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The Role of Vitamin D in CKD Stages 3 to 4: Report of a Scientific Workshop Sponsored by the National Kidney Foundation

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Deficiency of 25-hydroxyvitamin D (25[OH]D) is common in patients with chronic kidney disease stages 3 and 4 and is associated with poor outcomes. However, the evaluation and management of vitamin D deficiency in nephrology remains controversial. This article reports on the proceedings from a "controversies conference" on vitamin D in chronic kidney disease that was sponsored by the National Kidney Foundation. The report outlines the deliberations of the 3 work groups that participated in the conference. Until newer measurement methods are widely used, the panel agreed that clinicians should classify 25(OH)D "adequacy" as concentrations > 20 ng/mL without evidence of counter-regulatory hormone activity (ie, elevated parathyroid hormone). The panel also agreed that 25(OH)D concentrations < 15 ng/mL should be treated irrespective of parathyroid hormone level. Patients with 25(OH)D concentrations between 15 and 20 ng/mL may not require treatment if there is no evidence of counter-regulatory hormone activity. The panel agreed that nutritional vitamin D (cholecalciferol, ergocalciferol, or calcifediol) should be supplemented before giving activated vitamin D compounds. The compounds need further study evaluating important outcomes that observational studies have linked to low 25(OH)D levels, such as progression to end-stage kidney disease, infections, fracture rates, hospitalizations, and all-cause mortality. We urge further research funding in this field.

Complete author and article information provided before references.

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Aims of this Report

KDIGO (Kidney Disease: Improving Global Outcomes) recently published an updated guideline concerning the diagnosis, evaluation, prevention, and treatment of chronic kidney disease (CKD)–mineral and bone disorders.[1] However, due to a scarcity of novel high-quality evidence, there was little new guidance on how to manage secondary hyperparathyroidism (SHPT) in CKD stages 3 to 4. In 2014, Kramer et al[2] had published a National Kidney Foundation–Kidney Disease Outcomes Quality Initiative (NKF-KDOQI) controversies report on 25-hydroxyvitamin D (25[OH]D) testing and supplementation in CKD. Because there have been several recent publications on the topic,[3,4] the NKF concluded that this would be an opportune time to facilitate a "controversies conference" to examine clinical issues related to the evaluation, prevention, and management of SHPT and vitamin D deficiency in CKD stages 3 to 4. Topic experts in nephrology, vitamin D physiology, primary care, and pharmacology participated in the workshop held on May 18 and 19, 2017, in Atlanta, GA. The workshop was structured to allow faculty attendees to examine the current state of knowledge through targeted literature reviews presented to the group by invited speakers related to vitamin D physiology, evaluation, outcomes, and management associated with altered vitamin D metabolism in patients with reduced kidney function. This is a report on the extensive deliberations at the workshop, reviewing the highlights and recommendations. The report is divided into 3 sections representing a synopsis of the discussions from separate work groups (evaluation of vitamin D status, outcomes associated with low vitamin D levels, and management of low vitamin D levels and SHPT). Each section includes a discussion overview and a list of recommended research questions.

Introduction

Studies confirm that the prevalence of 25(OH)D deficiency (Table 1) is greater in individuals with CKD than in the general population.[5,6] Levin et al[7] reported that in CKD stage 3, ~20% of patients are found to have low 25(OH)D concentrations (defined as <15 ng/mL), whereas in CKD stages 4 and 5, >30% of patients are deficient. In an analysis of the National Health and Nutrition Examination Survey (NHANES), participants with estimated glomerular filtration rates of 15 to 29 mL/min/1.73 m^2 had 25(OH)D concentrations that were 4.7 ng/mL lower than for participants with estimated glomerular filtration rates > 90 mL/min/1.73 m^2.[8] 25(OH)D is hydroxylated to 1,25-dihydroxyvitamin D ($1,25[OH]_2D$), or calcitriol, the active form of vitamin D, by the 1α-hydroxylase enzyme found in the kidney and other tissues. Both 25(OH)D and $1,25(OH)_2D$ can then be inactivated by the 24-hydroxylase enzyme into 24,25-dihydroxyvitamin D ($24,25[OH]_2D$) (Fig 1). Therefore, low 25(OH)D concentrations contribute to a deficiency of $1,25(OH)_2D$,[9,10] ultimately driving an increase in parathyroid hormone (PTH) levels and the development of SHPT.[7] $1,25(OH)_2D$ assists in the regulation of mineral homeostasis by mobilizing calcium and phosphate through gastrointestinal absorption. Thus, adequate $1,25(OH)_2D$ concentrations are needed for normal bone formation and mineralization.

Table 1. Institute of Medicine Recommendations for Vitamin D Adequacy

25(OH)D[a]		
nmol/L[a]	ng/mL[a]	Health Status
<30	<12	Associated with vitamin D deficiency, leading to rickets in infants and children and osteomalacia in adults
30-<50	12-<20	Generally considered inadequate for bone and overall health in healthy individuals
≥50	≥20	Generally considered adequate for bone and overall health in healthy individuals
>125	>50	Emerging evidence links potential adverse effects to such high concentrations, particularly >150 nmol/L (>60 ng/mL)

Note: Based on the Institute of Medicine's Dietary Reference Intakes.[18]
Abbreviation: 25(OH)D, 25-hydroxyvitamin D.
[a]1 nmol/L = 0.4 ng/mL.

