Nutritional vitamin D use in chronic kidney disease: a survey of pediatric nephrologists

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Abstract

Background Vitamin D deficiency may contribute to risk of cardiovascular disease, diabetes, and infections, in addition to known effects on mineral metabolism. Controversy remains regarding the use of nutritional vitamin D supplementation in chronic kidney disease (CKD), and the supplementation practices of pediatric nephrologists are unknown. **Methods** An electronic survey containing eight vignettes was sent to physician members of the International Pediatric Nephrology Association in 2011 to identify physician and patient characteristics that influence nephrologists to supplement CKD patients with nutritional vitamin D. Vignettes contained patient characteristics including light vs dark skin, CKD stage, cause of renal disease, parathyroid hormone (PTH), and 25(OH) vitamin D levels. Multivariate logistic generalized estimating equation regression was used to identify predictors of supplementation.

Results Of 1,084 eligible physicians, 504 (46%) completed the survey. Supplementation was recommended in 73% of cases overall (ranging from 91% of those with vitamin D levels <10 ng/mL to 35% with levels >30). Greater CKD severity was associated with greater recommendation of supplementation, especially for patients with higher vitamin D levels (test for interaction $p < 0.0001$). PTH level above target for CKD stage was associated with greater recommendation to supplement in pre-dialysis CKD, but did not have an impact on recommendations in dialysis patients (test for interaction $p < 0.0001$). Skin color, cause of CKD, and albumin levels were not associated with supplementation recommendation.

Conclusions Recommending nutritional vitamin D is common worldwide, driven by CKD stage and vitamin D and PTH levels. Future studies are needed to establish the risks and benefits of supplementation.

Keywords Vitamin D · Nutrition · Case vignettes · Survey · Chronic kidney disease · Pediatrics

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Introduction

Multiple clinical practice guidelines for vitamin D supplementation in children and adults with chronic kidney disease (CKD) have been published in recent years. However, these guidelines contain conflicting recommendations regarding supplementation in renal disease and indications for assessment of 25-hydroxyvitamin D (25(OH)D) levels (Table 1) [1–4]. The most recent guidelines highlight the lack of outcomes data supporting supplementation in CKD and recommend the correction of vitamin D deficiency using strategies for the general population [1]. Observational studies in CKD have linked vitamin D deficiency with mortality, insulin

Table 1 Vitamin D supplementation recommendations in chronic kidney disease

Guideline	Year	Assessment	Treatment
K/DOQI Clinical Practice Guideline for Bone Metabolism and Disease in Chronic Kidney Disease	2003	In CKD stages 3–4: If iPTH > target, measure 25(OH)D at first encounter and, if normal, repeat annually Monitor 25(OH)D level in conjunction with serum calcium and phosphorus level If the serum level is <30 ng/mL, initiate supplementation with ergo- or cholecalciferol	In CKD stages 3–4: 25(OH)D <5 ng/mL (severe deficiency): 50,000 IU/week for 12 weeks then 50,000 IU/month for 6 months total, measure 25(OH)D at 6 months 25(OH)D 5–15 ng/mL (mild deficiency): 50,000 IU/week for 4 weeks then 50,000 IU/month for 6 months total, measure 25(OH)D at 6 months 25(OH)D 16–30 ng/mL (insufficiency): 50,000 IU/month for 6 months Once replete, continue supplementation with an MVI with vitamin D and reassess annually
K/DOQI Clinical Practice Guideline for Bone Metabolism and Disease in Children with Chronic Kidney Disease	2005	In CKD stages 2–4: If iPTH level > target, measure serum 25(OH)D Periodic assessment warranted if dietary or lifestyle changes have occurred Monitor 25(OH)D level in conjunction with serum calcium and phosphorus level If the serum level is <30 ng/mL, initiate supplementation with ergo- or cholecalciferol	In CKD stages 3–4: 25(OH)D <5 ng/mL (severe deficiency): 8,000 IU/day or 50,000 IU/week for 4 weeks then 4,000 IU/day or 50,000 IU twice a month for 2 months, measure 25(OH)D at 3 months 25(OH)D 5–15 ng/mL (mild deficiency): 4,000 IU/day for 12 weeks or 50,000 IU every other week for 12 weeks, measure 25(OH)D at 3 months 25(OH)D 16–30 ng/mL (insufficiency): 2,000 IU/day or 50,000 IU every 4 weeks for 12 weeks, measure 25(OH)D at 3 months Once replete, continue supplementation with an MVI with vitamin D and reassess annually
KDOQI Clinical Practice Guideline for Nutrition in Children with CKD: 2008 Update	2008	In CKD stages 2–5D: Measure 25(OH)D levels annually If the serum level is <30 ng/mL, initiate supplementation with ergo- or cholecalciferol During repletion phase, serum levels of corrected total calcium and phosphorus should be measured at 1 month after initiation or change in dose of vitamin D and at least every 3 months thereafter	In CKD stages 2–5D: Same as KDOQI pediatric guidelines above Once replete, maintain with 200–1,000 IU/day supplementation and reassess annually
KDIGO Clinical Practice Guideline for the Diagnosis, Evaluation, Prevention, and Treatment of Chronic Kidney Disease-Mineral and Bone Disorder (CKD-MBD)	2009	In CKD stages 3–5: Measure 25(OH)D at baseline with repeat testing determined by baseline values and interventions If iPTH > upper normal limit of assay, evaluate phosphorus, calcium, and 25(OH)D levels, and correct abnormalities. Initiate evaluation at CKD stage 2 in children	In CKD stages 3–5: Correct vitamin D deficiency and insufficiency using strategies for the general population

