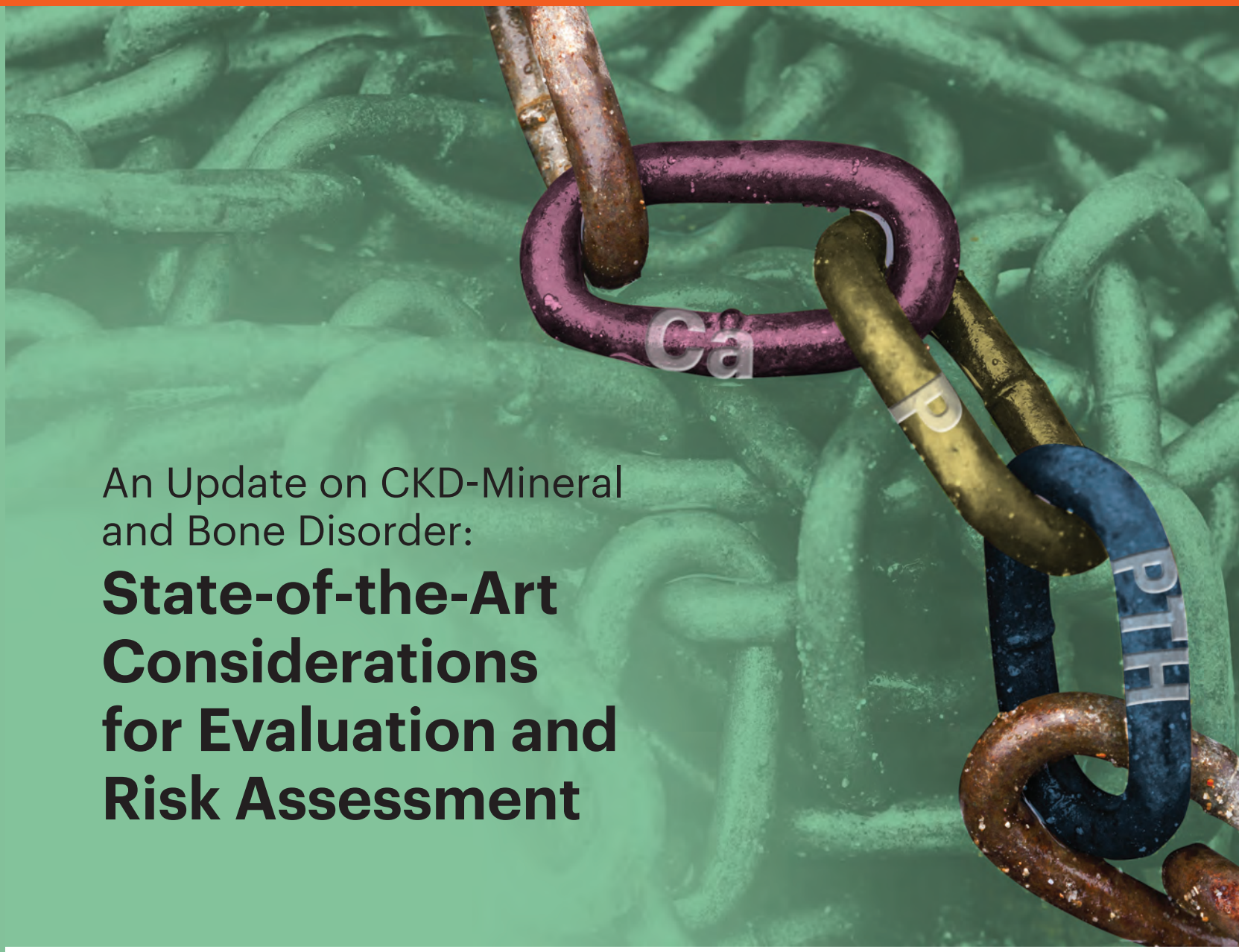

An Update on CKD-Mineral and Bone Disorder:

State-of-the-Art Considerations for Evaluation and Risk Assessment

National Kidney Foundation®

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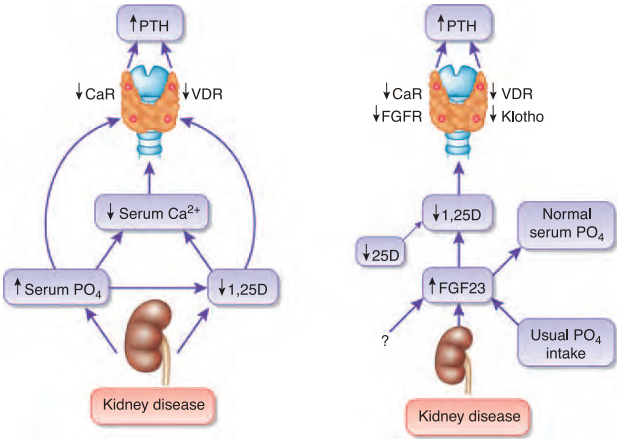
INTRODUCTION

