KDIGO 2017 Clinical Practice Guideline Update for the diagnosis, Evaluation, Prevention and Prevention of Chronic Kidney Disease–Mineral and Bone Disorder (CKD-MBD):
Indian commentary

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Introduction

CKD- MBD guidelines were framed in 2009.[1] Indian commentary was published in 2011.[2] The work group analysed the studies done after 2009 and a Controversies conference was held in 2013. Subsequently updated guidelines came in 2017[3] followed by KDIGO commentary.[4,5] There are 21 updated recommendations / suggestions reviewed in KDIGO 2017, 8 of them (38%) remain 'ungraded' and all of the others are graded Level 2 which, according to the KDIGO nomenclature and description for rating guideline recommendations, means that 'Different choices will be appropriate for different patients. As a result, management of CKD-MBD in patients should be individualised, multi-professional and often pragmatic in its approach. The most significant change in the update is a move away from treating to specific targets towards a more personalised approach. UK renal association published the UK commentary in 2018.[6] In view of recent updates by KDIGO 2017 and recent evidence there is a need to update the Indian commentary as well.

Chapter 3.1: Diagnosis of CKD–MBD: Biochemical Abnormalities

(KDIGO 2009 No change in 2017 UPDATE)

3.1.1: We recommend monitoring serum levels of calcium, phosphate,PTH, and alkaline phosphatase activity beginning in CKD G3a. (Grade1C recommendation)

3.1.2: In patients with CKD G3a to G5D, it is reasonable to base thefrequency of monitoring serum calcium, phosphate, and PTH on thepresence and magnitude of abnormalities, and the rate of progressionof CKD. (Not graded)

Reasonable monitoring intervals would be:

• In CKD G3a to G3b: for serum calcium and phosphate, every 6–12months; and for PTH, based on baseline level and CKD progression
• In CKD G4: for serum calcium and phosphate, every 3–6 months; andfor PTH, every 6–12 months
• In CKD G5, including G5D: for serum calcium and phosphate, every1–3 months; and for PTH, every 3–6 months
• In CKD G4 to G5D: for alkaline phosphatase activity, every 12months, or more frequently in the presence of elevated PTH (seeChapter 3.2)

In CKD patients receiving treatments for CKD–MBD, or in whombiochemical abnormalities are identified, it is reasonable to increasethe frequency of measurements to monitor for trends and treatmentefficacy and side effects. (Not graded)

3.1.3: In patients with CKD G3a to G5D, we suggest that 25-(OH)D(calcidiol) levels might be measured, and repeated testing determinedby baseline values and therapeutic interventions. (Grade 2Crecommendation) We suggest that vitamin D deficiency andinsufficiency be corrected using treatment strategies recommendedfor the general population. (Grade 2C recommendation)

3.1.4: In patients with CKD G3a to G5D, we recommend that therapeuticdecisions be based on trends rather than on a single laboratory value,taking into account all available CKD–MBD assessments. (Grade 1Crecommendation)

3.1.5: In patients with CKD G3a to G5D, we suggest that individual valuesof serum calcium and phosphate, evaluated together, be used toguide clinical practice rather than the mathematical construct ofcalcium–phosphate product (Ca × P). (Grade 2D recommendation)

3.1.6: In reports of laboratory tests for patients with CKD G3a to G5D, werecommend that clinical laboratories inform clinicians of the actualassay method in use and report any change in methods, samplesource (plasma or serum), and handling specifications to facilitate the appropriate interpretation of biochemistry data. (Grade 1Brecommendation)

Chapter 3.2: Diagnosis of CKD–MBD: Bone Abnormalities

(KDIGO 2009)

3.2.2. In patients with CKD G3a–G5D with evidence of CKD-MBD, 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 renal osteodystrophy (2B).

