Diagnosis and Management of Mineral Metabolism in CKD

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BACKGROUND: Chronic kidney disease (CKD) affects over 26 million Americans and is frequently complicated early in its course by disordered mineral metabolism and metabolic bone disease. Since CKD-related bone loss is often indistinguishable from osteoporosis by standard bone densitometry, many CKD patients may be inappropriately treated with bisphosphonates rather than CKD-specific therapies.

OBJECTIVE: To determine the prevalence of appropriate evaluation, diagnosis and management of metabolic bone disease among individuals with pre-dialysis CKD.

DESIGN AND PARTICIPANTS: Retrospective cohort study using electronic medical records of 69,215 ambulatory patients seen in the primary care clinics of an academic medical center.

MEASUREMENTS: Prevalence of CKD stages 3–4, frequency of diagnostic testing and treatment of metabolic bone disease.

MAIN RESULTS: Based on current diagnostic criteria and consistent with national data, CKD was present in 12% of the population. Bisphosphonates were used in 7.2% of patients, 20% of whom met criteria for CKD. Fewer than half of CKD patients underwent testing for parathyroid hormone (PTH) or 25-hydroxyvitamin D (25D) levels. Among those tested, vitamin D deficiency (25D <30 ng/ml) and secondary hyperparathyroidism (PTH >60 pg/ml) were present in 65% and 55%, respectively. Among patients with CKD, bisphosphonate use was nearly seven times as frequent as therapy with active vitamin D (12% vs. 1.7%, $p<0.0001$), a primary treatment for CKD-associated metabolic bone disease.

CONCLUSIONS: Disordered mineral metabolism in CKD is common, under-diagnosed and under-treated. As a result, bisphosphonates may be prescribed inappropriately in patients with CKD.

KEY WORDS: chronic kidney disease; bisphosphonate; osteoporosis.
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INTRODUCTION

Chronic kidney disease (CKD) is a growing public health epidemic that affects up to 13% of the US population.[1] Although end-stage renal disease requiring dialysis is its most widely appreciated consequence, CKD exerts a toxic toll on a variety of other organ systems beginning early in its course. This results in numerous complications that contribute to decreased quality of life and premature death.[2–5] Not surprisingly, the risk of death among patients with early stages of CKD dwarfs their risk of progression to end-stage renal disease.[6]

Metabolic bone disease with disordered calcium and phosphorus metabolism begins in early CKD, but often remains undiagnosed until advanced renal failure when serum calcium and phosphate levels first become abnormal.[7] In addition to contributing to bone loss and increased fracture risk, many components of metabolic bone disease have been independently associated with mortality in prospective studies of individuals receiving dialysis.[8,9] These observations have increased the urgency for early diagnosis and intervention. Clinical practice guidelines recommend specific laboratory screening for parathyroid hormone (PTH) and vitamin D levels followed by targeted treatment with combinations of nutritional and active vitamin D, and dietary phosphorus binders.[10–13]

Bisphosphonates are potent anti-resorptive agents that prevent bone loss and decrease fracture risk in osteoporosis, but they are contraindicated in advanced CKD and likely have a limited role in early CKD. Bisphosphonates do not address the specific metabolic alterations associated with CKD,[14,15] are less effective in the setting of these metabolic alterations[16,17] and have a markedly prolonged half-life in CKD that may contribute to adynamic bone disease.[18,19] Despite these concerns, bisphosphonates may be inadvertently prescribed in CKD because osteoporosis and CKD-related bone loss cannot be differentiated by standard bone mineral density testing.[20] Furthermore, awareness and appropriate management of CKD is low,[21,22] and clinically significant CKD may be present at a relatively normal serum creatinine level in elderly women,[23] the very population most commonly prescribed bisphosphonates. We used the electronic medical record of a major academic medical center to test the hypothesis that the appropriate evaluation, diagnosis and management of metabolic bone disease among individuals with pre-dialysis CKD is uncommon.

