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Full Length Article

International variation in the management of mineral bone disorder in patients with chronic kidney disease: Results from CKDopps

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ABSTRACT

Background and objectives: Chronic kidney disease (CKD) is commonly associated with mineral and bone metabolism disorders, but these are less frequently studied in non-dialysis CKD patients than in dialysis patients. We examined and described international variation in mineral and bone disease (MBD) markers and their treatment and target levels in Stage 3–5 CKD patients.
Design, setting, participants, and measurements: Prospective cohort study of 7658 adult patients with eGFR < 60 mL/min/1.73 m^2, excluding dialysis or transplant patients, participating in the Chronic Kidney Disease Outcomes and Practice Patterns Study (CKDopps) in Brazil, France, Germany, and the US. CKD-MBD laboratory markers included serum levels of phosphorus (P), calcium (Ca), intact parathyroid hormone (iPTH), and 25-hydroxyvitamin D (25-D). MBD treatment data included phosphate binders and vitamin D (nutritional and active). Nephrologist survey data were collected on target MBD marker levels.
Results: Over two-thirds of the patients had MBD markers measured at time intervals in line with practice guidelines. P and iPTH increased and Ca decreased gradually from eGFR 60–20 mL/min/1.73m^2 and more sharply for eGFR < 20. 25-D showed no relation to eGFR. Nephrologist survey data indicated marked variation in upper target P and iPTH levels. Among patients with P > 5.5 mg/dL, phosphate binder use was 14% to 43% across the four countries. Among patients with PTH > 300 pg/mL, use of active (calcitriol and related analogs) vitamin D was 12%–51%, and use of any (active or nutritional) vitamin D was 60%–87%.
Conclusions: Although monitoring of CKD-MBD laboratory markers by nephrologists in CKDopps countries is consistent with guidelines, target levels vary notably and prescription of medications to treat abnormalities in these laboratory markers is generally low in these cross-sectional analyses. While there are opportunities to increase treatment of hyperphosphatemia, hyperparathyroidism, and vitamin D deficiency in advanced CKD, the effect on longer-term complications of these conditions requires study.

1. Introduction

Chronic kidney disease (CKD) is commonly associated with disorders of mineral and bone metabolism, including abnormalities of serum calcium (Ca), phosphorus (P), parathyroid hormone (iPTH), and serum 25-hydroxyvitamin D (25-D). These abnormalities have been extensively investigated in patients with end-stage kidney disease where the disturbances and consequences of altered mineral metabolism are most apparent [1–3].

The cascade of pathophysiological events that results in CKD mineral bone disorders (MBD) progresses in parallel with CKD and contributes to parathyroid hyperplasia and impaired bone health. MBD

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alterations may also contribute to cardiovascular disease, through the development of vascular calcification, impaired arterial function, and left ventricular hypertrophy and fibrosis [2]. The onset, rate, and severity of CKD-MBD biochemical abnormalities can be highly variable across patients [4,5]. Additional characterization of MBD marker patterns and treatment practices across the CKD spectrum would assist in the development of prevention strategies.

The recently updated 2017 KDIGO guidelines [6] recommend initiating the evaluation of CKD-MBD markers in CKD Stage 3, with treatment decisions based on serial measurements of the full array of laboratory markers. We lack data on international practice with respect to the routine clinical frequency of MBD marker measurement and pharmacological treatment of MBD with phosphate binders, vitamin D, and related compounds in non-dialysis CKD patients.

To address these gaps in knowledge, we sought to examine and describe international variation in the assessment, prevalence, clinical targets, and treatment of MBD markers in non-dialysis (Stage 3–5) CKD patients.

2. Methods

2.1. Sample

CKDopps is an ongoing, international, prospective cohort study of adults (≥18 years old) with estimated glomerular filtration rate (eGFR) < 60 mL/min/1.73 m^2 receiving care in stratified random national samples of nephrology clinics. Patients were sequentially or randomly selected from national samples of nephrologist-run CKD clinics in Brazil, France, Germany, Japan, and the United States. The study rationale and design has been previously published [7]. Data for this analysis were drawn from Brazil (1009 patients from 21 CKD clinics, 2014–18 data), France (2969 patients, 40 clinics, 2013–16 data), Germany (1834 patients, 33 clinics, 2013–18 data), and the United States (US; 1765 patients, 38 clinics, 2014–18 data).

2.2. Data

At study enrollment, patient demographics and comorbid conditions are collected on the baseline medical questionnaire. Comorbidities were determined based on ICD-10 codes in Germany, and via medical record abstraction in Brazil, France, and the US. Laboratory data up to six months prior to enrollment and until one year after the first lab were recorded. CKD-MBD laboratory markers of interest included serum levels of P, Ca, iPTH, and 25-D. In Brazil, Germany, and the US, we collected routinely measured laboratory data during longitudinal follow-up (to a maximum frequency of monthly). In France, laboratory measurements and prescription information were collected according to a pre-defined study protocol [8], we did not analyze CKD-MBD lab-measurement frequency practices for this cohort. PTH is referred to as intact PTH (iPTH) because roughly 85%–90% of the PTH values were obtained through intact PTH assays. Whole PTH assay was used for about 10% of Brazilian and US patients, and 5% of Brazilian patients had missing assay type. The distributions of PTH were similar for patients with intact PTH and for patients with missing assay type, but the variability introduced by different assay types (even within iPTH assays) will render the reported iPTH values less accurate. Nephrologists in each clinic reported target MBD-related laboratory values using the Nephrologist Practice Questionnaire.