(2017 UPDATE)
3.2.1: In patients with CKD G3a to G5D with evidence of CKD–MBDand/or risk factors for osteoporosis, we suggest BMD testing toassess fracture risk if results will impact treatment decisions.(Grade 2B recommendation)

Commentary

Earlier Indian commentary stated that routine BMD testing by Dual-energy x-ray absorptiometry (DEXA-BMD) should not be performed as DEXA-BMD does not help in determining type of renal osteodystrophy and was earlier not thought of be predictive of fracture risk. Quantitative CT was suggested as a better tool for BMD assessment.[2,3] Four prospective cohort studies subsequently demonstrated that measurement of BMD by DXA predicted fractures in adults with CKD stages G3a to G5D.[8-11] Studies also demonstrated that the World Health Organization (WHO) T-score thresholds are predictive of fracture risk in CKD. BMD by DXA showed a low bone mass in 41.05% of patients and was more prevalent in CKD stage 5 in Indian study.[7] Fracture is painful and incapacitates the individual and is associated with increased mortality; therefore, patients with or at risk for fractures require treatment. Hence BMD is recommended to assess risk of fractures so that treatment can be initiated. Fracture Risk Assessment Tool (FRAX) can be considered in stratifying patient for risk of fracture. If BMD testing cannot be done due to cost, Indian FRAX score which is independent of BMD can be used[9]

(KDIGO 2009)

3.2.1. In patients with CKD G3a–G5D, 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 prior to therapy with bisphosphonates in patients with CKD-MBD (Not Graded).

(2017 UPDATE)
3.2.2: In patients with CKD G3a to G5D, it is reasonable to perform a bone biopsy if knowledge of the type of renal osteodystrophy will impact treatment decisions. (Not graded)

Order of guidelines changed as BMD may impact biopsy decision.

Commentary

Treatment for low BMD is recommended. However before initiating therapy adynamic bone disease or osteomalacia should be ruled out. Bone biopsy is the best test for ruling out adynamic disease or osteomalacia. However, biopsy is not universally available. The non availability of biopsy may not justify withholding treatment for patients at high risk for fracture. If Adynamic bone disease or osteomalcia can be ruled out noninvasively ie by biochemical tests ie PTH and alkaline phosphatase, treatment with an anti-resorptive agent can be started without the need for bone biopsy. If the clinician is not able to make the assessment by non invasive biochemical tests, bone biopsy should be performed. Nephrologists may consider referring patients with high fracture risk to physicians with expertise in metabolic bone disorders for decisions regarding treatment strategies that may include initiation of antiresorptive or anabolic agents.

Although bone biopsy is the best test to confirm bone disorders in CKD-MBD, it is currently not feasible in India, 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.

(KDIGO 2009, UPDATE 2017 No change)

3.2.3: In patients with CKD G3a to G5D, we suggest that measurementsof serum PTH or bone-specific alkaline phosphatase can be used toevaluate bone disease because markedly high or low values predictunderlying bone turnover. (Grade 2B recommendation)Total serum alkaline phosphatase (fasting sample) may be used instead of Bone specific alkaline phosphatase in patients who do not have liver disease, non pregnant patients and do not have neoplastic disease as TSAP is less costly.

(KDIGO 2009, UPDATE 2017 No change)

3.2.4: In patients with CKD G3a to G5D, we suggest not to routinelymeasure bone-derived turnover markers of collagen synthesis (such asprocollagen type I C-terminal propeptide) and breakdown (such astype I collagen cross-linked telopeptide, cross-laps, pyridinoline, or deoxypyridinoline). (Grade 2C recommendation)

Impact on clinical practice and recommendations to Indian nephrologists:

1. Serum calcium, Phosphorus 6-12 months G3, 3-6 months in G4, and 1-3 months G5 and 5D
2. PTH baseline in G3, 6-12 months in G4, and 3-6 months in G5 and 5D
3. Vitamin D baseline then as needed
4. BMD assessment suggested by DEXA
5. Fracture assessment by FRAX tool for India (available online with or without BMD) can be used if BMD cannot be done due to cost and use of anti resorptives as indicated
6. Development of centres of excellence for bone biopsy

Chapter 3.3: Diagnosis of CKD–MBD: Vascular Calcification (KDIGO 2009, UPDATE 2017 No change)

3.3.1: In patients with CKD G3a to G5D, 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. (Grade 2C recommendation)

3.3.2: We suggest that patients with CKD G3a to G5D with known vascular or valvular alcification be considered at highest cardiovascular risk. (Grade 2A recommendation) It is reasonable to use this information to guide the management of CKD–MBD. (Not graded)

3.2.5: We recommend that infants with CKD G2–G5D have their length measured at least quarterly, while children with CKD G2–G5D should be assessed for linear growth at least annually (1B).

