Title
Target Levels for Serum Phosphorus and Parathyroid Hormone

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D analogue in the presence of persistent or recurrent hypercalcemia (1B). In patients with CKD stages 3-5D and hyperphosphatemia, we suggest restricting the dose of calcium-based phosphate binders in the presence of arterial calcification (2C) and/or adynamic bone disease (2C) and/or if serum PTH levels are persistently low (2C)…." As also nicely remarked in the commentary by the Canadian Society of Nephrology (6), the recommendation to restrict the dose of calcium-based phosphate binders, although labeled as of high level (level 1) and based on studies of purportedly moderate quality of evidence (B), mainly rests, in reality, on observational findings. Common sense clearly dictates that limiting calcium intake in the presence of hypercalcemia and vascular calcifications is beneficial. However, how to implement such a recommendation is not an easy matter because no phosphate binder (including sevelamer and lanthanum carbonate) has emerged as unequivocally superior to others with respect to relevant clinical outcomes. Furthermore, longer dialysis is another option to implement such a recommendation. Trials investigating this issue are of obvious importance but these trials are less likely to be performed after the issuing of this recommendation. Given the difference in cost of calcium and noncalcium phosphate binders (at least a 15 fold difference), this suggestion has a huge impact on the total cost of ESRD care. I believe that a comparative effectiveness study—a direct comparison of different phosphate binders in real-world settings to determine the most effective treatment based on individual characteristics—is a priority in clinical research in patients with ESRD.

The KDIGO CKD–MBD guidelines represent the best available synthesis of clinical data on which to base the diagnosis, prognosis, and therapy of alterations in mineral metabolism as it relates to bone disease in patients with CKD. The open debate within the scientific community and the commentaries issued after the publication of these guidelines (5,6) represent powerful stimuli for advancing knowledge in this field and for ultimately generating more solid clinical research data to support nephrology practice. The ultimate goal is, and will remain, improving the still largely unsatisfactory clinical outcomes of dialysis patients.

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Target Levels for Serum Phosphorus and Parathyroid Hormone

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Introduction and Methodological Approach

Studies in the last decade have repeatedly shown that abnormalities in mineral and bone metabolism are associated with increased risk of death in patients on dialysis, mainly from cardiovascular disease (1–3). Concern for this risk prompted the National Kidney Foundation (NKF) Kidney Disease Outcome Quality Initiative (KDOQI) to issue its clinical practice guidelines for mineral and bone metabolism in 2003 (4). In August

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2009, the Kidney Disease Improving Global Outcomes (KDIGO), which reviewed more recent evidence, published its first clinical practice guidelines for the diagnosis, evaluation, prevention, and treatment of Chronic Kidney Disease-Mineral and Bone disorder (CKD-MBD) (5). The guidelines included interventions for treatment of hyperphosphatemia, secondary hyperparathyroidism, and bone disease in patients with CKD stages 3-5D. Given that the KDIGO guidelines are based on more recent literature, its recommendations are expected to replace those published previously by KDOQI.

The KDIGO Work Group agreed a priori to evaluate only randomized clinical trials (RCTs). Given the lack of definitive RCTs for hard clinical outcomes in CKD-MBD, most of the KDIGO clinical practice guidelines on this entity were labeled as weak or discretionary. Thus, like the K/DOQI guidelines, KDIGO relied heavily on expert opinion. We recognize the challenges that members of the KDIGO Work Group faced in developing these guidelines; they are to be commended on their extensive review of available evidence. Overall, the guidelines provide useful recommendations for the management of CKD-MBD. However, there are some areas that we believe should be the subject of further debate. Because of space constraints, we restrict our comments to only a few of the KDIGO recommendations as they apply to patients on dialysis (CKD stage 5D). In particular, we will focus on the KDIGO treatment target levels for serum phosphorus and iPTH.

Diagnosis of CKD-MBD: Biochemical Abnormalities

In Chapter 4, the Work Group suggests using individual values of calcium and phosphorus levels and recommends abandoning the previously appreciated calcium-phosphorus product (Ca × P), which may be dominated by the contribution of serum phosphorus concentration. The KDIGO does not specify a definite target range for serum phosphorus but recommends controlling serum phosphorus in patients on dialysis by targeting the normal range of the general population, i.e., 2.5–4.5 mg/dl. Whereas we agree with the comments advanced by the KDIGO working group that there are no prospective studies that have specifically examined the benefits of targeting different phosphorus levels on patients' outcome, clinical and experimental studies suggest a causal relationship between high phosphorus and secondary hyperparathyroidism (sHPT), bone abnormalities, calcitriol deficiency, and extraskeletal calcification (6–9). More importantly, data from multiple epidemiological studies showed that both high and low levels of serum phosphorus are associated with an increased relative risk of mortality (1–3). Thus, there is a compelling reason to control serum phosphorus in patients on dialysis; the question is to what level.