METHODS

Study Population

The Massachusetts General Hospital Primary Care (MGPC) network serves an ethnically diverse patient population in

Eastern Massachusetts. The network is comprised of 15 primary care practices, including 5 community health centers, 6 community-based practices and 4 hospital-based practices. It is the largest provider of free care services in Massachusetts. In 2004, more than 200 primary care physicians (PCPs) treated over 150,000 adult patients at more than 372,000 clinic visits.

A standardized electronic medical record (EMR) unifies the MGPC network and contains demographic data, past medical history, medications and laboratory results. All encounters are documented electronically, and internal data indicate that 74–89% of prescriptions written by providers are recorded in the electronic medical record. PCPs also document non-prescription medications in the record, though these data are likely less complete. Encounter data are merged with laboratory testing, diagnostic coding, billing and scheduling systems in the Partners Research Patient Data Registry (RPDR), a searchable, research-grade data warehouse used in several prior studies.[24–27]

We used the RPDR to identify all ambulatory patients who had a serum creatinine measured during 2002 and 2003 and had a subsequent visit with their primary care physician (PCP) during 2004 or later (Fig. 1). This ensured that all patients in the analysis had the opportunity for a diagnosis of CKD after the 2003 release of the National Kidney Foundation's Kidney Disease Outcomes Quality Initiative (K/DOQI) clinical practice guidelines for bone metabolism and disease in CKD.[10]

The purpose of this study was to focus on the diagnosis and management of disordered mineral metabolism and bone disease in early CKD. Therefore, we excluded patients with stage 5 CKD (eGFR <15 ml/min/1.73 m^2; n=123) and those on dialysis at baseline (n=397), as these individuals are primarily managed by nephrologists and have relevant laboratory testing and medications prescribed by protocol at their dialysis units, independent of their PCPs. We excluded patients whose bisphosphonate prescriptions originated in a subspecialty clinic and those who received intravenous bisphosphonates (n=639 total) because the indication for these was likely control of hypercalcemia or metastatic disease rather than bone loss. We also excluded patients with primary hyperparathyroidism (n=963; defined as a coded diagnosis or a PTH >60 pg/ml in association with a serum calcium >10.5 mg/dl), because it is a cause of bone loss and elevated PTH levels that is independent of CKD. Lastly, we excluded organ transplant recipients (n=1,133), who may be treated with bisphosphonates by protocol for prevention of transplant-associated bone loss.

Outcomes

Laboratory Testing. We queried the RPDR for all laboratory tests of creatinine, calcium, phosphorus, 25-hydroxyvitamin D (25D) and PTH between 2002 and 2007. The last outpatient creatinine result prior to January 1, 2004, was used to calculate eGFR at the beginning of the bisphosphonate observation period, which spanned through May 23, 2007 (Fig. 1). We could thus be confident that a certain level of CKD had developed prior to a subsequent PCP visit when a prescription for a bisphosphonate was provided. We used the simplified Modification of Diet in Renal Disease (MDRD) equation for eGFR, which has been a recommended screening tool for CKD since 2000.[23] Stage of CKD was defined based on eGFR expressed in ml/min/1.73 m^2: stage 3a, 45–59; stage 3b, 30–44; and stage 4, 15–29.[23] For the tests of mineral metabolism, we included assays from throughout the study period (2002–2007), because a PCP diagnosing CKD in 2004 might, justifiably, not repeat these tests if recent values were available. This reduced the likelihood of underestimating testing rates. The MGH laboratory uses isotope-dilution mass spectrometry (IDMS) creatinine test; automated eGFR reporting was not performed by the laboratory during the study period.