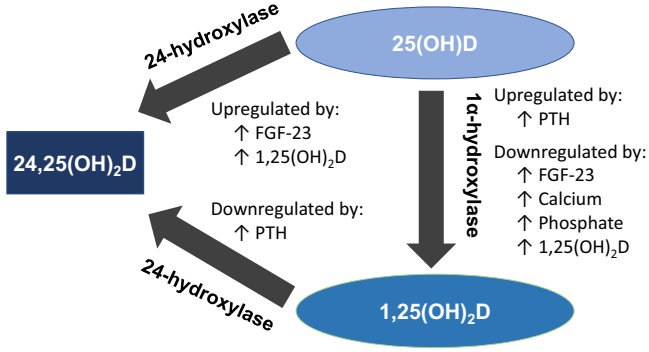

Figure 1. Vitamin D metabolism and primary regulators of 1α-hydroxylase and 24-hydroxylase enzymes. 1α-Hydroxylase (encoded by *CYP27B1*) is a cytochrome P450 enzyme that catalyzes the hydroxylation of 25-hydroxyvitamin D (25[OH]D) to 1,25-dihydroxyvitamin D (1,25[OH]$_2$D; the active form of vitamin D). 24-Hydroxylase (encoded by *CYP24A1*) catalyzes the 24-hydroxylation of 25(OH)D and 1,25(OH)$_2$D to their inactive 24 metabolites. Factors that regulate (up and down) each enzyme are depicted in the figure. Abbreviations: 24,25(OH)$_2$D, 24,25-dihydroxyvitamin D; FGF-23, fibroblast growth factor 23; PTH, parathyroid hormone.

Low 25(OH)D status is associated with the pathogenesis or worsening of various diseases and conditions such as bone disease, cardiovascular disease, autoimmune disorders, malignancies, musculoskeletal weakness, and insulin resistance, though randomized trials showing that treatment of vitamin D insufficiency or deficiency improves these conditions are lacking.[11-16]

Evaluation of Vitamin D Status

Measurement and Definition of Vitamin D Deficiency/Insufficiency in CKD

25(OH)D is a prehormone that ultimately acts in concert with a variety of paracrine and autocrine systems and intracellular signaling pathways to influence numerous cell actions throughout the body.[17] Although recommendations for adequate serum circulating 25(OH)D concentrations vary,[18,19] concentrations that may be sufficient for certain cell functions, such as the maintenance of skeletal health, may not suffice for others, such as cardiovascular function.[20] It is reasonable to define 25(OH)D deficiency as the concentration at which there is a clear adverse physiologic manifestation, whereas insufficiency may be considered a low serum concentration that is associated with activation of counter-regulatory systems and/or reduced capacity of many tissues to carry out their normal functions.[20] For instance, the fractional absorption of calcium increases with increasing 25(OH)D concentrations to a plateau of 32 ng/mL.[17] Additionally, serum 25(OH)D concentration is inversely associated with serum PTH level in individuals with[21] and without[22,23] CKD, until serum 25(OH)D concentration increases to 30 to 40 ng/mL (75-100 nmol/L), by which time PTH level achieves a stable nadir.[22]

Several plausible mechanisms have been proposed to explain the high prevalence of 25(OH)D deficiency in the CKD population.[5,24] Among these are: (1) possible reduced ingestion of foods high in 25(OH)D content (ie, fish, cream, milk, and butter) by patients with CKD, given that kidney diseease progression is associated with diminishing dietary intake in general, and because patients are frequently advised to follow a phosphorus-restricted diet[25]; (2) many patients with CKD spend less time outdoors, leading to lower sunlight exposure and reduced endogenous synthesis of vitamin D_3 in the skin[26]; and (3) among the main causes of CKD worldwide are type 2 diabetes and glomerulonephritis, which in many cases are associated with nephrotic-range proteinuria, itself associated with urinary loss of the major carrier protein for 25(OH)D, namely vitamin D–binding protein.[27]

Current Definitions

The optimal serum 25(OH)D concentration for patients with CKD and the concentration at which patients with CKD are considered deficient/insufficient is not well defined, but is generally considered to be the same as in the general population.[7] The recommended 25(OH)D concentration in the general population is controversial. It is generally acknowledged that 25(OH)D concentrations < 12 ng/mL are associated with marked increased risk for bone and mineral disorders and perhaps cardiovascular and other diseases.[18,19,28] However, a recent report from the Institute of Medicine recommended that serum vitamin D concentrations should be maintained at 20 to 50 ng/mL[18] (Table 1). The Endocrine Society recommends that 25(OH)D concentrations < 20 ng/mL be termed vitamin D deficiency, concentrations of 21 to 29 ng/mL be termed vitamin D insufficiency, and values > 30 ng/mL be considered normal,[19] and it seems reasonable to apply similar thresholds to individuals with CKD. It is important

to recognize that the terms deficient and insufficient do not necessarily represent explicit states of disease, but rather a spectrum of increased risk toward adverse outcomes,[17] and thus recommendations can vary based on the definition of terms. These designations may be even more difficult to characterize in CKD because circulating concentrations of vitamin D–related biomarkers of bone and mineral metabolism vary by CKD stage.[1,28] Further, at a population level, vitamin D deficiency/insufficiency may vary by age, race/ethnicity, and other characteristics.[18]

