REVIEW

Guidelines for Vitamin Supplements in Chronic Kidney Disease Patients: What Is the Evidence?

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Wide discrepancies exist in the use of vitamins in kidney disease, and evidence-based recommendations are sparse. Water-soluble vitamin levels may be inadequate in patients not receiving supplements and this may be associated with increased mortality, which deserves further attention to increase strength of evidence.

Supplements should be administered cautiously as renal mechanisms to prevent hypervitaminosis are no longer functional. The most reliable assays for vitamin status examine tissue mechanisms that rely on vitamins as cofactors. Vitamin A levels are generally quite high, vitamin D is low and requires supplementation, and the benefits of vitamin E may be linked to its usage in a modified dialysis membrane. Because of restricted diets that provide limited vitamin intake from food, many renal patients can benefit from a tablet that adds an amount equal to one recommended daily allowance of water-soluble vitamins, but larger amounts are not appropriate or beneficial.

Vitamin status is influenced by interaction of many variables, and individual attention to each patient is warranted to achieve optimal vitamin status.

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Providing multi-vitamin supplementation for patients with renal disease has never been uniformly practiced, since the beginnings of treatment for renal failure. The need for the active metabolite of vitamin D, calcitriol, was recognized very early because of the key role of the kidney in vitamin D activation, and this therapy has been almost universal for past 20 years (ref). For the other vitamins, during the period between the years 1970 and 1990, use of vitamin supplements was at the discretion of the practitioner or often the result of the individual patient decision. The observation of widespread vitamin C deficiency and the ability of folate/B-12/B-6 to lower homocysteine in patients on dialysis lead to a more widespread use of additional vitamin supplements, and by the year 2000, administration of a mixture of water-soluble vitamins was the standard recommendation in many countries, including the United States. However, this has not yet gained uniform acceptance, and a Dialysis Outcomes and Practice Patterns Study (DOPPS) study in 2004 illustrates the widely varying use of multivitamins in world-wide renal disease management. Although cost is a factor, it is not a dominant consideration because a typical renal multi-vitamin capsule costs from US $0.1 to $0.5 per day. Apart from universal acceptance of therapy with active vitamin D or its analogues, several factors are responsible for this variability in the usage of vitamins.

Although benefits were anticipated from introduction of vitamin E supplements in renal disease, following epidemiological studies between the years 1980 and 1995 that reported major cardiovascular benefits from high intakes of vitamin E, this was not substantiated in a controlled trial of vitamin E supplements and end-stage renal disease (ESRD) published in 2000, and vitamin E supplements have not been widely effective in decreasing heart disease in the general population. Therapy with folate/B12/B6 certainly lowers homocysteine, but in a variety of trials with nonrenal...
disease patients, only limited benefits for cardiovascular disease were reported. Vitamin A levels are already very high in ESRD because of the lack of the normal renal clearance mechanism, and vitamin A supplements are contraindicated.

Although there is a well-documented evidence for the ability of vitamin C to improve anemia management in ESRD, concerns about oxalosis have restricted vitamin C supplementation to relatively small doses that may have limited action on erythropoiesis.

Renal Disorders That Could Lead to Different Vitamin Requirements Than the Healthy Population

There are several ways through which renal disorders could affect vitamin requirements. The water-soluble vitamins are freely filtered into the glomerular filtrate, and the amounts released into the glomerular filtrate would readily lead to deficiency, except for active tubular resorption. For example, about 2 grams of vitamin C/day appears in the glomerular filtrate in a healthy adult, which is much more than typical dietary intake and larger than the total vitamin C body pool of 1.5 grams. The active vitamin C transporters in the proximal tubule are essential to conserve vitamin C and prevent the development of vitamin C deficiency. Other water-soluble vitamins with established active tubular resorption mechanisms that appear in the filtrate include thiamine, niacin, folate, B12, and riboflavin. In poorly-controlled diabetes, thiamine deficiencies are able to develop where a high level of glomerular filtration but a deficient thiamine resorption in the proximal tubule is reported, which may also be the case for other water-soluble vitamins. This could be a problem whenever there is tubular dysfunction as part of kidney disease, and supplements of water-soluble vitamins may be needed to maintain healthy tissue levels.

