Indian commentary on the 2009 KDIGO clinical practice guideline for the diagnosis, evaluation, and treatment of chronic kidney disease-mineral and bone disorders

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ABSTRACT

This commentary presents the view of an Expert Group of Indian nephrologists on adaptation and implementation of the Kidney Disease: Improving Global Outcomes (KDIGO) guidelines for evaluation and management of mineral and bone disorder in chronic kidney disease (CKD-MBD) for practice in India. Zonal meetings of nephrologists drawn from the cross-section were convened to discuss the KDIGO guidelines. Recommendations were presented in a central meeting of zonal representatives. The finalized recommendations were reviewed by all the participants. There was a broad agreement on most of the recommendations made by the KDIGO workgroup. Significant departures in the current guidelines from the previous Kidney Disease Outcome Quality Initiative (KDOQI) guidelines were also noted. The participants agreed that the available evidence did not allow more precise recommendations, and the recommended best practice suggestions were often based on relatively weak evidence. There is a remarkable lack of data from Indian patients. We comment on specific areas and amplify certain concepts where we feel that further guidance that goes beyond what is stated in the document might help Indian nephrologists in appropriate implementation of the KDIGO guidelines. This commentary is intended to help define practically implementable best practices based on current disease concepts and available research evidence, thereby positively affecting the quality of management of CKD-MBD in India, and eventually improving patient outcomes.

Key words: Chronic kidney disease, guideline, hyperparathyroidism, KDIGO, mineral and bone disorder

Introduction

There is no uniformity in the quality of care for managing abnormalities in the bone and mineral metabolism in chronic kidney disease (CKD) in India. An important step in this process is to have in place practice guidelines which can be applied for optimal management of the abnormalities in mineral and bone disorders (MBD) in the CKD patient.

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Kidney Disease: Improving Global Outcomes (KDIGO) was established in the year 2003 with the stated mission to "improve the care and outcomes of kidney disease patients worldwide through promoting coordination, collaboration, and integration of initiatives to develop and implement clinical practice guidelines."[1]

The KDIGO Clinical Practice Guidelines for the Diagnosis, Evaluation, Prevention, and Treatment of CKD-MBD were published in August 2009 after a two-year comprehensive review of relevant evidence in CKD-MBD.[2] The Indian nephrologists congratulate KDIGO on a fantastic review of the available evidence.

One of the principles of KDIGO is "think global, act local". KDIGO recognizes that international guidelines might need to be adapted for local situations. The guidelines have been translated into other languages and several national societies and professional organizations have commented on them.[3-8]To examine the applicability and implementation of the KDIGO guidelines for patients

with CKD in India, a committee of experienced Indian nephrologists was constituted. The group was broad-based and chosen from all parts from the country to represent the full range of nephrology practice in India.

This commentary presents the considered view of the group on the adaptation and implications of the KDIGO guidelines for practice in India. This commentary is intended to help define practically implementable best practices based on current disease concepts, available research evidence and economic and logistic constraints prevalent in the country.

Structure of this Commentary

The purpose of this commentary is not to critique the recommendations given by KDIGO but to understand and arrive at a consensus about its application in India. The members of the panel have used their clinical experience and expertise in the subject to examine the KDIGO recommendations that have been derived after a rigorously performed evidence review. The panel recognized that by and large, the biological and clinical behavior of patients is likely to be similar around the world and hence the derived guidelines and the science behind it would apply for the management of abnormalities in CKD-MBD in Indian patients as well. There was no additional evidence beyond that available to the KDIGO workgroup to allow changes in recommendations. However, because of perceived differences in clinical behavior, differences in dietary habits, financial issues, and a knowledge gap in the nephrology community, it was felt that certain issues might need to be emphasized or elaborated to ensure that the implementation of the guidelines is not felt to be difficult or even impossible by the ordinary nephrologists or physicians. The group also recognized the paucity of data in Indian subjects,[9-11] and the need to support endeavors that would help generate good quality evidence that specifically addresses clinical issues that might be of greater relevance to Indian patients.

Procedure Followed During Analysis of KDIGO Guidelines for the Management of CKD-MBD

Four zonal meetings were held across India, where selected nephrologists (Annexure I) discussed the guidelines and their adaptation to the Indian settings. The discussion in each zone was coordinated by two to three conveners, who then prepared a consensus statement from each zone. A meeting of the conveners then discussed the four drafts and arrived at a final consensus statement on the Indian adaptation of the KDIGO guidelines. The final document was sent for review to all participants and their comments incorporated. The key aspects of the final commentary are presented in the following sections.