Based on generally recommended cutoff concentrations, 25(OH)D deficiency/insufficiency is common in CKD populations and the manifestation of early counter-regulatory actions (eg, increased PTH) occurs earlier than in individuals with normal kidney function because patients with CKD have reduced capacity to fully hydroxylate 25(OH)D into $1,25(OH)_2D$. Given these nuances, the term "adequacy" may be a better word than "deficiency/insufficiency."

Possible Future Definitions

Because bone is typically recognized as the main organ affected by vitamin D activity, better understanding of biomarkers of bone and mineral metabolism (eg, PTH, fibroblast growth factor 23 [FGF-23], or creation of a bone and mineral disease panel) in patients with CKD and varying vitamin D concentrations may help define screening tests to help determine vitamin D adequacy without having to perform bone biopsies. Adequacy cannot be defined by simply measuring 25(OH)D because of issues related to the block in conversion to $1,25(OH)_2D$ and in the breakdown by 24-hydryoxylase, for which activity has been shown to be reduced in patients with CKD.[29] Instead, vitamin D status in CKD may be better assessed using both quantitative measures such as 25(OH)D concentrations and surrogate or functional measures of enzymatic activity in patients with CKD. To this end, the ratio of 25(OH)D to $24,25(OH)_2D$ (or vice versa) may be particularly useful in patients with CKD as a surrogate of 24-hydroxylase.[29,30] In support of this concept is a study showing that the ratio of 25(OH)D to $24,25(OH)_2D$ is higher in patients on hemodialysis therapy than in apparently healthy individuals or individuals with normal kidney function and vitamin D deficiency (Fig 2).[31] This suggests a functional block of $24,25(OH)_2D$ production in individuals with end-stage kidney disease, providing insight into 24-hydroxylase activity in these patients. To the extent to which 24-hydroxylase activity is the opposite of 1α-hydroxylase activity, this ratio may also reflect 1α-hydroxylase activity.[32] Evaluating the 25(OH)D to 1,25(OH)2D ratio may also provide critical insight into 1α-hydroxylase,[33] with important implications for understanding the physiologic capacity to activate vitamin D that integrates both quantitative 25(OH)D concentrations (the input) and the ability to convert 25(OH)D to $1,25(OH)_2D$ (the system's capacity).[33] For these reasons, instead of using single measurements of 25(OH)D to assess vitamin D adequacy in CKD, developing a vitamin D deficiency profile made of complementary markers of vitamin D status including 25(OH)D, the ratio of 25(OH)D to $24,25(OH)_2D$, possibly the ratio of 25(OH)D to 1,25(OH)2D, PTH, and FGF-23 levels at baseline and the change in these factors in response to vitamin D supplementation over time might help assess vitamin D adequacy and determine whether a patient with CKD is going to be responsive to therapy.

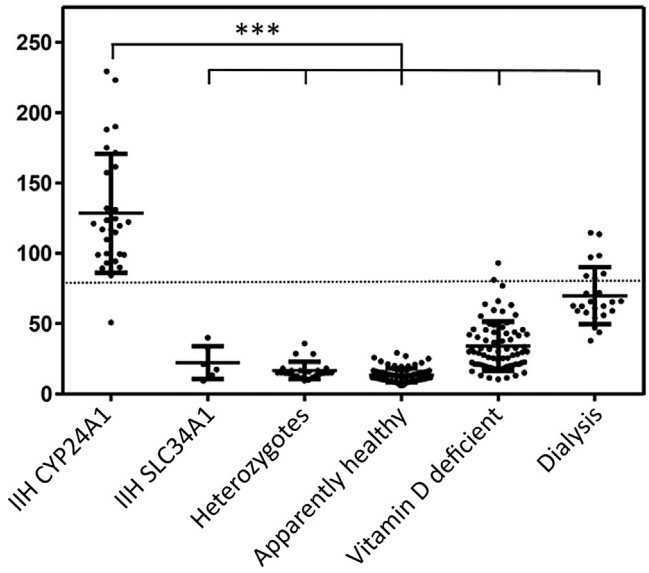

Figure 2. Ratio of 25-hydroxyvitamin D (25[OH]D) to 24,25-dihydroxyvitamin D ($24,25[OH]_2D$) observed in different groups of idiopathic infantile hypercalcemia (IIH) patients and comparators. The 25(OH)D to $24,25(OH)_2D$ ratios are depicted for patients with IIH due to genetic mutations of *CYP24A1* (24-hydroxylase) or *SLC34A1* (sodium/phosphate cotransporter), unaffected heterozygotes, apparently healthy controls, individuals who are vitamin D deficient, and patients treated by dialysis. Differences in ratios between *CYP24A1* patients and other groups were statistically significant (*** denotes $P < 0.001$). Adapted from a figure in Kaufmann et al[31] with permission of the copyright holder; original image © 2017 American Society for Bone and Mineral Research.