The cascade of pathophysiological events that results in chronic kidney disease-mineral and bone disorder (CKD-MBD) begins early in the development of CKD and contributes to the development and progression of vascular calcification, impaired arterial function, and ultimately cardiovascular events, as well as altered bone strength.[1,2] Phosphate (P), calcium (Ca), and intact parathyroid hormone (iPTH) are the primary biological parameters that are commonly evaluated in clinical practice to diagnose and treat CKD-MBD, but other emerging biomarkers, such as fibroblast growth factor 23 (FGF-23), are also being investigated.

Interrelationship Between Phosphorus, Calcium, Parathyroid Hormone, and Vitamin D

Alterations in P, Ca, iPTH, and vitamin D metabolism are involved in the pathogenesis of secondary hyperparathyroidism (Figure 1).[3] The disease cascade begins with increases in FGF-23 and reductions in Klotho leading to a decline in vitamin D levels. The resulting hypocalcemia, as well as changes in expression of parathyroid gland receptor, calcium sensing receptor, vitamin D receptor, and FGF receptor, lead to a rise in serum iPTH, which is seen as early as CKD stage 3 (GFR <60 mL/min/1.73m^2).[4] Available data suggest that the increases in FGF-23 and iPTH are effective in maintaining neutral phosphate balance and "normal" serum P levels.[5] However, serum P increases as CKD progresses from stage 2 through stage 4. Most individuals with CKD stage 5, eating a normal diet, will have elevated serum P as a result of the marked reduction in GFR despite profound elevations in FGF-23 and iPTH.

Figure 1.[3] Emerging views on the pathogenesis of disordered mineral metabolism in CKD



Isakova T, Wolf MS. FGF23 or PTH: which comes first in CKD? *Kidney Int.* 2010;78:947-949.

Due to these complex interrelationships, therapeutic regimens aimed at improving each of the CKD-MBD biological parameters simultaneously impacts the others, and naturally occurring changes in one parameter inevitably are reflected in changes in the other. For this reason, while it is tempting (and common) to try to isolate the independent effect of one parameter on clinical outcomes, Block et al. suggest that any attempt to estimate risks associated with each parameter individually may result in statistical over-adjustment that can mask biologic inter-relationships and therapeutic treatment effects.[6]

Dialysis Patients and CKD-MBD Risk

As described above, disturbances in phosphate metabolism are pivotal in the development of CKD-MBD. Although there has been a decrease in serum P concentrations over time, data from the nationally representative DOPPS Practice Monitor (DPM) indicate that approximately 60% of U.S. dialysis patients in 2013 had hyperphosphatemia (defined as serum P >4.5 mg/dl).[7,8] This suggests that the majority of dialysis patients are at risk for developing CKD-MBD.

Other trends for the U.S. dialysis population show that concentrations of serum Ca have decreased, with only 4.2% of patients having a serum Ca >10.2 mg/dL.[7,8] Median iPTH values have increased over time; currently 40% of DPM participants have iPTH levels between 300 and 600 pg/ml and ~ 19% have iPTH >600 pg/ml.[8]

Laboratory Trends vs. Single Laboratory Values

The most recent clinical practice guideline for CKD-MBD for patients on dialysis suggests lowering serum P levels toward the normal range, maintaining serum Ca within the normal range, and maintaining iPTH levels in the range of approximately two to nine times the upper normal limit for the assay.[9,10]

Assessment of CKD-MBD should begin in stage 3, taking all available CKD-MBD parameters into account. Due to assay and biological variations, it is important to base therapeutic decisions on trends rather than on a single laboratory value, particularly with iPTH.[9,10] Technical issues that impact laboratory measurements include assay type and its accuracy, interassay variability, blood sample handling, and physiological, postprandial, diurnal, and seasonal variations. Serum P levels, for example, undergo profound changes over the course of 24 hours with the highest values being around 4:00am and the lowest values being between 8:00am to 12:00am. Table 1 describes the sources and extent of variation in serum measurements of Ca, P, iPTH, and vitamin D sterols. This guide reinforces that laboratory tests should be measured using the same assays, and at similar times of the day/week for each patient, as well as the importance to evaluate trends in MBD markers vs. single values.[9,10]

Table 1. Sources and magnitude of the variation in the measurement of serum Ca, P, iPTH, and vitamin D sterols[9]

Variable	Calcium	Phosphorus	iPTH	Vitamin D sterols
Coefficient of variation	+	+	++	++
Diurnal variation	+	++	++	--
Seasonal variation				++
Variation with meals	+	+	+	--
Variation with dialysis time	+	+		
Assay Validity	+++	+++	+	+

PTH, parathyroid hormone; +, minimal or low; ++, moderate; +++, high or good; --, no variability; blank space, not tested.