Recommendation 1: Diagnosis of CKD–MBD: Biochemical Abnormalities

3.1.1. We recommend monitoring serum levels of calcium, phosphorus, parathyroid hormone (PTH), and alkaline phosphatase activity beginning in CKD Stage 3 (1C). In children, we suggest such monitoring beginning in CKD Stage 2 (2D).

3.1.2. In patients with CKD Stages 3-5D, it is reasonable to base the frequency of monitoring serum calcium, phosphorus, and PTH on the presence and magnitude of abnormalities and the rate of progression of CKD (not graded). Reasonable monitoring intervals would be: in CKD Stage 3: for serum calcium and phosphorus, every 6-12 months; and for PTH, based on baseline level and CKD progression. In CKD Stage 4: for serum calcium and phosphorus, every 3-6 months; and for PTH, every 6-12 months. In CKD Stage 5, including 5D: for serum calcium and phosphorus, every 1-3 months; and for PTH, every 3-6 months. In CKD Stages 4-5D: for alkaline phosphatase activity, every 12 months or more frequently in the presence of increased PTH levels (see Chapter 3.2). In patients with CKD receiving treatments for CKD-MBD or in whom biochemical abnormalities are identified, it is reasonable to increase the frequency of measurements to monitor for trends and treatment efficacy and side-effects (not graded).

3.1.3. In patients with CKD Stages 3-5D, we suggest that 25(OH)D (calcidiol) might be measured, and repeated testing determined by baseline values and therapeutic interventions (2C). We suggest that vitamin D deficiency and insufficiency be corrected using treatment strategies recommended for the general population (2C).

3.1.4. In patients with CKD Stages 3-5D, we recommend that therapeutic decisions be based on trends rather than on a single laboratory value, taking into account all available CKD-MBD assessments (1C).

3.1.5. In patients with CKD Stages 3-5D, we suggest that individual values of serum calcium and phosphorus evaluated together be used to guide clinical practice, rather than the mathematical construct of calcium-phosphorus product (2D).

3.1.6. In reports of laboratory tests for patients with CKD Stages 3-5D, we recommend that clinical laboratories inform clinicians of the actual assay method in use and report any change in methods, sample source (plasma or serum), and

handling specifications to facilitate the appropriate interpretation of biochemistry data (1B).

The panel agreed that monitoring of serum levels of calcium, phosphorus, PTH, and alkaline phosphatase activity should begin in Stage 3 in adults and Stage 2 in children, because of the impact on growth.

In patients with CKD stages 3-5D, the frequency of monitoring should be based on the presence and magnitude of abnormalities and the rate of progression of CKD, as suggested in the KDIGO guidelines. There was a lot of discussion on monitoring intervals and it was felt that there is no evidence behind suggested intervals, but some recommendations might be helpful. By consensus, the following were considered to be reasonable monitoring intervals:

- CKD Stage 3: Serum calcium and phosphorous every 3 months; PTH optional.
- CKD Stage 4: Serum calcium and phosphorous every 3 months; PTH once in 12 months unless clinical indications for more frequent estimation arise.
- CKD Stage 5: Serum calcium and phosphorous every month; PTH every 3-6 months.
- CKD Stages 4-5D: Total alkaline phosphatase every 3-6 months in Stage 4 and every 3 months in Stage 5.

In those receiving treatment for CKD-MBD or with identified biochemical abnormalities, it is reasonable to increase the frequency of measurements to monitor for trends, treatment efficacy and side-effects. Monitoring of trend rather than effecting abrupt treatment changes based on single values was emphasized, unless the values were clearly abnormal and correlated with the overall clinical picture.

With respect to vitamin D, the consensus was that a baseline value can be obtained and repeated once in 12 months in all stages of CKD.

