

## Vitamins in pre-dialysis patients

Date written: October 2004  
Final submission: August 2005  
Author: David Voss

### GUIDELINES

No recommendations possible based on Level I or II evidence

### SUGGESTIONS FOR CLINICAL CARE

(Suggestions are based on Level III and IV evidence)

- Chronic kidney disease (CKD) patients following a protein-restricted diet should receive supplementation with thiamine (>1 mg/day), B<sub>2</sub> (1–2 mg/day) and B<sub>6</sub> (1.5–2.0 mg/day). (Level IV evidence and Opinion)
- CKD patients with a GFR below 50 mL/min and with an elevated parathyroid hormone (PTH) level or histological evidence of osteodystrophy should receive vitamin D supplementation. (Level II evidence and Opinion)

(See Appendix for recommended daily intake of selected vitamins).

#### A. Water soluble vitamins:

Most B vitamins are supplied in a combined tablet form of 3 to 6 different vitamins. As they are water soluble, and when in excess easily cleared from the body, even in severe renal failure, supplementation is a safe way of ensuring deficiency of this group of vitamins is avoided.

#### Vitamin B<sub>1</sub> (thiamine):

Dietary sources of thiamine include fresh green vegetables, wholemeal grains and some meats. Potassium-restricted or protein-restricted diets may result in thiamine deficiency. It may take 12 months or more for the deficiency to develop.

For patients following a prolonged protein-restricted diet, supplementary thiamine (1.0–1.5 mg/day is adequate maintenance) should be added to their medication profile.

#### Vitamin B<sub>2</sub> (riboflavin):

Vitamin B<sub>2</sub> is plentiful in meat. As it is common (up to 40% of patients) for patients to become vitamin B<sub>2</sub> deficient on a protein-restricted diet, CKD patients following a prolonged protein-restricted diet should have their diet supplemented with vitamin B<sub>2</sub> by 1.0–2.0 mg/day.

**Vitamin B<sub>6</sub> (pyridoxine):**

Meat is a natural dietary source rich in pyridoxine. Pre-dialysis patients on erythropoietin and patients on protein-restricted diets can develop pyridoxine deficiency. Such at-risk patients should have supplementary pyridoxine (5 mg/day is adequate maintenance) added to their medication profile.

The relevance of reports of mega-dosing with vitamin B<sub>6</sub> (300 mg/day) being associated with a lowering of serum cholesterol is unknown in CKD patients.

**Vitamin B<sub>12</sub> (cobalamin):**

Vitamin B<sub>12</sub> is only plentiful in meat and meat product foodstuffs. B<sub>12</sub> requirements are low and deficiency is rare, and can take several years to develop after the introduction of a diet deficient in B<sub>12</sub>. Annual serum B<sub>12</sub> levels can be monitored in high-risk patients, especially vegans.

**Folic acid:**

Dietary sources of folic acid include fresh green vegetables but prolonged cooking destroys folic acid. Folic acid deficiency results in megaloblastic anaemia. There is no conclusive evidence for routine folic acid supplementation in pre-dialysis CKD patients. Only intra-cellular red corpuscle folic acid levels should be measured, as serum levels are not indicative of body stores. Pre-dialysis patients on supplementary erythropoietin may need folic acid supplementation with 200 mg per day, due to increased use of folate.

**Other B vitamins (biotin, niacin, pantothenic acid):**

Levels of these vitamins are elevated in CKD. The risk of deficiency is therefore low. There is no evidence for routine supplementation in the pre-dialysis CKD population.

**Vitamin C (ascorbic acid):**

Low potassium diets are also low in vitamin C. Patients on low potassium diets can become vitamin C deficient. Serum ascorbic acid levels are low in most pre-dialysis patients. Supplementary vitamin C of > 60 mg per day may increase the risk of hyper-oxalosis and associated nephrolithiasis (Kopple 1997).

A high intake of vitamin C is associated with hyperoxalosis, which may contribute to the vascular disease of renal failure patients or obstructive uropathy. Care should be taken not to exacerbate the CKD with oxalosis/urine crystal formation from the excessive administration of supplementary vitamin C.

Vitamin C supplementation may be given to assist the absorption of oral iron.

**B. Fat-soluble vitamins:**

**Vitamin A (retinol):**

Chronic kidney disease results in a rise in vitamin A levels by up to 20% above baseline. Retinol-binding protein (RBP) rises in renal failure and is associated with this vitamin A rise. Toxicity does not usually occur, as vitamin A is well

bound to the RBP. Supplementation is not required and regular monitoring of blood vitamin A level is also not required.