KDOQI Kidney Disease Outcomes Quality Initiative; *KDIGO* Kidney Disease: Improving Global Outcomes; *CKD* chronic kidney disease; *iPTH* intact parathyroid hormone; *IU* international units; *DRI* dietary reference intake

resistance, anemia, inflammation, and CKD progression [5–14]. A recent randomized controlled trial of ergocalciferol in children with CKD stages 2–4 who had 25-hydroxyvitamin D (25(OH)D) deficiency showed significantly longer time to development of hyperparathyroidism [15].

The Institute of Medicine (IOM) recently updated vitamin D intake recommendations in the healthy general population, lowering both the upper limit for toxicity to keep serum vitamin D levels below 50 ng/mL (125 nmol/L) and the definition of vitamin D deficiency to 20 ng/mL (40 nmol/L) to cover 97.5% of the healthy population [16]. Importantly,

these recommendations were based on the healthy general population and considered bone outcomes only, concluding that the evidence of a causal role of vitamin D deficiency in other outcomes (e.g., cancer, cardiovascular disease, and metabolic disease) was insufficient. The IOM report noted a marked increase in measurements of vitamin D levels and use of vitamin D supplements in the general population. Supplementation patterns in CKD have not been well-characterized; however, supplementation in children with all stages of CKD is suspected to be exuberant, as noted in a 2010 review article [17]. As future observational and interventional studies assess the impact of vitamin D supplementation in CKD, it will be essential to understand current practice patterns among pediatric nephrologists.

The objective of this study was to assess vitamin D supplement recommendations among pediatric nephrologists worldwide, and to delineate the physician and patient characteristics that influence pediatric nephrologists' decision to recommend supplementation in children and adolescents with CKD. We hypothesized that supplementation would be recommended less often in CKD stage 5 and dialysis, given that those stages have only been included in more recent practice guidelines and that the kidney's ability to activate nutritional vitamin D is severely diminished in those stages. We also hypothesized that the most robust supplementation recommendation would be below vitamin D levels of 10 ng/mL with minimal supplementation above 30 ng/mL. In light of the recent changes in guidelines for healthy populations, we believed that there would be wide variation in recommendations to supplement in the range of 20 ng/mL to 30 ng/mL.

This study employed established survey methods with clinical vignettes to minimize survey burden. This approach was previously used to examine patient and physician factors that were associated with recommendations for hemodialysis versus peritoneal dialysis among pediatric and adult nephrologists [18]. The use of vignettes is accepted as a valid method of assessing clinical practice. In multiple studies, vignettes were equal or superior to standardized patient evaluation and chart review as a measure of physician practices [19–23]. These results will provide insight into the impact of current clinical guidelines and may inform the design of future observational studies and clinical trials of nutritional vitamin D supplementation.