Chapter 4.1: Treatment of CKD–MBD Targeted at Lowering HighSerum Phosphate and Maintaining Serum Calcium

(KDIGO 2009)

4.1.1. In patients with G3a–G5, we suggest maintaining serum phosphate in the normal range (2C). In patients with CKD G5D, we suggest lowering elevated phosphate levels toward the normal range (2C).

UPDATE 2017

4.1.1: In patients with CKD G3a to G5D, treatments of CKD–MBDshould be based on serial assessments of phosphate, calcium, andPTH levels, considered together. (Not graded)

4.1.2: In patients with CKD G3a to G5D, we suggest lowering elevated phosphate levels toward the normal range. (Grade 2C recommendation)

(KDIGO 2009)

4.1.2. In patients with CKD G3a–G5D, we suggest maintaining serum calcium in the normal range (2D).

UPDATE 2017

4.1.3: In adult patients with CKD G3a to G5D, we suggest avoidinghypercalcemia. (Grade 2C recommendation)

(KDIGO 2009)

4.1.3. In patients with CKD G5D, we suggest using a dialysate calcium concentration between 1.25 and 1.50 mmol/l (2.5 and 3.0 mEq/l) (2D).

UPDATE 2017

4.1.4: In patients with CKD G5D, we suggest using a dialysatecalcium concentration between 1.25 and 1.50 mmol/L (2.5 and 3.0mEq/L). (Grade 2C recommendation)

(KDIGO 2009)

4.1.4. In patients with CKD G3a–G5 (2D) and G5D (2B), we suggest using phosphate-binding agents in the treatment of hyperphosphatemia. It is reasonable that the choice of phosphate binder takes into account CKDstage, presence of other components of CKD-MBD, concomitant therapies, and side effect profile (Not Graded).

UPDATE 2017

4.1.5: In patients with CKD G3a to G5D, decisions aboutphosphate-lowering treatment should be based on progressivelyor persistently elevated serum phosphate. (Not graded)

4.1.6: In adult patients with CKD G3a to G5D receivingphosphate-lowering treatment, we suggest restricting the dose ofcalcium-based phosphate binders. (Grade 2B recommendation)

(KDIGO 2009)

4.1.5. In patients with CKD G3a–G5D 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).

4.1.7: In patients with CKD G3a to G5D, we recommend avoiding thelong-term use of aluminum-containing phosphate binders and, inpatients with CKD G5D, avoiding dialysate aluminum contamination toprevent aluminum intoxication. (Grade 1C recommendation)

UPDATE 2017

4.1.8: In patients with CKD G3a to G5D, we suggest limiting dietaryphosphate intake in the treatment of hyperphosphatemia alone orin combination with other treatments. (Grade 2D recommendation)
It is reasonable to consider phosphate source (e.g., animal,vegetable, additives) in making dietary recommendations. (Notgraded)

(KDIGO 2009. *UPDATE 2017 No change*)

4.1.9: In patients with CKD G5D, we suggest increasing dialyticphosphate removal in the treatment of persistent hyperphosphatemia.(Grade 2C recommendation)

Commentary

The KDIGO statement of lowering high phosphorus and maintaining serum calcium level to normal level was widely in agreement to all. However, phosphorus value may depend on nutritional status, dietary intake and dietary pattern whether patient is vegetarian or non-vegetarian. Study form India had observeda very high prevalence to malnutrition at beginning of dialysis from our CKD cohort, 68% of patients had mild to moderate malnutrition and 7% had

severe malnutrition. [12]. The study also observed that the average protein intake was also low than recommended. In view of high prevalence of malnutrition and low protein intake in Indian subjects, the interpretation of low- normal phosphorus value become complex. Moreover, enforcing excessive dietary restrictions for control of hyperphosphatemia in those with protein energy malnutrition mayensue deterioration in nutritional status. Low phosphate levels should be managed by first judging the protein intake and nutritional status of the patients.

