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Incident isolated $1,25(OH)_2D_3$ deficiency is more common than 25(OH)D deficiency in CKD

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Abstract

Introduction: **Vitamin D deficiencies are well described in general populations and in those with chronic kidney disease (CKD). Although serum 25(OH)D may be a good indicator of vitamin D status in healthy individuals, the hydroxylated product, $1,25(OH)_2D$, essential for important biological functions such as mineral metabolism, bone turnover, regulation of protein synthesis, cell differentiation and proliferation may be a more suitable indicator for individuals with CKD.**

Methods: **We report an observational prospective cohort study of the incidence after 12 months of new isolated $1,25(OH)_2D$ and new 25(OH)D deficiency in CKD patients (estimated glomerular filtration rate [eGFR] <60 ml/min), who were vitamin D replete at baseline. All analyses were run in a central laboratory.**

Results: **Of 1,256 patients who completed the study at 12 months, 631 were replete in both 25(OH)D and $1,25(OH)_2D$ at baseline; at 12 months, 65% remained replete, 25% developed an isolated $1,25(OH)_2D$ deficiency, whereas only 6% developed an isolated 25(OH)D deficiency. Based on the multinomial logistic regression model, factors that were associated with 12-month changes in vitamin D status were diabetes, baseline values of eGFR, albumin and both 25(OH)D and $1,25(OH)_2D$ (all p values <0.03). Patients with diabetes, lower albumin, lower eGFR, lower levels of 25(OH)D and $1,25(OH)_2D$ at baseline were at increased risk of developing isolated $1,25(OH)_2D$ deficiency.**

Conclusions: **The high incidence of new isolated $1,25(OH)_2D$ deficiency as compared with new 25(OH)D deficiency, in the presence of 25(OH)D sufficiency, brings into question the value of measuring 25(OH)D levels in CKD. The significance of these findings and implications for replacement strategies require further study.**

Key words: *$1,25(OH)_2D_3$, 25(OH)D, Chronic kidney disease, Deficiencies*

Introduction

Vitamin D deficiencies are well described in the general population and in those with chronic kidney disease (CKD) (1, 2). Recently, increased attention has focused on the different forms of vitamin D and their biological relevance in both health and disease. Of particular interest is the association between 25-hydroxyvitamin D (25(OH)D) and its active form, 1,25-dihydroxyvitamin D ($1,25(OH)_2D$). Serum 25(OH)D is the best circulating measure of vitamin D status in healthy individuals, due to its long half-life. It is hydroxylated to $1,25(OH)_2D$, which is the biologically active moiety well known for its role in mineral metabolism and bone turnover, and recently identified as a key regulator of protein synthesis, cell differentiation and proliferation. Its role in immune function and vascular health is becoming more completely understood (3).

There is ongoing debate as to whether the deficiencies of $1,25(OH)_2D$ observed in the CKD population are due primarily to a deficiency in the substrates vitamin D_3 or 25(OH)D, or the inability of the damaged kidney to produce 25-hydroxyvitamin D-1α hydroxylase enzyme required for the activation of 25(OH)D (4, 5). Although many extrarenal sites also have the ability to metabolize 25(OH)D, questions remain as to biological relevance of these sites, and their potency (6, 7). The importance of $1,25(OH)_2D$ is that its target is the vitamin D receptor (VDR), which is ubiquitous, and important in numerous biological processes. In health, low $1,25(OH)_2D$ levels are usually associated with low substrate levels, thus leading to recommendations of supplementing the latter to increase the former. However in CKD, this many not hold true (8). It is possible the substrate dependency may be enhanced in CKD patients as well, though no conclusive data exist for either theory. Improved understanding of the relative changes in these deficiencies may lead to alterations in current diagnostic and therapeutic strategies.

