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Special Report

25-Hydroxyvitamin D Testing and Supplementation in CKD: An NKF-KDOQI Controversies Report

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The benefits of and thresholds for 25-hydroxyvitamin D administration in individuals with chronic kidney disease (CKD) remain uncertain. In this report, NKF-KDOQI (National Kidney Foundation–Kidney Disease Outcomes Quality Initiative) endeavors to provide health care providers with the latest information on a controversial area in the management of CKD, the role for nutritional vitamin D. Although knowledge of the biological mechanisms of vitamin D for bone maintenance in individuals with all stages of CKD has expanded, no consensus currently exists within the medical community regarding methods for 25-hydroxyvitamin D supplementation or optimal 25-hydroxyvitamin D levels in individuals with CKD. Within this report, existing CKD guidelines are summarized and scrutinized and ongoing clinical trials are cited as sources for future guidance on the optimal management of vitamin D in CKD.
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PERSPECTIVE

The NKF-KDOQI (National Kidney Foundation–Kidney Disease Outcomes Quality Initiative) definition and staging system for chronic kidney disease (CKD),[1] which published in 2002, facilitated the development of clinical practice guidelines for managing the complications associated with kidney disease for stages earlier than kidney failure. Subsequent guidelines from NKF-KDOQI include 2 publications concerning bone metabolism and disease in patients with CKD (recommendations for adults[2] published in 2003, and for children,[3] in 2005). In the document focusing on adults, guideline 7 describes the prevention and treatment of vitamin D insufficiency and vitamin D deficiency in patients with CKD and includes the suggestion to measure 25-hydroxyvitamin D (25[OH]D) in individuals with stages 3-4 CKD in the setting of secondary hyperparathyroidism in order to identify individuals who would benefit from 25(OH)D supplementation. Guideline 7 was based on opinion, given the absence of clinical trial data to support 25(OH)D supplementation in individuals with CKD.

In 2009, KDIGO (Kidney Disease: Improving Global Outcomes) published clinical practice guidelines on the diagnosis, evaluation, prevention, and treatment of CKD–mineral and bone disorders[4] and the care of kidney transplant recipients.[5] These guidelines also provided opinion-based recommendations regarding measurement of 25(OH)D in patients with CKD stages 3-5, including those receiving dialysis, and in CKD stages 1-5 in kidney transplant recipients. The recommendations by KDIGO regarding 25(OH)D testing and supplementation did not necessarily mirror the KDOQI recommendations.

During the past decade, knowledge of the biological mechanisms of vitamin D for bone maintenance in individuals with all stages of CKD has greatly expanded. However, no consensus currently exists within the medical community regarding methods for 25(OH)D supplementation or optimal 25(OH)D levels in individuals with CKD.[2-4,6-8] This lack of consensus was highlighted in a report from the Institute of Medicine (IOM) Committee to Review Dietary References Intakes for Vitamin D and Calcium published in 2011.[9] In this article, we focus on the debate regarding thresholds for 25(OH)D supplementation and risks and benefits of 25(OH)D supplementation for adults with stages 3-5 non–dialysis-dependent CKD.

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BACKGROUND

Chemistry and Biological Activity

Vitamin D, an essential nutrient for all individuals regardless of CKD status, may be categorized into 2 major forms: vitamin D_2 and vitamin D_3. Vitamin D_2 (ergocalciferol) is produced by UV irradiation of yeast ergosterol and frequently is added to processed foods such as cereals and bread.[10] Vitamin D_3 (cholecalciferol) is synthesized in the skin by UVB radiation of 7-dehydrocholesterol[10] and occurs naturally in certain foods such as oily fish. Also, in the United States, synthetic vitamin D_3 is added to milk. Although both vitamin D_2 and D_3 may be synthesized commercially, their biological activity is limited until they undergo hydroxylation by 25-hydroxylase in the liver. This hydroxylation step forms 25(OH)D, which then is hydroxylated by 1α-hydroxylase in the kidney and other organs to 1,25-dihydroxyvitamin D (1,25[OH]$_2$D), the biologically active form of vitamin D known as calcitriol (Fig 1).[10]

Because 25(OH)D has a substantially longer half-life than 1,25(OH)$_2$D, the former is considered the major biomarker of total vitamin D stores obtained from cutaneous synthesis or foods.[10] However, it currently is not established to what extent 25(OH)D