There is general consensus that phosphorus level should be brought towards the normal value. The recent KDIGO guidelines and the recent commentary by KDOQI (unlike older KDOQI) on KDIGO guideline agree for that part statement.[3]Although, they have not set forth any target phosphate values, but we feel that the older KDOQI targets, though less evidence-based, might still be useful to guide therapy in different stages of CKD in Indian scenario, where general physicians treat large number of early CKD patients and a general guidance will be required for them. It was suggested that the recommended targets for CKD 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.

KDIGO also emphasized that calcium, phosphorus and PTH should be interpreted together, however the single values may be misleading and serial trending values should be encouraged particularly in stage -5D as these values may be dynamic on follow-up and substantial biological variability in PTH may complex it further. We agree that hypercalcemia should be avoided. However, we should also keep in mind that there is low dietary intake of calcium in the diet in both adult and children in general population in India and Asia during dietary prescription.[13,14]

Serum calcium and corrected value for serum albumin level particularly in patients with malnutrition should also be considered in Indian scenario. Age appropriate serum calcium level is important for children of growing age.

The awareness about dialysate calcium content in India is low and not prevalent in practice in dialysis unit, however it is important to emphasize 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 not very strong evidence supporting the use of one phosphate binder over others. Strong evidences for lesser use of calcium based phosphate binders are lacking, emphasis should be there on calcium level and calcium must be adjusted for age in children. The choice of binders 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, cost of therapy 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.

In order to achieve desired serum phosphorus level, aluminum based phosphate binder should be avoided in general and should only be advocated for a brief period, preferably 8-12 weeks when phosphorus level is very high and not well controlled with non-aluminum based binders. The suggested for limited period has been set arbitrarily in absence of any evidence.

Studies regarding measurement of the daily phosphate consumption in various Indian meals are lacking. Bioavailability of phosphorus in phytate based diet is inferior compared to animal protein based phosphorus and phosphorus containing in processed food. An assessment of protein and phosphorus intake should be made 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. However, trained dietician for all calculation and providing dietary prescription is lacking in majority of Indian dialysis center and we feel that there is a need to develop this capability. We feel that in difficult scenario where serum phosphorus is difficult to control with measures like dietary intervention, and phosphate binders, the change in dialytic modality should be considered.

Impact on clinical practice and recommendations to Indian nephrologists:

1. Recommendation 4.1. by KDIGO (2017) is valid in Indian Scenario as well.
2. Serum phosphate level should be maintained within the normal range in patients with G3a–G5 and try lowering elevated phosphate levels toward the normal range in dialysis patients.
3. Maintaining serum calcium within normal range and attempt should be made to avoid not only hypercalcemia, but hypocalcemia as well.
4. In patients with poor nutritional status, suppressed appetite and inadequate dialysis, a prevalent situation in Indian scenario, we should look for calcium intake and corrected calcium for serum albumin level as well. Hypocalcemia may worsen secondary hyperparathyroidism and hypercalcemia vascular calcification. Low dialysate calcium should be used in patients with hypercalcemia.
5. Consider analysing calcium, phosphorus, hypovitaminosis D and PTH level altogether to optimize the CKD-MBD management.
6. Instead of single value, serial changes in the values of biochemical parameters should be taken in account to decide the treatment.

Chapter 4.2: Treatment of abnormal PTH levels in CKD-MBD

(KDIGO 2017)

4.2.1. In patients with CKD G3a–G5 not on dialysis, the optimal PTH level is not known. However, we suggest that patients with levels of intact PTH above the upper normal limit of the assay are first evaluated forhyperphosphatemia, hypocalcemia, and vitamin D deficiency (2C).

It is reasonable to correct these abnormalitieswith any or all of the following: reducingdietary phosphate intake and administeringphosphate binders, calcium supplements, and/or native vitamin D (Not Graded).

UPDATE 2017

4.2.1. In patients with CKD G3a–G5 not on dialysis, the optimal PTH level is not known. However, we suggest that patients with levels of intact PTH progressively rising or persistently above the upper normal limit for the assay be evaluated for modifiable factors, including hyperphosphatemia, hypocalcemia, high phosphate intake, and vitamin D deficiency (2C).

