not been further studied.

Coadministration of thiamine and pyridoxine did not affect blood levels of advanced glycation end products or markers of oxidative stress in patients on HD (49). However, in uremic rats treated with peritoneal dialysis, pyridoxamine improved structural and functional abnormalities thought to be induced by advanced glycation end products or by carbonyl stress (35,36).

Peripheral Neuropathy

PLP levels correlated with symptoms of peripheral neuropathy in elderly unsupplemented patients on PD, and improved in 8 of 12 most symptomatic patients after 1 month's treatment with 30 mg daily (50). In a blinded randomized trial of 26 patients on high-flux HD who had peripheral neuropathy, B6 50 mg/day compared with B12 500 mg/day resulted in improvement in peripheral neuropathy scores (effect shown graphically, $p < 0.05$, effect size not reported) (45).

Cardiovascular Disease and Thrombosis

Inadequate B6 leads to hyperhomocysteinemia; genetic hyperhomocysteinemia is associated with venous thrombosis and arterial atherosclerosis; patients with low glomerular filtration rate or on dialysis have very high levels of homocysteine, and are at high risk for both thrombosis and atherosclerosis (51). Because of these connections, it has been hypothesized that hyperhomocysteinemia accounts for some of the excess cardiovascular risk associated with low kidney function, and that lowering homocysteine levels with B6, B12, and folate, especially in high-dose combination, might ameliorate this risk. Randomized trials of multiple B vitamins in the treatment of hyperhomocysteinemia in patients on dialysis have been conducted and are largely disappointing; results are summarized in detail in the section on B12, below, and in Table 4.

Summary

The recommended dose has varied between none, 10 mg, and 300 mg/day (42). Levels of PLP in patients on either HD or PD have been very low in most, but not all, studies, suggesting that some supplementation is warranted. In high-flux hemodialysis, some regard 10 mg daily as adequate supplementation, but other data suggest that somewhat higher doses of 12–17 mg daily are needed to normalize PLP. In peritoneal dialysis, 10 mg appears to be adequate for all patients, based on one small study (42). However, studies have been conducted in prevalent patients who may have become deficient over some time, and it is possible that lower doses would be needed if started earlier in the course of kidney disease or at the initiation of dialysis.

Vitamin B7 (biotin)

Background

Discovered by Kögl in 1948, B7 is a cofactor responsible for carbon transfer in several carboxylase reactions (31). Gross deficiency states are rare, as a large but variable proportion of B7 absorbed by humans is produced by alimentary tract bacteria (31). Egg white contains a glycoprotein, avidin, that tenaciously binds B7; excessive consumption of egg white (more than 20 a day) can lead to frank clinical deficiency, called egg-white disease, and characterized by scaly dermatitis and skin dryness, atrophy of lingual papillae, graying of mucous membranes, depression, lassitude, and muscle pain (31). Other studies of experimental B7 deficiency in humans have identified seborrhoeic dermatitis as the cardinal manifestation (52).

Dietary sources include yeast, liver, egg yolk, tomato, soybeans, rice, and bran (31).

Plasma B7 levels are not a sensitive indicator of deficiency. Plasma B7 was in the normal range in half of patients fed raw egg white to induce deficiency and in some cases of overt deficiency (53). In the general population, urinary excretion of B7 and B7 metabolites is thought a more reliable indicator of sufficiency (53).

Toxicity appears to be low, with no syndrome reported (31,54). Excess B7 is excreted in the urine in patients with normal renal function and those with low glomerular filtration rate not on dialysis (55).

General Population

The RDA varies from 20 to 35 mcg/day for adolescents and adults: 20 mcg for an adolescent male, and somewhat higher recommendations with increasing age, pregnancy, and lactation (37). There are few reports of frank deficiency syndromes and to our knowledge, no large-scale epidemiologic

TABLE 4. Summary of randomized controlled trials of water-soluble vitamin supplementation in patients with renal disease that reported a clinical outcome

Study	Intervention	Patients	N	Follow up	Outcome	Result
Jamison (129)	40 mg folic acid, 100 mg pyridoxine, 2 mg vitamin B12 daily (vs matched placebo)	Aged ≥21yo eCrCl ≤30 ml/minute or ESRD and high homocysteine level (≥15 umol/L)	2056	3.2 years (median)	*Primary* All-cause mortality *Secondary* Myocardial infarction Stroke Lower extremity amputation Composite of above with all-cause mortality Time to dialysis Time to AV access thrombosis	*Primary* No effect on mortality (HR 1.04 CI 0.91–1.18) *Secondary* No effect on all secondary and adverse outcomes.
Heinz (121)	5 mg folic acid, 50 μg vitamin B12, and 20 mg vitamin B6 vs 0.2 mg folic acid, 4 μg vitamin B12, and 1 mg vitamin B6 thrice weekly	ESRD on dialysis	650	6 month	*Primary* Total mortality *Secondary* Fatal and non-fatal cardiovascular events	*Primary* No difference on mortality (HR 1.13 CI 0.85–1.5 $p = 0.51$) *Secondary* No difference on cardiovascular outcomes (HR 0.80 CI 0.60–1.07 $p = 0.13$)
Mann (130)	Folic acid 2.5 mg, vitamin B6 50 mg, and vitamin B12 1 mg vs placebo daily	Aged ≥50 years GFR <60 ml/minute	619	5 years	*Primary* Composite of death from cardiovascular causes, myocardial infarction, and stroke *Secondary* Total ischemic events Total mortality Hospitalization for unstable angina Hospitalization for congestive heart failure Revascularization Cancer incidence/death	*Primary* No difference (RR 1.19 CI 0.88–1.61 $p = 0.25$) *Secondary* No difference
Okada NDT 2000 (45)	Vitamin B6 50 mg daily vs B12 500 mg daily	High flux HD all with peripheral neuropathy 4.6 to 5.8 years	26	4 weeks	Peripheral neuropathy symptom score	Improved in B6 compared with B12-treated patients, $p < 0.05$, effect size not given, results presented graphically only

eCrCl: estimated creatinine clearance; HR: hazard ratio; CI: confidence interval; GFR: glomerular filtration rate; ESRD: end stage renal disease; HD: hemodialysis.

assessment of the effect of lower vs. higher levels on clinically important outcomes.