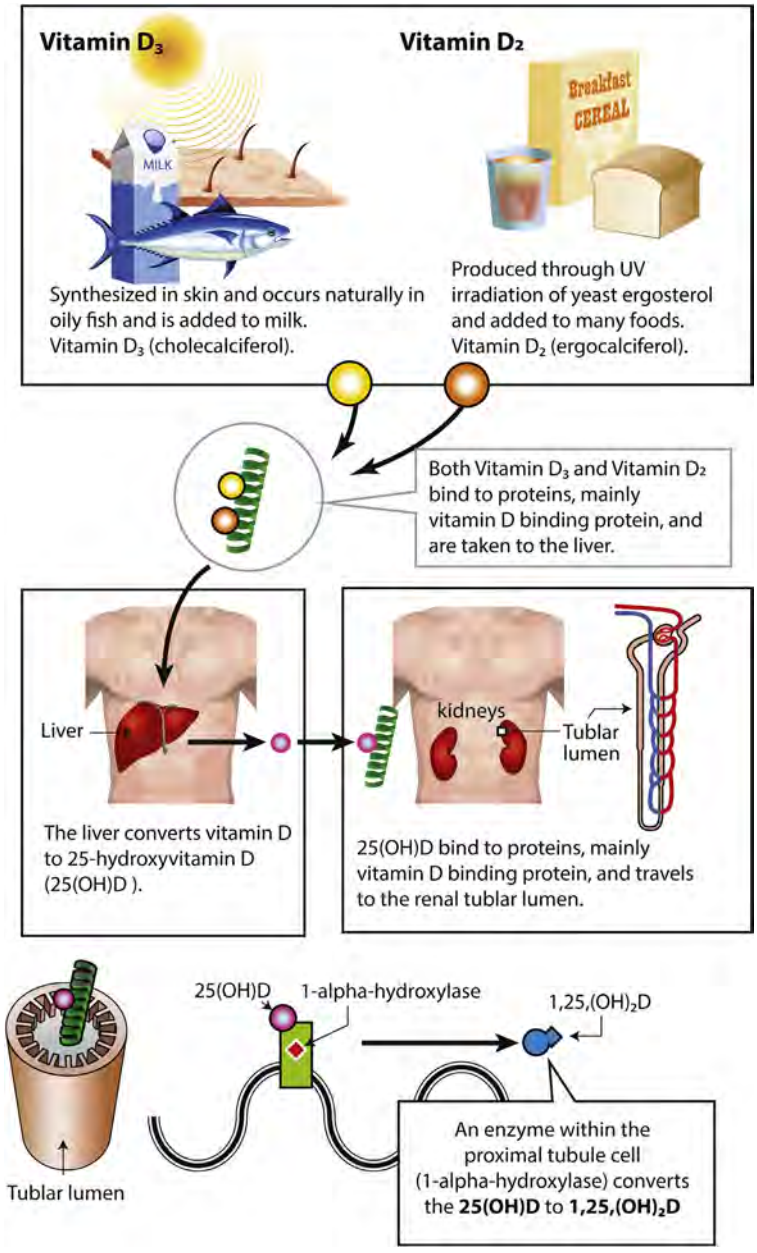

Figure 1. Overview of vitamin D metabolism. Abbreviations: 25(OH)D, 25-hydroxyvitamin D; 1,25(OH)$_2$D, 1,25-dihydroxyvitamin D. Figure courtesy of T. Mattix.

levels serve as a biomarker of the effects of vitamin D.[9] 25(OH)D must bind to vitamin D–binding protein, which is capable of carrying both 25(OH)D and $1,25(OH)_2D$. Biological actions of active vitamin D are mediated through binding of $1,25(OH)_2D$ to a vitamin D receptor, which is located in the nuclei of target cells. Because vitamin D is fat soluble[11] and uptake of ingested vitamin D depends on fat content in the intestinal lumen, vitamin D supplements are absorbed most efficiently when taken with meals that contain fat. Vitamin D also is stored in adipose tissue and when an individual loses weight, 25(OH)D levels increase.[12,13] Higher doses of vitamin D_2 or D_3 are needed to increase serum 25(OH)D levels in individuals who are obese compared with those who are not.[14]

In contrast, the biologically active $1,25(OH)_2D$ does not reflect overall vitamin D status because of its very short half-life (hours) and the fact that its net formation is not directly regulated by vitamin D intake or cutaneous synthesis of vitamin D.[9] Instead, the production of 1α-hydroxylase in the kidney is regulated tightly by plasma parathyroid hormone (PTH), fibroblast growth factor 23 (FGF-23), and serum calcium and phosphorus levels.[10]

The dominant role of active vitamin D is to interact with PTH to maintain serum calcium and phosphorus levels within a narrow range for bone maintenance.[15] We now know that the vitamin D–PTH axis also includes FGF-23, which is produced predominantly by osteoblasts and osteocytes and regulates renal tubular phosphate reabsorption by inhibition of the solute carrier 34 member family 1 and 3 sodium-dependent cotransporters in the proximal tubules.[15] FGF-23 also acts as a counter-regulatory hormone of $1,25(OH)_2D$ by decreasing production of 1α-hydroxylase and stimulating expression of 24α-hydroxylase, an enzyme that converts 25(OH)D and $1,25(OH)_2D$ to the inactive forms 24,25-dihydroxyvitamin D ($24,25[OH]_2D$) and calcitroic acid, respectively.[15] A reduction in $1,25(OH)_2D$ levels then leads to decreased intestinal absorption of calcium and increased PTH production given that $1,25(OH)_2D$ inhibits the expression of messenger RNA coding for PTH.[16] Moreover, the reduction in $1,25(OH)_2D$ levels alters the cellular effects of FGF-23. FGF-23 signaling in the proximal tubule is dependent on FGF-23 binding with α-klotho, a cofactor protein expressed in the kidney.[15] Because $1,25(OH)_2D$ levels induce α-klotho expression in the kidney and parathyroid gland, reductions in $1,25(OH)_2D$ levels are accompanied by reduced α-klotho expression,[17] which leads to cellular resistance to FGF-23.[15]