We have previously reported, in a cross-sectional study, a cohort of patients in the United States, with estimated glomerular filtration rate (eGFR) less than 60 ml/min, and the prevalence of deficiencies of 25(OH)D and $1,25(OH)_2D$ at each decile of eGFR (9). We have described the association of these abnormalities with calcium, phosphate and intact parathyroid hormone (iPTH) values and noted that lower levels of $1,25(OH)_2D$ were evident at relatively higher levels of eGFR than previously reported, and that the prevalence of deficiency of $1,25(OH)_2D$ showed a stepwise increase over the range of eGFR, while 25(OH)D deficiency prevalence remained relatively constant over the range of eGFR values. There is a need to improve our understanding of the natural history of vitamin D deficiencies in CKD, given the importance of VDR activation in multiple processes. Thus the current analysis describes the incidence of new deficiencies of both $1,25(OH)_2D$ and 25(OH)D alone, and in combination, in those patients who were replete in both at baseline, and describes the factors associated with developing these isolated deficiencies in an untreated cohort.

Methods

Study population and design

The Study for the Evaluation of Early Kidney Disease (SEEK) was a prospective, observational, multicenter, community-based cohort study with baseline and 12-month data collected. Patients were enrolled if they had an eGFR less than 60 ml/min at initial screening, from general practice charts. Details of the cohort derivation and characteristics have been published previously (9). Twelve-month follow-up data was obtained on all patients enrolled in the SEEK study. Repeat blood work was drawn, and all analysis was run in a central laboratory. Predialysis serum creatinine (sCr) was converted into GFR estimates using the original 4-variable Modification of Diet in Renal Disease (MDRD) Study equation. Predictions were based on unstandardized sCr: GFR = $186 \times sCr^{-1.154} \times Age^{-0.203} \times 1.21$ (if African American) $\times$ 0.742 (if female). Based on currently recommended clinical laboratory cutpoints, $1,25(OH)_2D$ deficiency was defined as a level <25 pg/mL, while 25(OH)D deficiency was defined as a level <15 ng/mL. Both $25(OH)D_3$ and $1,25(OH)_2D_3$ were determined using the DiaSorin radioimmunoassay kit (Stillwater, MN, USA). Calcium, P and creatinine were analyzed with a routine autoanalyzer. Serum iPTH was determined by a chemiluminescence assay (DPC, Los Angeles, CA, USA). The lab references are 10-65 pg/mL for iPTH, 8-60 ng/mL for $25(OH)D_3$ and 25-65 pg/mL for $1,25(OH_2)D_3$.

Statistical methods

Descriptive statistics are presented as means with standard deviation or medians with interquartile range and percentages. Unpaired Student's *t*-test (for normally distributed variables) and Wilcoxon signed-rank test (for nonnormally distributed variables) were used to compare the baseline characteristics between those with 12-month follow-up and those without. Categorical variables were compared by using chi-square test or Fisher exact test where appropriate.

The study cohort was categorized into 4 groups based on the clinical laboratory cutpoints for $1,25(OH)_2D$ deficiency and 25(OH)D deficiency statuses at 12 months. One-way ANOVA and Kruskal-Wallis tests were conducted to determine whether baseline data significantly affected vitamin D level at 1 year.

Multinomial logistic regression modeling technique was employed to investigate baseline factors that were associated with vitamin D deficiency status at 12 months. Variables that were univariately associated with vitamin D deficiency status (defined as $p<0.15$), as well as potential confounders, were all simultaneously entered into a single multinomial logistic regression model. Since creatinine and eGFR are highly correlated, as with urinary albumin to creatinine ratio (UACR) and albumin, only eGFR and serum albumin were included in the model. The same applied to hematocrit and hemoglobin, thus only hemoglobin was included in the model. Values for iPTH were logarithmically transformed before analysis, because of their positively skewed distribution. A p value of less than 0.05 for 2-sided test was considered statistically significant. All statistical analyses were performed using SAS, version 9.1 (SAS Institute, Cary, NC, USA).

Results

Population cohort

Figure 1 describes the derivation of the cohort from the SEEK database, including at baseline and subsequent follow-up visits. Of the original 1,821 patients in SEEK, 1,256 completed the study at 12 months; reasons for nonparticipation in the 12-month follow-up are described in the figure.