Based on the laboratory's reference range, the following cut points were used to define clinically relevant abnormal results associated with CKD: vitamin D deficiency was defined as a 25D level <30 ng/ml; secondary hyperparathyroidism as a PTH >60 pg/ml; hypocalcemia as a serum calcium <8.5 mg/dl, unadjusted for albumin; and hyperphosphatemia as a serum phosphate >4.5 mg/dl. For patients with multiple measure-

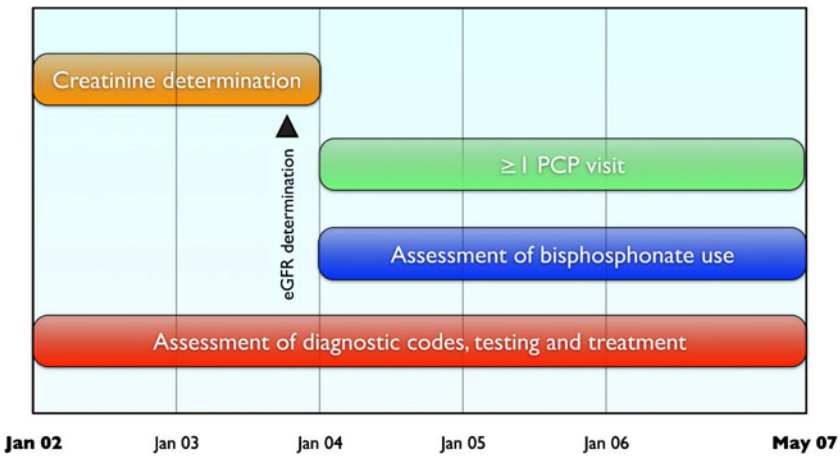

Figure 1. Data collection strategy. Patients who had at least one serum creatinine measured in 2002–2003 and at least one PCP visit thereafter were included. The last creatinine prior to 2004 was used to determine eGFR. Bisphosphonate prescriptions from January 2004 through May 2007 were determined. Clinical diagnoses, laboratory test results and other medications were assessed throughout the study period. PCP = primary care physician. eGFR = estimated glomerular filtration rate.

ments, nadir levels of 25D and calcium and peak levels of PTH and phosphate were analyzed.

Medications. Bisphosphonate use was ascertained by the presence of a new prescription for an oral bisphosphonate beginning after January 1, 2004, after there had been an opportunity for CKD status to be determined. Prescriptions for calcium supplements, phosphorus binders (calcium acetate, lanthanum carbonate or sevelamer hydrochloride), nutritional vitamin D (ergocalciferol, cholecalciferol or "vitamin D") and active vitamin D (calcitriol, paricalcitol or doxercalciferol) were coded as positive for any prescription during the study period. Combination medications (e.g., a calcium plus vitamin D supplement) were coded as positive for both classes.

Documented Diagnoses. Diagnosis lists were available for all patients and were derived from clinic notes, problem lists and centralized billing records. Patients were considered as having a CKD code based on the presence of a diagnosis that identified "chronic kidney disease," "nephrotic," "nephritic," "cystic kidney," "atheroembolism of kidney," "unspecified disorder of kidney" or "renal," but excluded diagnoses related to infectious or neoplastic kidney diseases, nephrolithiasis and isolated renal cysts. Osteoporosis was identified by documentation of the term "osteoporosis."

As PCPs would not need to replicate testing and treatment performed by subspecialists, laboratory testing, diagnoses and medications (other than bisphosphonates) that originated in a subspecialty clinic were also included in the analysis.

Statistical Analysis

Groups of patients were compared according to the presence or absence of CKD as defined by the study, and by incident prescription of bisphosphonates versus no bisphosphonate treatment. Each index group was compared with the remainder of the population; for example, patients with and without CKD were compared. Comparisons within subgroups were also performed: patients with CKD receiving bisphosphonates were compared with CKD patients not receiving bisphosphonates. Continuous variables were compared using two-sample *t* tests, while categorical variables were compared with the chi^2 test. Chi^2 testing and multivariable logistic regression were used to compare odds of laboratory testing, laboratory abnormalities, diagnostic coding and prescription writing between groups. Analyses were performed using SAS 9.1.3 (SAS Institute, Cary, NC). The study was approved by the institutional review board of Massachusetts General Hospital, which waived the requirement for informed consent.