Materials and methods

The survey was conducted in 2011 among active physician members of the International Pediatric Nephrology Association (IPNA). Participants' names and emails were acquired from a membership list obtained from the IPNA leadership in February 2011. The study protocol was approved for

exemption by the Institutional Review Board of the Children's Hospital of Philadelphia (CHOP). The identification of respondents was tracked in order to guide follow-up contact; however, the content of the responses was de-identified.

Questionnaire format

Each questionnaire contained eight case vignettes describing hypothetical patients. Patient characteristics included light vs dark skin, stage of CKD, cause of kidney disease, serum 25(OH)D level and PTH level at or above the target for CKD stage. Table 2 summarizes the categories for each characteristic. These parameters were chosen based on a literature review of current guidelines for vitamin D supplementation in CKD [1–4] and pilot surveys administered to pediatric and adult nephrologists at CHOP and the University of Pennsylvania respectively. Age, sex, and season were not included, as these factors likely influence the decision *to measure* a vitamin D level rather than the decision to supplement after a level has been obtained. Disease categories were limited to congenital anomalies of the kidney and urinary tract (CAKUT) and focal segmental glomerulosclerosis (FSGS) because these represent the majority of children and adolescents with CKD stage 2–5 [24]. The albumin level among FSGS patients was specified based on feedback from the pilot survey. PTH at or above target level was chosen based on KDOQI guidelines in children and adolescents [3].

The case characteristics were randomized into groups of eight vignettes, ensuring that each combination of vignettes included cases across the range of vitamin D levels. A total of 68 different surveys were created, representing 540 unique cases and ensuring that all possible permutations of the variables appeared once within each questionnaire. For example, 50% of all cases had dark skin because there were two categories for skin and 11% of cases had a vitamin D level between 10 and 12 ng/mL (25–30 nmol/mL) because there were nine categories for vitamin D level. The surveys were then examined to make certain that no single category appeared in all vignettes within a questionnaire. When sent out to IPNA membership, each survey was assigned to at least 17 physicians. This ensured that a range of variables would be answered, regardless of response rate.

Participants were instructed to assume that the patient:

1. Had stable CKD
2. Was not pregnant
3. Had no history of transplantation
4. Got minimal sun exposure
5. Was treated with an active vitamin D sterol if indicated
6. Had serum ionized calcium and phosphorus concentrations within normal limits

Table 2 Clinical variables included in the case vignettes

Variables	Categories
Skin pigmentation	Light skinned
	Dark skinned
CKD stage	CKD stage 2
	CKD stage 3
	CKD stage 4
	CKD stage 5 (pre-dialysis)
	Dialysis
Cause of renal disease	CAKUT
	FSGS with normal serum albumin level (3.5–4.0 g/dL)
	FSGS with low serum albumin (1.5–1.8 g/dL)
25(OH)D level	3–5 ng/mL (7.5–12.5 nmol/L)
	6–9 ng/mL (15–22.5 nmol/L)
	10–12 ng/mL (25–30 nmol/L)
	13–15 ng/mL (32.5–37.5 nmol/L)
	16–18 ng/mL (40–45 nmol/L)
	19–21 ng/mL (47.5–52.5 nmol/L)
	22–26 ng/mL (55–65 nmol/L)
	27–31 ng/mL (67.5–77.5 nmol/L)
PTH level at vs above target for CKD stage	32–36 ng/mL (80–90 nmol/L)
	For CKD stage 2:
	At target: 50 pg/mL (5.3 pmol/L)
	Above target: 100 pg/mL (10.6 pmol/L)
	For CKD stage 3:
	At target: 50 pg/mL (5.3 pmol/L)
	Above target: 150 pg/mL (15.9 pmol/L)
	For CKD stage 4:
	At target: 80 pg/mL (8.48 pmol/L)
	Above target: 300 pg/mL (31.8 pmol/L)
	For CKD stage 5 and dialysis:
	At target: 200 pg/mL (21.2 pmol/L)
	Above target: 600 pg/mL (63.6 pmol/L)

CKD chronic kidney disease; CAKUT congenital anomalies of the kidney and urinary tract; FSGS focal segmental glomerulosclerosis; PTH parathyroid hormone

Participants were asked if they would recommend nutritional vitamin D supplementation (either ergocalciferol or cholecalciferol) for each case. The dose of nutritional vitamin D was not specified.