The inflection point at which circulating phosphorus appears to become significantly associated with increased all-cause mortality in patients on dialysis has generally been found to be > 5.0 mg/dl (1–3). However, the level that may be associated with cardiovascular calcification is probably lower than 5.0 mg/dl (8). Kestenbaum et al. showed that there is a 21% increased risk of coronary artery calcification for each 1 mg/dl increase in serum phosphorus above 3 mg/dl (8). Based on these observations, we agree that the upper end of target serum phosphorus should be 5.0 mg/dl or less. However, with respect to the lower end of serum phosphorus, levels < 3.0 mg/dl, although less common, have also been shown to be associated with increased risk of death; the critical level was < 3.0 mg/dl in a large study from DaVita dialysis clinics and < 2.0 mg/dl from the Dialysis Outcomes and Practice Patterns Study (DOPPS) (2,9). These low levels may be caused by severe dietary restriction, malnutrition–inflammation–cachexia syndrome (MICS), or overuse of phosphate binders. Thus, by recommending that serum phosphorus levels < 3.0 mg/dl is an acceptable target, the working group may inadvertently persuade patients and health care providers to adopt a more strict dietary restriction, which may lead to malnutrition and increased risk of death (2,10).

Based on the previous discussion, we believe that there is reasonable evidence from recent observational studies that can be used to make an ungraded statement on target range for serum phosphorus level. According to KDIGO, ungraded statements provide guidance that is based on common sense. Notwithstanding the possible association of higher phosphorus intake with poor outcomes (11), in our opinion, a serum phosphorus level of 3.0–5.0 mg/dL level meets the common sense criterion as it would minimize the adverse effects of hyperphosphatemia and at the same time avoids the risk of attaining the malnutrition range (Table 1). Moreover, this target is best achieved by appropriate phosphate binder therapy rather than by strict dietary restriction (10). In this regard, we believe that the best binder that can control serum phosphorus is the one which is affordable, potent, has the lowest pill burden, and which the patient is willing to take (and tolerate), especially because nonadherence is a major cause of uncontrolled hyperphosphatemia in patients on dialysis (12). However, the imminent implementation of bundled payments for dialysis services may limit access to expensive medications such as patented phosphate binders. We do hope that in the near future, more effective and palatable phosphate binders will become available to make this target achievable in most patients.

Treatment of Abnormal PTH in CKD-MBD

In Chapter 4.2.3, the KDIGO recommends a target range for iPTH level in patients on dialysis that has already become quite controversial. The Work Group raised concerns about problems with sample collection for PTH and assay variability and questioned the validity of absolute levels of PTH and their strict use as a clinically relevant biomarker for targeting specific values. In particular, the group felt that using narrow

TABLE 1. Recommended target levels for serum phosphorus, calcium, and iPTH and the frequency of measuring alkaline phosphatase in patients with chronic kidney disease stage 5 on dialysis

Organization	Serum phosphorus	Serum calcium	iPTH	Alk phos
Kidney Disease Outcome Quality Initiative	3.5–5.5	8.4–10.2	150–300	Not specified
Japanese Society for Dialysis Therapy	3.5–6.0	8.4–10.0	80–180	Monthly
Kidney Disease Improving Global Outcomes	Normal range	Normal range	130–585	Yearly
Authors	3.0–5.0	9.0–10.5	100–300	Monthly

ranges of PTH defining an "optimal" or "target" range was neither possible nor desirable. Nonetheless, the group expressed concern about the clinical consequences of not measuring PTH and treating sHPT.

In an attempt to balance the methodological issues of PTH measurement with the known risks and benefits of excess PTH and treatment strategies, KDIGO recommends an iPTH level that is 2–9 times the upper limit of normal, i.e., approximately 130–600 pg/ml for patients on dialysis. This wide range is a major departure from the target level of 150–300 pg/ml (2–3 times the upper limit of normal) that was recommended by the KDOQI in 2003. Interestingly, for CKD stages 3–5 not on dialysis, KDIGO recommends treating patients in whom serum PTH is progressively rising and remains persistently above the upper limit of normal for the assay despite correction of modifiable factors, with calcitriol or vitamin D analogs. Thus, the working group recommends keeping the iPTH levels for these patients below the 65 pg/ml, the upper limit of normal range. Therefore, the pathophysiologic basis for the KDIGO recommendations with respect to PTH level in various CKD stages seems inconsistent. Moreover, the recommended target range for iPTH is excessively wide and implies that no treatment is necessary for iPTH levels up to 600 pg/ml. Thus, in following this guideline, clinicians may not be willing to employ any intervention for managing patients on dialysis with such obvious degrees of sHPT particularly in the new era of bundling. Unfortunately, such an approach is bound to result in an increased prevalence of osteitis fibrosa, and patients with such high levels of PTH may become resistant to medical therapy alone.