A few studies have reported beneficial effects on glucose metabolism, atherogenic markers, and coronary risk factors in people with type 2 diabetes (given in conjunction with chromium) (56–58). Little work appears to have been conducted on patient-important outcomes. Two small RCTs, one in women with alopecia and one in infants with seborrhoeic dermatitis (both negative) have been conducted (52,59).

People with Low Glomerular Filtration Rate & End-Stage Renal Disease

In a comparative study of patients with and without chronic kidney disease, normal controls and patients with renal transplants ingested 37 (SD 12) mcg of B7 daily, compared with 30 (SD 9) mcg in people with low GFR not on dialysis and 19 (SD 5) mcg in unsupplemented patients on dialysis.

In prevalent patients on low-flux or high-flux HD, almost all patients had values in the normal or high range (Table 3) (2,60); 70% of patients had values above 1000 ng/l, which would be highly unusual in the general population. Patients on HD for longer than 5 years had levels that were higher than those on of more recent vintage (mean: 1642 vs. 1274 ng/l, $p < 0.01$), and anuric patients had higher values than patients with residual renal function (mean: 1581 vs. 1116, $p < 0.01$) (2). In a different study, these factors were not examined, but plasma B7 concentrations were not associated with duration or frequency of dialysis, high-flux vs. low-flux dialysis, Qb, smoking, body mass index, or age (55).

As neurologic disease is not part of the described deficiency syndrome and because we now know that levels of B7 are not low in patients on dialysis, it is hard to understand the finding, in 1985, of dramatic clinical improvement in an uncontrolled trial of B7 10 mg daily given to nine patients who had developed dementia or peripheral neuropathy while on dialysis (54).

Summary

Given the large proportion of B7 derived from intestinal flora, the documented high levels of B7 in unsupplemented dialysis patients, the extreme rareness of clinical syndromes associated with B7 deficiency, it seems unlikely that B7 supplementation in dialysis patients would be useful. However, all studies addressed sufficiency by assaying B7 concentrations in blood, which are known not to be sensitive indicators of deficiency; furthermore, no toxicity has been described. Perhaps this rationale explains the large amounts of B7 found in some dialysis supplements (e.g., Replavite at 300 mcg/day contains 10 times the RDA for adults).

Vitamin B9 (folic acid, folate)

Background

Folate is derived from polyglutamates in food which are deconjugated in the upper jejunum and actively transported across mucosal epithelia (61). Folate circulates as 5-methyltetrahydrofolate, which is further demethylated to tetrahydrofolate in a reaction, catalyzed by B12, which requires homocysteine as a methyl acceptor (leading to methionine generation). Tetrahydrofolate is responsible for one-carbon transfer reactions in the body, most notably in the reactions needed for DNA synthesis. The cardinal clinical manifestation of frank deficiency is megaloblastic anemia (61).

Green leafy vegetables, whole grains, yeast, and liver are particularly rich in folate, particularly when raw or not heavily processed (31,62). Intestinal bacteria also synthesize folate (64). The RDA is given as dietary folate equivalents (DFE; 1 DFE = 1 μg food folate = 0.6 μg of folate from fortified food or as a supplement consumed with food = 0.5 μg of a supplement taken on an empty stomach) and is 300–600 mcg/day for adolescents and adults, with the higher end of that range recommended for pregnant and lactating women, and older people (37). In many countries, flour and bread are fortified with folate as a public health measure, and many breakfast cereals are also fortified with 25–100% of the RDA per serving (62). This resulted in a decrease from 4.9% to 1.9% in the proportion of the people in the general population who were frankly deficient (64).

Folate stores are low, so deficiency can occur 21–28 days of severe dietary deficiency (63). Red cell folate, rather than plasma folate, is thought the better reflection of tissue stores, and is the recommended blood measurement for the assessment of folate status (65).

Toxicity appears to be low, and no syndrome associated with excess consumption has been described (63). Very high doses (in excess of 1000 mcg/day) can correct the anemia associated with B12 deficiency and lead to delay in diagnosis (66), and folate supplementation can precipitate neurologic deterioration in B12-deficient patients (61,66).

General Population

In the general population, frank deficiency of folate leads to megaloblastic anemia. This is most commonly due to inadequate intake such as occurs in anorexia nervosa, malabsorption, or alcoholism; or increased demand, as in hyperthyroidism, pregnancy or lactation (63).

Neural Tube Defects

Folate deficiency is associated with fetal neural tube defects (including spina bifida). Following

recognition that many people had diets inadequate in folate and that the benefits of folate supplementation would be greatest preconception and in the first month of pregnancy, the US Food and Drugs Administration issued a regulation, effective 1998, that all enriched cereals (included flour and products of flour) should be fortified with 140 mcg of folate per 100 g (in addition to the iron, thiamine, riboflavin and niacin already added to these products) (64), and Canada soon followed suit (67). Follow-up indicates that food fortification has been among the most successful public health programs in reducing the rates of neural tube defects in the United States and Canada (68) and a number of reports show reduction in the incidence of neural tube defects by 20–78% (69).