Medication use and dosage extracted from the paper or electronic medical records was collected, using a summary questionnaire, on a secure, web-based data collection system. Analysis of medication was performed at the time of patient inclusion and 30 days before, until up to one year after, the CKD stage index date.

We obtained ethics approval for CKDopps from a central institutional review board, supplemented by additional study approvals as required by national and local ethics committees. All patient data are used in accordance with the written informed consent of the patients.

2.3. Statistical analyses

The unit of analysis was patient-stage, based on the patient's CKD stage at study entry or the first identified date of entry into another CKD stage during study follow-up (except in France, where one observation per patient, based on CKD stage at study entry, was used). Baseline patient characteristics were provided by patient-stage. Timing of follow-up laboratory measurements within a particular CKD stage was assessed using Kaplan-Meier curves with censoring at the earliest of transition to a new CKD stage, initiation of renal replacement therapy, death, departure from the study for any reason, or the end of study follow-up. Timing of laboratory measurement was compared to the 2017 KDIGO recommendations [6,9]. Reported laboratory values were the first available, from 30 days before until up to one year after the CKD stage index date. Medication prescription (yes/no) was assessed as any recorded medication prescription from 30 days before until up to one year after the CKD stage index date We conducted statistical analyses using SAS version 9.4 (SAS Institute Inc., Cary, NC).

3. Results

Our analysis cohort included 7577 patients; we excluded 73 subjects who had out of range or missing eGFR values (Table 1). Allowing patients to be reassigned after transition to a new CKD stage (patient-stage

Table 1
Patient sample and characteristics.

Country	Brazil				Germany				United States				France			
Sample																
Consented patients	1012				1836				1769				3033			
GFR < 60 and non-missing	1009				1834				1765				2969			
Patients in final dataset	1009				1834				1765				2969			
Patient-stages[a] in analyses	1367				3155				2413				2969			
CKD stage	3a	3b	4	5	3a	3b	4	5	3a	3b	4	5	3a	3b	4	5
N	126	351	612	278	193	620	1554	788	226	632	1075	480	471	1135	1240	123
N from Prior Stage	0	65	163	130	0	157	438	726	0	125	266	257	0	0	0	0
Age (mean, years)	64	66	66	62	68	71	72	72	66	69	69	67	64	67	68	69
Male	62%	54%	51%	49%	64%	57%	57%	63%	61%	54%	50%	50%	71%	66%	63%	61%
Comorbidities																
Diabetes	46%	45%	47%	50%	36%	41%	42%	40%	54%	55%	56%	58%	38%	44%	44%	42%
Hypertension	89%	92%	91%	91%	82%	83%	82%	82%	92%	94%	93%	93%	86%	91%	92%	97%
Heart failure	11%	14%	19%	14%	8%	12%	14%	11%	11%	16%	18%	18%	9%	13%	15%	15%
Coronary artery disease	19%	21%	24%	20%	23%	26%	29%	27%	30%	31%	34%	29%	22%	24%	28%	25%

[a] Each time a patient entered a new CKD stage while in follow-up, their data during that stage was used to inform all tables relevant to that CKD stage.

analyses) yielded 9904 patients—distributed as 32% from Germany, 30% from France, 24% from the US, and 14% from Brazil. Male patients were more common than women in most countries and CKD stages. Mean age was higher in Germany than in other countries. The most common comorbidity was hypertension, which varied from 82% to 97% by country and CKD stage. The US had the highest percentage of diabetic patients in each CKD stage. The prevalences of heart failure (HF) and coronary artery disease (CAD) increased from CKD Stage 3a to 3b to 4, then stabilized or declined in CKD Stage 5.

3.1. CKD-MBD laboratory target levels as identified in the Nephrologist Practice Survey

Nephrologists (n = 273) associated with the participating clinics were asked to indicate their preferred target values for MBD laboratory values (Fig. 1a–c). The reported maximum P target for CKD Stage 4/5 varied from a low of 4 mg/dl to a high of > 7 mg/dl; the modal target value was 4.5 mg/dl for Brazil and France, 5.5 mg/dl for the US, and 6 mg/dl for Germany. The upper iPTH target for CKD Stage 4/5 also varied, with a modal target range of 200–500 pg/mL for all countries. The majority of respondents in each country selected a lower target of 30 ng/mL for 25-D.

3.2. Probability of repeat measurement of CKD-MBD-related labs over time

For each specific CKD-MBD marker value identified near the index date, we determined the patient's cumulative probability of a repeat lab measurement over the following 12 months (Table 2). The probability of a repeat measurement increased over 12 months, and with increasing CKD stage, for all CKD-MBD markers. For example, the probability of a repeat serum phosphorous measurement among patients with CKD Stage 3a was 34% within three, 61% within six, 73% within nine, and 79% within 12 months.

In situations where KDIGO has published recommendations regarding time intervals for repeat testing, the recommendations were achieved or surpassed at least 69% of the time (Table 2). The probability of repeat lab measurement was typically higher in Germany than the US and Brazil (not shown). Despite the absence of a specific recommendation for repeat testing for iPTH in CKD Stage 3, the probability of repeat testing within 12 months was relatively high at 61% (Stage 3a) and 73% (Stage 3b). The probability of iPTH testing within 12 months increased further in CKD Stage 5 to 83%, although adherence to the KDIGO recommendation to test every 3–6 months in CKD Stage 5 was considerably lower (43% at three months, 69% at six months). Despite the absence of a specific KDIGO recommendation for frequency of 25-D testing, 25-D was assessed on a yearly basis in the majority of the patients, ranging from 55% (Stage 3a) to 80% (Stage 5).