**Vitamin D (cholecalciferol):**

Care must be taken not to allow hypercalcaemia to ensue with vitamin D supplementation. Administration of vitamin D and dose adjustment should be prescribed initially at low doses with careful monitoring of serum calcium, phosphorus and PTH (Ando 2004). Vitamin D is potentially valuable for patients at high risk of developing secondary hyperparathyroidism (Sanchez et al 1999).

**Vitamin E (tocopherol):**

Levels of vitamin E in platelets drop with CKD and correct with supplementation. Serum levels have been documented to be low, normal and high in patients with CKD, with both normal and restricted-protein diets (Gilmour et al 1998).

Erythropoietin therapy has been noted to raise vitamin E levels. At present, no recommendation with regards to vitamin E supplementation in CKD patients can be made.

**Vitamin K:**

There is no information on vitamin K in relation to CKD. At present, no recommendation with regards to vitamin K supplementation in CKD patients can be made.

## **Background**

Water soluble vitamins, of the B and C class, cannot be stored in the body and are lost in the urine when taken in excess. It is theoretically possible, therefore, that in advanced renal failure, especially with oral supplementation, the pre-dialysis patient may become vitamin overloaded. Most B and C class vitamins have a high toxic:therapeutic ratio, and therefore vitamin levels are unlikely to accumulate to toxic levels with a normal diet. Vitamin C is a notable exception, in that excessive vitamin C may result in oxalate-containing nephrolithiasis, and exacerbation of renal failure.

The major dietary source of B vitamins is protein and implementation of a protein-restricted diet may lead to a deficiency of these vitamins (Mitch 1991, Ballmer et al 1995, Molitoris et al 1989, Gilmour et al 1998).

This guideline aims to outline the recommended daily intake and dietary requirements of vitamins: A, B<sub>1</sub>, B<sub>2</sub>, B<sub>3</sub>, B<sub>6</sub>, B<sub>12</sub>, folic acid, biotin, niacin, pantothenic acid, C, D, E and K. It will assess any evidence of an association between mortality/morbidity and abnormal levels of these vitamins. These include blood test/plasma, serum levels and dietary intake levels.

## **Search strategy**

**Databases searched:** MeSH terms and text words for kidney disease were combined with MeSH terms and text words for vitamins then combined with the Cochrane highly sensitive search strategy for randomised controlled trials and search filters for identifying prognosis and aetiology studies. The search was carried out in Medline (1996 – November Week 2 2003). The Cochrane Renal Group Trials Register was also searched for trials not indexed in Medline.

**Date of searches:** 27 November 2003.

## **What is the evidence?**

Observational studies have shown the presence of low levels of thiamine (B<sub>1</sub>), riboflavin (B<sub>2</sub>) and pyridoxine (B<sub>6</sub>) in pre-dialysis patients (Kopple et al 1981).

Homocystine levels are known to increase in progressive renal failure, prior to dialysis. Hyperhomocystinaemia may result in increased cardiovascular disease. A dose of 1–2 mg/day of folate is sufficient to reduce these homocystine levels in dialysis patients. It is not known if hyperhomocystinaemia in CKD is the cause of increased cardiac disease. One interventional study (ASFAST, Zoungas et al 2004), is enrolling 315 CKD patients and 213 healthy controls, and will hopefully clarify if intervention with high-dose folic acid reduces cardiovascular morbidity and mortality.

The suppression of calcitriol by hyperphosphataemia and its reduced synthesis (from the reduced nephron mass) in CKD both lead to a deficiency in calcitriol (1,25-dihydroxycholecalciferol) once the GFR falls below 40 mL/min (Portale et al 1989, Hamdy et al 1995).

One prospective multicentre study (Hamdy et al 1995) that was placebo-controlled and run over a two-year period, showed that 0.25 µg/day of alfacalcidol, increasing to 1.0 µg/day, lowers PTH levels and improves bone turnover histological parameters.

## **Summary of the evidence**

Vitamin B supplementation should be instigated in protein-restricted diets in the pre-dialysis phase of renal care.

## **What do the other guidelines say?**

**Kidney Disease Outcomes Quality Initiative:**  
No recommendation.

**British Renal Association:**  
No recommendation.

**Canadian Society of Nephrology:**

No recommendation.

**European Dialysis & Transplant Nurses Association/ European Renal Care Association:**

The dietician/nutrition advisor will ensure that the dietary intake of vitamins in the pre-dialysis patient is adequate and advise on supplements as required.