Seasonal Variations in Vitamin D Concentrations

Sunlight and temperature increase conversion of 7-dehydrocholesterol to previtamin D to vitamin D_3 and subsequently 25(OH)D. For this reason, circulating 25(OH)D concentrations demonstrate marked seasonal variations.[18] Despite a seasonal variation in 25(OH)D, $1,25(OH)_2D$ concentrations are not subject to seasonal change, likely due to tight feedback regulation,[34] but may vary based on select vitamin D–binding protein polymorphisms.[35]

Impact of Race on the Definition of Vitamin D Adequacy in CKD

In the general population, African Americans or blacks typically have lower serum 25(OH)D concentrations

than their peers of European ancestry, suggesting that they would be at greater risk for adverse health effects of low vitamin D levels. However, African Americans maintain better indexes of musculoskeletal health and have fewer bone fractures than those of European ancestry despite having lower 25(OH)D concentrations, suggesting that the relationship between vitamin D deficiency/insufficiency and racial health disparities may be complex.[36] This is highlighted by the finding of major heterogeneity in the association of 25(OH)D levels and cardiovascular outcomes, for which 25(OH)D concentrations correlate with cardiovascular disease events in whites, but not blacks.[37-39] African American dialysis patients have lower 25(OH)D concentrations and higher PTH levels,[40,41] but increased bone mineral density[42] and reduced fracture rates compared with their white peers.[43,44] These findings and other reports indicate that vitamin D and potentially FGF-23 metabolism may have important differences by race, especially in CKD,[38,45-47] and that serum 25(OH)D concentrations in the range of 12 to 15 to 20 ng/mL may lead to adverse outcomes in populations of European ancestry, but may not have the same degree of deleterious effects in African Americans. This is possibly due to a different prevalence of select vitamin D–binding protein polymorphisms that may affect concentrations of bioavailable and free serum 25(OH)D.[48] Thus, recent advances in our understanding of free 25(OH)D concentrations with similar vitamin D metabolite ratios (VMRs; eg, serum 25[OH]D to 24,25[OH]2D ratio) suggest that racial differences in vitamin D status may be mitigated when comparing bioavailable 25(OH)D concentrations or VMRs. Thus, bioavailable 25(OH)D or VMRs may serve as better physiologic indicators of vitamin D adequacy for all populations, and it is unlikely that similar cutoffs for defining sufficiency and insufficiency should be applied equally to all populations.[49] In summary, although much of the existing data suggest the possible need for a different reference range of serum 25(OH)D concentrations for blacks as compared with whites, advances in our understanding of mineral and bone disorder and vitamin D metabolite profiles may help overcome the effect of differences in issues such as the prevalence of select vitamin D–binding protein polymorphisms and/or decreased kidney function.[49]

Identifying High-Risk Patients

Patients at increased risk for 25(OH)D deficiency/insufficiency include those with high body mass index, poor sunlight exposure, poor intake of vitamin D–enriched dairy products, high use of sunscreen, limited skin exposure to sun due to clothing coverage (for personal, cultural, or religious reasons), high Northern or low Southern latitudes due to the cold because the conversion of previtamin D to vitamin D in the skin is temperature sensitive,[50] and CKD itself.[8]

Testing Frequency

Although it is difficult to determine with certainty how often testing for 25(OH)D adequacy should be performed, it often depends on individual factors such as patient risk, follow-up for low 25(OH)D concentrations, how low the concentrations are, and evidence of activation of vitamin D counter-regulatory systems such as increased PTH levels.

Evaluation of Altered Vitamin D Metabolism in the Pediatric CKD and Transplantation Populations

Children may be more prone to overt clinical manifestations of low 25(OH)D concentrations, with findings such as poor bone mineralization. Treatment of vitamin D deficiency/insufficiency may require a more liberal approach in terms of which thresholds to use because in children with CKD, 25(OH)D deficiency can have important implications for bone growth and overall bone health. Similar approaches should be considered for patients who have received a kidney transplant who are at risk for bone mineralization abnormalities from long-standing CKD acquired before transplantation, superimposed with immunosuppressive therapy, and the frequent presence of persistent hyperparathyroidism.[51] In these settings, the use of "nutritional" forms of vitamin D supplementation should be prioritized to limit or avoid the need to use activated vitamin D analogues to treat the underlying hyperparathyroidism. However, one should use caution or avoid the use of vitamin D in patients with high-normal serum calcium levels and avoid in patients with high serum calcium levels.