Of interest, a substantial proportion (n=631, 50%) of the individuals who completed the 12-month follow-up, were both 25(OH)D and $1,25(OH)_2D$ replete, as defined by conventional values, at baseline. It is these patients who form the cohort of interest as they were "eligible" to develop a deficiency of either or both 25(OH)D and $1,25(OH)_2D$.

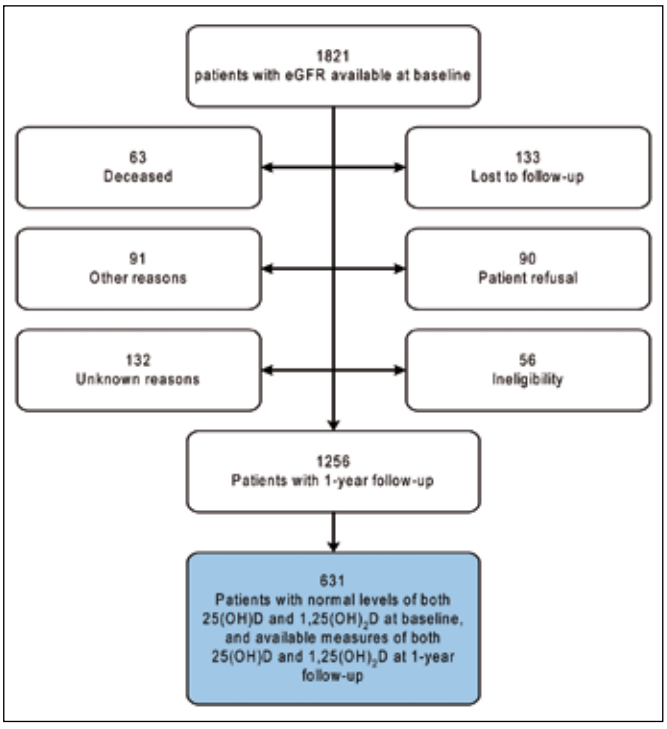

Fig. 1 - Derivation of patient cohort from all patients enrolled from 152 sites in the United States in the original SEEK study. Note that the cohort of interest includes only those who are replete in both 25(OH)D and 1,25(OH)$_2$D at baseline, as these were the only ones eligible for the outcome of interest: deficiency of either or both. eGFR = estimated glomerular filtration rate.

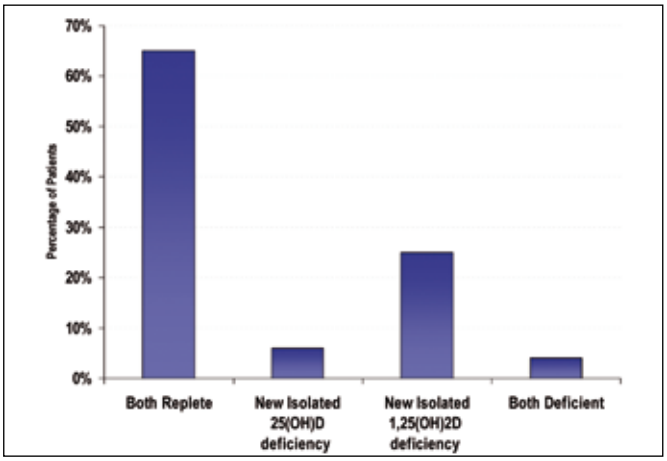

Fig. 2 - Incidence of vitamin D deficiency at 12 months, among the population who were replete in both 25(OH)D and 1,25(OH)$_2$D at baseline, for the outcomes of interest: continued "acceptable" levels of both 25(OH)D and 1,25(OH)$_2$D or deficiencies of either or both. Note that over 20% of this population developed laboratory deficiency of 1,25(OH)$_2$D in isolation.

Those who were available for 12-month follow-up differed from the original cohort in that they had a higher eGFR (49 vs. 43 ml/min; p<0.0001) higher 1,25(OH)$_2$D and 25 vitamin D levels (30 vs. 27 ng/mL; p<0.0001), lower iPTH level (72 vs. 102 pg/mL; p<0.0001), lower previous hospitalization rates (p=0.04) and lower myocardial infarction rates (MI) (14% vs. 21%; p=0.001) (data not shown).