Thus, as glomerular filtration rate (GFR) decreases to < 60 mL/min/1.73 m^2 (CKD stage 3a), the ability to excrete a phosphorus load and maintain calcium homeostasis becomes progressively impaired (Fig 2).[17] When GFR declines to < 30 mL/min/1.73 m^2 (CKD stage 4), compensatory increases in FGF-23 and PTH levels may no longer maintain serum phosphorus levels within a normal range and $1,25(OH)_2D$ levels and 1α-hydroxylase activity become low. Emerging research also has suggested that reduced GFR is associated not only with diminished ability to produce $1,25(OH)_2D$, but also with a reduction in 25(OH)D and $1,25(OH)_2D$ catabolism, as reflected by an inverse correlation between $24,25(OH)_2D$ levels and GFR.[18] Whether this state of stagnant vitamin D metabolism is compensatory or harmful remains an area in need of further research.[18,19]

Existing Guidelines for 25(OH)D Testing and Supplementation in CKD

Development of the KDOQI clinical practice guideline for bone metabolism in adults with CKD was preceded by several key research findings for vitamin D and kidney disease. In 1976, Eastwood et al[20] showed low levels of 25(OH)D in patients with both CKD and osteomalacia and that supplementing these patients with 25(OH)D lowers PTH levels.[20-22] In 1975, Chertow et al[23] discovered that administration of the active form of vitamin D, $1,25(OH)_2D$, reduces PTH secretion in rats. Approximately 10 years later, several investigators showed that $1,25(OH)_2D$ suppresses parathyroid hormone transcription and parathyroid cell prolifeation via the vitamin D receptor.[16,24,25] This discovery dramatically changed the clinical approach for managing bone disease in individuals with kidney disease and facilitated the discovery of active vitamin D analogues for the treatment of secondary hyperparathyroidism in end-stage renal disease. Subsequently, a cross-sectional study reported a lack of

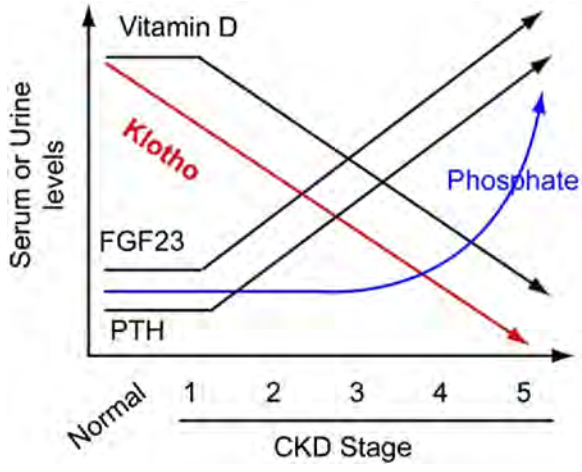

Figure 2. Changes in phosphate-regulating factors by chronic kidney disease (CKD) stages. Abbreviations: FGF23, fibroblast growth factor 23; PTH, parathyroid hormone. Reproduced from John et al[100] with permission of the National Kidney Foundation.

inappropriately elevated PTH levels or subperiosteal resorption patterns in pelvic or hand x-rays in hemodialysis patients with 25(OH)D levels > 40 ng/mL.[26] In addition, a seminal article published in 1998 reported a high prevalence of 25(OH)D deficiency, defined as 25(OH)D level ≤ 15 ng/mL, in hospitalized adults with chronic medical conditions, including CKD.[27] Although 25(OH)D deficiency was known to associate with secondary hyperparathyroidism (which may be reversed with repletion of 25[OH]D levels),[22] measurement of 25(OH)D in adults with CKD was not routinely performed.

Guideline 7 in the 2003 KDOQI clinical practice guideline suggested to measure serum 25(OH)D at the first encounter in patients with stages 3-4 CKD if plasma PTH level is above the target range for the stage of CKD (Table 1). If 25(OH)D levels are normal, measurement of 25(OH)D should be repeated annually. The guideline also suggested that for serum 25(OH)D levels < 30 ng/mL, supplementation with vitamin D_2 (ergocalciferol) should be initiated using dosing regimens recommended for the general population. Such regimens could include supplementation with ergocalciferol, 50,000 IU, for 4 weekly doses, then monthly for 5 months. Sufficient 25(OH)D levels were defined as ≥30 ng/mL, and the guideline suggested that when 25(OH)D levels reached this threshold, patients should be continued on a vitamin D–containing multivitamin preparation, with measurement of serum 25(OH)D annually and total calcium and phosphorus every 3 months.