Cardiovascular Disease

Folate is also required for one-carbon transfer in homocysteine metabolism. Higher levels of folate intake are associated with lower levels of homocysteine in general populations, but the relationship is not linear and seems to plateau at around dietary intake of 300 mg/day (70). Whether folate intake is associated with vascular disease is still controversial (71). Randomized trials have usually included the other B vitamins involved in homocysteine pathways (B6 and B12) and are discussed in the section on B12 and summarized in Table 4.

Cognitive Function

A Cochrane review of a limited number of studies found no benefit of folate supplementation, with or without B12, on cognitive function for prophylaxis in unselected elderly people or for treatment in people with cognitive decline (72). Three RCTs of 247 people provided limited support for the idea that folate might be a useful adjunct in the treatment of depression (73).

People with Low Glomerular Filtration Rate & End-Stage Renal Disease

Mean predialysis serum folate concentrations were in the normal range in all 36 patients studied on high-flux thrice weekly hemodialysis, although dialytic losses documented in this study were thought likely to be clinically important (Table 3), and 3/36 (9%) had levels suggestive of deficiency (1). However, RBC folate concentrations were normal in all patients in this study (1). This study was conducted in Canada around the time that mandatory food fortification came into effect. Two other studies of 50–60 unsupplemented patients on HD found that 10% had folate or RBC folate below the lower limit of normal (74,75), while none of 34 patients on CAPD had folate deficiency (74). These studies were conducted in Korea (74) where plasma

folate levels in the general population are higher than in other countries without mandatory fortification (76), likely because of relatively high content of leafy green vegetables in the diet, and in France (75), where recommendations rather than regulations govern the addition of folate to cereal. This probably has not led to clinically important increases in folate consumption, judged by the lack of effect on the rates of neural tube defects in France) (77).

Importance of Assessment of RBC Folate rather than Serum Folate

Assessment of folate status in patients on dialysis may be particularly liable to error if plasma rather than RBC folate is measured: in one of these studies, estimating folate stores by plasma folate rather than RBC folate would have led to 3% of CAPD and 72% of HD patients being thought folate-deficient, rather than 0% and 10%, respectively (74). Discordance between serum and RBC folate was also noted in a study from Canada in 2000 (1). Patients on HD consistently have lower RBC folate that those on CAPD (74,78).

Extended Hours Dialysis

Extended hours dialysis did not have an impact on serum levels of folate in 52 HD patients, 38% of whom were taking a multivitamin (17).

Sevelamer

In one small pre–post study, sevelamer use was associated with a decrease in serum folate levels (5.5 vs. 4.79 ng/ml, $p < 0.05$) and an increase in homocysteine levels (51 vs. 68 nmol/ml) (79).

Summary

While some experts have recommended that folate supplementation is not necessary in patients on HD, findings of 10% of prevalent patients with levels in the range associated with deficiency call this recommendation into question. The countries' policy on folate fortification may be relevant, as at least 2 of the 3 studies available were conducted in populations that were not exposed to mandatory cereal supplementation. Fortification is in effect in Canada, United States, Chile, and Australia (69), but not in any European countries (80). However, no documentation of adequate folate stores in countries that practice fortification has appeared, and toxicity and costs are low, so perhaps the most reasonable approach until further evidence is developed is fortification with small quantities (perhaps 2–7 mg/week). Use of large doses, usually in conjunction with other B vitamins, appears to lower homocysteine, but not to prevent cardiovascular events and cannot be recommended.

Vitamin B12

Background

The main source of cobalamin is from dietary intake of animal and dairy products. Cyanocobalamin, another name for vitamin B12, is an artefactual molecule based on previously used isolation methods from liver specimens and does not have direct biologic activity. The actual biologically active forms proceed from cobalamin. Ingested cobalamin complexes with salivary haptocorrin, which is released from cobalamin by pancreatic proteases in the duodenum. Intrinsic factor secreted from the parietal cells of the stomach then complexes with the released cobalamin. When this complex arrives at the distal ileum, it binds to cubilin on the enterocytes and is endocytosed. The cobalamin molecule is separated from intrinsic factor and transferred to transcobalamin II, which is a plasma transport protein (81,82).

At the target cell, the complex is endocytosed into the cellular lysosome where cobalamin is released from transcobalamin. It is metabolized to two active forms: adenosylcobalamin in the mitochondria and methylcobalamin in the cytosol.

Methylcobalamin is a methyl-transferring cofactor to the enzyme methionine synthase. Catalyzed by methionine synthase, methyltetrahydrofolate surrenders a methyl group to cobalamin, which then methylates homocysteine and forms methionine. Methionine is an essential amino acid required in the synthesis of nucleotides and phospholipids.

Adenosylcobalamin is formed within mitochondria and is a cofactor for a mutase known as methylmalonyl-CoA-mutase. This enzyme converts methylmalonyl-CoA into succinyl CoA and is important in the catabolism of various aminoacids and fatty acids. These processes may also require pyridoxine (vitamin B6) as a cofactor.

Unlike cobalamin acquired from dietary sources, pharmacologic sources provide either cyanocobalamin or hydroxocobalamin (2). Gastrointestinal absorption is saturable. After a 5–50 mcg dose, the maximum amount of absorbed B12 is 1.5 mcg (83). Dairy products, fish, and shellfish appear to continuously increase plasma vitamin B12 levels with increased daily intake. Meat and meat products, on the other hand, appear to have a plateau effect beyond 4 μg/day (83). Beyond 10 μg/day, plasma vitamin B12 levels plateau, independent of the food source (83).

Total body stores are about 2–5 mg of vitamin B12, 0.1% of which is in serum. The daily utilization of vitamin B12 amounts to approximately 2–5 mcg: several years of deficiency are necessary to deplete body stores (84,85).

The doses and levels for systemic toxicity in humans have not been established. Reports of pruritus, skin lesions, and diarrhea have been documented. Animal studies with intravenous doses up to 100 mg/kg for 26 weeks did not demonstrate any toxicity (82).