Future Research Priorities

Despite significant advances, the optimal definition of vitamin D adequacy and potential threshold concentrations most strongly linked to vitamin D toxicity in persons with CKD remain unclear. Differences in outcomes by serum 25(OH)D concentration may vary by levels of vitamin D–binding protein, as well as vitamin D–binding protein polymorphisms. Emerging data for the ability of VMRs and other markers of bone and mineral disorders to better assess the physiologic adequacy of vitamin D shows much promise, and how these levels differ by stage of CKD and in patients after kidney transplantation is yet to be determined. In particular, increasing our understanding of VMRs across the spectrum of kidney function and how they dynamically change in response to vitamin D supplementation may help develop a more rational approach to assessing vitamin D adequacy that integrates both quantitative 25(OH)D measurements with key counter-regulatory hormones (PTH and FGF-23) and functional measures of 24-hydroxylase and 1α-hydroxylase activity. See Box 1 for recommendations related to evaluation of vitamin D status.

Box 1. Research Questions From Workshop and Comparison to Recommendations From KDIGO Guideline and NKF-KDOQI Controversies Report

Evalution of Vitamin D

NKF Scientific Workshop on Vitamin D (this article)
- Research is needed to develop a profile of deficiency/insufficiency or alternatively "adequacy" that encompasses the response to supplementation and 24-hydroxylase and 1α-hydroxylase activity, using the ratio of serum 25(OH)D to $24,25(OH)_2D$ (VMR) and hormones that affect these factors, particularly PTH and FGF-23.
- Research is needed to evaluate whether the use of VMRs or vitamin D–binding protein may help overcome differences by race, providing more accurate assessments of vitamin D status in racially diverse populations.
- Separate research is needed in children due to their high susceptibility to growth abnormalities related to bone disease.
- Research is needed as to whether children may need more liberal thresholds to activate therapy and avoid the need for more aggressive therapy later on with attendant side effects.
- Research on VMR and candidates for a deficiency or "adequacy" profile (PTH, FGF-23, others) are needed to assess the effects of treatment.
- Research on whether we should use seasonally adjusted vitamin D levels to assess average 12-month values is needed.
- Research is needed on optimal frequency of 25(OH)D measurement.

KDIGO 2017 Guidelines on CKD-MBD[28]
"Multicenter RCTs should be conducted in children and adults to determine the benefits or harms of calcitriol or vitamin D analogs in patients with CKD G3a to G5; patient-level outcomes including falls, fractures, sarcopenia, muscle strength, physical function, progression to end-stage kidney disease, cardiovascular events, hospitalizations, and mortality should be assessed. Additional important patient level outcomes to include are bone pain, pruritus, and health-related quality of life. Studies should also include patients with more severe SHPT and should determine the impact of reducing PTH to different target levels, such as the normal range versus higher levels."[1(p35)]

NKF-KDOQI Controversies Report[2]
Need "well executed clinical trials" to determine:
- Risks and benefits of 25(OH)D supplementation
- 25(OH)D thresholds for supplementation
- Long-term goals for treatment

"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."[2(p506)]

Outcomes Related to Low Vitamin D

NKF Scientific Workshop on Vitamin D (this article)
The body of existing evidence related to vitamin D in populations with or at risk for kidney disease requires greater attention to the clinical context. Ongoing and future studies will benefit from:
- More precise tools to define vitamin D deficiency
- Focusing treatment of clinically apparent vitamin D deficiency
- Targeting therapy toward likely "responders"
- Evaluating surrogate outcomes related to intermediate bone or kidney outcomes to help identify subpopulations and dosing targets for long-term treatment trials
- Targeting subpopulations at high risk, such as the elderly

KDIGO 2017 Guidelines on CKD-MBD[1]/NKF-KDOQI Controversies Report[2]
[Not addressed]

Management of Low Vitamin D & SHPT in CKD

NKF Scientific Workshop on Vitamin D (this article)
- Research is needed in an adequately powered trial (pragmatic trial may be easier than traditional clinical trials) to evaluate meaningful outcomes:
  - Hospitalizations
  - Progression to ESRD
  - All-cause mortality
  - Patient-centered outcomes

(Continued)

Box 1 (Cont'd). Research Questions From Workshop and Comparison to Recommendations From KDIGO Guideline and NKF-KDOQI Controversies Report

- Future research studies should be stratified by vitamin D status, PTH level, and FGF-23 level.
- Future research should focus on cost-effectiveness of the intervention.
- Further research may include an interventional trial 2×2 factorial comparing cholecalciferol, calcitriol, and calcifediol vs placebo.
- Further studies especially needed in children and transplant recipients.

KDIGO 2017 Guidelines on CKD-MBD[1]/NKF-KDOQI Controversies Report[2]
[Not addressed]

Abbreviations: 25(OH)D, 25-hydroxyvitamin D; $24,25(OH)_2D$, 24,25-dihydroxyvitamin D; CKD, chronic kidney disease; CKD-MBD, chronic kidney disease–mineral and bone disorder; ESRD, end-stage renal disease; FGF-23, fibroblast growth factor 23; KDIGO, Kidney Disease: Improving Global Outcomes; NKF-KDOQI, National Kidney Foundation–Kidney Disease Outcomes Quality Initiative; PTH, parathyroid hormone; RCT, randomized controlled trial; SHPT, secondary hyperparathyroidism; VMR, vitamin D metabolite ratio.