3.3. CKD-MBD laboratory values, by eGFR level and country

Increases in mean P and iPTH, and decreases in Ca, were generally gradual from eGFR 60 to 20 mL/min/1.73m^2 but accelerated at eGFR < 20 mL/min/1.73m^2. 25-D showed no relation to eGFR; the small deviations in 25-D at the eGFR extremes reflect lower sample size rather than pathophysiologic patterns. These trends were similar for all four countries. Supplementary Fig. 1 shows median P, Ca, iPTH, and 25-D in relation to eGFR.

Categorical distributions of MBD laboratory markers by CKD stage

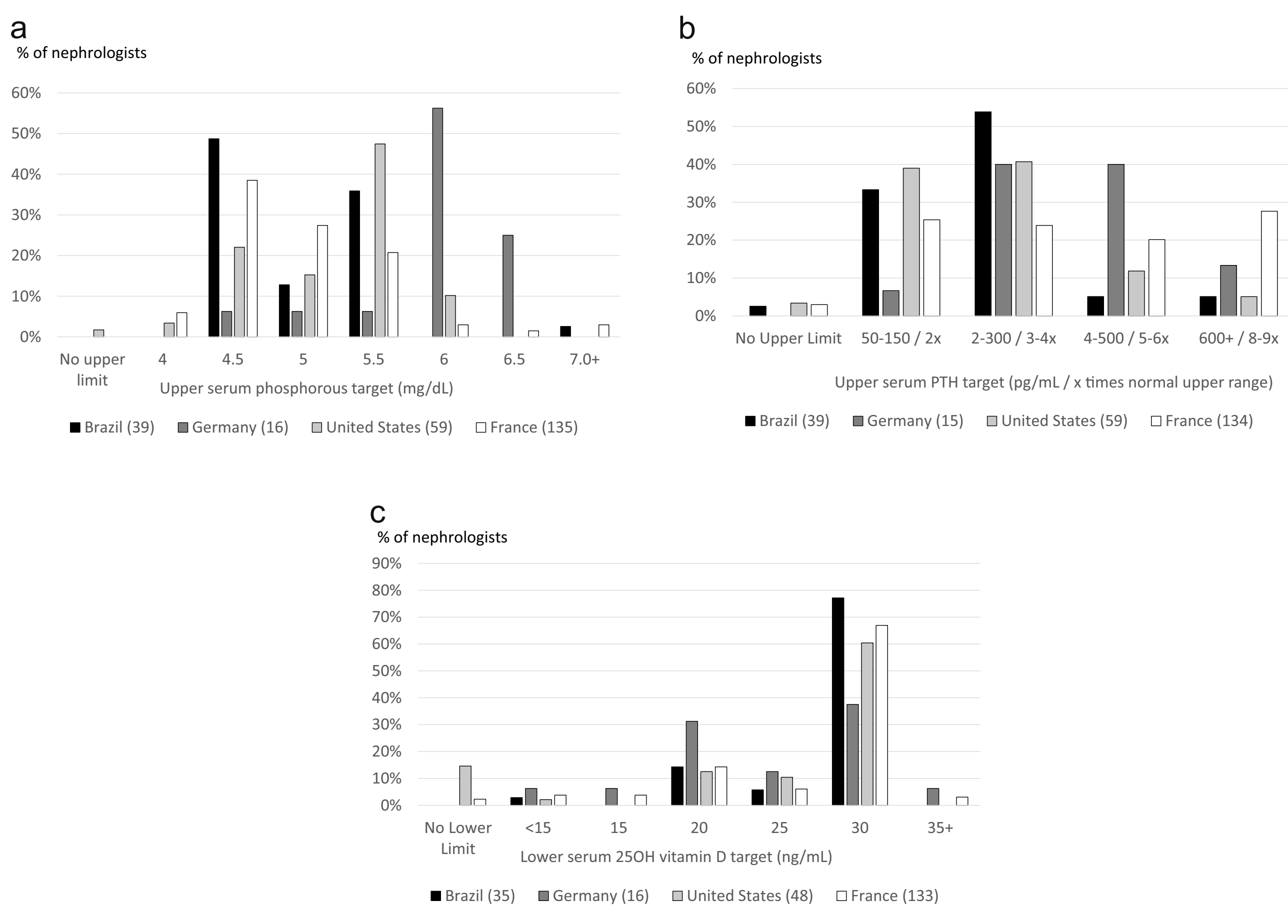

Fig. 1. a–c: Nephrologists (n = 273) associated with the participating clinics were asked to indicate their preferred upper and/or lower target values for MBD laboratory values for patients in the indicated CKD stages.

Table 2
Probability of repeat measurements of MBD-related laboratory data, by CKD stage.