General Population

Epidemiology

Sufficiency Data. Low serum levels may not represent tissue vitamin deficiency. One study observed that approximately 10% of patients with serum levels <150 pmol/l had normal tissue levels (85). The current definition of vitamin B12 sufficiency is a serum level >210 pmol/l. This definition is based on the analysis of the NHANES cohort and represents the 95th percentile for vitamin B12-replete subjects (86).

Marginal deficiency is defined by a serum level of 148–221 pmol/l; deficiency is defined by a serum level <148 pmol/l; and severe deficiency is defined as serum levels <120 pmol/l. More definite evidence of vitamin B12 deficiency is based on the elevation of serum methylmalonic acid (>270 nmol/l) (87).

In North Americans, the prevalence of vitamin B12 deficiency was 3% of those aged 20–39 years, 4% of those aged 40–59 years, and 6% of persons aged $\geq$ 60 years (86). Marginal deficiency was more common and occurred in 14–16% of those aged 20–59 years and 20% of those $\geq$ 60 years. The mean methylmalonic acid level was 137 nmol/l (134–140 nmol/l). These findings demonstrate an increased incidence of deficiency with age (87).

The recommended daily allowance for vitamin B12 is 2.4 mcg/day for adult males and females (88). This recommendation is based on daily utilization data and the prevention of megaloblastic anemia.

Determinants of Sufficiency. Diet is an important determinant of vitamin B12 status. Dietary vitamin B12 consumption increases from 0.4 mcg/day in vegans to 7.2 mcg/day in people who eat meat (88). These dietary patterns directly correlate with serum B12 levels. Current data suggest that, in general, serum B12 levels respond similarly for supplements, fortified cereals, and animal sources.

Malabsorption is another important determinant. Increasing age leads to gastric inflammation and atrophy. The resulting hypochlorhydria prevents the release of vitamin B12 from salivary haptocorrin and subsequent ileal absorption. This is corroborated by the observation of increased gastrin levels with increasing age (89). Other causes of malabsorption include proton pump inhibition (90), immunologic, intrinsic factor status, transcobalamin variants (91), postgastric surgery, bowel disease, or constipation (92).

This malabsorption may be circumvented by providing supplemental vitamin B12. Some authorities recommend routine supplemental vitamin B12, especially for the elderly (93,94).

Megaloblastic Anemia. Macrocytic anemia is the most common manifestation of vitamin B12 deficiency; it is rarely seen with serum levels >148 pmol/l (85). The macrocytosis may be normalized with folate repletion, leading to delay in

recognition and possible worsening of neurologic sequelae (61,66).

Hyperhomocysteinemia. Vitamin B12 deficiency is the major cause of elevated plasma total homocysteine in folate-fortified populations (95). Determinants of homocysteine levels include the status of folic acid, vitamin B6, and vitamin B12. A normal homocysteine level is <10 μmol/l (96). The estimated prevalence of hyperhomocysteinemia is between 5% and 10%. It can be categorized as mild (12–30 μmol/l), intermediate (31–100 μmol/l), and severe (>100 μmol/l) (97).

Homocysteine has been proposed as a vascular toxin ever since the first observations of premature vascular morbidity in patients with inherited homocysteinemia (98). Observational studies, summarized in a recent Cochrane review (97), have convincingly demonstrated an association between increasing homocysteine levels and cardiovascular outcomes. Approximately 4.1% of cardiovascular events can be attributed to elevated homocysteine levels (99).

Cognitive Status. Impairment of cognitive status is observed with vitamin B12 deficiency, usually in elderly people. Homocysteine levels have been predictive of cognitive decline in healthy older people (100). Other studies have found methylmalonic acid levels, but not B12 levels, to predict cognitive status, perhaps because this is the better marker of sufficiency (101). Neuropsychiatric disorders related to B12 deficiency present without anemia or metabolic derangements in the elderly in about 30% of cases (102).

Neurologic Complications. Long-standing vitamin B12 deficiency can lead to various neurologic sequelae including peripheral neuropathy, cognitive impairments, and subacute combined degeneration of the spinal cord.

Prostate Cancer. Elevated vitamin B12 levels (>376 pmol/l) showed a trend toward an increased risk of prostate cancer (OR 1.17 CI 0.95–1.43 $p = 0.06$). Other metabolites in the vitamin B12 cascade were also weakly linked to prostate cancer. This association remains to be confirmed, but it is relevant to the debate about food fortification with vitamin B12 as a public health measure (103).

Trials

Deficiency. Patients with frank deficiency can present with hematologic or neuropsychiatric syndromes. The risk for deficiency and symptom presentation increases with age. Traditional treatment involves parenteral replacement of vitamin B12. A recent Cochrane review identified two randomized trials comparing oral vs. intramuscular vitamin B12 therapy, and concluded that oral vitamin B12 therapy may be as effective as intramuscular therapy (87).

Homocysteine and Cardiovascular Effects and Mortality. As folic acid, vitamin B6, and vitamin B12 have a role in the generation of homocysteine, many cardiovascular studies examining the effects of vitamin supplements employed all three vitamins. To date, there are at least four major meta-analyses (97,104–106). Dosing varied for each vitamin depending on the trial: folic acid 0.5–40 mg/day, vitamin B12 0.4–2 mg/day, and vitamin B6 25–100 mg/day. Follow-up in these studies ranged from 6 months to 7.3 years. The main primary outcome measures were myocardial infarction, stroke, and all-cause mortality. Most studies also reported the effect of vitamin B supplementation on total homocysteine levels. Details of these trials are summarized in Table 4.