Outcomes Associated With Altered Vitamin D Metabolism in CKD

Overview of Vitamin D and Outcomes

The association of 25(OH)D concentrations with outcomes in CKD continues to be an area of great clinical and public interest, yet also a matter of controversy. Epidemiologic studies and clinical trials have addressed a wide variety of outcomes, including those related to mineral metabolism, SHPT, bone and muscle disease, hypertension, new-onset diabetes, cardiovascular outcomes, kidney disease progression, infectious events, cancer, and overall and cause-specific mortality.[15,52-54] Although observational data appear to reveal strong associations, small clinical trials have not revealed effects. Our group of experts considered the broad set of existing studies to highlight limitations and promising areas for additional investigation with an emphasis on areas most relevant to CKD.

Relevance of Vitamin D in Bone

In general, higher 25(OH)D concentrations are thought to have a positive impact on bone health because of the endocrine actions of its active metabolite, $1,25(OH)_2D$, on the intestine, parathyroid glands, and bone.[55] However, it appears that 25(OH)D has beneficial effects on bone that are independent of circulating $1,25(OH)_2D$ concentrations. van Driel et al[56] showed that 1α-hydroxylase is present in human osteoblasts, and after incubation with 25(OH)D, these cells synthesize sufficient $1,25(OH)_2D$ to modulate their osteoblastic activity, leading to bone mineralization. In addition, vitamin D deficiency is the most common cause of osteomalacia, a generalized bone disorder in which impaired mineralization results in accumulation of unmineralized matrix or osteoid in the skeleton. Moreover, 25(OH)D has been observed to suppress PTH synthesis in primary cultures of bovine parathyroid cells.[57] Taken together, these autocrine/paracrine actions suggest that 25(OH)D may play a role in regulating both calcium and PTH metabolism, separate from the hormonal effects of kidney-synthesized $1,25(OH)_2D$.

Clinically, in patients with kidney disease, nutritional forms of vitamin D (precursors/analogues of 25(OH)D: ergocalciferol, cholecalciferol, and calcifediol) have all been associated with modest reductions in PTH levels.[3,58] Some studies suggest that nutritional vitamin D supplementation is either not effective or inferior to vitamin D receptor (VDR) agonists in lowering PTH levels. However, many of these studies used fixed doses or titrated to vitamin D concentrations as opposed to PTH levels, as is commonly performed with VDR agonists.[59,60] For all formulations, gaps remain in understanding how a reduction in PTH levels may translate to improvement in bone mineral density, bone strength, or fracture outcomes. In the general population, several large randomized clinical trials evaluating the effects of cholecalciferol on fracture risk have shown negative or adverse outcomes.[13,61] Such large trials have not been performed in patients with kidney disease.

Relevance of Vitamin D in CKD Outcomes

Definitive studies identifying the potential benefits of vitamin D administration to reduce cancer, cardiovascular disease, and mortality are eagerly awaited.[62,63] Ancillary studies focused on the prevention of de novo kidney disease may provide particularly relevant insights on potential benefits to patients with or at risk for kidney disease.[64] Although these large trials underway will inform vitamin D treatment globally, the goal of CKD-specific guidance may be to adapt these broader recommendations to the context of kidney disease. Safety concerns that may be particularly relevant for patients with kidney and urologic disease should be investigated, including risks for hypercalcemia, hyperphosphatemia, vascular calcification, nephrocalcinosis, and nephrolithiasis.[15,65-67] Additionally, the relative efficacy of vitamin D derivatives, including 25(OH)D and $1,25(OH)_2D$ and analogues across a range of kidney function, is an area of particular importance to recommendations in the CKD population. An emphasis of research on these CKD priority areas may aid in carefully adapting general population recommendations to those with CKD.

In addition, novel CKD-related outcomes should be an area of focus. These would include whether vitamin D

therapy can prevent de novo CKD; improve CKD-related metabolic complications, such as SHPT, CKD-related bone disease, sarcopenia, or frailty; or improve the natural history of CKD either in terms of the rate of progression of CKD or accelerated development of cardiovascular disease (Table 2). These latter end points may identify potential CKD-specific treatment indications for vitamin D supplementation.

Challenges in Vitamin D Outcomes Research in Kidney Disease

Measurement and Confounding

A major challenge in reconciling the large literature related to 25(OH)D and outcomes relates to differences in 25(OH)D measurement and uncertainty about the ideal definition of 25(OH)D adequacy in populations with kidney disease. Differences in sunlight exposure may be important proxies for health status, including institutionalization and physical activity limitations that are more prevalent among patients with kidney disorders.[68,69] The effects of these factors may substantially confound 25(OH)D-outcome associations in ways that are difficult to measure and account for in epidemiologic analyses, resulting in divergence of observational and trial results.

Heterogeneity and Disparities

As mentioned, racial differences in vitamin D, which may be related to underlying polymorphisms in vitamin D–binding protein, VDR, or regulatory hormones such as 24-hydroxylase, may account for different associations between 25(OH)D concentrations and outcomes in different racial and ethnic groups.[48,70-72] Whether these differences underscore true biological heterogeneity or reduced levels of confounding due to sun exposure or other factors remains to be elucidated. In contrast, studies among older adults, a population with high risk for CKD, often reveal stronger associations between 25(OH)D concentrations and outcomes.[73,74] These differences may relate to increased indoor activity and institutionalization among older adults, placing them at risk for clinically meaningful 25(OH)D deficiency.