	KDIGO suggested frequency	% with repeat measure within			
		3 months	6 months	9 months	12 months
S. Phosphorus					
Stage 3a	6–12 months	34%	61%	73%	79%
Stage 3b	6–12 months	31%	63%	77%	84%
Stage 4	3–6 months	47%	77%	86%	89%
Stage 5	1–3 months	70%	86%	91%	92%
S. Calcium					
Stage 3a	6–12 months	37%	66%	78%	83%
Stage 3b	6–12 months	36%	67%	81%	87%
Stage 4	3–6 months	49%	80%	88%	92%
Stage 5	1–3 months	73%	90%	94%	94%
iPTH					
Stage 3a	[a]	17%	38%	53%	61%
Stage 3b	[a]	16%	42%	61%	73%
Stage 4	6–12 months	27%	53%	70%	78%
Stage 5	3–6 months	43%	69%	80%	83%
25OH vitamin D					
Stage 3a	[a]	14%	30%	49%	55%
Stage 3b	[a]	12%	41%	63%	73%
Stage 4	[a]	24%	49%	67%	76%
Stage 5	[a]	40%	67%	80%	80%

French data were not available for this table. Percentages based on Kaplan-Meier curves of time to next lab measurement, censored on departure, death, and change to another CKD stage if not accompanied by the specific lab. Includes patients with an initial measurement after 30 days prior to and before 1 year after their entry into a given CKD stage during study follow-up. Suggested frequencies based on KDIGO 2017 guidelines 3.1.3 (not graded).

[a] No time interval given in KDIGO 2017 guidelines. For iPTH, the guideline states that frequency should be based on baseline level and CKD progression. For 25OH vitamin D, the guideline states that 25OH vitamin D levels might be measured, and repeated testing determined by baseline values and therapeutic interventions.

are provided in Fig. 2. Although median P increased with CKD stage, there were some patients with $P < 3.5$ mg/dl in all CKD stages. The proportion of patients with iPTH < 70 pg/mL declined steeply with increasing CKD stage. Ca values < 8.5 mg/dl were seen across CKD stage but were more common in more advanced CKD stages. 25-D levels did not vary meaningfully by CKD stage. Of note, 25-D levels were not reported for 65%–71% of patients from the US and Brazil or for 45% of German patients. Overall, differences between countries in distributions of these four serum MBD laboratory markers were modest.

We explored the relation between iPTH and 25-D, the prohormone of calcitriol (Fig. 3). Amid large variation, iPTH showed a negative association with 25-D. Median iPTH was 49 pg/mL lower for patients with 25-D 40–49 ng/mL versus 0–10 ng/mL. In a multivariable logistic model, iPTH > 300 pg/mL was more common at 25-D < 20 ng/mL than 30–44 ng/mL (OR = 1.54, 95% confidence interval 1.25–1.90; Supplemental Table 1).

3.4. CKD-MBD treatments

We examined CKD-MBD treatment patterns in relation to relevant lab values, with a focus on patients with CKD Stage 4 or 5 (Fig. 4). Phosphate binder use varied by P and country (Fig. 4a). Among patients with P > 5.5 mg/dl, phosphate binder use ranged from 14% in the US to 43% in France. Among patients with serum P < 4.5 mg/dl, phosphate binder use ranged from 5% in Germany to 18% in France. Calcium-based phosphate binders were the primary treatment used in Germany, Brazil, and the US, whereas almost exclusively non-calcium-based binders were prescribed in France.

The prescription of nutritional and active (calcitriol and related analogs) vitamin D varied by iPTH and country (Fig. 4b). Generally, use of active vitamin D was higher among patients with higher iPTH values, especially ≥300 pg/mL, while the use of nutritional vitamin D was more constant across iPTH values (Fig. 4b). France had the highest use of nutritional vitamin D and Germany had the highest use of active vitamin D. France and Brazil had the lowest simultaneous use of active and nutritional vitamin D (Fig. 4b). Among patients with iPTH > 300 pg/mL, the use of active vitamin D ranged from 12% in France to 51% in Germany. The percentage of vitamin D use did not appear to be consistently related to 25-D levels (Fig. 4c).

4. Discussion

CKD-MBD is an important complication of CKD, and frequent monitoring of biomarkers is required to optimally guide treatment. The main findings of our study are that frequency of monitoring of CKD-MBD markers by nephrologists in CKDopps countries is in keeping with guidelines, but prescription of medications to treat CKD-MBD abnormalities is generally low – even in this study of patients under nephrologist care. Target MBD biomarker levels vary notably, and prescription patterns vary somewhat, across countries.

CKD-MBD affects a large number of persons with advanced CKD and influences the risk of bone, mineral, and cardiovascular complications. Block et al. (2013) found many phenotypes of abnormal iPTH, Ca, and P, each with its own risks of death, parathyroidectomy, and cardiovascular hospitalization [2]. Similarly, DOPPS showed that abnormalities in CKD-MBD markers were linked with adverse outcomes in hemodialysis patients [1]. Despite this increased risk, Liabeuf et al. found that a large proportion of HD patients have CKD-MBD biomarker values outside the KDIGO recommended targets [10]. While the majority of epidemiological studies related to CKD-MBD focus on late stages of kidney disease, many reports illustrate the importance of studying CKD-MBD at earlier CKD stages. Indeed, a recent study of bone histomorphometric data among persons with CKD Stages 2–5 reported a gradual increase in bone resorption, associated with decreased bone formation and impaired bone mineralization, with increasing CKD stage [11].