Vitamin B supplementation reduced homocysteine levels especially in populations that were not exposed to dietary folate fortification. Baseline levels were between 10 and 13 μmol/l and net reduction was between 2 and 4 μmol/l (20–40%) over the course of follow-up (97,104–106).

Myocardial infarctions and other cardiac outcomes were not improved with vitamin B supplementation. The pooled relative risks for these events consistently surrounded unity with strong evidence of homogeneity in the trials pooled (low I^2 values) [RR 1.03 (CI 0.94–1.13, 7 RCTs, I^2 0%) (98), RR 1.04 (CI 0.94–1.16, I^2 31%) (106), RR 1.03 (CI 0.97–1.1) (106)]. Significant heterogeneity was not demonstrated in these analyses.

The effect of B12 supplementation on stroke outcomes remains debatable, with some studies showing a tendency or marginally statistically significant reduction in the risk of stroke (107,108), and others observing no benefit (104–106,109,110).

Vitamin B supplementation did not impact all-cause or cardiovascular mortality. In most studies, mortality was either part of a combined primary outcome or a secondary outcome [RR 1.00 (CI 0.92–1.09, 6 RCTs, I^2 0%) (98), RR 1.01 (CI 0.95–1.07, 13 RCTs, I^2 0%) (106), RR 1.02 (CI 0.97–1.08) (106)].

Cognitive Status. The evidence for vitamin supplementation on cognitive status is sparse (111). Most studies show no benefit in dementia, including Alzheimer's disease, or in cognitive deficits (112–119). A Cochrane review in 2009 identified only three trials evaluating the ability of vitamin B12 supplementation to prevent or retard cognitive deficits in elderly patients with low vitamin B12 levels (120). Cognitive and dementia scores did not improve. This review, however, was limited by small studies with less than one-year follow-up. Another Cochrane review of combined folic acid and vitamin B12 supplementation reached similar conclusions (72).

People with Low Glomerular Filtration Rate & End-Stage Renal Disease

Sufficiency Data

Vitamin B12 status in the renal population is dependent on the extent of uremia and the impact on nutrition. At baseline, in a recent trial in dialysis patients, mean plasma vitamin B12 level was around 350 pmol/l (ranging from 154 to 932 pmol/l) (121).

Extended duration hemodialysis (>15 hours/week), hemofiltration or hemodiafiltration does not lead to increased risk of vitamin B12 deficiency in comparison with standard hemodialysis (17,122).

Homocysteine and Cardiovascular and Mortality Outcomes. Elevated homocysteine levels in renal patients are not necessarily due to vitamin B insufficiency, but may reflect reduction in the enzymes present in normal kidney parenchyma. Uremia may also reduce the activity of methionine synthase. Average homocysteine levels in people with ESKD are approximately 25 μmol/l in patients who eat a folate-fortified diet and 35 μmol/l in patients eating an unfortified diet (123).

A recent meta-analysis assessed the influence of homocysteine levels on cardiovascular outcomes in patients with end-stage renal disease (123). Most studies involved hemodialysis patients. The pooled risk estimate for all-cause mortality was not significant (RR 1.02), nor was the risk of cardiovascular events (HR 0.99). However, when analyzing studies where there was no supplementation or folate fortification, there was a small, statistically significant association with mortality (HR 1.07 CI 1.03–1.13 $p = 0.001$) and morbidity (HR 1.09 CI 1.03–1.14).

Neuropsychiatric Complications. The association of vitamin B12 and homocysteine with cognitive status, to our knowledge, has not been investigated in the renal population despite the high prevalence of cognitive abnormalities. Lower cobalamin levels have been associated with depression in hemodialysis patients (124).

Trials

Homocysteine and Cardiovascular and Mortality Outcomes. Because the intrinsic factor pathway is saturable and independent of intrinsic factor absorption has limited capacity, leading to the absorption of about 1% of an oral dose, intravenous therapy has the potential to raise B12 levels to a larger extent than achievable with oral therapy. It has been suggested that these pharmacologic effects may lead to more dramatic homocysteine lowering than therapeutic or near-therapeutic replacements (125). Intravenous hydroxycobalamin given to vitamin B12-replete patients on dialysis led to 14-fold increases in B12 and 23% reductions in homocysteine (126). In a randomized crossover trial, hydroxycobalamin 1 mg intravenously every 4 weeks resulted in a 40-fold increase in serum B12 levels in patients on hemodialysis, whereas cyanocobalamin levels increased 10-fold; however, reduction in homocysteine was similar with both treatments, around 33% (127). Oral vitamin B12 combined with folic acid and pyridoxine has been shown, in randomized controlled trials, to reduce total homocysteine levels by 30–50% in patients with low glomerular filtration rate or end-stage renal disease (121,128–130).

In a recent, multicenter, randomized trial, 650 patients with end-stage renal disease who had average homocysteine levels of 28.2–30.0 μmol/l were randomized to two B vitamin regimens given postdialysis (121). The active regimen consisted of 5 mg folic acid, 50 μg cobalamin, and 10 mg vitamin B6, whereas the placebo regimen consisted of 0.2 mg folic acid, 4 μg cobalamin, and 1 mg vitamin B6. Homocysteine levels fell significantly with active treatment (-10.4 μmol/l vs. -1.8 μmol/l). However, there was no difference in all-cause mortality (31% vs. 28%) or cardiovascular events (25% vs. 30%). Interestingly, the change in cobalamin levels from baseline was similar in both groups despite differing doses of cobalamin supplementation (100–125 pmol/l rise).

Multiple studies have demonstrated similar effects of vitamin B12 therapy on homocysteine levels and a lack of efficacy with regard to cardiovascular outcomes in patients with low glomerular filtration rate and on dialysis (129–131).