RESULTS

General Subject Characteristics

A total of 150,024 patients were identified as having seen a PCP at one of the study sites from 2004–2007. Of these patients, 71,928 had at least one creatinine measurement in 2002–2003. After applying the exclusion criteria, 69,215 patients remained; their characteristics are presented in Table 1 and Table 2. Twelve percent (n=8,472) of the study population met criteria for moderate-severe CKD (eGFR 15–59 ml/min/1.73 m^2); 75% stage 3a, 21% stage 3b, and 4% stage 4.

Laboratory Testing for Mineral Metabolism

Serum calcium, which is part of the basic metabolic panel at this center, was measured in 97% of all patients, while serum phosphorus was measured in only 54%. Compared with patients without CKD, patients with CKD were somewhat more likely to have serum calcium (99% vs. 97%, p<0.0001) and phosphorus testing (69% vs. 52%, p<0.0001). In contrast, evaluation of 25D levels was performed in only 15% of all patients. Although more commonly tested in patients with CKD, 25D testing was not routine even in this population (25%). Evaluation of PTH levels was similarly uncommon overall (8%), although higher among patients with CKD (15%). Only 10% of patients with CKD had all four recommended tests of calcium, phosphorus, 25D and PTH at any time during follow-up.

Abnormalities in Mineral Metabolism

Vitamin D deficiency was observed in 65% of the 2,105 patients with CKD in whom 25D was measured, a proportion similar to that seen in the general population (66%, p=0.62). Secondary hyperparathyroidism was observed in 55% of the 1,252 patients with CKD in whom PTH was tested. Hypocalcemia (32% of 8,381 tested) and hyperphosphatemia (18% of 5,866 tested) were less common. After adjusting for age, sex and race, patients with CKD were significantly more likely than those without CKD to have hypocalcemia (OR 1.6, 95%CI 1.5, 1.6), hyperphosphatemia (OR 2.6, 95%CI 2.3, 2.8) and secondary hyperparathyroidism (OR 2.8, 95%CI 2.4, 3.2).

Management of Bone Disease: CKD-Specific vs. Bisphosphonate Therapy

Only 17% of patients were documented as receiving supplementation with calcium and only 16% with nutritional vitamin

Table 1. Demographic Characteristics of Subjects with and without CKD. Values Are Reported as Mean ± Standard Deviation or Percentage of Population Along with P-values for Differences Between Groups. CKD = Chronic Kidney Disease

Parameter	CKD	Non-CKD	p-value
	N=8,472	N=60,743	
Age (years)	70.9±12.6*	50.8±15.7	<0.0001
Race, ethnicity (%)			
White	87.0	76.7	<0.0001
Hispanic	2.5	8.6	<0.0001
Black	3.3	6.0	<0.0001
Asian	4.4	5.2	0.002
Other	2.8	3.5	0.002
Sex, (% female)	63.6	56.5	<0.0001

Table 2. Laboratory Characteristics of Subjects with and without CKD. Means ± Standard Deviations and P-value for the Differences Between Groups Are Reported. Calcium, Creatinine, Potassium and Hemoglobin Levels Were Available in >95% of All Subjects, While Phosphorus Levels Were Available in 54%. CKD = Chronic Kidney Disease

Parameter	CKD	Non-CKD	p-value
	N=8,472	N=60,743	
Calcium (mg/dl)	9.3±0.4	9.3±0.4	0.47
Phosphorus (mg/dl)	3.2±0.5	3.1±0.5	<0.0001
Creatinine (mg/dl)	1.3±0.4	0.9±0.2	<0.0001
Potassium (mg/dl)	4.2±0.3	4.0±0.3	<0.0001
Hemoglobin (g/dl)	12.9±1.6	13.8±1.5	<0.0001

D. CKD-specific therapies were considerably less common: 1.9% were documented as receiving active vitamin D, while 0.9% received a phosphorus binder.