The KDOQI guideline went on to suggest use of ergocalciferol versus cholecalciferol (vitamin D_3) for 25(OH)D supplementation due to data (mainly animal studies) reporting less metabolic risk with use of vitamin D_2 versus D_3.[28] The guideline also recommended discontinuation of vitamin D supplementation (ergocalciferol and all other forms) if serum levels of corrected total calcium were > 10.2 mg/dL or serum phosphorus levels were > 4.6 mg/dL despite use of phosphate binders. In addition, the guideline recommended initiating active vitamin D (1,25 $[OH]_2D$) use in patients with stage 2-4 CKD when 25(OH)D levels were > 30 ng/mL and PTH levels exceed the target range for the respective CKD stages. For patients with stage 5 CKD, active vitamin D use should be initiated when PTH levels are > 300 pg/mL regardless of 25(OH)D level.

This 2003 KDOQI guideline was followed 2 years later by publication of the KDOQI clinical practice guideline for bone metabolism and disease in children with CKD.[3] Guideline 8 in this document addressed vitamin D insufficiency and deficiency and suggested that children with both stages 2-4 CKD and PTH levels that exceed respective targets for CKD stage be screened for 25(OH)D deficiency or insufficiency (defined as 25[OH]D < 30 ng/mL). For 25(OH)D levels < 30 ng/mL, children with stages 2-4 CKD and elevated PTH levels should be supplemented with 2,000-4,000 IU of ergocalciferol daily for 12 weeks. All forms of vitamin D supplementation should be discontinued if serum calcium level is > 10.2 mg/dL. When patients are 25(OH)D sufficient, they should be placed on a multivitamin containing 25(OH)D and be assessed annually for 25(OH)D deficiency or insufficiency. For children with stage 5 CKD, the guideline

Table 1. Comparison of Recommendations for 25(OH)D Testing and Supplementation for CKD

	KDOQI 2003 (Adults)	KDOQI 2005 (Children)	KDIGO 2009	ERBP 2010
Patient population for 25(OH)D measurement	CKD 3-4 if PTH above target range	CKD 2-4 if PTH above target range	CKD 3-5 and 5T	CKD 3-4
25(OH)D threshold for supplementation	30 ng/mL	30 ng/mL	None[a]	12.5 ng/mL
Methods for 25(OH)D supplementation	If 25(OH)D < 5 ng/mL, use oral ergocalciferol, 50,000 IU/wk for 12 wk, then 50,000 IU/mo for 3 mo; if 5-15 ng/mL, use 50,000 IU/wk for 4 wk then 50,000 IU/mo for 5 mo; if 16-30 ng/mL, use 50,000 IU/mo for 6 mo	Recommended ergocalciferol over cholecalciferol; dose of ergocalciferol should not exceed 2,000-4,000 IU/d or 50,000 IU/mo; use 2,000-4,000 IU/d for 12 wk	Recommended treatment strategies used for general population; no specific recommendations for use of cholecalciferol vs ergocalciferol	Recommended cholecalciferol or other 25(OH)D analogues; no specific treatment strategy specified

Note: Conversion factor for 25(OH)D in ng/mL to nmol/L, ×2.496.

Abbreviations: 25(OH)D, 25-hydroxyvitamin D; CKD, chronic kidney disease; ERBP, European Renal Best Practice; KDIGO, Kidney Disease: Improving Global Outcomes; KDOQI, Kidney Disease Outcomes Quality Initiative; PTH, parathyroid hormone.

[a]KDIGO clinical practice guideline regarding the care of kidney transplant recipients suggested treating vitamin D deficiency and insufficiency in all stages of CKD in transplant recipients using treatment strategies recommended for the general population. Vitamin D deficiency and insufficiency was identified as level < 40 nmol/L (<16 ng/mL) and 40-75 nmol/L (16-30 ng/mL), respectively.[5]

did not recommend routine screening for 25(OH)D levels or supplementation with 25(OH)D, but rather recommended using active vitamin D for management of secondary hyperparathyroidism when PTH levels are > 300 pg/mL.[3]