## **Implementation and audit**

1. All pre-dialysis patients who are following a protein-restricted diet should have B vitamin supplementation. Most proprietary formulations have an adequate amount of the required vitamins. One or two B vitamin complex tablets daily is usually adequate. The prescribing physician should ensure that the prescribed medication contains the recommended content.
2. The diet could be supplemented with at least 1 mg of folate per day. Higher doses may be required in cases of erythropoietin administration. If available, therapy efficacy and compliance could be followed by regularly taking blood homocysteine levels.
3. Vitamin C supplementation may be appropriate to assist supplementary oral iron absorption (see separate iron and erythropoietin guidelines). Mega-dosing of vitamin C (e.g. prevention of common cold) must be avoided.
4. Parathyroid hormone level should be measured once GFR is below 60 mL/min. Regular monitoring of PTH levels (3–6 monthly) should be performed, and oral vitamin D dose should be adjusted to maintain near-normal PTH levels. Pulse oral dosing (two or three days per week) has a greater effect in lowering PTH levels, with less provocation of hypercalcaemia. Care must be taken not to induce hypercalcaemia with supplementary vitamin D therapy, which may result in nephrolithiasis, and exacerbate renal failure. Regular review of the patient's diet by a renal dietician must also occur, as the calcium content of foods in the diet may vary (e.g. calcium-supplemented foods, milks and juices).

## **Suggestions for future research**

No recommendations.

## **References**

Ando R. [Vitamin D therapy in predialysis renal failure]. *Clin Calcium* 2004; 14: 73–77.

Ballmer PE, McNurlan MA, Hulter HN et al. Chronic metabolic acidosis decreases albumin synthesis and induces negative nitrogen balance in humans. *J Clin Invest* 1995; 95: 39–45.

Gilmour ER, Hartley GH, Goodship TH. Trace elements and vitamins in renal disease. In: Mitch WE, Klahr S, editors. *Handbook of nutrition and the kidney*. 3<sup>rd</sup> ed. Philadelphia: Lippincott-Raven; 1998. p. 107–22.

Hamdy NA, Kanis JA, Beneton MN et al. Effect of alfacalcidol on natural course of renal bone disease in mild to moderate renal failure. *Br Med J* 1995; 310: 358–63.

Kopple JD. Nutritional management of non-dialysed patients with chronic renal failure. In: Kopple JD, Massry SG, editors. *Nutritional management of renal disease*. Baltimore: Williams and Wilkins; 1997. p. 479–531.

Kopple JD, Mercurio K, Blumenkrantz MJ et al. Daily requirement for pyridoxine supplements in chronic renal failure. *Kidney Int* 1981; 19: 694–704.

Mitch WE. Dietary protein restriction in chronic renal failure: nutritional efficacy, compliance, and progression of renal insufficiency [editorial]. *J Am Soc Nephrol* 1991; 2: 823–31.

Molitoris BA, Froment DH, Mackenzie TA et al. Citrate: a major factor in the toxicity of orally administered aluminium compounds. *Kidney Int* 1989; 36: 949–53.

Portale AA, Halloran BP, Morris RC Jr. Physiologic regulation of the serum concentration of 1,25-dihydroxyvitamin D by phosphorus in normal men. *J Clin Invest* 1989; 83: 1494–99.

Sanchez CP, Goodman WG, Salusky IB. Prevention of renal osteodystrophy in predialysis patients. *Am J Med Sci* 1999; 317: 398–404.

Zoungas S, Branley P, Kerr PG et al. Atherosclerosis and folic acid supplementation trial in chronic renal failure: baseline results. *Nephrology* 2004; 9: 130–41.

## Appendix

**Table 1 Recommended daily intake of selected vitamins**

<b>Vitamin</b>	<b>Males</b>	<b>Females*</b>	<b>Comments</b>
Vitamin A (retinol)	750 µg retinol equivalents	750 µg retinol equivalents	
Vitamin B <sub>1</sub> (thiamine)	0.9–1.1 mg	0.7–0.8mg	See note below if administering protein-restricted diet
Vitamin B <sub>2</sub> (riboflavin)	1.3–1.7 mg	1.0–1.2 mg	See note below if administering protein-restricted diet
Niacin	16–19 mg niacin equivalents	11–13 mg niacin equivalents	
Folate	200 µg	200 µg	See note regards homocystine, and if on erythropoietin therapy
Vitamin B <sub>6</sub> (pyridoxine)	1.0–1.9 mg	0.8–1.4 mg	See note regards if administering protein-restricted diet
Vitamin B <sub>12</sub> (cobalamin)	2.0 µg	2.0 µg	
Vitamin C (ascorbic acid)	40 mg	30 mg	May use more to aid iron absorption
Vitamin E (tocopherol)	10 mg (α-tocopherol equivalents)	7 mg (α-tocopherol equivalents)	

\* Additional supplementation is recommended for pregnant and lactating women.