Vitamin Deficiencies in Chronic Kidney Disease, Forgotten Realms

Related Articles, p. 360, p. 380, and p. 407

NOTWITHSTANDING THE IMPORTANCE of nutritional deficiencies in the etiology and associated adverse outcomes of the protein energy wasting syndrome of chronic kidney disease (CKD),[1] the knowledge of the burden and bioactivity of many nutrients and their effect on the health of the patients with CKD is very incomplete. This is relevant for defining desirable intake ranges of energy-producing nutrients, such as carbohydrates, proteins, and fats, as well as vitamins, minerals, and trace elements. Without sufficient data and understanding, the use of nutritional supplements to prevent inadequate intake may result in either excessive or insufficient intake of micronutrients for people with CKD, with consequences in many cases yet to be explored.

Micronutrients are excellent examples of this scientific void. Vitamins, minerals, and trace elements are essential to metabolic function. In a person without a chronic disease, variable intake of these nutrients is typically sufficient to allow normal functionality due to tight regulation. Increasing bioavailability and decreasing excretion are two mechanisms which work well to regulate micronutrient concentrations with day-to-day variations in intake. However, when a person has a chronic condition which impacts intake, absorption, utilization, and/or excretion of nutrients, the ability to maintain optimal concentration of any one nutrient is compromised. This is certainly a truism in the setting of CKD, and one with which we are probably all familiar. Contemporary reports of CKD describe the commonness of vitamin deficiencies, affecting in general around 50% of screened patients.[2-6] In the United States, as in many other countries, established dietary reference intakes (DRIs) have been produced based on expert consensus and systematic reviews of the literature. DRI ranges and optimal intake levels are based on the assumption of a healthy population,[7] with recommended dietary allowances (RDAs) defined as "the average daily dietary nutrient intake level sufficient to meet the nutrient requirement of nearly all (97%-98%) healthy individuals in a particular life stage and gender group".

Although DRIs and RDAs are important for public health targets and policies, they fall short when working with patients with chronic diseases and particularly those with CKD.[8] The Kidney Disease Outcomes Quality Initiative (KDOQI)[9] and European Renal Best Practice[10] guidelines generally suggest that "…it is prudent to supplement, rather than risk deficiency, especially when supplementation is safe at the recommended levels…". A problem in that statement is that, with few exceptions, recommended levels for most vitamins are mostly based on extrapolation from RDAs. Unfortunately, limited amounts of vitamin data exist in the literature on patients with CKD, with a representativeness and design that makes it difficult to determine whether the vitamin status is altered due to the disease state per se or due to signs and symptoms from or treatment of the disease (e.g., nausea or anorexia from uremia or diet restrictions and medications used to manage CKD).[11,12] Nephrologists and dietitians are left with their understanding of vitamin metabolism in CKD to determine whether a patient is at risk for or has already developed a nutrient deficiency/overdose.

In this issue of the journal, we are presented with three reports that collectively inform us on the commonness of vitamin deficiencies, the importance of assessing for micronutrients starting with clinical signs as a part of the overall nutrition assessment, and the still unknowns of repletion, overall illustrating the complexity of this issue. Park *et al.*[13] discuss the relationship between eGFR, albuminuria-to-creatinine ratio, and 25 hydroxyvitamin D concentrations (25[OH]D) in the large and well-phenotyped 2011-2012 Korean National Health and Nutrition examination Survey. The authors show that in the Korean general population, serum 25[OH]D are incrementally lower as markers of kidney function are worse. Their results are in line with previous reports from the other Western countries, emphasizing the role of kidney dysfunction in nutrient deficiencies and requirements in the community. Although recent observational studies link vitamin D deficiency with CKD progression,[14-16] lack of interventional trials in this regard precludes causality. The prevalence of hypovitaminosis D in the Korean CKD subpopulation (38.2%) was notably lower than that found in other societies,[14-16] a finding that in our opinion illustrates the difficulties of establishing uniform adequate dietary vitamin ranges. For the case of vitamin D, adequate intake will be affected by many

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factors such as sun exposure, use of sun screen, vitamin D levels in each country's habitual diet[17] or the culture/tradition of prescription of vitamin D–related medication in CKD patients.[18]

This issue also includes the case report by Kittisakmontri *et al.*[19] which discusses the clinical manifestations of vitamin C deficiency (scurvy) in a 6-year-old female patient undergoing dialysis. Vitamin C deficiency is also common in CKD patients and typically explained by dietary restrictions as well as losses due to use of diuretics or through dialyzate.[20] Vitamin C concentrations are not measured routinely in patient encounters, and this case report reminds us on the subtle clinical manifestations of scurvy, often not easy to separate from the normal manifestations of uremia. The patient is seen to have bleeding gums, gingival swelling, and petechial hemorrhaging on her legs. Such signs are classic for vitamin C deficiency and actually included in a nutrition focused physical examination that dietitians are encouraged to follow carefully in connection with their nutrition assessment.

Finally, the study from Obi *et al.*,[21] reports on an open-label, randomized control trial where 56 patients undergoing maintenance hemodialysis and resistant to erythropoiesis-stimulating agents (ESAs) were randomized to 60 mg of thrice-weekly intravenous vitamin B6. The rationale of this study builds on the role of vitamin B6 in the synthesis of hemoglobin, and previous observational and uncontrolled studies suggesting a potential benefit of vitamin B6 depletion in this pathway. About 40% of included patients were vitamin B6 deficient at study inclusion, and 10% more were found vitamin insufficient according to reference values. After 26 weeks, vitamin B6 deficiencies were repleted, but the intervention was not able to lower ESA resistance. On the contrary, the authors observed instead increased resistance to ESA treatment irrespective of baseline vitamin B6 status. Furthermore, there was a trend toward higher endogenous erythropoietin concentrations, which may be the compensatory response to increased resistance. Negative findings of this kind are important to move the field forward, and the authors are commended for their undertaking. They touch in the discussion on an interesting point above alluded, which is whether we need to reconsider the traditional definition of vitamin B6 deficiency (>20 nmol/L) in this population.

Tucker *et al.*[22] discussed in the journal 1 year ago whether routine multivitamin supplementation is necessary in hemodialysis patients. The interested reader may find in that systematic review an excellent argumentation on the insufficient knowledge that we currently have on vitamin deficiencies and vitamin interventions for CKD. Their conclusions[22] are an excellent corollary for this editorial. Present literature offers no strong rationale for routine multivitamin supplementation, with many uncertainties on desired ranges, potential benefits, and risks. Supplementation needs to be individualized on each patient's needs and risk profile, and the field urgently needs more rigor with well-powered evidence to define vitamin requirements for our patients. Currently, KDOQI and the Academy of Nutrition and Dietetics are investing great efforts in developing new "guidelines for nutritional management in kidney disease", with a dedicated chapter to micronutrient deficiencies. We look forward to this awaited initiative, scheduled for public review in early 2018. We hope it may bring new considerations for these, at times, forgotten realms.

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