The KDIGO guideline on CKD–bone and mineral disorders published in 2009 also provided opinion-based recommendations regarding measurement of 25(OH)D in patients with CKD stages 3-5, including those receiving dialysis. KDIGO recommended correcting 25(OH)D deficiency or insufficiency using treatment strategies used for the general population.[4] In patients with non–dialysis-dependent CKD stages 3-5 in whom plasma PTH levels are progressively increasing and remain persistently above the assay's upper limit of normal despite correction of modifiable factors (hyperphosphatemia, hypocalcemia, and vitamin D deficiency), the KDIGO guideline suggested initiating treatment with active vitamin D such as calcitriol or vitamin D analogues. The KDIGO guideline acknowledged a lack of established consensus regarding optimal PTH levels for CKD. However, KDIGO recommended that patients with PTH levels above the upper limit of normal for the PTH assay be screened for 25(OH)D deficiency, along with hyperphosphatemia and hypocalcemia. It should be noted that the KDIGO guidelines did not provide a specific 25(OH)D level for initiating 25(OH)D supplementation or maintenance, but instead discussed the lack of consensus within the scientific community concerning the definition of 25(OH)D adequacy and encouraged clinicians to individualize testing and treatment decisions regarding 25(OH)D (see discussion of 25[OH]D thresholds next).[4] The level of evidence supporting these recommendations was graded as 2C by KDIGO, indicating that recommendations were based on low-quality evidence, meaning the true effect of the intervention could be substantially different from the estimated effect (Table 1).[4]

The KDOQI US commentary on this KDIGO guideline characterized the KDIGO recommendations for 25(OH)D testing and supplementation as an expansion of the KDOQI 2003 guideline.[6] The commentary discussed the lack of clinical trial data for use of 25(OH)D and clinical outcomes, but stated that the risks of 25(OH)D use likely are minimal and treatment might be beneficial. The commentary also highlighted the lack of standardization of 25(OH)D measurement, which complicates the ability to determine definitions for 25(OH)D sufficiency.[6]

This lack of laboratory standardization for 25(OH)D measurement currently is being addressed by the Vitamin D Standardization Program. Launched in 2010 by the National Institutes of Health Office of Dietary Supplements, the program includes the collaborative efforts and support of the National Institutes of Health, Centers for Disease Control and Prevention, National Institute for Standards and Technology, and Ghent University in Belgium.[29] It will take a few years before standards and regulatory requirements for 25(OH)D testing will be fully implemented. Until the National Institute of Standards and Technology reference standards using a validated liquid chromatography–tandem mass spectrometry method are fully implemented for 25(OH)D testing, interpreting and comparing studies on 25(OH)D levels must be done with caution.

The European Renal Best Practice Group (ERBG) endorsed the KDIGO guideline for 25(OH)D testing and supplementation but stated that specific 25(OH)D targets for supplementation and long-term treatment would be clinically useful.[7] The ERBG argued that 25(OH)D levels < 12.5 ng/mL should indicate supplementation using vitamin D_2 or D_3 and 25(OH)D should be remeasured after 6 months of therapy. They stated that although it remains unclear whether 25(OH)D supplementation should be given to individuals with 25(OH)D levels of 12.5-30 ng/mL, one could argue that the potential benefits of 25(OH)D repletion may outweigh the risks. However, data from clinical trials are not available to support such a strategy.[7] Differences between recommendations in the KDOQI guidelines published in 2003 and 2005, the KDIGO guideline published in 2009, and the ERBG commentary with regard to 25(OH)D testing and supplementation are shown in Table 1.

Existing evidence at the time the KDOQI and KDIGO guidelines were published suggested that 25(OH)D supplementation may be a more cost-effective and safer alternative for management of secondary hyperparathyroidism in non–dialysis-dependent CKD.[30] However, findings from studies examining the association between ergocalciferol or cholecalciferol use and reduction in PTH levels among patients with stages 2-4 CKD or non–dialysis-dependent stage 5 CKD have been inconsistent.[31-38] A summary of these studies by Kandula et al[39] found that many, but not all, patients in these studies achieved 25(OH)D levels > 30 ng/mL with ergocalciferol or cholecalciferol supplementation. In addition, not all studies showed significant declines in PTH levels with 25(OH)D supplementation compared with baseline values.[34,38,40] Differences in doses of 25(OH)D supplementation,[41] adiposity,[42] length of treatment,[39] and CKD severity may have all contributed to the lack of congruent findings across studies.

RECENT CLINICAL FINDINGS

In 2010, the first randomized clinical trial of 25(OH)D versus active vitamin D for the management of secondary hyperparathyroidism in patients with stages 3-4 CKD was published.[30] In this randomized, blinded, 3-month trial, adults with 25(OH)D levels ≤ 20 ng/mL and either stage 3 CKD and PTH

levels > 100 pg/mL or stage 4 CKD and PTH levels > 150 pg/mL were randomly assigned to either cholecalciferol, 4,000 IU, daily for 1 month followed by 2,000 IU daily for 2 months or doxercalciferol 1 μg tablets daily for 3 months. Allocation was stratified by CKD stage. Exclusion criteria for this study included PTH level > 400 pg/mL, corrected calcium level > 9.7 mg/dL, serum phosphorus level > 5.0 mg/dL, and use of calcimimetics or vitamin D therapy 30 days before enrollment. A total of 55 patients were randomly assigned and 47 of them had at least one follow-up visit (22 and 25 in the cholecalciferol and doxercalciferol groups, respectively).