There is widespread ignorance about the impact of the methodological issues on PTH assays. Proper collection, storage and transport conditions must be ensured. Samples need to be collected properly (in prechilled tubes), and transported on ice (especially important during summer and monsoon months). This is often not implemented by commercial laboratories which get samples through their collection centers and then transport them to a central lab which might take a couple of days. There is a need to educate personnel on these aspects. Differences across laboratories also occur because of variation in the methodologies. Because of all these issues, the PTH assays are often imprecise, often underestimate the true value and variations in results lead to further confusion. KDIGO does not insist on the actual values of PTH, but emphasizes on a 'normal' range given by a particular laboratory. There is a need to standardize the methodology of PTH estimation; and normal range and method used should be mentioned with the results. Since PTH assays are expensive, the decision to obtain PTH should be taken judiciously until all these problems are sorted out. As it is difficult to set any target values, calcium and phosphorus might be appropriate to guide initial therapy in the early stages of CKD. However, PTH should be measured at diagnosis to establish baseline values.

As bone-specific alkaline phosphatase assay is not commercially available, total alkaline phosphatase can be used to guide therapy for high-turnover bone disease. It is also cost-effective.

KDIGO recommends that therapeutic decisions should be based on trends rather than on a single laboratory value for all the biochemical parameters. Quick changes in treatment make it difficult to assess whether changes in the parameter are as a result of lab variation or true treatment effect. A trend of increasing or decreasing values gives greater confidence in deciding change in treatment. It is important that values from the same laboratory be used to study the trend. However, if there is a clearly abnormal value that correlates with the clinical picture, it is appropriate to make changes in treatment.

The corrected serum calcium levels should be taken into consideration rather than the actual laboratory values. Measuring ionized calcium levels is not required routinely when both serum calcium and albumin levels have been assessed. An important issue that needs to be reiterated is the recommendation to do away with calculation of the CaxP product, a practice that is of little clinical utility but still followed widely in India.

Vitamin D controls not only PTH levels and bone health, but also a number of other biological processes. It must be emphasized that optimal or even "normal" vitamin D level in different Indian ethnicities is not known, and the proposals reflect data from elsewhere. Using these norms, widespread vitamin D deficiency has been shown in Indians, both in the general population and in those with CKD. This could be because of several factors, including rapid urbanization, darker skin color, lack of fortification of food with vitamin D and high intake of phytates that prevent vitamin D absorption. Therefore, measuring the level may not be essential and a case could be made for supplementing vitamin D as soon as CKD is diagnosed, more so as this is cheap. However, studies form different

parts of the country in different times of the year are needed to establish the true prevalence of deficiency. Moreover, if levels are measured and found to be normal, then supplementation is not needed.

Recommendation 2: Diagnosis of CKD–MBD: Bone

3.2.1. In patients with CKD Stages 3-5D, it is reasonable to perform a bone biopsy in various settings, including, but not limited to, unexplained fractures, persistent bone pain, unexplained hypercalcemia, unexplained hypophosphatemia, possible aluminum toxicity, and before treatment with bisphosphonates in patients with CKD-MBD (not graded).

3.2.2. In patients with CKD Stages 3-5D with evidence of CKD-MBD, we suggest that bone mineral density (BMD) testing not be performed routinely because BMD does not predict fracture risk as it does in the general population and BMD does not predict type of renal osteodystrophy (2B).

3.2.3. In patients with CKD Stages 3-5D, we suggest that measurements of serum PTH or bone-specific alkaline phosphatase can be used to evaluate bone disease because markedly high or low values predict underlying bone turnover (2B).

3.2.4. In patients with CKD Stages 3-5D, we suggest not to routinely measure bone-derived turnover markers of collagen synthesis (such as procollagen Type I C-terminal propeptide) and breakdown (such as Type I collagen cross-linked telopeptide, cross-laps, pyridinoline, or deoxypyridinoline) (2C).

3.2.5. We recommend that infants with CKD Stages 2–5D should have their length measured at least quarterly, while children with CKD Stages 2–5D should be assessed for linear growth at least annually (1B).

Although bone biopsy is the best test to confirm bone disorders in CKD-MBD, it is currently not feasible, since there is an extreme paucity of centers that can perform this test and interpret it appropriately according to the guidelines. Incidentally, the use of bone biopsy is limited in the industrially advanced nations also and is mostly done for research purposes. Indian clinicians and researchers need to develop this capability. Finally, there are no randomized controlled trials that suggest that changes in treatment based on bone biopsy impacts outcomes.

Evaluating the bone density in a patient with CKD-MBD is not of much value. DEXA machines are widely available and there is a tendency to get test this done without adequate justification, even by non-nephrologists. Although it is of value for diagnosing osteoporosis in the general population, it should not be done routinely in CKD cases. Quantitative computed tomography (QCT) is probably more specific in terms of assessing bone density than DEXA.[9] So, in situations where a need for BMD testing is felt, QCT should be preferred over DEXA.