In addition to the case vignettes, information was collected regarding physician demographics (if they see pediatric nephrology patients, year of completion of nephrology training, country in which they practice, and availability of nutritional vitamin D supplements). Following the vignettes,

physicians were asked to comment on their sources of information about nutritional vitamin D supplementation (KDOQI, KDIGO, or regional society guidelines, original research, and other) and to assess the applicability of international guidelines to their practice.

The questionnaires were managed using REDCap which is a secure, web-based application designed to support data capture for research studies [25]. This provided an intuitive interface for validated data entry; audit trails for tracking data manipulation and export procedures; and automated export procedures.

Sampling of pediatric nephrologists and follow-up

In February 2011, the IPNA provided an active membership list of 1,176 physicians from 100 countries. Each was randomly assigned an identification number. Then, stratifying by country, each physician was randomly assigned a survey number (1–68). The survey was administered by email. The following strategies were used to increase response rates:

1. Introductory email from the Secretary General of the IPNA
2. Emails from IPNA representatives from regional pediatric nephrology societies to increase awareness of the study
3. A personalized email from a pediatric nephrologist at CHOP
4. A raffle for 1 year's paid membership to the IPNA (value US\$ 175)
5. Follow-up contact via postcard with information directing the recipient to the online survey [26]

In order to capture data on IPNA members who no longer see patients, an email requesting a response if no longer seeing patients was sent to the IPNA membership separate from the survey.

Statistical analysis

Stata 11.0 (Stata, College Station, TX, USA) was used for all statistical analyses. A p value <0.05 was considered statistically significant, and two-sided tests of hypotheses were used in all analyses. Group differences were assessed using Student's t test for comparisons of means of normally distributed variables. Differences in proportions were assessed using the Chi-squared test. Predictors of supplementation (both patient and physician characteristics) were assessed using multiple logistic regression with supplementation (yes or no) as the outcome. All results were also tested using generalized estimating equation (GEE) methods to account for non-independence of the eight vignette responses within each respondent. Vitamin D level analyses were grouped as <10 ng/mL, 10–19 ng/mL, 20–29 ng/mL, and ≥ 30 ng/mL, based on definitions of deficiency established by the IOM

and KDOQI. Associations between time to response and recommendation of supplementation were also assessed.

Results

Response rate

Survey collection was conducted over 13 weeks from 20 March 2011 through 17 June 2011. The survey link was sent via email a maximum of five times. The response rate is shown in Fig. 1. Among the IPNA members with emails returned as “undeliverable,” none responded to the subsequent postcard. A total of 1,084 physicians were deemed eligible for participation in the survey, and 504 completed the survey for an overall response rate of 46%. The response rate was 66% in the USA and 39% elsewhere. Our response rate provided adequate coverage of the 68 surveys distributed. The median number of times (IQR) a survey was answered was 8 (range 7–10). The distribution of each category remained the same as the original survey design.

Characteristics of nephrologists surveyed

Twenty-two respondents (4%) reported that they were still in training and the remainder had completed training a median of 15 (interquartile range (IQR) 6–22) years earlier. Table 3 summarizes the geographic distribution of IPNA members and survey respondents as well as the availability of nutritional vitamin D supplementation and overall percentage of vignettes for which supplementation was recommended in each region. Ten physicians (2%) reported that nutritional vitamin D supplements were not available in their country (Chile, Jamaica, Japan, South Korea, Malaysia, Nigeria, Taiwan, and Turkey). Most respondents (80%)

agreed that the international guidelines, like KDIGO, were applicable to their practice, while 16 (3%) disagreed. Respondents reported their sources of information on vitamin D supplementation to be KDIGO (63%), journal articles and original research (62%), KDOQI (60%), and other regional society recommendations (27%).

Factors influencing recommendation of supplementation

Overall, supplementation was recommended in 73% of cases. Six physicians (1%) did not recommend supplementation for any of their 8 cases, and 93 (18%) recommended supplementation for all cases. The median (IQR) of cases to which respondents answered yes to supplementation was 6 (range 5–7) of the 8 vignettes in each survey. In logistic modeling, greater time to respond, measured by the time stamp on the survey in days since the first email, was marginally associated with lesser odds of supplementation recommendation (OR 0.997; 95% CI [0.994–0.999] $p=0.04$). When divided into supplementation recommendation based on interventions to increase response rate, there was no difference between those who answered immediately and those who answered after additional measures to increase response.