There are three important outcomes that should be considered when recommending a target range for iPTH level (Fig. 1). The first is the PTH relationship to bone histomorphometry and risk of bone fracture. The second is its association with cardiovascular calcification (CVC) and all-cause mortality, and lastly the potential of high PTH levels for systemic toxic effects.

PTH and Bone Turnover

We agree that a precise diagnosis of the underlying bone histology in patients on dialysis can only be made by bone biopsy. However, because of the invasiveness and cost of the procedure along with other practice related constraints, iPTH level has been used as a marker to predict bone histology in patients on dialysis. Extreme values of iPTH correlate with bone turnover. Levels between these extremes generally do not predict bone histology well and have not been associated with patient-level outcomes. Moreover, most data on the relationship between PTH and bone turnover have been obtained with older assays that are no longer in use. The recently introduced second generation iPTH assays have their own limitations and their usefulness in predicting the type of bone lesion in patients on dialysis is yet to be determined.

In this regard, two recent studies that used the newer Immulite assay to measure iPTH confirmed the dissociation between PTH levels and bone turnover (13,14). Interestingly, in the study by Barreto et al. (14), 80% of their patients with iPTH level < 100 pg/ml had LT while 100% of those with iPTH level > 400 had high bone turn over (HT) after 1 year of treatment (F. Barreto, personal communication). It is important to note, however, that a

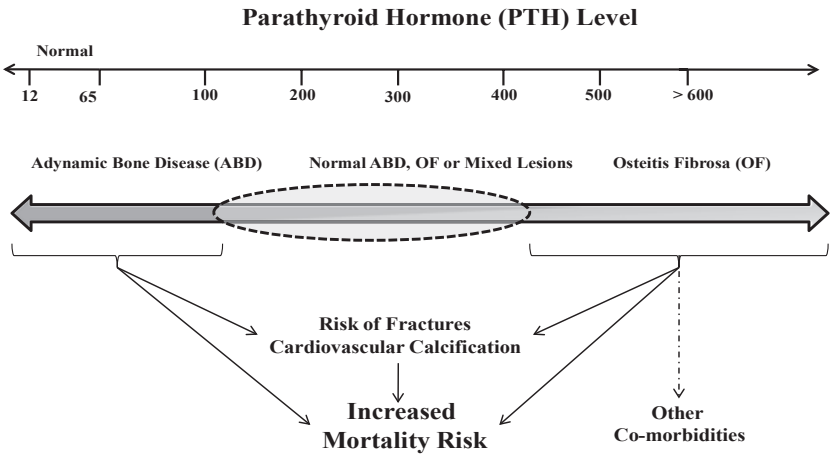

FIG. 1. Consequences of abnormal PTH level.

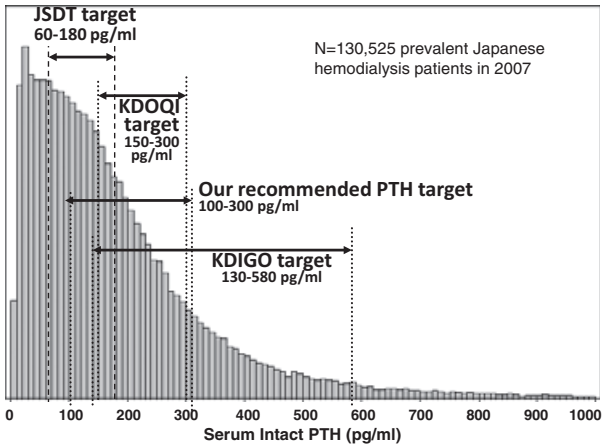

FIG. 2. Recommended iPTH target range.

low iPTH level may not necessarily reflect a low turnover (LT) disease but be a correlate of diverse conditions including MICS (15). Thus, targeting a range of 100–400 may reduce the risk of both LT and HT. We believe that currently there is no single biochemical marker that can accurately predict the type of bone turnover in patients on dialysis. However, a combination of markers such as iPTH, alkaline phosphatase, and bone-specific alkaline phosphatase levels may afford a more precise noninvasive assessment of turnover in this population.