Evaluating CKD-MBD and Vascular Risk

Vascular calcification and arterial dysfunction related to CKD-MBD are likely to contribute to the higher cardiovascular morbidity and mortality experienced by patients with CKD as compared to the general population.[11,12] More effective methods of evaluating and treating CKD-MBD and vascular risk may help clinicians improve patient outcomes.

Findings from the Dialysis Outcomes and Practice Patterns Study (DOPPS)

In the international DOPPS cohort, associations between CKD-MBD markers and mortality data show the lowest mortality risks as follows: P 3.6-5.0 mg/dl, Ca 8.0-10.0 mg/dl, and iPTH 101-300 pg/ml.[7,8] The greatest mortality risks were associated with serum P >7.0 mg/dl, Ca >10.0 mg/dl, and iPTH >600 pg/ml. Combinations of high levels of these biomarkers were associated with higher mortality risk. Mortality risk is also higher for patients with low phosphorus levels.[7] These findings provide important insights for clinicians to manage CKD-MBD, however they may be susceptible to the issues previously described related to over-adjustment of inter-related biologic parameters.

Composite risk categories

A recent study looked at risk relationships using P, Ca, and iPTH to categorize patients into mutually exclusive, naturally occurring composite risk categories. The authors used multivariable Cox proportional hazards to first identify a baseline risk for death or the composite outcome of death or cardiovascular (CV) hospitalization. They then added an individual's unique profile of P, Ca, and iPTH to determine if their MBD characteristics modified their clinical outcome.[6]

The most important findings from this approach were that the specific composite risk categories of MBD were very strongly related to their risk of death or CV hospitalization. While those with high calcium were at the greatest risk, this represented a small fraction of patients. However, a large group of patients at increased risk were those with iPTH >300 pg/ml with a high serum P, and many of those with iPTH >600 pg/ml. The authors concluded that this novel method for establishing CKD-MBD — related mortality and CV hospitalization avoids statistical over-adjustment of a single parameter and may help practitioners determine priorities in treating CKD-MBD.

Alkaline phosphatase

Another important biomarker of CKD-MBD is alkaline phosphatase (Alk Phos). Guidelines support monitoring serum levels of Alk Phos activity beginning in stage 3 CKD, with increased frequency as kidney disease progresses and iPTH becomes elevated.[9,10] Although it is difficult to diagnose bone turnover disease using laboratory values, Alk Phos may be useful in detecting high bone-turnover disease, since bone has high concentrations of Alk Phos and Alk Phos is typically not elevated in low bone-turnover disease.

Studies of hemodialysis and peritoneal dialysis patients show an increase in all-cause and cardiovascular mortality as serum Alk Phos levels rise.[13-15] Due to the significant association of osteodystrophy with cardiovascular calcification, cardiovascular disease, and death, close management of high bone-turnover disease may be effective to improve outcomes in patients with CKD. Overall, Alk Phos may be a useful marker in the care of dialysis patients.

Similar to dialysis patients, elevated levels of serum Alk Phos in pre-dialysis CKD is associated with poor outcomes and faster progression to kidney failure.[16] Likewise, among CKD-MBD surrogates, higher serum Alk Phos before kidney transplantation is associated with worse post-transplant outcomes.[17]

Novel biomarkers

Emerging biomarkers of CKD-MBD show various associations with regard to CKD progression, cardiovascular events, and death in patients with CKD (Table 2).[18]

Table 2. Emerging CKD-MBD Biomarkers[18]

Promoter of Calcification in CKD	Inhibitors of Calcification in CKD	Other
Osteoprotegerin	Fetuin-A	FGF-23
Osteocalcin	Matrix-Gla protein	Klotho
	Osteopontin	Vitamin D

Studies of the following novel biomarkers related to CKD-MBD show association with cardiovascular events and death in CKD.[18, 19]

1. Osteoprotegerin (OPG) is a regulator of vascular calcification. High levels are associated with vascular calcification and all-cause mortality in pre-dialysis CKD and dialyzed patients. Elevated serum OPG levels may be useful for the detection of cardiovascular risk in these patients. [20, 21]
2. FGF-23 regulates P and vitamin D metabolism. Increased levels of FGF-23 are independently associated with an increased risk for cardiovascular mortality in patients on hemodialysis, and predictive of cardiovascular events in CKD stages 2-5.[22, 23]

While of great scientific interest, these biomarkers are not ready for routine application in the clinical setting. Further studies are needed to determine if they are superior to traditional parameters in their contribution to the evaluation and clinical management of CKD-MBD.

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