In univariate analyses, recommendations for vitamin D supplementation were inversely associated with vitamin D levels, as shown in Fig. 2, ranging from 91% of cases with levels <10 ng/mL to 35% of cases with levels >30 ng/mL. Of the 9% of cases with vitamin D levels <10 ng/mL for whom supplementation *was not* recommended, 56% were CKD stages 2–3, and 66% had PTH levels within the target range. On the other hand, of the 35% of cases with vitamin D levels >30 ng/mL for whom supplementation *was* recommended, 72% had CKD stages 4–5D, and 60% had PTH levels above target. Recommendations for supplementation

Fig. 1 Response rates.

Physician members who met criteria for inclusion and subsequent survey response rate, shown as total response, response among physician members from the United States, and response among members from all other countries. *IPNA* International Pediatric Nephrology Association; *CKD* chronic kidney disease; *US* United States; *International* IPNA members from countries other than the United States

Table 3 Regional representation in the IPNA and among respondents

Continent	Number of IPNA members, <i>n</i> (% of total)	Number of respondents, <i>n</i> (% of total)	Number indicating supplementation available, <i>n</i> (% of total)	Cases for which supplementation was recommended, <i>n</i> (% of total)
North America	379 (32)	222 (44)	222 (100)	1,398 (79)
Central/South America	114 (10)	33 (7)	31 (93)	194 (73)
Europe	343 (29)	133 (26)	131 (98)	722 (68)*
Asia	286 (25)	88 (18)	83 (94)	482 (68)*
Africa	26 (2)	17 (3)	16 (94)	93 (68)*
Australia/New Zealand	28 (2)	11 (2)	11 (100)	60 (68)*
Total	1,176 (100)	504 (100)	494 (98)	2,949 (73)

*Significantly different from North America, $p < 0.05$

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were greater among cases with more severe CKD (69% of cases with CKD stages 2–3 vs 77% in CKD stages 4–5D, $p < 0.0001$). Recommendations for supplementation were also greater among cases with a PTH level above the CKD stage-specific target range (70% of cases with PTH levels within the target range versus 76% of cases with a PTH above target for CKD stage, $p < 0.0001$).

In the GEE multivariate logistic regression analysis, lower vitamin D level, more advanced CKD stage, and PTH level above the target range were significantly and

independently associated with greater odds of supplementation. Dark skin vs light skin, FSGS with normal serum albumin level vs CAKUT, and FSGS with low serum albumin level vs CAKUT were not associated with recommendation for supplementation. The final GEE logistic regression model is presented in Table 4. This shows significant interactions between CKD stage and vitamin D level and between CKD stage and PTH level.

Analyses stratified by CKD stage illustrate the directions of these interactions. The association between recommendation

Fig. 2 Supplementation recommendation by vitamin D Level. Percentage of case vignettes for which supplementation was recommended for each range of vitamin D levels. IOM Institute of Medicine; KDOQI National Kidney Foundation Disease Outcomes Quality Initiative

Table 4 Generalized estimating equation (GEE) model for supplementation recommendation

Characteristic	Group	Adjusted odds ratio (95 % CI)	p value
CKD stage	2–3	Reference	
	4–5	1.21 (1.13–1.29)	<0.0001
	Dialysis	1.28 (1.17–1.40)	<0.0001
PTH level	At target for stage	Reference	
	Above target for stage	1.12 (1.08–1.16)	<0.0001
Vitamin D level	≥30 ng/mL	Reference	
	20–29 ng/mL	1.48 (1.40–1.56)	<0.0001
	10–19 ng/mL	1.81 (1.72–1.91)	<0.0001
	<10 ng/mL	1.92 (1.81–2.03)	<0.0001
CKD stage by vitamin D	CKD 2–3, vitamin D >30	Reference	
	CKD 4–5, vitamin D 20–29	0.94 (0.87–1.02)	0.14
	CKD 4–5, vitamin D 10–19	0.88 (0.82–0.94)	<0.0001
	CKD 4–5, vitamin D <10	0.90 (0.83–0.97)	<0.01
	CKD 5D, vitamin D 20–29	0.88 (0.80–0.97)	<0.05
	CKD 5D, vitamin D 10–19	0.85 (0.78–0.94)	<0.001
	CKD 5D, vitamin D <10	0.84 (0.76–0.94)	<0.01
CKD stage by PTH category	CKD 2–3, PTH at target	Reference	
	CKD 4–5, PTH above target	0.94 (0.91–1.01)	0.11
	CKD 5D, PTH above target	0.90 (0.85–0.96)	<0.001
Skin pigmentation	Light	Reference	
	Dark	1.02 (0.99–1.04)	0.15
CKD cause	CAKUT	Reference	
	FSGS, normal albumin	1.01 (0.99–1.04)	0.33
	FSGS, low albumin	0.99 (0.97–1.02)	0.64