Vitamin D status over time

Figure 2 describes the 12-month vitamin D status of the 631 individuals who were replete in both 25(OH)D and 1,25(OH)$_2$D at baseline. At 12 months, 65% remained replete, while 25% developed an isolated 1,25(OH)$_2$D deficiency, whereas only 6% developed an isolated 25(OH)D deficiency; a smaller proportion of patients developed a combined deficiency over the follow-up period.

Table I describes the baseline characteristics of the cohort who were replete at baseline and the 4 groups, categorized by their vitamin D status at 12 months. The mean age of the cohort replete in vitamin D at baseline was 70 years, 49% were males and 9% were African-American, the mean eGFR was 52 ± 16 ml/min. In the whole group of those replete in vitamin D at baseline, the mean eGFR change was 2.6 ml/min (p<0.0001), change in iPTH was −3.0 pg/mL (p=0.002), and change in phosphate was +0.1 mmol/L (p<0.0001), over the 12-month observation period.

Factors that were associated with change in vitamin D status at 12 months were diabetes, cardiovascular comorbidities, body mass index (BMI), eGFR, UACR, iPTH, phosphate, serum albumin, hemoglobin, hematocrit and bicarbonate (see Tab. I, all p≤0.01). Those who developed an isolated 1,25(OH)$_2$D deficiency had lower eGFR, UACR, serum albumin, hemoglobin, hematocrit, bicarbonate and phosphate levels and were more likely to have diabetes than those patients who retained stable. In contrast, those who developed an isolated 25(OH)D deficiency were more likely to be male, with higher cardiovascular comorbidities, a higher BMI and a higher iPTH than the group who remained stable at 12 months. Those with an isolated 1,25(OH)$_2$D deficiency had a greater drop in eGFR than those with an isolated 25(OH)D deficiency between baseline and 12 months (p<0.01).

Multivariate predictors of isolated deficiencies

Based on the multinomial logistic regression model, factors that were associated with the vitamin D status at 12 months were diabetes, baseline GFR, baseline albumin and both 25(OH)D and 1,25(OH)$_2$D levels at baseline (p<0.03). Figure 3 demonstrates the odds ratios and the corresponding 95% confidence intervals. Compared with patients with repletion of both forms of vitamin D at 12 months, patients