In 2017, KDIGO issued updated guidelines that recognized the complexity and challenges involved with management of CKD-MBD markers [6,9]. The 2017 guidelines are more specific than prior iterations regarding the recommended frequency of routine CKD-MBD lab measurements. In this study, we focused on the probability of repeat lab measurements within specific time intervals in order to accurately report on adherence to KDIGO measurement frequency recommendations, showing that the majority of patients underwent repeat lab testing in accordance with the 2017 KDIGO recommended timeline (Table 2). KDIGO also recommends that CKD patients receive an initial measurement of each of these MBD markers, ideally when the patient is still in Stage 3. It has been reported [12] that the majority of Stage 3 patients do not receive these initial measurements for PTH, P, and 25-D, and investigations (not shown) using CKDopps data corroborate this. As the majority of our data were collected prior to publication of these guidelines, these results demonstrate that nephrologists were aware previously of the importance of careful monitoring for CKD-MBD, whether influenced by prior guidelines or for other reasons, but that these measurements were often not initiated immediately for new CKD patients.

The 2017 KDIGO guidelines encourage efforts to normalize laboratory markers but lack specific target recommendations. Clinical uncertainty about optimal and attainable lab targets is evident in the variation in the target lab values for P and PTH selected by nephrologists participating in CKDopps. As previously shown in HD patients [10], it appears to be difficult to attain target levels for all CKD-MBD markers simultaneously, a goal achieved in only 3% to 15% of CKD Stage 5 patients.

This work expands our understanding of CKD-MBD and its management across the CKD stage and geographic spectrum. In the study cohort, the prevalence of MBD abnormalities increased as expected with CKD progression. The percentage of CKD Stage 4 patients with

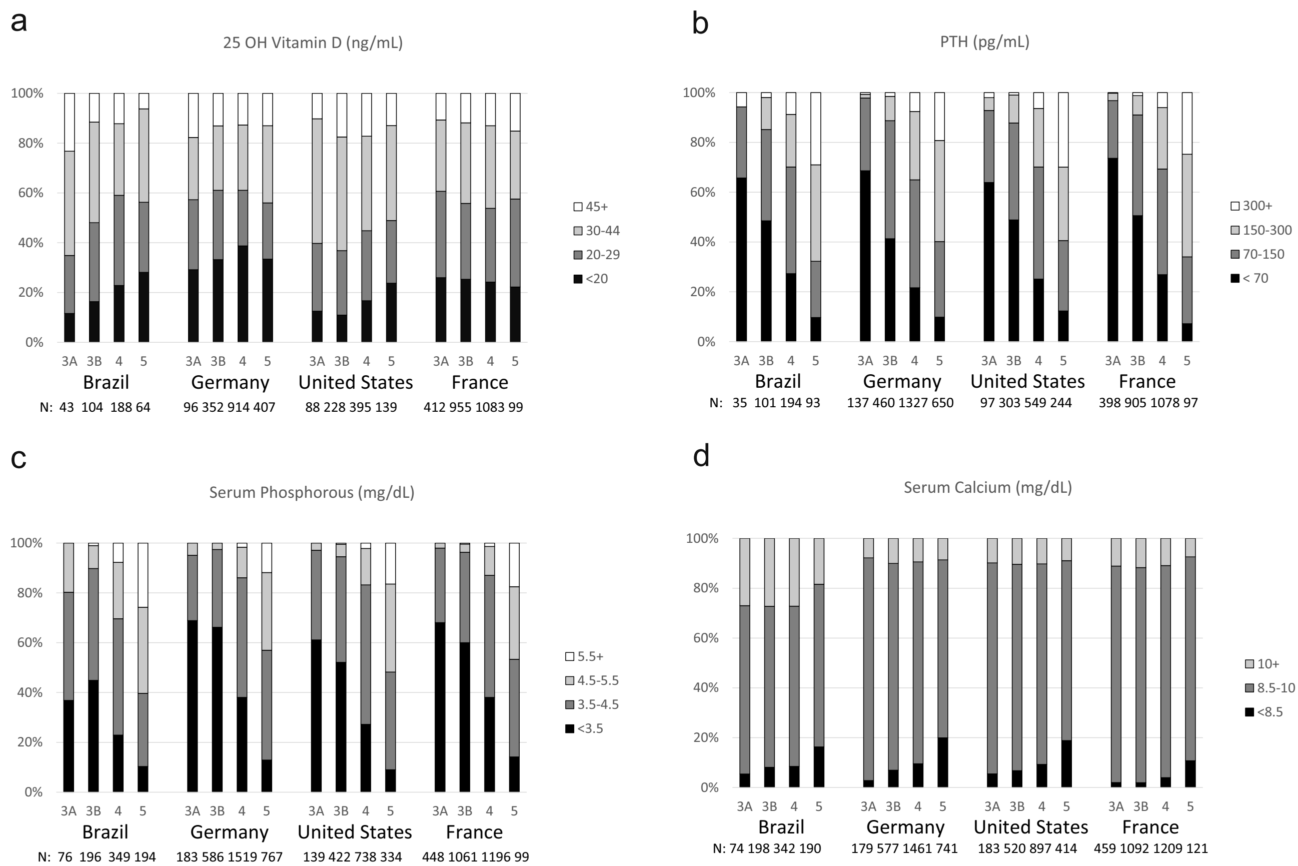

Fig. 2. a–d: Baseline MBD marker lab measurements were used once per patient per CKD stage. If a patient, during follow-up, had multiple lab measurements in multiple CKD stages, at most one per stage was used. A lab measurement was used if it was taken between 30 days before or up to one year after the first lab during study follow-up indicating that the patient had entered a given CKD stage. N represents the number of patients with available data.