Bone-specific alkaline phosphatase (BSAP) best correlates with serum PTH levels. If both PTH and bone-specific alkaline phosphatase levels are low on repeated testing, one can be reasonably confident in making a diagnosis of low bone turnover or even adynamic bone disease. However, as BSAP is not commercially available, serial measurements of total alkaline phosphatase can be used in conjunction with PTH levels. These values could be evaluated once every 6-12 months in stable patients; more frequent testing may be necessary in unstable patients. There is no need to routinely measure other bone-derived turnover markers since they provide limited clinically relevant information.

The importance of measuring linear growth in infants and children with CKD in order to assess the extent of bone disorders was emphasized.

Recommendation 3: Diagnosis of CKD–MBD: Vascular Calcification

3.3.1. In patients with CKD Stages 3-5D, we suggest that a lateral abdominal radiograph can be used to detect the presence or absence of vascular calcification, and an echocardiogram can be used to detect the presence or absence of valvular calcification as reasonable alternatives to computed tomography–based imaging (2C).

3.3.2. We suggest that patients with CKD Stages 3-5D with known vascular/valvular calcification be considered at highest cardiovascular risk (2A).

There is a paucity of data on vascular calcification and its contribution to overall and/or cardiovascular mortality amongst Indian CKD patients. The A lateral abdominal radiograph can be easily obtained at most places and is cheap, but an echocardiogram is not as widely available and is relatively expensive. The former can therefore be routinely performed and the latter whenever possible. It is unclear, however, as to how this will change patient management. One suggestion is to not use calcium-containing phosphate binders in those with calcification. An attempt should be made to differentiate medial from intimal calcification on the basis of radiologic patterns, since the risk of mortality depends on the calcification type: patients with intimal calcification are at a higher risk compared to those with only medial calcification.

It is important to follow proper methodology, which includes proper patient preparation, use of optimized exposure settings and an experienced reader. These tests could be repeated once every year to detect progression. Data on prevalence of vascular calcification using high-speed CT scan needs to be generated amongst Indian patients.

Recommendation 4: Treatment of CKD–MBD Targeted at Lowering High Serum Phosphorus and Maintaining Serum Calcium

4.1.1. In patients with CKD Stages 3-5, we suggest maintaining serum phosphorus levels in the reference range (2C). In patients with CKD Stage 5D, we suggest decreasing increased phosphorus levels toward the reference range (2C).

4.1.2. In patients with CKD Stages 3-5D, we suggest maintaining serum calcium levels in the reference range (2D).

4.1.3. In patients with CKD Stage 5D, we suggest using a dialysate calcium concentration between 1.25 and 1.50 mmol/L (2.5 and 3.0 mEq/) (2D).

4.1.4. In patients with CKD Stages 3-5 (2D) and 5D (2B), we suggest using phosphate-binding agents in the treatment of hyperphosphatemia. It is reasonable that the choice of phosphate binder takes into account CKD stage, presence of other components of CKD-MBD, concomitant therapies, and side-effect profile (not graded).

4.1.5. In patients with CKD Stages 3-5D and hyperphosphatemia, we recommend restricting the dose of calcium-based phosphate binders and/or the dose of calcitriol or vitamin D analog 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).

4.1.6. In patients with CKD Stages 3-5D, we recommend avoiding the long-term use of aluminum-containing phosphate binders and, in patients with CKD Stage 5D, avoiding dialysate aluminum contamination to prevent aluminum intoxication (1C).

4.1.7. In patients with CKD Stages 3-5D, we suggest limiting dietary phosphate intake in the treatment of hyperphosphatemia alone or in combination with other treatments (2D).

4.1.8. In patients with CKD Stage 5D, we suggest increasing dialytic phosphate removal in the treatment of persistent hyperphosphatemia (2C)

There was a general agreement on the KDIGO recommendations targeted at lowering high serum phosphorus and maintaining serum calcium. Because of the high prevalence of malnutrition in Indian subjects, it is especially important to interpret low-normal phosphate values in light of the nutrition status, and to resist the temptation of enforcing excessive dietary restrictions for hyperphosphatemia in those with protein energy malnutrition as this would mean severe curtailment of dietary protein intake.