TABLE I
BASELINE CHARACTERISTICS OF STUDY COHORT GROUPED WITH RESPECT TO VITAMIN D STATUS AT 12 MONTHS

Characteristics	Cohort (vitamin D replete at baseline)	Stable at 12 months	New isolated 25(OH)D deficiency	New isolated $1,25(OH)_2D$ deficiency	New dual deficiency	p Value
Number (%)	631	413 (65%)	36 (6%)	160 (25%)	22 (4%)	
Age in years	70 ± 10.53	70 ± 10.83	71 ± 8.50	70 ± 10.46	72 ± 8.57	0.796
Male, no. (%)	307 (48%)	211 (51%)	11 (31%)	77 (48%)	8 (36%)	0.070
Ethnicity African-American, no. (%) Other	55 (9%) 576 (91%)	36 (9%) 377 (91%)	6 (17%) 30 (83%)	11 (7%) 149 (93%)	2 (9%) 20 (92%)	0.31
Diabetic, no. (%)	240 (38%)	124 (30%)	16 (44%)	87 (54%)	13 (59%)	<0.0001
Cardiovascular comorbidity, no. (%)	563 (89%)	359 (87%)	36 (100%)	147 (92%)	21 (96%)	0.033
Body mass index (calculated as kg/m^2)	29.56 ± 6.86	29.06 ± 6.21	31.22 ± 6.70	30.17 ± 7.94	32.43 ± 9.50	0.029
$1,25(OH)_2D$, pg/mL	42.33 ± 17.27	44.93 ± 17.41	41.82 ± 22.02	36.93 ± 14.79	33.62 ± 10.35	<0.0001
25(OH)D, ng/mL	32.87 ± 11.80	34.97 ± 12.38	24.64 ± 7.64	30.91 ± 9.31	21.13 ± 6.23	<0.0001
Serum creatinine, mg/dL	1.3 (1.1-1.6)	1.2 (1.0-1.5)	1.3 (1.1-1.5)	1.4 (1.1-1.8)	1.6 (1.1-2.2)	<0.0001
eGFR, ml/min	52.36 ± 16.00	55.16 ± 15.57	52.94 ± 17.33	46.15 ± 14.19	44.15 ± 19.41	<0.0001
Urinary albumin to creatinine ratio, mg/g	8.0 (4.0-28.0)	8.0 (4.0-21.0)	9.0 (4.0-23.0)	11.0 (4.0-82.0)	43.5 (4.0-95.0)	<0.0001
iPTH, pg/mL	49.0 (32.0-74.0)	48.0 (31.0-68.0)	53.5 (38.5-102.0)	52.0 (35.0-79.0)	72.0 (47.0-120.0)	0.002
Corrected calcium, mg/dL	9.12 ± 0.44	9.11 ± 0.45	9.16 ± 0.42	9.16 ± 0.40	9.02 ± 0.40	0.381
Phosphorus, mg/dL	3.57 ± 0.58	3.53 ± 0.56	3.59 ± 0.49	3.66 ± 0.59	3.85 ± 0.93	0.011
Serum albumin, g/dL	4.31 ± 0.30	4.35 ± 0.31	4.28 ± 0.29	4.23 ± 0.28	4.23 ± 0.25	<0.0001
Hemoglobin, g/dL	13.38 ± 1.55	13.59 ± 1.59	12.91 ± 1.57	13.01 ± 1.44	12.79 ± 0.78	<0.0001
Hematocrit (10%)	39.81 ± 4.42	40.43 ± 4.48	38.15 ± 4.43	38.74 ± 4.12	38.56 ± 2.57	<0.0001
Bicarbonate, mEq/L	22.53 ± 2.82	22.75 ± 2.73	22.89 ± 2.64	21.89 ± 2.92	22.50 ± 3.43	0.011

Values are means ± SD, or median (IQR), unless specified otherwise.
BMI = body mass index; eGFR = estimated glomerular filtration rate; iPTH = intact parathyroid hormone.