With advanced chronic kidney disease (CKD), the major pattern is that little if any vitamin excretion occurs, and there is the possibility of very high levels. With a large dose of water-soluble vitamins, amounts of each normally appear in the urine because the renal threshold has been exceeded. However, in late-stage CKD, this “overflow” mechanism does not operate, and vitamins can accumulate to high levels in the bloodstream.

With development of ESRD, there is a very unstable pattern, with vitamins reaching high levels between hemodialysis treatments and then falling dramatically during hemodialysis. Substantial amounts of vitamins could be lost during dialysis, resulting in deficiency. Because of variation over time, plasma levels are a poor marker for status in ESRD and concentrations in white cells and red cells are more reliable. With typical levels of supplementation, cellular levels are almost always normal or even elevated.

In addition, each form of renal failure might impose special requirements for vitamin intakes. Because the normal renal catabolism of vitamin A is lost in renal disease, intakes of vitamin A should be conservative, and supplements should be avoided because they might result in harmful tissue levels. As reviewed elsewhere (Handelman, the current volume), the accumulation of stored iron in renal failure can often justify substantial doses of vitamin C to aid in mobilization of iron, but care is needed to avoid damage from oxalosis. In some cases of ESRD, there is an unusual form of thiamine deficiency linked to Wernicke's encephalopathy, which can be treated with thiamine supplements; this dangerous condition indicates that occasional screening of all ESRD patients for thiamine status is warranted.

Adherence to Vitamin Supplementation in Different Countries

In 2004, it was reported by DOPPS that there was a striking international variation in the usage of vitamin supplement for patients on dialysis, and usage was low in some countries that have favorable patient outcomes. When vitamin usage was controlled between individual patients, there were a strong positive effect on survival associated with vitamin usage (Fig. 1). The lack of universal acceptance of this nutritional approach can be attributed to the shortage of controlled trials with patient outcomes, which are otherwise the basis for much clinical decision-making.

Dietary Factors That Justify Prudent Supplement Use in CKD Patients

In 2002, it was reported in Hong Kong that the dietary restrictions imposed on patients undergoing peritoneal dialysis led to diets with 50% to 75% of the normal content of all vitamins; this was largely because of restrictions on potassium- and phosphate-rich foods. This pattern can justify
The routine administration of a vitamin tablet containing 1 RDA of the major vitamins (except for vitamin A); doses larger than this should be avoided because renal disease patients can readily be brought into a state of high levels of vitamins, as a component of renal failure.

**Vitamin E Dialyzers: A Special Case That Might Improve Hemoglobin Levels, Through Interaction With RBC Survival**

Evidence for increased hemoglobin with long-term use of the vitamin E-coated dialyzer has been reported with a gradual corresponding reduction in EPO requirements. Because RBC lifetimes are often greatly compromised in ESRD through factors that seem to damage the RBC membrane, it is of interest to evaluate the effects of these dialyzers on RBC survival in the circulation, as this could lead to both higher achieved hemoglobin levels and decreased EPO dosage.

**Conclusions**

Wide discrepancies exist in the use of vitamins in kidney disease. Evidence-based recommendations are sparse. Water-soluble vitamin levels may be inadequate in patients who do not receive supplements and this may be associated with increased mortality, which deserves further attention to increase strength of evidence.

The transition between severe chronic kidney disease and dialysis needs examination because dialysis adds new features to metabolic disposition of vitamins. Care is needed to avoid use of large supplements because the normal renal mechanism to remove excess water-soluble vitamins no longer operates reliably. Supplement dose should be ideally adjusted to achieve normal physiological function.

Vitamin A levels are generally quite high, vitamin D is low and requires supplementation, and the benefits of vitamin E may be linked to its usage in a modified dialysis membrane.

Vitamin status depends on the interaction of demographics, previous and current vitamin intake, dialysate losses, residual kidney function, dialysis dose, type of dialyer, and, possibly, changes in metabolism; thus, individual attention to each patient is warranted to achieve optimal vitamin status.

**References**