CI confidence interval; CKD chronic kidney disease; PTH parathyroid hormone; CAKUT congenital anomaly of the kidney or urinary tract; FSGS focal segmental glomerulosclerosis

for supplementation and vitamin D level varied according to CKD stage, adjusted for PTH level within or above the target for CKD stage. For example, in analyses stratified by CKD stage, the odds ratio (OR; 95% confidence interval [CI]) for recommending supplementation for vitamin D levels <10 ng/mL (vs >30 ng/mL) was 1.94 (1.83–2.06) in CKD stages 2–3, 1.73 (1.64–1.82) in CKD stages 4–5, and 1.66 (1.52–1.82) in dialysis patients. This difference in ORs was driven by the lower supplementation rates in CKD stages 2–3 at vitamin D levels >30 ng/mL compared with CKD stages

4–5D. This is illustrated in Table 5, which shows the percentage supplemented by CKD stage and vitamin D level. Overall, supplementation was higher in CKD stages 4–5 and 5D with the gap narrowing at levels <30 ng/mL.

Similarly, the association between recommendation for supplementation and PTH level also varied with CKD stage, adjusted for vitamin D level. In GEE modeling stratified by CKD stage, the OR (95% CI) for recommending supplementation for PTH levels above vs within the target range were 1.12 (1.08–1.16) in CKD stages 2–3, 1.08 (1.05–1.12) in

Table 5 Impact of CKD stage on supplementation recommendation for vitamin D level

CKD stage	Vitamin D level											
	≤10 ng/mL (<25 nmol/L)			10–19 ng/mL (25–47.5 nmol/L)			20–29 ng/mL (50–72.5 nmol/L)			≥30 ng/mL (≥75 nmol/L)		
	All (%)	NA (%)	Other (%)	All (%)	NA (%)	Other (%)	All (%)	NA (%)	Other (%)	All (%)	NA (%)	Other (%)
CKD stages 2–3	87	94	82	82	96	74	61	67	57	23	23	23
CKD stages 4–5	94	97	92	85	93	80	72	79	67	42	31	49
CKD stage 5D	91	95	88	86	98	78	67	59	72	43	34	50

CKD chronic kidney disease; NA North America

CKD stages 4–5, and 1.01 (0.96–1.07) in dialysis patients. In a comparison of supplementation rates according to PTH levels, the impact of PTH levels was greatest among patients with less severe CKD; PTH levels did not influence the decision to supplement in dialysis patients. For example, 64% of cases with CKD stages 2–3 and PTH within target were recommended for supplementation compared with 73% of cases with PTH above target. For CKD stage 5D, 75% of cases with PTH within target and 75% of cases with PTH above target were recommended for supplementation.

Regional differences in supplementation

As shown in Table 3, supplementation was recommended most often amongst respondents from North America and was less frequently recommended in Europe, Asia, Africa, and Australia/New Zealand. The lowest rate of availability of nutritional vitamin D was in Central/South America (93%), compared with 100% in North America. Despite this difference, respondents from Central/South America recommended supplementation in 73% of cases, a rate that was not significantly different from the 79% in North America.