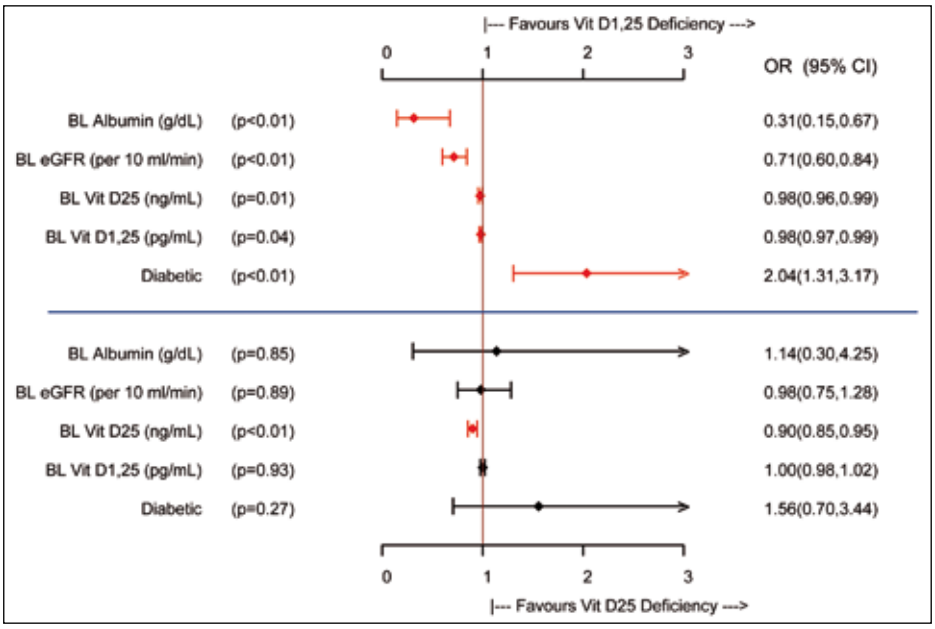

Fig. 3 - Factors associated with vitamin D deficiency status at 12-month follow-up (relative to both vitamin D replete at 12-month follow-up): odds ratios (OR) and 95% confidence intervals (95% CI) for those factors which were independently associated with isolated 1,25(OH)$_2$D deficiency (upper panel) vs. 25(OH)D deficiency (lower panel). Note that while both models include baseline levels (BL) of each of 25(OH)D and 1,25(OH)$_2$D, all levels at baseline were above current thresholds for diagnosis of "insufficiency" – i.e., they were within the normal laboratory range. eGFR = estimated glomerular filtration rate.

with diabetes, lower albumin, lower eGFR, lower level of 25(OH)D and 1,25(OH)$_2$D levels at baseline had increased the risk of developing isolated 1,25(OH)$_2$D deficiency. Only lower levels of baseline 25(OH)D increased the risk of developing isolated 25(OH)D deficiency, when compared with having the 2 forms of vitamin D replete at 12 month.

Discussion

This is the first population-based study in the current era to prospectively describe incident vitamin D deficiency in a cohort of patients with reduced kidney function, predominantly followed by general practitioners, in whom no treatments aimed at correcting mineral metabolism were administered. The key finding is the high incidence of new isolated 1,25(OH)$_2$D deficiency which was more common than new 25(OH)D deficiency in this cohort. While many would postulate that this is expected in those with reduced kidney function, the fact that it occurs in the presence of preserved sufficient levels of 25(OH)D levels is interesting. Current diagnostic and treatment strategies would suggest that measurement and subsequent supplementation of the 25(OH)D would lead to improved 1,25(OH)$_2$D status. The findings herein suggest that despite these deemed acceptable levels of 25(OH)D, even a minimal reduction in kidney function may result in either direct or indirect aberrations of the ability to complete the second hydroxylation step, leading to deficiencies of 1,25(OH)$_2$D. It is possible that higher levels of 25(OH)D are required in CKD patients than those that we currently deem "acceptable" or sufficient. In support of this, Stubbs et al have described supplementation with very high doses of cholecalciferol with subsequent improvement in calcitriol levels in dialysis patients (10). Alternatively, 2 possible, but not mutually exclusive, explanations for the current findings can be entertained. It may be that the extrarenal sites known to be capable of hydroxylation of 25(OH)D, are not as functional as previously thought in the presence of impaired kidney function. Alternatively, other factors, such as fibroblast growth factor-23 (FGF-23), are playing a modulatory role even early in CKD (11). Unfortunately, FGF-23 was not assessed in these blood samples given the era in which these samples were collected, and no blood remains for reanalysis, so this latter hypothesis cannot be tested. It is possible that all 3 explanations: need for higher levels of 25(OH)D, nonfunctionality of extrarenal conversion sites and high levels of FGF 23 are all acting or interacting to explain the findings.

The individuals who were identified as having a new isolated 1,25(OH)$_2$D deficiency with preserved 25(OH)D levels differed from those who did not develop that deficiency, in that they had a lower eGFR, were older, had lower albumin, lower 25(OH)D levels (albeit not deficient by current definitions) and were more likely to be diabetic than those who remained 1,25(OH)$_2$D replete. These observations support the argument that reduced renal reserve leads to deficiencies in endocrine function, here manifest as lower 1,25(OH)$_2$D levels. It has been well described that CKD patients do have higher levels of FGF-23, and thus it is possible that lower eGFR, less renal reserve and associated higher FGF-23 levels account for these findings.

It may be useful also to consider that current "threshold" values to define deficiency of either 25(OH)D or $1,25(OH)_2D$ may not be appropriate in the context of CKD or an aging population. Current established values describing deficiency are based on population norms, and CKD may alter tissue response to physiological concentrations of various compounds in the blood, thus leading to the need for reexamination of these values in the context of CKD. Further studies are needed in this area.