For studies of CKD progression and proteinuria, the underlying kidney disease and its pathophysiology is often not specifically considered. Beneficial associations of vitamin D on CKD progression may relate to direct inhibition of the renin-angiotensin-aldosterone system (RAAS). This proposed mechanism is most biologically relevant to diseases characterized by RAAS activation and proteinuria. Choosing the most appropriate populations for studies may be important to properly identify benefits in particular diseases, such as diabetes or other proteinuric kidney diseases.[73,75] Some negative studies of vitamin D and CKD progression might have failed to focus on these target diseases or have evaluated 25(OH)D concentrations only, without evaluating vitamin D therapy that could plausibly be effective irrespective of baseline vitamin D status.[47,75]

Limited Randomized Controlled Trial Evidence of Clinical Outcomes in CKD

Despite promising findings highlighted in the observational literature, the literature connecting vitamin D therapy with improved outcomes in trials is limited.[54,76-78] In CKD populations, most trials have focused on surrogate outcome measures such as changes in PTH levels, cardiovascular surrogates, or proteinuria.[60,65,66,79-86] Vitamin D administration may lower proteinuria through inhibition of the RAAS. Trials such as the VITAL Study demonstrated promising results of 1 to 2 μg daily of paricalcitol to reduce proteinuria in diabetic kidney disease.[75,82,83] Two recent trials showed that paricalcitol decreases proteinuria in the setting of high-salt diets, but not low-salt diets.[87,88] The effects of nutritional vitamin D, such as ergocalciferol, cholecalciferol, or calcifediol, on proteinuria are less clear, with both positive and null results.[89,90] Such intermediate end point trials may help identify populations of

Table 2. Vitamin D–Related Outcomes Most Relevant to CKD Guidelines, With Selected Supporting Publications

CKD-Specific Benefit Possible	Evidence for Effect Based on Level of	
	Ergocalciferol/Cholecalciferol/ Calcifediol or 25(OH)D	Activated Vitamin D (Calcitriol, Paricalcitol) or 1,25(OH)$_2$D
Reduction in parathyroid hormone	Ritter (2006)^{B} Kandula (2011)^{M} Sprague (2016)^{R}	Coyne (2006)^{R} Coyne (2014)^{R} Thadhani (2012)^{R}
Improvement in bone and muscle disease (sarcopenia)	Theodoratou (2014)^{M} Bischoff-Ferrari (2006)^{M}	van Driel (2006)^{M}
Reduction in proteinuria	Melamed (2009)^{O}	de Zeeuw (2010)^{R} Cheng (2012)^{M}
Reduction in CKD progression	Melamed (2009)^{O}	
Reduction in CV complications in CKD	Robinson-Cohen (2013)^{O}	
All-cause mortality	Afzal (2014)^{O} Melamed (2008)^{O}	Kalantar-Zadeh (2011)^{O}

Note: Level of evidence (^{R}, randomized clinical trial; ^{B}, basic science study; ^{O}, observational study; ^{M}, meta-analysis). For other outcomes, there is a need for evidence to adapt to the CKD context: efficacy of nutritional vitamin D versus calcifediol versus calcitriol and other vitamin D receptor agonists; dosing and titration of vitamin D preparations in CKD; risk for cardiovascular calcification; risk for hypercalcemia/hypercalciuria/nephrolithiasis; risk for hyperphosphatemia.
Abbreviations: 1,25(OH)$_2$D, 1,25-dihydroxyvitamin D; 25(OH)D, 25-hydroxyvitamin D; CKD, chronic kidney disease; CV, cardiovascular.

responders, most effective agents, and optimal doses for treatment before moving to clinical outcome studies.

Current Knowledge and Gaps Regarding Vitamin D and Outcomes, Overall and in CKD

Definitive effects of vitamin D therapy on hard outcomes such as cardiovascular disease, fractures, kidney disease progression, and mortality are not well established. Although ongoing trials may provide new data,[63] recent systematic reviews suggest that large impacts on mortality, cardiovascular disease, and other hard outcomes in the general population are unlikely.[76] These trials are built on a large body of evidence linking low 25(OH)D concentrations with each of these outcomes observationally, but they may be subject to substantial confounding.[54] More rigorous designs, such as Mendelian randomization studies, continue to suggest potentially causal associations between 25(OH)D, mortality, cancer, and hypertension in particular,[91,92] but not cardiovascular disease.[91,93,94] These designs evaluate the contribution of genetic influences on 25(OH)D concentrations to outcomes, thereby removing confounding due to physical activity, outdoor exposure, diet, and other health habits. Results of these genetic studies continue to support current interest in the importance of adequate 25(OH)D in maintaining optimal health in some domains, but suggest that confounding is a major factor in observational 25(OH)D–cardiovascular outcome studies.