Low phosphate levels should be managed by first judging the protein intake and then reducing the phosphate binders. The KDIGO guidelines do not set any target phosphate values. While this is sound evidence-based advice, some guidance may be required for the general physicians who treat a large number of early-stage CKD patients in India. The older KDOQI targets, though less evidence-based, might still be useful to guide therapy in different stages of CKD. It was suggested that the recommended targets for Stage 3- 4 could be 3-4.6 mg/dl, whereas it is appropriate to try and bring the phosphate towards 3.5–5.5 mg/dl in Stage 5.

Given the low awareness of the significance of dialysate calcium, it is important to emphasize the KDIGO guideline that calcium dialysate should be used at a concentration of 5–6 mg/dL in patients on dialysis. Its value also lies in the fact that this allows increased use of the cheaper calcium-containing phosphate binders.

There is no evidence supporting the use of one phosphate binder over others. The choice of binder depends on the overall clinical and biochemical evaluation and economic factors. A judgment needs to be made regarding individualization of therapy based on cardiovascular disease (CVD) risk including vulnerability to vascular calcification, and the reimbursement status. It might be prudent to restrict the use of calcium-based phosphorus binders in high-risk subjects, such as those with vascular calcification.

It is okay to use aluminum-containing phosphate binders for a brief period if the phosphorus levels are very high. Their use, however, should be restricted to less than 8-12 weeks. This limit has been set arbitrarily.

There are no studies that have measured the daily phosphate consumption in various Indian meals. An assessment of protein and phosphorus intake should be made so far as possible before restricting phosphorus. In patients where a high protein intake is mandatory because

of severe protein energy malnutrition, phosphate binders are preferred over dietary restrictions. It is also important that managing the various dietary issues requires the skills of an experienced dietician, even better if he/she is expert in taking care of patients with kidney disease. Sadly, such people are not available in most Indian centers, and there is a need to develop this capability.

Recommendation 5: Treatment of Abnormal PTH Levels in CKD–MBD

4.2.1. In patients with CKD Stages 3-5 not on dialysis therapy, the optimal PTH level is not known. However, we suggest that patients with iPTH levels higher than the upper reference limit of the assay are first evaluated for hyperphosphatemia, hypocalcemia, and vitamin D deficiency (2C). It is reasonable to correct these abnormalities with any or all of the following: decreasing dietary phosphate intake and administering phosphate binders, calcium supplements, and/or native vitamin D (not graded).

4.2.2. In patients with CKD Stages 3-5 not on dialysis therapy in whom serum PTH levels are progressively increasing and persistently remain higher than the upper reference limit for the assay despite correction of modifiable factors, we suggest treatment with calcitriol or vitamin D analogs (2C).

4.2.3. In patients with CKD Stage 5D, we suggest maintaining iPTH levels in the range of approximately 2-9 times the upper reference limit for the assay (2C). We suggest that marked changes in PTH levels in either direction within this range prompt an initiation or change in therapy to avoid progression to levels outside of this range (2C).

4.2.4. In patients with CKD Stage 5D and increased or increasing PTH levels, we suggest calcitriol, vitamin D analogs, calcimimetics, or a combination of calcimimetics and calcitriol or vitamin D analogs be used to decrease PTH levels (2B).

It is reasonable that the initial drug selection for the treatment of increased PTH levels be based on serum calcium and phosphorus levels and other aspects of CKD-MBD (not graded). It is reasonable that calcium-based or non–calcium-based phosphate-binder dosage be adjusted so that treatments to control PTH levels do not compromise levels of phosphorus and calcium (not graded).

We recommend that in patients with hypercalcemia, calcitriol or another vitamin D sterol be reduced or stopped (1B).

We suggest that in patients with hyperphosphatemia, calcitriol or another vitamin D sterol be reduced or stopped (2D).

We suggest that in patients with hypocalcemia, calcimimetics be reduced or stopped depending on severity, concomitant medications, and clinical signs and symptoms (2D). We suggest that if iPTH levels decrease to less than two times the upper reference limit for the assay, calcitriol, vitamin D analogs, and/or calcimimetics be reduced or stopped (2C).

4.2.5. In patients with CKD Stages 3-5D with severe hyperparathyroidism that fail to respond to medical/pharmacologic therapy, we suggest parathyroidectomy (2B).

All the aspects of the KDIGO recommendations concerning treatment of abnormal PTH levels in CKD-MBD should be implemented.