There are conflicting studies which describe the results of supplementation on $1,25(OH)_2D$ levels. Some intervention studies supplementing vitamin D_3 (cholecalciferol) in non-dialysis CKD patients demonstrate a lack of any impact with substrate on $1,25(OH)_2D$ levels in the absence of fully functioning kidneys. These studies show statistical increases in 25(OH)D and statistical falls in PTH, without effect on $1,25(OH)_2D$ levels (8, 12). Chandra et al recently conducted a 12-week randomized controlled trial of cholecalciferol versus placebo in a population of vitamin D deficient subjects with CKD (stages 3 and 4). While levels of 25(OH)D increased there was not a significant increase in $1,25(OH)_2D$ levels (13). Interestingly, between 93% and 83% of the unselected patients entered into these studies had a prevalent 25(OH)D deficiency or insufficiency, much higher than the present cohort. It is not clear what reasons exist for these differences. Conversely there are a few small studies, mostly in dialysis patients, which describe increases in $1,25(OH)_2D$ levels with supplementation (4, 5). Ravani et al have described correlations between 25(OH)D and PTH and $1,25(OH)_2D$ levels, in a CKD cohort, but these were predominantly referred patients, whereas in the current cohort they are more reflective of the general population, and earlier underappreciated reduction of eGFR (14).

The predictors of 25(OH)D deficiency in this population were factors suggesting alternative comorbidities rather than CKD per se: larger BMI, use of steroids and warfarin, and higher eGFR in this group, all suggest a different "phenotype" of patient becoming 25(OH)D deficient relative to those with $1,25(OH)_2D$ deficiency.

As in all observational studies, there are a number of limitations and benefits. The benefits include the relatively unselected population from general practitioners' offices, as well as the unbiased sampling of all continuing patients in the cohort. A central laboratory was used for measurement of 25(OH)D and $1,25(OH)_2D$ thus ensuring standardization of laboratory testing. One limitation is that a proportion of individuals were not available for the second study visit. However, given that the remaining cohort participants appeared healthier based on baseline parameters, this limitation is relative, and may even raise the question of conservative estimates of true prevalence and incidence. In addition, while efforts were made to collect all medications, in particular use of vitamin D supplementation, this information was by self-report and therefore could have been subject to error, though again this is a relative consideration and unlikely. Lastly, as we are not able to measure FGF-23 values, the mechanisms for the isolated deficiencies remain unknown, and we are unable to pursue them in the current cohort. Given the increasing awareness of the value of vitamin D in the lay public, and increasing consumption of supplements, we believe that this may represent a lost opportunity to study a naïve cohort, which may not be so easy to amass in the future, given the change in public awareness and behaviors.

In summary, we describe a cohort in which new isolated $1,25(OH)_2D$ deficiency is more frequent than a new isolated 25(OH)D deficiency, in those with lower, albeit relatively well-preserved eGFR. Furthermore this new isolated deficiency is associated with a fall in eGFR. These findings would suggest that it is the presence of CKD, and its attendant aberrations in internal milieu, including impaired hydroxylation of 25(OH)D and likely the inhibitory effect of FGF-23 that explains these findings. Specific mechanisms and outcomes need to be tested in further detailed studies. We wonder if the current recommendation of measuring 25(OH)D in CKD patients prior to dialysis may not be as clinically useful as previously thought, given the dissociation between the 25(OH)D and $1,25(OH)_2D$ deficiencies demonstrated herein. Further studies are required to both document and examine best thresholds for the diagnosis of $1,25(OH)_2D$ and 25(OH)D deficiency in CKD populations, by determining the link between these values with outcomes and other lab tests. This will permit the development of a systematic approach to evaluating therapeutic choices for supplementation in those with CKD.

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Conflicts of interest: Dr Levin has received grant support from Abbott Laboratories, however this particular analysis has been conceived and executed independently. Dr Andress is an employee of Abbott.

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