In analyses by CKD stage, relative change in PTH levels for CKD stage 3 was −15.9% ± 20.3% in cholecalciferol-treated individuals and −25.1% ± 37% for the 13 doxercalciferol-treated patients. For CKD stage 4, relative change in PTH levels was −1.3% ± 33% in the 7 cholecalciferol-treated individuals, but −30.3% ± 29.3% for the 8 doxercalciferol-treated individuals. Overall, PTH levels decreased by 10% ± 31% in the cholecalciferol group and 27% ± 34% in the doxercalciferol group. In the group that received cholecalciferol, 25(OH)D levels increased from a baseline mean of 14.0 ± 6.1 to 37.1 ± 10.1 ng/mL at study completion. Overall, there was no significant difference in PTH lowering between the cholecalciferol and doxercalciferol groups, but sample sizes were small. No change in 25(OH)D levels was noted in the group that received doxercalciferol.[30]

The findings that cholecalciferol had a greater impact on lowering PTH levels in patients with CKD stage 3 versus stage 4 is consistent with several other published studies that demonstrated differences in PTH lowering with either cholecalciferol or ergocalciferol by CKD stage.[35,36,38] Other studies have shown no significant changes in PTH levels with cholecalciferol, 2,000 IU, daily in children with non–dialysis-dependent stages 2-5 CKD[43] or with ergocalciferol in adults (CKD stages 3-4) after 6 months of therapy. Differences in PTH lowering with 25(OH)D supplementation by CKD severity may be a function of the inhibition of 1α-hydroxylase activity by FGF-23, PTH fragments, and uremic solutes, factors that are higher in CKD stages 4-5 versus stage 3.[39] In patients receiving dialysis, studies have not consistently demonstrated significant lowering of PTH levels with 25(OH)D supplementation.[44,45]

THRESHOLDS FOR SUPPLEMENTATION

Bone Disease Indications for 25(OH)D Supplementation

25(OH)D cutoff values defining deficiency are based on levels associated with rickets in children.[10] Despite the large amount of research on vitamin D and its association with health that has been produced over the past decade, no consensus has emerged within the medical community regarding 25(OH)D thresholds that define 25(OH)D deficiency or insufficiency.[10] In the last decade, many studies have focused on 25(OH)D levels < 30 ng/mL for disease outcomes.[46] This threshold is supported by a clinical guideline on evaluation, treatment, and prevention of vitamin D deficiency from the Endocrine Society, which defines 25(OH)D levels < 20 ng/mL as a state of deficiency and 20-29 ng/mL as a state of insufficiency.[8] In contrast, the Pediatric Endocrine Society recommends that a 25(OH)D level > 20 ng/mL be used to define 25(OH)D sufficiency, with 25(OH)D levels of 15-20 and ≤ 15 ng/mL defining insufficiency and deficiency, respectively.[47] The American Academy of Pediatrics also suggests that 25(OH)D levels ≥ 20 ng/mL define sufficient 25(OH)D.[48]

The selection of 25(OH)D levels ≥ 30 ng/mL as a marker of 25(OH)D sufficiency was based on several published studies reporting maximal PTH suppressed at this 25(OH)D threshold.[27,49,50] Studies showing maximal PTH suppression at a 25(OH)D threshold of 30 ng/mL included one based on a female population with osteoporosis, many of whom were receiving bisphosphonates (which increases PTH levels), and one that used a statistical approach that did not account for the nonlinear association between PTH and 25(OH)D levels.[51] None included adults with CKD. Sai et al[52] summarized data from 70 studies that examined serum 25(OH)D levels by serum PTH levels in a variety of populations and settings. In 59 studies, no consistent 25(OH)D cutoff was associated with maximal PTH suppression. PTH values demonstrated a plateau at serum 25(OH)D levels ranging as low as 15 ng/mL to as high as 50 ng/mL, whereas 8 studies showed no plateau, but rather a linear and indirect association between serum PTH and 25(OH)D levels. The other 3 studies showed no association between 25(OH)D and serum PTH levels.[52] It should be noted that none of these studies focused on populations with CKD.

Due to the controversy regarding 25(OH)D thresholds for treatment, the association between 25(OH)D levels and clinical outcomes and the rapid growth in vitamin D testing and supplementation in North America, the US and Canadian governments requested that the IOM review the existing evidence regarding 25(OH)D requirements and identify dietary reference intakes. The IOM Committee to Review Dietary References Intakes for Vitamin D and Calcium examined the evidence, including consideration of the impact of 25(OH)D intake on chronic disease indicators such as cancer, cardiovascular disease, diabetes, and CKD and other nonchronic disease indicators and assessed the ability of each outcome/indicator to serve as the basis for specifying adequate or excess intake.[9] The