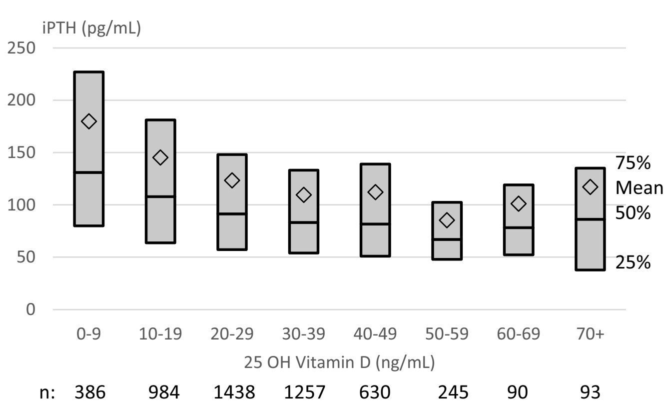

Fig. 3. Distributions of PTH within each category of 25-D indicated are shown, from 25th percentile to 75th percentile, with the median (line) and mean (diamond) indicated.

phosphorus > 4.5 mg/dl was similar in Germany (14%), US (15%), and France (13%), but higher in Brazil (26%). The distribution of iPTH levels was similar across the four countries. The proportion of patients with 25-D < 30 ng/mL was consistent across CKD stages, and was approximately 55% overall, though slightly higher in the US. Country differences could be explained by differences in sunlight exposure and intake of nutritional vitamin D, differences in costs of medications, or health coverage. Similarly, a study evaluating US patients with early stage CKD showed differences in mean and median iPTH levels, but not 25-D levels, across deciles of eGFR [5]. In our analysis, iPTH levels varied inversely with 25-D levels, although with wide variation and a relatively small effect (Fig. 4), a result similar to results found in prior analyses [13]. Furthermore, a recent analysis of a prospective study showed that progressive reductions in iPTH were achieved as mean post-treatment serum 25-D rose from 13.9 ng/mL to 92.5 ng/mL, irrespective of CKD stage [14]. Interestingly, both studies [14,15] found that 25-D levels far above 30 ng/mL are needed to suppress iPTH in non-dialysis CKD patients.

Only 15%–39% of patients with P > 5.5 mg/dL in this study were prescribed phosphate binders. The type of phosphate binder used differed across countries. Few patients in Germany, Brazil, or the US received non-calcium-based phosphate binders, whereas these agents were the treatment of choice in France. The 2017 KDIGO guidelines suggest limiting the dose of calcium-based phosphate binders in adult patients with CKD G3a–G5D who are receiving phosphate-lowering treatment.

Studies evaluating use of phosphate binders in early CKD stages have shown significant decrease in phosphaturia without a large change in serum phosphate [16,17]. These data indicate that serum P may not accurately reflect phosphate balance in early CKD stages. Nephrologists may avoid the use of phosphate binders in non-dialysis CKD patients because of the lack of reliable outcome-based clinical trials and from safety concerns related to a possible association of phosphate binder use, especially calcium-based binders, with vascular calcification [17].

The CKDopps cohort demonstrates national differences in the use of nutritional vitamin D or calcitriol and related analogs. A substantial proportion of CKD Stage 4/5 patients with a potential clinical indication were not prescribed vitamin D (23%–51% of those with vitamin D < 30; 13%–41% of those with iPTH > 300 pg/mL across the four countries). Prescription of nutritional vitamin D appears to be inconsistently associated with 25-D and iPTH levels. The percentage of