Serum PTH Level and Mortality

Epidemiologic studies have shown that high PTH level is associated with increased risk of death and cardiovascular disease (CVD) events. In nondialyzed patients with CKD, Bhuriya et al. reported that iPTH levels >70 pg/ml were independently associated with CVD events (16). In patients on dialysis, the inflection point at which PTH becomes significantly associated with increased all-cause mortality varied from >400 pg/m/(2) to >600 pg/ml (1). In experimental animals, high PTH levels increase cardiac contractility, induce myocardial hypertrophy and interstitial fibrosis. Clinical studies have also shown that high PTH may contribute to the development of left ventricular hypertrophy, hyperlipidemia, insulin resistance, and impaired glucose tolerance (17,18). Moreover, high PTH contributes to arterial stiffness and hypertension via its effect on vascular endothelial function and its role in vascular calcification (19). In addition, these high levels may worsen anemia (20) and immunodeficiency of patients on dialysis (21). Finally, high PTH levels are associated with increased percentage of patients with hyperphosphatemia.

There are clearly no RCTs that examined the effects of various levels of PTH on the various clinical outcomes discussed above. For that reason, the KDIGO Work Group considered that levels of iPTH <2 or >9 times the upper limit of normal to represent extreme ranges of risk. The major departure from KDOQI guidelines is only in the upper end of the PTH range leaving the impression that KDIGO was more concerned about adynamic bone disease (ABD) than the potential for the adverse consequences associated with high iPTH level. The implication here is that ABD is more serious as it is suspected to be associated with higher fracture rate and faster progression of cardiovascular calcification. However, there are no prospective studies that compared the fracture rate or rate of progression of CVC in patients with LT vs. those with HT bone disease. Moreover, there are no RCTs that established a causative link between ABD and cardiovascular outcomes. Indeed, studies have shown that patients on dialysis who underwent parathyroidectomy have better survival and lower fracture risk despite their low PTH levels (22,23). Finally, the Japanese Society for Dialysis Therapy (JSDT) has indicated the lowest mortality of patients on dialysis when PTH is maintained in 60–180 pg/ml range (see Fig. 2) (24).

Conclusions

In the absence of evidence from RCTs, we believe that a narrower target range for iPTH of 100–300 pg/ml in patients on dialysis would probably be more reasonable. In this range, a target level above 100 pg/ml would probably avoid inducing LT disease, while a maximum high level of 300–400 pg/ml would minimize HT bone lesions. We also believe that a routine practice that incorporates measuring both iPTH- and bone-specific alkaline phosphatase would enhance our ability to noninvasively assess bone turnover in patients on dialysis. Finally, targeting these levels may have value beyond that of bone disease because markedly high or low levels of PTH and alkaline phosphatase are associated with increased risk of death and higher coronary artery calcium scores (25) (Table 1). In this regard, it is remarkable that while JSDT recommends an even lower iPTH range of 60-180 pg/ml, their patients experience superior patient survival rate and better clinical outcomes (24).

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Universal or Individual Screening for Vascular Calcification?

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In the recently published international clinical practice guideline – Kidney Disease Improving Global Outcomes (KDIGO) for Chronic Kidney Disease-Mineral Bone Disorder (CKD-MBD) – one can read the following statements:

> "In patients with chronic kidney disease (CKD) stages 3–5D, we suggest that a lateral abdominal radiograph can be used to detect the presence or absence of vascular calcification (VC), and an echocardiogram can be used to detect the presence or absence of valvular calcification as reasonable alternatives to CT-based imaging (2C)."
>
> "We suggest that patients with CKD stages 3–5D with known vascular/valvular calcification be considered at highest cardiovascular risk (2A). It is reasonable to use this information to guide management of CKD-MBD (not graded)" (1).

There is no recommendation for universal screening for VC because of the absence of hard evidence that current treatment strategies have an impact on morbidity and mortality associated with VC.

The assessment of VC was left to the discretion of the caring physician and was deemed warranted in special situations such as patients with significant hyperphosphatemia or on a transplant waiting list in whom VC may impact therapeutic decision-making. Furthermore, the majority of the KDIGO Work Group felt that: "….approaches to limit calcium intake from phosphate binders in CKD patients with known vascular/valvular calcification are appropriate until definitive studies are conducted" (1). The discord on this point can be read in the fact that although the document points out that it is reasonable to use the presence of VC to guide management, this was not a graded recommendation.

It is well known that VC is highly prevalent in CKD stage 5D and its prevalence increases steadily through the stages of CKD. Its presence has been associated with a several-fold increased risk of morbidity and mortality both in the general population and in CKD stage 5D patients. Because VC has a rapidly progressive character and prognostic implications in CKD (as reported in the KDIGO publication), its identification may become crucial for the implementation of effective preventive and therapeutic strategies. Therefore, the question of screening should arise in the mind of physicians regarding individual patients' treatment strategies. Should

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