In GEE modeling, the odds of recommending supplementation (OR [95 % CI], *p* value) were significantly less for Europe (0.91 [0.87–0.96], <0.0001), Asia (0.91 [0.86–0.96], <0.0001), and Australia/New Zealand (0.88 [0.77–0.99], *p* <0.05), compared with North America. The odds of recommending supplementation were not significantly different for Africa (0.96 [0.86–1.07], *p* = 0.49) or Central/South America (0.95 [0.88–1.03], *p* = 0.23), compared with North America. The factors influencing supplementation amongst all participants—vitamin D level, PTH level, and CKD stage—remained significant in models stratified by North America and non-North American respondents. Amongst North American respondents, vitamin D level had the greatest effect on increasing odds of recommending supplementation, across all CKD stages. Amongst non-North American respondents, this effect was less pronounced with higher supplementation rates in severe CKD (stage 4 or worse) across all vitamin D ranges. This difference in consideration of CKD stage was especially true at high vitamin D levels (>30 ng/mL) when, for example, supplementation was recommended in 50% of cases on dialysis amongst non-North America respondents compared with 34% of cases on dialysis amongst North American respondents. The interaction between PTH and CKD stage remained for both groups, with the impact of PTH levels being greatest among patients with less severe CKD and PTH levels not influencing the decision to supplement in dialysis patients. The differences in percentages for which supplementation was recommended are shown in Table 5.

Discussion

Vitamin D remains an important topic of debate in CKD. When and how to supplement nutritional vitamin D are challenging, complicated questions, and more research is needed to discern the influence of nutritional vitamin D on outcomes of interest in CKD. Vitamin D levels have been associated with metabolic, cardiovascular, immune, and renal protective effects [5–14, 27–30]. A recent trial in children with CKD stages 2–4 showed a beneficial effect of ergocalciferol on PTH levels [15]; however, in the few adult prospective clinical trials performed, no significant benefits at a variety of doses have been shown [31–34]. As we work toward more definitive answers, clinicians are tasked with balancing the benefit and harm to their patients. The high rate of reported nutritional vitamin D availability (98%) and supplementation recommendation (73%) in this survey suggests that nutritional vitamin D is often being considered for pediatric nephrology patients with CKD worldwide.

The factors that were significant in the choice to supplement were vitamin D level, CKD stage, and PTH level. In addition, between CKD stages, vitamin D level and PTH level had a different influence on the choice to supplement. As expected, recommending supplementation increased as vitamin D levels decreased. However, we were surprised by the level of supplementation recommendation at levels >30 ng/mL; nutritional vitamin D was recommended in 35% of cases. This finding may reflect the varying theories regarding the definition of an adequate vitamin D level [16, 35]. Supplementing with nutritional vitamin D when the level is adequate may also be recommended for maintenance of that level. KDIGO and KDOQI guidelines as well as Endocrine Society guidelines recommend supplementation to maintain 25(OH) levels in at-risk patients, including those with CKD [1–4, 36]. This study did not address dosing nor did it ask about the reason for supplementation, which may have demonstrated that supplementation of levels above 30 ng/mL was recommended in order to maintain levels. Also a surprise to us, recommendation of supplementation was greater in severe CKD (stages 4, 5, and dialysis) across all vitamin D levels (see Table 5). We hypothesized that supplementation would be recommended less often in severe CKD because renal hydroxylation of vitamin D would be diminished. However, mass effect and the extra-renal 1- α -hydroxylation of nutritional vitamin D may be justification for supplementation despite poor renal function [37, 38]. Respondents were told to assume that patients would receive an active vitamin D sterol as necessary, in addition to the recommendation for nutritional supplementation. Hence, it seems unlikely that respondents were recommending nutritional vitamin D because a sterol was not available in these hypothetical cases. This survey method did not assess the availability of active vitamin D sterol in respondents' actual practices. As expected, patients

with PTH levels above target were more likely to be recommended for supplementation. However, in patients on dialysis, having a high PTH did not lead to increased supplementation recommendations. This is most likely because there was already such a high level of nutritional vitamin D recommendation at that stage overall (75%), or maybe because respondents would rather have used active vitamin D sterols instead of nutritional vitamin D supplementation in those patients on dialysis with a PTH above target. Physicians answering this survey seemed to consider the complex interactions of vitamin D level, CKD stage, and PTH level in deciding when to recommend nutritional vitamin D supplementation.