committee did not create a definition for 25(OH)D deficiency or sufficiency per se, but instead defined 25(OH)D level < 12 ng/mL as a state of risk of deficiency[9] and stated that some, but not all, individuals may be at risk for insufficiency with 25(OH)D levels of 12-20 ng/mL.[9] The report highlighted the fact that enhancing calcium absorption remains the key role of vitamin D; thus, the effects of 25(OH)D deficiency may depend on calcium intake. Their review of the existing evidence revealed a trend toward maximum calcium absorption at 25(OH)D levels of 12-20 ng/mL, with no further increase at higher 25(OH)D levels. The terms risk of deficiency and risk of insufficiency were used to emphasize the likely heterogeneity of effects of low 25(OH)D levels on bone maintenance across degrees of calcium intake.[9] Individuals with low 25(OH)D levels may not be at risk for rickets or osteomalacia if calcium intake is adequate, but no amount of vitamin D can compensate for inadequate calcium intake.[9] The recommended dietary allowance was set as 600 IU daily for children and adults (male and female) aged 1-69 years. For adults older than 70 years, recommended dietary allowance for 25(OH)D was 800 IU/d. The IOM report also included a review of studies that examined the dose-response relationship with 25(OH)D supplementation. Lower doses of 25(OH)D (<1,000 IU/d) are associated with a steeper increase in 25(OH)D levels regardless of baseline 25(OH)D levels.[41,53,54] Overall toxicity was shown to be low in studies that used 25(OH)D doses < 10,000 IU/d, but more common in studies that used doses of 50,000 IU/d.

Determining a one-size-fits-all threshold for 25(OH)D supplementation is especially problematic for patients with CKD if these thresholds are based on maximal suppression of PTH. First, there is no consensus regarding optimal PTH levels for CKD stages and the distribution of serum PTH levels across the spectrum of 25(OH)D levels likely differs by CKD severity[30] due to differences in 1α-hydroxylase activity. This issue is complicated further in minority racial/ethnic groups, which carry a disproportionate burden of CKD.[55-58] Darker skin pigmentation is associated with a leftward shift in the distribution of 25(OH)D levels[59] and studies have reported that only a small fraction of African Americans have sufficient 25(OH)D levels.[60-62] Persons with African ancestry demonstrate PTH plateaus at much lower 25(OH)D levels than whites.[63,64]

The association between 25(OH)D levels and bone mineral density and response to 25(OH)D supplementation with regard to bone mineral density also differs by race/ethnicity.[63,65-68] Racial differences in associations between 25(OH)D level, PTH level, and bone maintenance at least in part may be a function of genetic variants in *GC*, the gene encoding vitamin D–binding protein. Variation in this gene was first described in 1959.[69] Subsequent studies have identified *GC* variants in more than 150 different populations and have demonstrated that the distributions of these genetic variants differ by race/ethnicity and correlate with skin pigmentation.[70] Genetic variants may influence protein level and its binding properties and may account for some of the variance in total 25(OH)D levels between populations.[71-74] Thus, use of total 25(OH)D, which includes both free and vitamin D–binding protein–bound 25(OH)D, as the biomarker of vitamin D's biological activity may lead to misleading conclusions.[74] Further research is needed to clarify the role of *GC* variants on 25(OH)D levels and clinical outcomes, especially in patients with CKD.

Non–Bone Disease Indications for 25(OH)D Supplementation

Over the past 2 decades, emerging research has demonstrated that vitamin D receptors exist in most tissues and cells of the human body.[10] Such findings have fueled investigations on the role of 25(OH)D in multiple chronic diseases,[75,76] including diabetes, heart disease, cancer, autoimmune diseases, and hypertension,[77-80] and has led to marked increases in serologic testing and use of vitamin D supplements.[81,82] A range of population and clinical research has implicated less severe vitamin D deficiency as a potential risk factor for several chronic diseases, including hypertension, obesity, diabetes, cardiovascular diseases, autoimmune diseases, asthma, and depression.[13,77,78,80,83-90] The 1α-hydroxylase enzyme is located primarily in the kidney, and nephrectomy or reduced kidney function equate with marked reduction in conversion of 25(OH)D to $1,25(OH)_2D$.[91,92] However, the discovery of 1α-hydroxylase in the placenta, gastrointestinal tract, skin, blood vessels, and granulomatous tissue demonstrated that $1,25(OH)_2D$ production is not limited to the kidney.[91-93] Vitamin D receptors also have been located in multiple tissues not associated with calcium or phosphorus homeostasis, and vitamin D–responsive elements have been discovered in numerous human genes. Such discoveries promoted the autocrine/paracrine hypothesis that local production of active vitamin D may promote health by enhancing cellular immunity or endothelial function.[93] However, the contribution of extrarenal 1α-hydroxylase to vitamin D metabolism remains largely unknown.[93]

Low 25(OH)D levels also have been associated with rapid decline of kidney function and higher mortality in adults with established CKD.[94] All-cause mortality is increased significantly at the low end of the 25(OH)D distribution in US adults with and without CKD.[95,96] However, 25(OH)D levels may be influenced by multiple factors, such as sun exposure and diet, which may correlate with other health

behaviors. Observational studies remain an efficient method for examining associations between chronic diseases and 25(OH)D levels, but they cannot determine whether these associations are causal.