Cognitive Effects. As in the nonrenal population, supplementation has not been shown to improve cognitive outcomes. A 1-year study involving patients with low glomerular filtration rate and patients on dialysis found that supplementation with a vitamin B complex reduced homocysteine levels in the treatment group, but had no beneficial outcomes on cognitive functioning in comparison with placebo (49).

Summary. Vitamin B12 is an important vitamin in the catabolism of aminoacids and fatty acids. Deficiency has been linked to neurologic, hematologic, and cognitive effects. Current recommendations require a daily intake of 2.4 μg to maintain sufficiency. Given the effects of age and the prevalence of vitamin B12 malabsorption, use of routine low-dose supplementation to prevent overt deficiency in elderly patients, whether or not on dialysis, may be reasonable (132).

Given the strong observation of the association between homocysteine and cardiovascular outcomes, many studies have examined the effects of vitamin B12 in the prevention of these outcomes. Unfortunately, the evidence overall shows no role of vitamin B12 therapy with other B vitamins for the reduction of cardiovascular, cerebrovascular, or mortality outcomes.

Vitamin C

Background

Vitamin C (ascorbic acid) is a water-soluble vitamin produced from metabolism of glucose. Only the L enantiomer has biologic activity. Most animals possess the enzyme (L-gulonolactone oxidase: GULO) required for its synthesis, so that they do not require exogenous dietary ascorbic acid: for these animals, ascorbic acid is not a vitamin (133). Loss of the enzyme appears to have occurred at more than one point in evolution; some primates, including humans, guinea pigs and capybara, and some passerine birds require dietary vitamin C.

The frank deficiency syndrome of scurvy has a unique place in the history of clinical medicine. In 1753, the British naval surgeon (ship's doctor) Joseph Lind described in five paragraphs of his 358-page treatise his nonrandomized controlled experiment on sailors with scurvy ($n = 2$ per group) that is often credited as the first description of a controlled clinical trial (134). Scurvy, the clinical syndrome resulting from vitamin C deficiency, is characterized by gum disease, tooth loss, skin rash, corkscrew hairs (poikilocytosis), and fatigue. In Lind's time, it was a life-threatening disease that commonly reduced crews on long sea voyages by more than 50%, resulting from the consumption of a ship's diet devoid of fresh vegetables. The two seamen who received two oranges and a lemon daily for 6 days recovered, one to the point of return to duty and the other to the capacity of nurse for the other afflicted men; controls remained poor or deteriorated.

The serendipitous discovery, in the search for animal models of beriberi, that guinea pigs developed scurvy in response to vitamin C deficiency led to a reliable animal model and facilitated the identification of the anti-scorbutic substance in citrus fruits.

A number of critical roles for vitamin C have been identified: it is a cofactor in pathways for collagen synthesis, explaining many of the clinical manifestations of scurvy. It is a potent antioxidant, perhaps the most quantitatively important free radical scavenger in blood (135).

Dietary Sources and RDA

Usual dietary sources are citrus fruits, but some green vegetables such as broccoli and spinach are rich in vitamin C. Usual dietary intake on a western diet is around the RDA, which was increased in 2000 to 60 to 90 mg/day for men and 75 to 90 mg/day for women (136,137). As for vitamin D, the difference between required and optimal is controversial. Nonhuman primates who also lack the GULO enzyme required for vitamin C de novo synthesis typically consume 2–6 g of vitamin C daily; wild fruits and new shoots are particularly rich sources. Animals that possess GULO synthesize much larger quantities that the RDA also: for example, goats synthesize 13 g daily and can triple this in times of stress. For this reason, some scientists, most notably Nobel Laureate Linus Pauling, have advocated for daily intakes of 1–2 g/day, sometimes referred to as megadosing (138). The American Medical Association/Nutrition Advisory Group recommends 100 mg/day in total parenteral nutrition. A typical dialysis vitamin such as Replavite contains 100 mg (136).

Absorption and Bioavailability

Vitamin C is absorbed actively and passively, and is highly bioavailable, with 75–90% absorbed in a typical diet. Absorption may fall to as low as 16% in people who are vitamin C-replete who have high intakes (139).

Excretion and Metabolism

In people with normal renal function, excess ingested vitamin C is rapidly excreted in the urine (31). Some is also metabolized to oxalate, leading to concerns that supplements, especially megadoses, may lead to kidney stones. However, the initial studies reporting very large increases in urinary oxalate used heat in the analytic process that may have converted urinary vitamin C to oxalic acid. Subsequent studies avoiding this problem have shown more modest increases in oxalate, within the normal range, and the possibility that this too resulted from artefactual conversion from vitamin C in vitro remains (38).

In people whose GFR is low, there is also the concern that the calcium oxalate saturation threshold may be exceeded in blood leading to systemic oxalosis and vascular calcification (140).

Toxicity

Other than these concerns about oxalate accumulation or stones, it appears that vitamin C itself is, at least acutely, very safe (31).

General Population

In keeping with theory about antioxidant properties, cohort data consistently show a strong relationship between low vitamin C levels, cardiovascular death and death from all causes (summarized in (135)). The cut-point beyond which risk of events decreases appears to be around levels of 40–50 mmol/l (141). Observational data relating use or dose of supplemental vitamin C to outcomes are not, to our knowledge, available. However, the Medical Research Council/British Heart Foundation Heart Protection Study randomized 20,536 adults to antioxidant vitamins (vitamin C 250 mg daily, vitamin E 600 mg daily, carotene 20 mg daily) or placebo and found no difference between groups in cardiovascular or all-cause mortality (rate ratio cardiovascular death 1.04; death from all causes 1.04) (142).

While megadose vitamins have been implicated in kidney stones or renal oxalosis in individual cases, some authorities feel that these data do not stand up to critical review and that harm from doses of 1–2 g/day in people without preexisting low GFR or kidney stones has not been well documented (summarized in (38,140)).