In the overall population, 7.2% of patients received bisphosphonates during the study period. Among bisphosphonate users, 20% met criteria for CKD prior to initiation of therapy vs. 12% of non-users [odds ratio (OR) 1.9; 95% confidence interval (CI) 1.8, 2.1; p<0.0001]. The association between CKD and bisphosphonate use was driven largely by stage 3 CKD; the rate of bisphosphonate use was not significantly different between CKD stage 4 patients and those without CKD (8.3 vs. 7.0%, p=0.40).

After excluding the 19 patients who received both treatments, individuals with CKD were nearly seven times as likely to receive a bisphosphonate than active vitamin D (12% v 1.7%; p<0.0001), a result that persisted in analyses restricted to the subset of patients with CKD stages 3b and 4 (11% v. 4.8%, p=0.004). Furthermore, 24% of patients with CKD who were treated with bisphosphonates received these agents despite having untreated vitamin D insufficiency, hyperphosphatemia or hyperparathyroidism. When this analysis was restricted to those with stage 4 CKD, this percentage rose to 62%.

Documented Diagnoses

The two most common documented diagnoses were "unspecified hyperlipidemia" (n=43,110; 62%) and "unspecified essential hypertension" (n=39,137, 57%). Only 20% of patients with CKD based on laboratory criteria carried a documented diagnosis reflecting kidney disease by 2004; an additional 19% received a CKD diagnosis during follow-up. In contrast, the vast majority (84%) of patients treated with bisphosphonates had a documented diagnosis of osteoporosis. We examined the effect of CKD awareness on management of mineral metabolism by identifying those patients who had a coded diagnosis for kidney disease at any point during the study period. Among patients with CKD, the presence of a documented diagnosis of kidney disease significantly increased the likelihood of testing for calcium (100% vs. 98%), phosphorus (87% vs. 57%), 25D (29% vs. 22%) and PTH (24% vs. 9%; p<0.0001 for all comparisons), however, testing remained far from universal. Although patients documented to have CKD were more likely to be treated with active vitamin D or a phosphorus binder, only 5% were treated with either (Fig. 2), whereas 10% were treated with bisphosphonates.

DISCUSSION

In this retrospective study of 69,215 patients from primary care clinics throughout a large academic health system, we observed a high prevalence of CKD, but low rates of testing or treatment for associated metabolic bone disease. Although a documented diagnosis of kidney disease did increase the likelihood of targeted testing and treatment, the majority of CKD patients remained untested and untreated with recommended therapies. While the goal of the study was not to determine whether the presence of CKD was independently associated with bisphosphonate use, bisphosphonate therapy