There is a tendency of starting activated vitamin D therapy in incompletely worked up CKD subjects, and this practice needs to be resisted. However, if serum PTH is progressively rising and remains persistently above the upper limit of normal despite correction of modifiable factors, then treatment with vitamin D analogs should be initiated.

The range of PTH given by the KDIGO (2-9 times) is too large and creates confusion in the mind of an average practitioner. However, it needs to be clarified that this is based on an honest appraisal of the available evidence, and one cannot be more specific on the basis of published data. This shows the knowledge gap and calls for more extensive studies in this area. Combinations of calcitriol with zinc and calcium carbonate (available in Indian markets) should be avoided, since it could lead to hypercalcemia.

The choice of vitamin D or its analogs should be left to individual nephrologists who would make their decisions based on assessment of risk of developing hypercalcemia and the economic realities. Vitamin D analogs or calcimimetics can be started in patients with Stage 5D depending on their biochemical profile. Physicians need to be made aware of the need to stop vitamin D therapy and be careful with the use of calcium-containing phosphate binders in those with low iPTH levels.

Recommendation 6: Treatment of Bone with Bisphosphonates, other Osteoporosis Medications, and Growth Hormone

4.3.1. In patients with CKD Stages 1-2 with osteoporosis and/or high risk of fracture, as identified by World

Health Organization criteria, we recommend management as for the general population (1A).

4.3.2. *In patients with CKD Stage 3 with PTH levels in the reference range and osteoporosis and/or high risk of fracture, identified using World Health Organization criteria, we suggest treatment as for the general population (2B).*

4.3.3. *In patients with CKD Stage 3 with biochemical abnormalities of CKD-MBD and low BMD and/or fragility fractures, we suggest that treatment choices take into account the magnitude and reversibility of the biochemical abnormalities and progression of CKD, with consideration of a bone biopsy (2D).*

4.3.4. *In patients with CKD Stages 4-5D with biochemical abnormalities of CKD-MBD and low BMD and/or fragility fractures, we suggest additional investigation with bone biopsy before therapy with antiresorptive agents (2C).*

4.3.5. *In children and adolescents with CKD Stages 2-5D and related height deficits, we recommend treatment with recombinant human growth hormone when additional growth is desired, after first addressing malnutrition and biochemical abnormalities of CKD-MBD(1A).*

All the aspects of the KDIGO recommendations concerning treatment of bone with bisphosphonates, other osteoporosis medications, and growth hormone can be accepted as such.

Bisphosphonates do not reduce fracture rates in CKD subjects. Their use is associated with many issues, including nephrotoxicity, especially at higher dosages. They bind to hydroxyapatite and impair bone resorption, thus reducing the bone turnover rate. Patients with adynamic bone disease are unable to buffer calcium. Bisphosphonates can increase the fracture risk and soft tissue calcification in these patients.

A key issue with bisphosphonates is the dosage and frequency of therapy. It could be given parenterally, once a month (e.g., pamidronate), or orally, once a week (e.g. alendronate). In CKD patients, ibandronate once a month is preferred.

KDIGO guidelines suggest bone biopsy to rule out low bone turnover and adynamic bone disease before initiating bisphophonate therapy. It is important to educate the practicing doctors, so that indiscriminate use of antiresorptive agents can be avoided. This also represents a serious limitation of expertise, and there is a major need of developing this field in India.

Recommendation 7: Evaluation and Treatment of Kidney Transplant Bone Disease

5.1. *In patients in the immediate post-kidney-transplant period, we recommend measuring serum calcium and phosphorus at least weekly, until stable (1B).*

5.2. *In patients after the immediate post-kidney-transplant period, it is reasonable to base the frequency of monitoring serum calcium, phosphorus, and PTH on the presence and magnitude of abnormalities, and the rate of progression of CKD (not graded). Reasonable monitoring intervals would be:*

- *In CKD Stages 1–3T, for serum calcium and phosphorus, every 6–12 months; and for PTH, once, with subsequent intervals depending on baseline level and CKD progression.*
- *In CKD Stage 4T, for serum calcium and phosphorus, every 3–6 months; and for PTH, every 6–12 months.*
- *In CKD Stage 5T, for serum calcium and phosphorus, every 1–3 months; and for PTH, every 3–6 months.*
- *In CKD Stages 3–5T, measurement of alkaline phosphatases annually, or more frequently in the presence of elevated PTH (see Chapter 3.2).*
- *In CKD patients receiving treatments for CKD–MBD, or in whom biochemical abnormalities are identified, it is reasonable to increase the frequency of measurements to monitor for efficacy and side-effects (not graded). It is reasonable to manage these abnormalities as for patients with CKD Stages 3–5 (not graded) (see Chapters 4.1 and 4.2).*