The variables of skin color, cause of CKD, and albumin level were not influential in determining supplementation recommendation. Although our pilot studies identified albumin level as a potentially important covariate, this was not observed in the actual survey. Albumin levels are considered because low albumin is representative of the severity of proteinuria and loss of serum proteins, including vitamin D-binding protein [39, 40]. It may be that cause of disease, proteinuria, and skin color are more important factors in considering if or when to measure a vitamin D level and less influential in actual supplementation recommendation. A limitation of this survey was the lack of capacity to test more variables of interest, including calcium and phosphorus levels, vitamin D dosing and level monitoring strategies. A review of current guidelines reveals the complex nature of administering vitamin D to a patient with CKD [1–4]. Monitoring of calcium and phosphorus levels plays a key role in when to measure vitamin D levels and whether or not to continue supplementation with vitamin D in the pediatric guidelines [3, 4]. For that reason, we decided to hold calcium and phosphorus within normal ranges in order to clearly examine patient and physician factors that prompt the recommendation of vitamin D supplementation rather than how to begin, monitor, and adjust nutritional vitamin D supplementation.

This survey allowed comparisons with guidelines for initiation of nutritional vitamin D supplementation. Current international guidelines (KDIGO) were listed as the primary source of information on vitamin D supplementation for 63% of respondents. KDIGO recommends measuring vitamin D annually and when PTH is above the upper limit of the assay [1]. Supplementation should be initiated when the level is <30 ng/mL and the KDIGO is broad in strategies for vitamin D repletion, recommending use of strategies used in the general population. However, incongruent with those guidelines, supplementation was not recommended for 15% of cases with vitamin D levels <30 ng/mL and PTH levels above target. In addition, supplementation was recommended for 35% of cases with vitamin D levels above 30 ng/mL, which as discussed above may be due to desire to

maintain adequate vitamin D levels once achieved. This survey shows that guidelines are generally adhered to, but may not yet be the standard of care.

In terms of generalizing these findings to the international pediatric nephrology community, a few considerations need to be taken into account. Our survey method allowed us to sample many physicians who were potentially influenced by unique characteristics in their practice, resulting in residual confounding. However, the literature on case vignettes supports their use as an accurate way to measure practices compared with use of standardized patients and retrospective chart review [19–23]. Importantly, this method allowed the sampling of many physicians by a method known to approximate actual practice patterns without the confounders encountered in the chart review of a limited number of institutions. Survey response rates remain the greatest challenge to this method, and our response rate exceeded the rate reported in published studies using internet and mail surveys [41–43]. It was difficult to assess how respondents compared with nonrespondents because the only data available in nonrespondents were name and contact information. For example, we did not have information regarding time since completion of training among nonrespondents; however, the median (range) of time since training among respondents matched the most recent board certification data for practicing pediatric nephrologists in the United States [44, 45]. Although we used an electronic survey, responses were obtained across the range of practice duration. Respondents may be more interested in vitamin D in general and therefore more likely to supplement with vitamin D than nonrespondents. However, the lack of a difference in supplementation recommendation rates in early vs late responders suggests that the study did not suffer significant bias. To minimize the possibility that review of available guidelines immediately prior to completing the survey had an impact on vitamin recommendations, we asked questions regarding guideline use at the end of the survey [46]. However, it is still possible that physicians tailored responses to perceived standards of care. While the directions of these potential influences on supplementation recommendation patterns are unknown, the overwhelming number of supplementation recommendations seen in this survey is impressive and most likely does reflect international supplementation recommendation patterns.

In conclusion, physicians are recommending vitamin D supplementation at all vitamin D levels and CKD stages, but especially at low vitamin D levels and in severe CKD. PTH is a consideration in predialysis CKD. As more research sheds light on the consequences of nutritional vitamin D supplementation, including the safety of supra-therapeutic vitamin D levels and the effects of vitamin D on other organ systems, changes in recommendation patterns and decision-making could be assessed using a case vignette method

similar to this one. In addition, future studies of practices could assess indications for measuring vitamin D levels, dosing regimens and ongoing monitoring of levels. For the time being, it seems as though many physicians in the international pediatric nephrology community are recommending nutritional vitamin D supplementation for their patients. Continued discussion of when and how to use nutritional vitamin D is warranted and should be encouraged as our understanding of vitamin D continues to develop.

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