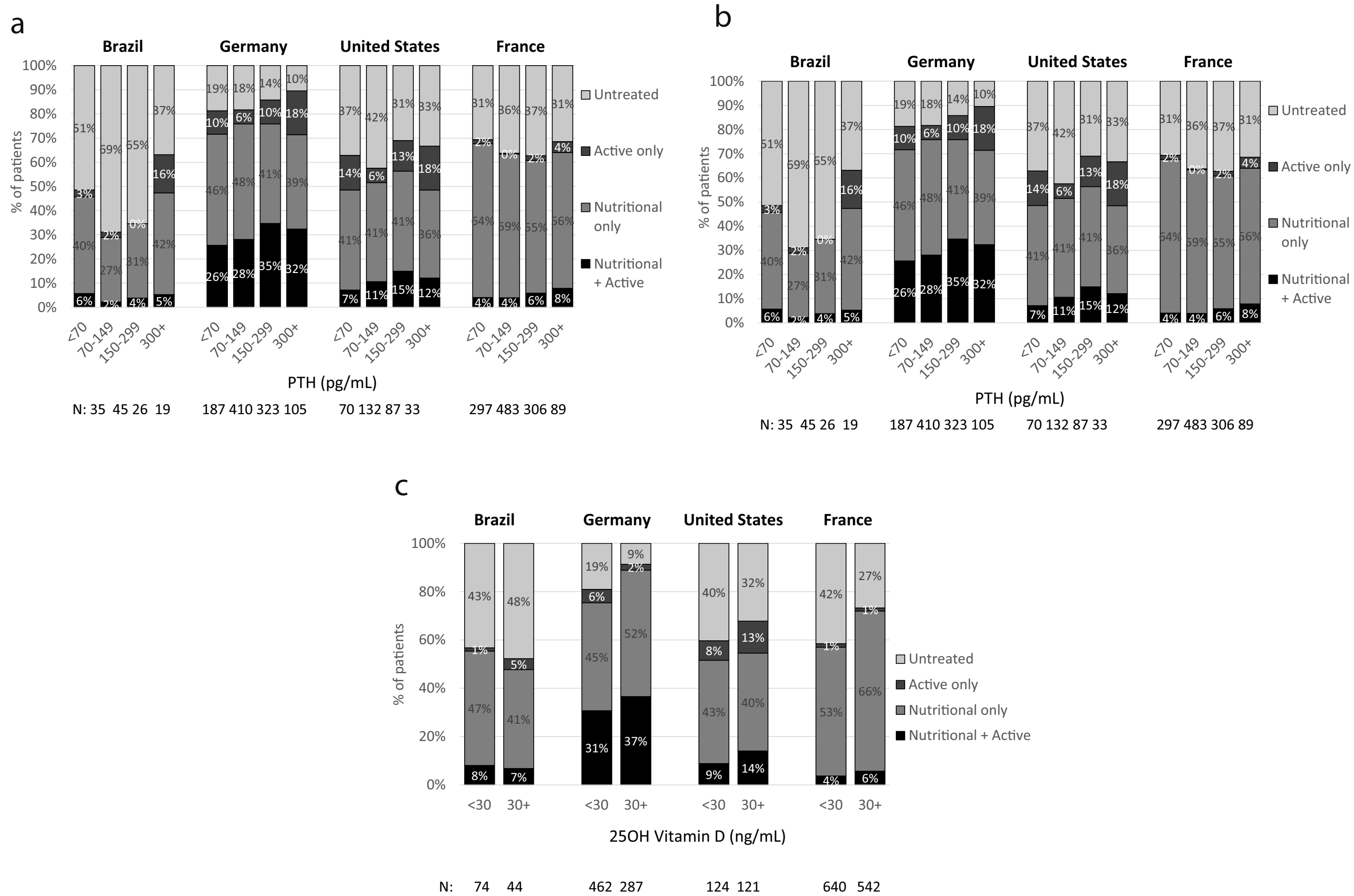

Fig. 4. a–c: Baseline MBD marker lab measurements and prescription information were used once per patient per CKD stage. At most one value for each patient per stage was used. A lab measurement or prescription was used if it was taken between 30 days before or up to one year after the first lab during study follow-up indicating that the patient had entered a given CKD stage. N represents the number of patients with available data.

patients treated by vitamin D varied widely across the studied countries, with Germany having the highest prescription rate (Fig. 4). National variations in clinical target preferences may contribute to these practice differences. Only 6%–7% of French and Brazilian patients received active vitamin D, while 15% of US and 32% of German patients did. This difference could be due to differences in national formularies and pharmacologic markets; for example, the French National Drug Agency and food and drug administration does not authorize paricalcitol use. The revised KDIGO recommendation suggested that calcitriol and vitamin D analogs should be routinely used only for CKD Stage 4–5 patients with severe and progressive hyperparathyroidism. This guideline's authors indicated that this revision was supported because recent randomized controlled trials of vitamin D analogs failed to demonstrate improvements in clinically relevant outcomes, while demonstrating increased risk of hypercalcemia [6,20,21].

In this international cohort, nutritional vitamin D was the most frequently used treatment. Yet 34% to 61% of patients still had 25-D levels below 30 ng/mL (Fig. 3A), often despite treatment with nutritional vitamin D, although dosage levels were not analyzed. Further investigation in clinical trials is necessary to determine whether more effective vitamin D replacement can ameliorate secondary hyperparathyroidism in CKD patients.

Readers should interpret these results in the context of study limitations—as this work was observational and cross-sectional in nature, we were unable to evaluate causal relationships. In addition, in some groups (including Stage 5 patients) the sample size is small, there was substantial missing data on medication use, and routine lab monitoring practices for French participants could not be included in the analysis because of their specific protocol. As included patients were prevalent, it was not possible to evaluate the date of mineral bone disease drug initiations and correlate this with a lab value. The medication use in relation to the serum biochemical parameters is difficult to interpret, as we do not have a record of medication at each laboratory value. Due to the period of inclusion (3% of patients included after July 2017), we could not evaluate the impact of the 2017 KDIGO CKD-MBD updated guidelines. Due to the limited time of follow up, we could not evaluate the changes over time for medications. These two points could be evaluated in CKDopps when longer follow up is available.

Laboratory values were routinely collected and not centrally measured, so differences between PTH and 25-D assays could interfere with the interpretation of difference across countries. Despite these limitations, the present study expands our knowledge on the prevalence of MBD abnormalities and management in a large, international sample of CKD patients, allowing for comparisons between geographically and culturally disparate regions. The nephrologist survey allowed inter-country comparisons of nephrologist preferences for biomarker targets.

Studies of patients with end-stage renal disease contribute the majority of our knowledge regarding MBD in kidney disease patients. The treatment of CKD-MBD remains a challenging task, and the high frequency of MBD marker abnormalities among CKD patients warrants further study. Well-designed clinical trials based on hard outcomes have not yet tested the use of calcitriol and related analogs, nutritional vitamin D, or phosphate binders, leading to a lack of strong evidence to guide use of these therapies.

We have shown that MBD practices among patients with kidney disease vary internationally and by CKD stages. Physicians are clearly aware of the need to monitor this multisystem interaction of pathophysiological events related to mineral and bone metabolism. However, target levels vary notably and prescription of medications to treat abnormalities in these laboratory markers is generally low. While there are opportunities to increase treatment of hyperphosphatemia, hyperparathyroidism, and vitamin D deficiency in advanced CKD, the effect on longer-term complications of these conditions requires study. Early intervention and preventive efforts, perhaps begun while laboratory markers are within target limits, may result in better overall and longer-term management.