5.3. *In patients with CKD Stages 1–5T, we suggest that 25(OH)D (calcidiol) levels might be measured, and repeated testing determined by baseline values and interventions (2C).*

5.4. *In patients with CKD Stages 1–5T, we suggest that vitamin D deficiency and insufficiency be corrected using treatment strategies recommended for the general population (2C).*

5.5. *In patients with an estimated glomerular filtration rate greater than approximately 30 ml/min per 1.73m^2, we suggest measuring BMD in the first three months after kidney transplant if they receive corticosteroids, or have risk factors for osteoporosis as in the general population (2D).*

5.6. *In patients in the first 12 months after kidney transplant with an estimated glomerular filtration rate greater than approximately 30 ml/min per 1.73m^2 and low BMD, we suggest that treatment with vitamin D, calcitriol/ alfacalcidol,*

or bisphosphonates be considered (2D).

We suggest that treatment choices be influenced by the presence of CKD–MBD, as indicated by abnormal levels of calcium, phosphorus, PTH, alkaline phosphatases, and 25(OH)D (2C).

It is reasonable to consider a bone biopsy to guide treatment, specifically before the use of bisphosphonates due to the high incidence of adynamic bone disease (not graded). There are insufficient data to guide treatment after the first 12 months.

5.7. *In patients with CKD Stages 4–5T, we suggest that BMD testing not be performed routinely, because BMD does not predict fracture risk as it does in the general population and BMD does not predict the type of kidney transplant bone disease (2B).*

5.8. *In patients with CKD Stages 4–5T with known low BMD, we suggest management as for patients with CKD Stages 4–5 not on dialysis, as detailed in Chapters 4.1 and 4.2 (2C).*

All the aspects of the KDIGO recommendations concerning evaluation and treatment of kidney transplant bone disease should be implemented.

There is a tendency to not evaluate the CKD-MBD abnormalities after transplantation, resulting in failure to identify abnormalities and institute appropriate measures at an appropriate time. It is important to do so at regular intervals as in the case of CKD.

Recommendation 5.3 is important because vitamin D levels are low in our patient population and early detection would help in early initiation of treatment.[11] Recommendation 5.5 is especially relevant in postmenopausal women or patients with diabetes mellitus. Caution should be exercised while prescribing bisphosphonates to avoid low turnover bone disease. The pretransplant bone disease can be used as a guide. Bisphosphonates may be beneficial in the early post-transplant period up to six months, but may not show much benefit when given after six months of transplant. In view of some Indian data that shows decline in BMD in the first six months after transplant, BMD may be monitored for 6-12 months post transplant.[9]

Bone Mineral Disorder in Patients on Peritoneal Dialysis

This area was not discussed in the KDIGO guidelines. It is important to monitor PTH levels and vascular calcification in patients on peritoneal dialysis (PD). Growth should be monitored in infants and children.

Adynamic bone disease is a significant concern in patients on PD compared to those on hemodialysis. Indian data is lacking in this area. One of the factors for this increased occurrence is the iatrogenic factor of giving a high or normal calcium dialysate in the PD. Hence, it may be prudent to make available a low calcium dialysate solution (5 mg/dl). This can be used in patients with calcium levels >9.5 mg/dl and also in those with a low PTH. The usage of low calcium dialysate PD bags gives the nephrologists more options for the administration of calcium-based phosphate binders as well as vitamin D. This holds true even in cases without hypocalcaemia. The other advantage of using these bags in patients without hypocalcaemia is that with this the calcium load is taken care of. It is reasonable to initiate patients with calcium levels >8.5 mg/dl on dialysis with low calcium dialysate. Dietary restriction of phosphates is difficult in patients on PD, because they are on a high-protein diet to compensate for the protein loss in the PD fluid. So, the phosphate intake is higher in these patients compared to those on HD.

The paucity of Indian data is a cause for concern, and the consensus statement was based more on suggestions and on the published Western data; and had been designed to assist in decision making. The obvious lack of Indian data reinforces the urgent need for large-scale studies, both observational and interventional to fill this knowledge gap. The cost of therapy is an important factor, impacts on all treatment decisions.

Annexure 1: Members of the Working Committee

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