In critical illness, blood levels appear to fall rapidly and recovered only after days on high-dose supplementation (more than 1000 mg/day) (143). In these patients, high urinary losses were seen with high-dose supplementation, in the face of plasma levels that remained extremely low for several days after the initiation of supplements.

Common Cold

A Cochrane meta-analysis of 29 RCTs of 11,306 people suggests that while prophylaxis with high-dose vitamin C (defined as more that 200 mg/day for the purpose of the review) does not affect the incidence of colds (RR 0.97, 95% CI 0.94–1.00), it does reduce severity and duration (144). Taking vitamin C after the onset of a cold had no effect on either severity or duration. In a planned subgroup analysis of five RCTs of 598 people engaged in extreme activity or working in extreme cold, a protective effect on the incidence of colds was noted (RR 0.48, 95% CI 0.35–0.64). Interesting although these findings are, these doses should not be used in people with low GFR or people on dialysis outside studies, because of the risks of oxalosis, discussed in detail below.

Iron Absorption

By preventing the formation of insoluble and unabsorbable iron compounds and by promoting the conversion from ferric to ferrous iron (which is more readily absorbed), vitamin C increases the absorption of dietary and supplemental iron in the gut by up to 60% (145).

People with Low Glomerular Filtration Rate & End-Stage Renal Disease

Dietary Intake and Levels

In a cross-sectional study of patients with low GFR, vitamin C levels were positively associated with GFR, suggesting that either spontaneous or prescribed dietary restrictions limits adequate intake in people with advanced chronic kidney disease (145). Many vitamin-C-rich foods are also high in potassium, which may lead to their restriction in patients with advanced renal failure and in those on dialysis. Another cross-sectional study estimated dietary intake from dietary records at 94 mg/day in patients with low GFR and 66 mg/day in patients on dialysis (146). In cross-sectional studies, 15% of patients on HD had levels <10 mcmol/l (147), and 12% of patients on PD had levels below 2 mg/l

(148), generally considered below the scorbutic threshold. Supplementation appears to improve the situation, but not in all patients: an Australian study of patients on PD found 44% of unsupplemented patients and 17% of patients receiving around 100 mg daily had vitamin C levels less than 2 mg/l (149). In addition to low dietary intake, the dialysis procedure also contributes to deficiency: removal of this water-soluble nonprotein-bound small molecule has been estimated at mean 66 mg per HD session (150) and 29 mg per PD exchange (43). In PD, transport status was not predictive of levels (149).

Oral or intravenous vitamin C supplementation increases levels. For example, in patients on PD 100 mg daily for 4 weeks increased levels by 45% (151), and in another study, when patients on PD whose initial level was less than 4 mg/l were treated for 12 months with a multivitamin containing 120 mg vitamin C, levels rose from 1.7 (IQR 1.2–2.2) mg/l to 22.5 (IQR 16.7–32.9) mg/l (149).

Because of the nonspecific nature of many of the symptoms of vitamin C deficiency (fatigue, weakness, poor connective tissue, mental disturbances, anemia), it is possible that subclinical or unrecognized vitamin C deficiency contributes to the disturbances as part of the uremic syndrome in people with low GFR or people on dialysis.

As in the general population, lower vitamin C levels in patients on dialysis predict fatal and nonfatal major cardiac outcomes: adjusted hazard ratios were 3.90 (95% CI 1.42–10.67; $p = 0.008$) and 3.03 (95% CI 1.03–8.92; $p = 0.044$) for the lower (<32 mcmol/l and middle (32–60 mcmol/l) thirds compared with people in the upper third (>60 mcmol/l) (135). To the best of our knowledge, no trials of the effects of vitamin C supplementation in dialysis patients on cardiovascular events or death from all causes have been conducted or are planned (152).

Secondary Hyperoxaluria and Oxalosis

Oxalate is a product of metabolism of vitamin C and though dialyzable, accumulates in patients on dialysis (153). High levels of oxalate are seen in patients on peritoneal dialysis (33.1 ± 9.3 mcmol/l) and hemodialysis (40.3 ± 9.8 mcmol/l) (153): levels are similar to those seen in type 1 primary hyperoxaluria (47,149,153), an inborn error of metabolism associated with clinically important damage to the heart, vessels, joints, and muscles. In a 1985 study of seven patients, a strong correlation between vitamin C levels and oxalate levels was observed (154). Long-term intravenous supplemental vitamin C in moderate doses of 250–500 mg weekly led to increases in plasma oxalate levels that exceeded the supersaturation threshold for calcium oxalate in some patients (140). We do not know to what extent hyperoxalemia contributes to morbidity in patients with low GFR, but the possibility of vascular and tissue damage from calcium oxalate

precipitation means that large or even moderate doses cannot be recommended without caution. Further work is needed in this area.

Functional Iron Deficiency and Erythropoietin Hyporesponsiveness

Functional iron deficiency, defined as a low transferrin saturation with normal or high ferritin levels (>100 mcg/l), is thought to result when iron stores are adequate, but iron cannot be released from storage forms for hematopoiesis. The clinical syndrome is one of persistent anemia and erythropoietin hyporesponsiveness. Vitamin C, acting as a reducing agent, mobilizes iron from storage sites and also plays a direct role in the integration of iron into the heme moiety (155). A 2007 meta-analysis identified six trials of 327 patients treated with intravenous or oral vitamin C in doses of 200–500 mg once to three times weekly (155). Random-effect models were without important statistical heterogeneity and identified a rise in hemoglobin (9 g/l, 95% CI 0.5–1.2 g/l), fall in erythropoietin requirements (−17 units/kg/week, 95% CI –26 to –8 units/kg/week), and rise in transferrin saturation, without change in ferritin concentration. This suggests a potential role for larger doses of vitamin C in anemia management. However, this conclusion is qualified by the variable quality of the original studies. Furthermore, there were no measures of oxalate, adverse effect reporting was suboptimal, and the sample sizes and duration of studies were insufficient to detect possible increases in patient-important outcomes such as cardiovascular events (from calcium oxalate precipitation).