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Declaration of competing interest

Sophie Liabeuf has no conflicts of interest to disclose; Helmut Reichel reports honoraria and consulting fees from Amgen and Hexal AG; Friedrich K. Port has consultancy contract with Arbor Research Collaborative for Health and no other conflicts to declare; Bénédicte Stengel reports grants for the CKD-REIN cohort study (which contributes French data to CKDopps) from Amgen, Baxter, Fresenius Medical Care, GlaxoSmithKline, Merck Sharp and Dohme-Chibret, Sanofi-Genzyme, Lilly, Otsuka, and Vifor Fresenius, as well as speaker honoraria at the French Society of Diabetology from Lilly, and at the French-speaking Society of Nephrology, Dialysis and Transplantation from MSD; Philipp A. Csomor is an employee of Vifor Pharma Management Ltd.; Marie Metzger has no conflicts of interest to disclose; Ziad A. Massy reports grants for CKD REIN and other research projects from Amgen, Baxter, Fresenius Medical Care, GlaxoSmithKline, Merck Sharp and Dohme-Chibret, Sanofi-Genzyme, Lilly, Otsuka and the French government, as well as fees and grants to charities from Astellas, Baxter, Daichii, and Sanofi-Genzyme; these sources of funding are not necessarily related to the content of the present manuscript.

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References

[1] F. Tentori, et al., Recent changes in therapeutic approaches and association with outcomes among patients with secondary hyperparathyroidism on chronic hemodialysis: the DOPPS study, Clin. J. Am. Soc. Nephrol. 10 (2015) 98–109.
[2] G.A. Block, R.D. Kilpatrick, K.A. Lowe, W. Wang, M.D. Danese, CKD–mineral and bone disorder and risk of death and cardiovascular hospitalization in patients on hemodialysis, Clin. J. Am. Soc. Nephrol. 8 (2013) 2132–2140.
[3] P. Ureña-Torres, et al., Association of kidney function, vitamin D deficiency, and circulating markers of mineral and bone disorders in CKD, Am. J. Kidney Dis. 58 (2011) 544–553.
[4] O. Moranne, et al., Timing of onset of CKD-related metabolic complications, J. Am. Soc. Nephrol. 20 (2009) 164–171.
[5] A. Levin, et al., Prevalence of abnormal serum vitamin D, PTH, calcium, and phosphorus in patients with chronic kidney disease: results of the study to evaluate early kidney disease, Kidney Int. 71 (2007) 31–38.
[6] KDIGO, 2017 Clinical practice guideline update for the diagnosis, evaluation, prevention, and treatment of chronic kidney disease–mineral and bone disorder (CKD-MBD), Kidney Int. Suppl. 7 (2017) 1–59.
[7] L. Mariani, et al., The CKD outcomes and practice patterns study (CKDopps): rationale and methods, Am. J. Kidney Dis. 68 (2016) 402–413.
[8] B. Stengel, et al., The French chronic kidney disease-renal epidemiology and information network (CKD-REIN) cohort study, Nephrol. Dial. Transplant. 29 (2014) 1500–1507.
[9] M. Ketteler, et al., Executive summary of the 2017 KDIGO Chronic Kidney Disease-Mineral and Bone Disorder (CKD-MBD) Guideline Update: what's changed and why it matters, Kidney Int. 92 (2017) 26–36.
[10] S. Liabeuf, et al., Attainment of guideline targets in EURODOPPS haemodialysis patients: are differences related to a country's healthcare expenditure and nephrologist workforce? Nephrol. Dial. Transplant. 32 (2017) 1737–1749.
[11] F.G. Graciolli, et al., The complexity of chronic kidney disease-mineral and bone disorder across stages of chronic kidney disease, Kidney Int. 91 (2017) 1436–1446.
[12] N.S. Roetker, Y. Peng, A. Ashfaq, D.T. Gilbertson, J.B. Wetmore, Adherence to kidney disease: improving global outcomes mineral and bone guidelines for monitoring biochemical parameters, Am. J. Nephrol. 49 (2019) 225–232.
[13] M. Metzger, et al., Relation between circulating levels of 25(OH) vitamin D and parathyroid hormone in chronic kidney disease: quest for a threshold, J. Clin. Endocrinol. Metab. 98 (2013) 2922–2928.
[14] S.A. Strugnell, S.M. Sprague, A. Ashfaq, M. Petkovich, C.W. Bishop, Rationale for raising current clinical practice guideline target for serum 25-hydroxyvitamin D in chronic kidney disease, Am. J. Nephrol. 49 (2019) 284–293.
[15] J.L. Ennis, E.M. Worcester, F.L. Coe, S.M. Sprague, Current recommended 25-hydroxyvitamin D targets for chronic kidney disease management may be too low, J. Nephrol. 29 (2016) 63–70.
[16] S. Liabeuf, et al., Randomized clinical trial of sevelamer carbonate on serum klotho and fibroblast growth factor 23 in CKD, Clin. J. Am. Soc. Nephrol. 12 (2017) 1930–1940.
[17] G.A. Block, et al., Effects of phosphate binders in moderate CKD, J. Am. Soc. Nephrol. 23 (2012) 1407–1415.
[20] N.A. Hamdy, et al., Effect of alfacalcidol on natural course of renal bone disease in mild to moderate renal failure, BMJ 310 (1995) 358–363.
[21] R. Thadhani, et al., Vitamin D therapy and cardiac structure and function in patients with chronic kidney disease: the PRIMO randomized controlled trial, JAMA 307 (2012) 674–684.