In reconciling observational and trial data, another consideration is that benefits may accrue to only some patients, such as those with evidence of functional 25(OH)D deficiency, with differences in genetic susceptibility to adverse effects of 25(OH)D deficiency, and with 25(OH)D-sensitive diseases or with other comorbid regulatory alterations such as increased oxidative stress and/or inflammation.[95,96] Specifically, how these results in the general population may extrapolate to patients with CKD, who have disease-related changes in vitamin D metabolism, is not known. From a teleological perspective, it is unlikely that humans evolved in a manner that modest reductions in a ubiquitous hormone such as vitamin D alone would lead to severe disease. However, deficiency could cause adverse effects in the setting of other abnormalities such as states of increased oxidative stress or inflammation or others.[95,96] Future studies may benefit from more targeted approaches to vitamin D supplementation focused on clinical deficiency, genetic predisposition, or other clinical conditions, including CKD. Additionally, the balance of efficacy and safety of nutritional vitamin D (cholecalciferol and ergocalciferol) versus calcifediol (older short-acting and newer long-acting derivatives) versus VDR agonists (calcitriol and other agents) in stages 3 and 4 CKD and the role of repletion (ie, treatment) versus supplementation (ie, prevention) requires further study.[79]

Research recommendations related to outcomes are listed in Box 1.

Management of Low Vitamin D and SHPT in CKD

Timing and Mechanism of Vitamin D Repletion

Although there was no consensus at the meeting about frequency of measurement of 25(OH)D in CKD, there was a general consensus that 25(OH)D concentrations < 15 ng/mL in CKD should be treated.

The Case for Repletion With Nutritional Vitamin D

Among different cell types, the capacity for synthesizing $1,25(OH)_2D$ depends on the presence of both 25(OH)D (obtained from circulating plasma) and 1α-hydroxylase. A study of cultured vascular smooth muscle cells found that $1,25(OH)_2D$ generation increases in step with increasing availability of 25(OH)D, reaching a plateau at a 25(OH)D concentration of 200 ng/mL (500 nmol/L), with a K_m (Michaelis constant) of 25 ng/mL (50 nmol/L).[97] In various extrarenal tissues, a threshold serum 25(OH)D concentration of at least 30 ng/mL (75 nmol/L) seems to be sufficient for $1,25(OH)_2D$ generation.[5,24,55,97-100] This extrarenally synthesized $1,25(OH)_2D$ predominantly performs autocrine or paracrine cell-specific roles, not endocrine functions. Thus, in contrast to that originating from the kidney, extrarenally produced $1,25(OH)_2D$ does not normally join the circulating pool of $1,25(OH)_2D$.[98] Of note, at extrarenal sites, 1α-hydroxylase is regulated substantially differently than that of the renal enzyme. Consistent with the autocrine and paracrine roles of $1,25(OH)_2D$, its synthesis and degradation rates in these tissues are mediated by a number of local factors, such as cytokines and growth factors that may adjust intracellular $1,25(OH)_2D$ concentrations to levels optimal for cell-specific actions.[98]

Extrarenally synthesized $1,25(OH)_2D$ binds to the nuclear VDR in an autocrine/paracrine manner.[98] The ubiquitous availability of 1α-hydroxylase and VDRs, in addition to the diverse effects of 25(OH)D on extrarenal tissues, supports the possibility that the primary function of the autocrine/paracrine vitamin D system is to address immediate local requirements through complex and coordinated local regulation,[5,24,98] avoiding reliance on the circulating $1,25(OH)_2D$ pool, which is under the control of systemic calcium homeostatic factors.

Thus, the panel concluded that patients with CKD should be treated with nutritional vitamin D before initiating activated vitamin D therapy. There was also consensus that there are few data to support one formulation of nutritional vitamin D over another in CKD stages 3 and 4.[4,101] However, in the general population, there appears to be some advantage of using cholecalciferol over ergocalciferol.[102,103] The panel agreed that there was no evidence of benefit of combining nutritional and activated vitamin D.

Research recommendations related to management are listed in Box 1.

Conclusions

To summarize, the consensus among conference participants was that there is still much work to be done to facilitate our understanding of how to use vitamin D in patients with CKD stages 3 and 4. Most agreed that newer measurement techniques (ie, a ratio of 25[OH]D to 24,25 $[OH]_2D$, or adjusting for vitamin D–binding protein) may help clarify functional 25(OH)D deficiency. Until newer measurement methods are widely used, the panel agreed that clinicians should classify 25(OH)D adequacy as concentrations > 20 ng/mL without evidence of counter-regulatory hormone activity (ie, elevated PTH). The panel also agreed that 25(OH)D concentrations < 15 ng/mL should be treated irrespective of PTH level. Patients with 25(OH)D concentrations between 15 and 20 ng/mL may not require treatment if there is no evidence of counter-regulatory hormone activity. The panel agreed that cholecalciferol may be preferable to ergocalciferol supplementation. A modified-release form of calcifediol recently received regulatory approval and provides another option for treating low 25(OH)D concentrations in CKD stages 3 and 4,[3] but requires further study comparing it with other vitamin D preparations. All the compounds need further study evaluating important outcomes such as progression to end-stage kidney disease, fracture rate, all-cause mortality, and hospitalizations. We urge further research funding in this field.

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