Randomized trials of vitamin C in dialysis patients have either examined the effects on blood levels of vitamin C and its metabolites or have focused on anemia outcomes. Blood levels rise predictably in HD and PD patients with oral or parenteral supplements; however, in patients on HD, supplementation with 500 mg weekly for a year led to a rise in oxalate level that was associated with around 40% of patients exceeding the saturation threshold for calcium oxalate product in blood (140). No clinical adverse events were noted.

Extended Hours Dialysis

Vitamin C levels were lower in patients on extended hours hemodialysis (0.30 vs. 1.14 mg/dl, $p < 0.001$) with 7/26 patients (27%) in the extended hours group having levels less than 0.18 mg/dl and 16/26 (73%) having levels less than the lower limit of normal (0.48 mg/dl) (17), compared with no patients in the conventional group. There was wide interindividual variation in vitamin C dose in this study; all patients received a multivitamin with 45 mg vitamin C, but a third of patients took additional vitamin C; mean dose in these patients was 151 mg/day.

B6 to Lower Oxalate

In a pre–post study of seven patients, vitamin B6 administration was temporally associated with a decline in serum oxalate levels in ascorbic acid-supplemented patients (48). B6 is a cofactor for glyoxalate conversion to glycine, reducing the substrate available for degradation into oxalate (47). To our knowledge, whether this might be clinically useful has not been further evaluated.

Multiple Pathways

Novel mechanistic insights into vitamin C in patients on dialysis are being elucidated. For example, high-dose vitamin C was shown to ameliorate dialysis-associated blood reactive oxygen species and total antioxidant score, decrease peroxidation of plasma lipid and red cell membranes, reduce hemolysis and levels of proinflammatory cytokines (156). Vitamin C administration also leads to shifts in several polypeptides identified in proteomic analysis from abnormal expression levels observed in patients on dialysis toward the expression levels seen in normal controls (157). Finally, in a randomized trial of vitamin C in patients with renal transplants, some, but not all, indices of vasomotor function were improved when assessed by intravascular ultrasound (158).

Treatment of Cramps

One trial compares the use of oral vitamin C 250 mg daily, vitamin E 400 mg daily, both, or placebo in the treatment of cramps, and showed a reduction of 61%, 54% and 97%, respectively, for the active treatment, compared with 7% for placebo (159). However, the concerns that cardiovascular events from systemic calcium oxalate deposition might increase, as discussed above, apply when considering whether to use vitamin C for this indication also.

Treatment of Iron Overload

In a small randomized trial of patients on hemodialysis with iron overload secondary to intravenous iron, vitamin C 200 mg iv three times weekly improved erythropoietin responsiveness more than desferrioxamine or controls, but did not lead to increases in iron loss or mobilization compared with either group (160).

Ongoing Studies

In hemodialysis patients, trials of vitamin C to reduce hyperpigmentation, and to alleviate restless legs syndrome, are ongoing (152). One trial in patients with chronic kidney disease will examine antioxidant properties by comparing vitamin C with N-acetylcysteine for prevention of contrast nephrotoxicity (152).

Summary

Vitamin C deficiency is prevalent in unsupplemented patients on dialysis, with perhaps 10% having severe deficiency, below the scorbutic threshold. It is also possible that most dialysis patients, or even most humans, eating a typical western diet, have intakes and levels that are far from optimal. Pending rigorous randomized trials in dialysis patients, powered to examine cardiovascular and infectious outcomes and the possibility of harm from calcium oxalate, it seems reasonable to administer low-dose vitamin C supplementation, perhaps 60–100 mg daily, to patients on hemodialysis, and to consider the diagnosis of vitamin C deficiency in patients whose anemia or fatigue is disproportionate to their known comorbidities, in patients on extended-hours hemodialysis treatments, and in those who have difficulty in maintaining a balanced diet within the restrictions imposed by dialysis. Short-term use of parenteral vitamin C can be considered for patients with functional iron deficiency, but strong evidence of the efficacy of this approach is lacking, and there are no long-term safety data.

Multivitamin Supplements

In patients on dialysis, the evidence summarized above suggests that supplementation with low doses, similar to the RDAs, for at least some of the B vitamins (in particular B1, B6, B9 [folic acid] and B12) and for vitamin C is warranted, although no randomized trials have been performed. Vitamins formulated for patients on dialysis tend to include these vitamins in doses that seem reasonable (161,162). We are not aware of strong reasons to choose one over another. Because of the factors associated with advanced chronic kidney disease that lead to poor intake, at least one agency recommends the use of a vitamin B and C multivitamin in patients with low GFR, not on dialysis, who have poor eating habits, are consuming less than 50% of meals or fewer than 1500 kcal/day, or who have appetite changes, food aversions, or weight loss (162). We believe general multivitamin tablets should be avoided, at least in patients on dialysis. They tend to contain somewhat lower doses of B vitamins, which might not adequately cover needs. They often contain doses of vitamin C in excess of those recommended for people on dialysis. They contain vitamin A, which is unnecessary and may lead to toxicity. Finally, general multivitamin tablets contain vitamin D, often in doses lower than public health recommendations for the general population. The effects of nutritional vitamin D supplementation in patients with very low GFR and patients on dialysis are currently unclear (163). When supplementation of nutritional vitamin D to patients on dialysis is desired, we believe, it is likely safer to prescribe this separately so that its pharmacologic effects can be taken into account in the interpretation of calcium, phosphate, and parathyroid hormone values.

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