After reviewing the evidence linking 25(OH)D levels and supplementation with chronic diseases published through 2010, the IOM vitamin D committee concluded that no level I evidence from randomized controlled trials demonstrated a clinical impact of 25(OH)D on a chronic disease other than modulating bone disease and turnover.[9] NKF-KDOQI and KDIGO guidelines did not recommend supplementing 25(OH)D for non–bone-related chronic diseases in patients with CKD.[2-4] Similarly, the Endocrine Society clinical practice guideline did not recommend prescribing 25(OH)D supplements beyond recommended daily needs for the primary or secondary prevention of cardiovascular disease or mortality or to improve quality of life.[8] However, this guideline recommended 25(OH)D supplementation for fall prevention (a noncalcemic benefit of vitamin D) and for prevention of rickets and osteomalacia (a calcemic benefit).[8] The IOM subsequently published a commentary that outlined their disagreement with the Endocrine Society's recommendation of 25(OH)D supplementation for fall risk.[51] The IOM specifically pointed out major flaws in a meta-analysis of studies examining the association between 25(OH)D supplementation and fall risk published in 2009.[97] The IOM committee reanalyzed data from this meta-analysis and found no significant dose-response relationship between fall risk and achieved 25(OH)D level.[51] Currently, use of 25(OH)D to maintain skeletal health remains the only health indicator with enough evidence to create dietary reference intakes.[9]

RESEARCH RECOMMENDATIONS AND CONCLUSION

Given the widespread testing and use of 25(OH)D supplements, there remains an urgent need for well-executed clinical trials investigating the risks and benefits of 25(OH)D supplementation in adults and children with CKD.[98] Studies need to determine 25(OH)D thresholds for supplementation and long-term goals for treatment and subsequent risks and benefits. Such studies will need to address the fact that multiple facets of 25(OH)D treatment, such as thresholds to initiate treatment, dose, and maintenance, may differ across race/ethnicity and by CKD stages. The 2003 and 2005 NKF-KDOQI guidelines suggested that 25(OH)D level >30 ng/mL indicates sufficiency. However, this threshold contrasts with the 20-ng/mL cutoff indicated by the IOM committee, the Pediatric Endocrine Society, and the US Academy of Pediatrics.[9,47,48] The existing controversy over 25(OH)D concentrations requiring supplementation

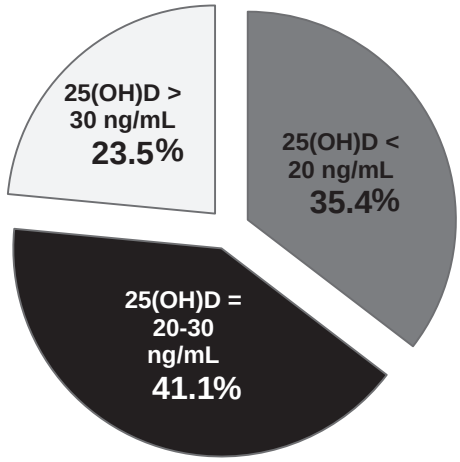

Figure 3. Serum 25-hydroxyvitamin D (25[OH]D) concentration category of US patients with stages 3-4 chronic kidney disease (CKD). Stages 3-4 CKD correspond to estimated glomerular filtration rate of 15 to <60 mL/min/1.73 m^2. Data source: Third National Health and Nutrition Examination Survey.

carries substantial clinical relevance for CKD management because the majority of US adults with stages 3-4 CKD have 25(OH)D levels within a range in which supplementation offers uncertain benefits (12-29.9 ng/mL).[96,99] Thus, most individuals with CKD and 25(OH)D levels <30 ng/mL are not being treated for 25(OH)D deficiency (Fig 3).

To date, a few clinical trials have suggested that 25(OH)D supplementation lowers PTH levels in individuals with CKD stage 3, but may be less effective in individuals with stages 4-5 CKD. Given the limited amount of level 1 evidence regarding the risks and benefits of 25(OH)D supplementation, clinicians must continue to use their best clinical judgment and individualize treatment decisions.[4] Clinicians also must be cognizant of the current lack of standardization of 25(OH)D measurement, so caution must be used when comparing and interpreting studies of 25(OH)D thresholds for clinical outcomes. To date, no clinical practice guideline has recommended 25(OH)D supplementation for any non–bone-related chronic medical condition, except for falls, due to lack of strong evidence. Ongoing clinical trials such as the DIVINE (Dialysis Infection and Vitamin D in New England) Study (ClinicalTrials.gov identifier NCT00892099) and VITAL (Vitamin D and Omega-3 Trial; ClinicalTrials.gov identifier NCT01169259) hopefully someday will answer the many clinical questions regarding the role of 25(OH)D in health and disease and provide better guidance for 25(OH)D testing and supplementation.

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