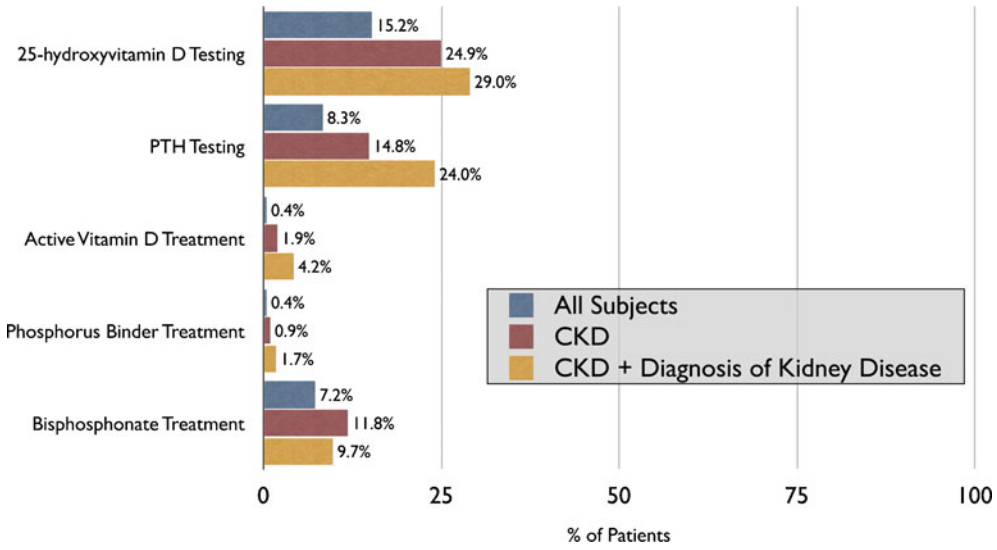

Figure 2. Metabolic bone disease evaluation and management. Percentage of all patients (n=69,215), patients with CKD (n=8,472) and CKD patients with a coded diagnosis of kidney disease (n=3,320) who underwent testing or treatment for metabolic bone disease. PTH = parathyroid hormone. CKD = chronic kidney disease.

was not significantly lower among CKD versus non-CKD patients as would be expected given their relative contraindication in CKD. These results suggest that CKD and its associated mineral disorders are under-recognized, underdiagnosed and under-treated, which may result in increased cost and decreased quality of care.[28] When clinicians consider bisphosphonate therapy for presumed osteoporosis, a thorough evaluation for potential causes of metabolic bone disease, including CKD, is warranted. Furthermore, the finding of bone loss could serve as a gateway to earlier diagnosis and tailored therapy of CKD itself.

The pathogenesis of disordered mineral metabolism in CKD involves inadequate renal conversion of 25-hydroxyvitamin D to its active hormonal form, 1,25-dihydroxyvitamin D, which may be further exacerbated by concomitant nutritional deficiency of 25-hydroxyvitamin D.[29] Deficiencies in the vitamin D axis impair dietary calcium absorption and release the parathyroid glands from feedback inhibition.[14] Impaired phosphorus excretion and decreased expression of the calcium sensing receptor in the parathyroid glands also promote increased PTH levels.[11,30] The resultant secondary hyperparathyroidism helps maintain normocalcemia by accelerating bone resorption that decreases bone mineral density in a pattern that can be radiographically indistinguishable from osteoporosis.[7] Bone biopsy studies confirm that histological abnormalities in bone turnover, mineralization and volume begin early in CKD.[31]

Although their contraindication in CKD stems more from a lack of safety data rather than proven toxicity, the efficacy and rationale for bisphosphonates are uncertain when there is untreated vitamin D deficiency or hyperparathyroidism,[16,17] which are core mechanisms of bone loss in CKD. While one meta-analysis suggested that risedronate reduced fractures in CKD patients,[32] long-term, dedicated safety and efficacy studies are lacking. Given recent concern over increased fracture rates because of excessive suppression of bone remodeling among long-term bisphosphonates users,[33–36] particular caution may be warranted in CKD, as decreased renal clearance can markedly increase the half-life of these drugs.

Despite these concerns, prescription of bisphosphonates was common in patients with CKD; even in the subset with CKD stage 4 (eGFR 15–29 ml/min/1.72 m^2), bisphosphonate use was no less prevalent than in the non-CKD population. The latter finding is especially noteworthy given that CKD stage 4 is usually clinically evident. Thus, the similar rates of therapy in stage 4 and the overall population strongly suggest a lack of awareness of the contraindications and potential toxicities of these agents in advanced CKD. Furthermore, patients with CKD were nearly seven times more likely to receive a bisphosphonate than active vitamin D. The infrequency of vitamin D therapy even among those found to have secondary hyperparathyroidism suggests providers were unaware of the potentially important role of this treatment in patients with CKD. Indeed, while vitamin D agents are recommended to treat vitamin D deficiency and secondary hyperparathyroidism in patients with pre-dialysis CKD, recent pharmaco-epidemiological studies suggest a potential survival benefit of therapy.[37,38] Collectively, these results suggest important gaps in understanding the potential risks and benefits of specific treatments for disordered mineral metabolism in CKD.

This large-scale study of real-world clinical practice was enabled by the presence of an institution-wide EMR. Despite the breadth of available data, this approach is accompanied by certain limitations. Data regarding care received outside the institution were unavailable; hence, it is possible that we underestimated the frequency of diagnostic testing and therapy. Nevertheless, the focus of this study was the role of PCPs, all of whom were based in the single institution encompassed by the EMR. In addition, we did include prescriptions for active vitamin D and phosphate binders from other providers, acknowledging that PCPs may co-manage CKD patients with nephrologists. It is also possible that the low rates of diagnosis, targeted laboratory testing and treatment were the result of documentation failure rather than deficits in clinical care. However, given that these rates were extremely low, it is unlikely that the conclusions of the study would be dramatically altered by perfect documentation.

Defining CKD based on a single creatinine test used to calculate eGFR is another potential limitation. Although our study design ensured that PCPs had access to at least one measure of renal function before the observation period, it could be argued that we overestimated the prevalence of CKD.[39] Indeed, some individuals labeled as having CKD might actually have had only a transient reduction in GFR, and others might have had a sustained, age-dependent reduction in GFR without any other objective evidence of kidney disease. It is important to note however, that despite these limitations, an eGFR <60 ml/min/1.73 m^2 has been independently associated with increased future risk of major cardiovascular events and mortality.[3] Furthermore, evidence of disordered mineral metabolism, either hypocalcemia, hyperphosphatemia or hyperparathyroidism, was present in 76% of patients we identified as having CKD who were tested, and the results were qualitatively similar even when we excluded patients with eGFR of 45–60 ml/min/1.73 m^2, the population most likely to include false-positive screens for CKD. Indeed, the limited precision of eGFR should promote, rather than obviate, the need for confirmatory testing of disordered mineral metabolism. Despite this, we found rates of such testing to be low.

Recommendations to screen for vitamin D deficiency in the evaluation for osteoporosis are inconsistent. Kaiser Permanente's osteoporosis/fracture prevention clinical practice guidelines recommend testing and repletion of 25-hydroxyvitamin D to a level of ≥30 ng/ml before initiation of bisphosphonates.[40] Guidelines from the National Osteoporosis Foundation recommend considering testing for vitamin D insufficiency and obtaining calcium and creatinine levels prior to treating with bisphosphonates.[41] However, many guidelines do not include routine screening for vitamin D levels in osteoporosis. If some PCPs in our study tested 25-hydroxyvitamin D levels as part of an evaluation for osteoporosis, this suggests that even fewer patients received the testing for CKD-related bone disease, further strengthening our findings.

An explicit goal of this report was not to criticize the care of exceptionally busy PCPs. Instead, we aimed to explore the obstacles in the primary care setting that prevent the appropriate diagnosis and treatment of one of the main complications of CKD. While bisphosphonates may have been deliberately used in some CKD patients after careful weighing of potential risks and benefits, their frequent use in CKD, along with infrequent targeted laboratory testing, suggests underlying knowledge deficits. These may include underappreciation of underlying CKD, of CKD as a cause of bone

loss, of recommended testing and treatment for disordered mineral metabolism in CKD or of the contraindication of bisphosphonates in advanced CKD. Indeed, other studies similarly found significant knowledge deficits in CKD diagnosis and management, even among recently trained physicians.[42] Interventions to fill these gaps might include automatic eGFR reporting, automated clinical reminders to prompt clinicians to consider appropriate metabolic bone disease testing for all patients in whom bisphosphonates are being considered and CKD-specific diagnostic testing for those with eGFR <60 ml/min/1.73 m^2. Publication of additional reviews on CKD management in the general medical literature[43] is also needed to increase awareness among PCPs. Ultimately, these interventions could pave the way for improved care of CKD and its various complications.

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I.B. was involved in conception and design, acquisition of data, analysis and interpretation of data, drafting and critical revision of the manuscript, and statistical analysis. M.W. was involved in conception and design, analysis and interpretation of data, drafting and critical revision of the manuscript, and supervision. A.D. was involved in acquisition of data, critical revision of the manuscript, and technical support.

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