Commentary

A major departure from the 2009 guidelines is that clinicians are advised to react to *the trend*of iPTH values rather than a single elevated value. The basis for this recommendation is that iPTH elevation is a compensatory phenomenon to promote phosphaturia, which aids in maintaining serum phosphate within the normal range, besides implying skeletal resistance to iPTH. In addition, intra and inter-assay coefficient of variation, diurnal[15] and dietary[16] variations, and individual patients' adherence to prescribed medications17, all of which impact iPTH, serum phosphate and serum calcium levels, add to the inherent variability of iPTH levels. In light of these factors, aggressive lowering of iPTH based on a single value that is above the upper normal limit is no longer justifiable. While this approach may seem conservative, the recommendation to act on "progressively rising" iPTH levels and not just values that are "persistently above the upper normal limit", suggests that a rising trend, even in patients whose iPTH values lie within the normal range for the assay, should prompt clinicians to intervene. This is a pro-active rather than reactive approach, and of special relevance to CKD Stage G3-4 patients on follow up, in whom the management of CKD-MBD is often accorded low priority. The scope for intervention is huge, given that, 52-70% of incident Indian CKD Stage G3, and 73-89% of incident Indian CKD Stage G4 and 5 patients have iPTH values more than 2 times the upper limit of normal[7,18-]

[21]. However, it is important to note that the response to persistently elevated or rising iPTH levels should take the form of an active search for modifiable factors, rather than the blanket administration of activated vitamin D to reduce iPTH levels, which is commonly practiced in India. The wisdom in this approach is amply brought out by the fact that hyperphosphatemia, hypocalcemia and vitamin D deficiency are present in 32-83%, 25-71% and 50-95% of Indian CKD Stage G3-5 patients [7,18-21]. Targeting these risk factors has been shown to lower iPTH levels[22,23]. The 2017 guidelines have included high dietary phosphate intake as a modifiable risk factor, acknowledging that high phosphate intake can elevate PTH without a corresponding rise in serum phosphate levels. Upto 20% of incident Indian CKD Stage G4-5 patients are vegan[20], and the remaining are lacto-ovovegetarians or nominal non-vegetarians. Barring regional, religious and cultural variations, dietary phosphate intake is unlikely to be a major driver of hyperparathyroidism in India, though with rising incomes, changing food habits and greater consumption of dairy products, processed food and carbonated beverages, this is likely to change. While we agree with these updates to the KDIGO recommendation, we believe it is important to recognize that in the Indian context, where CKD patient follow up is poor, many clinicians may not have access to more than one iPTH value, and the failure to act on modifiable risk factors at the first instance may be deleterious to the patient.

Points that need further clarification:

Despite the 2017 KDIGO guidelines laying emphasis on sequential monitoring of iPTH to determine the trend of iPTH values, the magnitude of increase in iPTH and the time period that must elapse before such increase becomes actionable, have not been defined. This assumes importance because KDIGO has not suggested any alteration in the frequency of iPTH measurement in Chapter 3.1. The frequency of iPTH monitoring remains at the discretion of the clinician in Stage G3, 6-12 monthly in Stage G4, and 3-6 monthly in Stage G5.

Impact on clinical practice and recommendations to Indian nephrologists:

1.We suggest that in CKD Stage G3-5, iPTH be monitored as follows:

CKD Stage G3: Once at baseline and yearly thereafter

CKD Stage G4: Once every 6 months

CKD Stage G5 and G5D: Once every 3 months

2.We agree with the KDIGO recommendation that modifiable factors must be identified if there is either a persistent rise in iPTH levels or persistently high iPTH levels above the normal range of the assay

3.We further suggest, that in CKD Stage G3-5 patients presenting with iPTH above the normal range of the assay who are likely to be irregular on follow up, modifiable risk factors be addressed at the first instance.

KDIGO 2009

4.2.2. In patients with CKD G3a–G5 not on dialysis, in whom serum PTH is progressively rising and remains persistently above the upper limit of normal for the assay despite correction of modifiable factors, we suggest treatment with calcitriol or vitamin D analogs (2C).

UPDATE 2017

4.2.2. In adult patients with CKD G3a–G5 not on dialysis, we suggest that calcitriol and vitamin D analogs not be routinely used (2C). It is reasonable to reserve the use of calcitriol and vitamin D analogs for patients with CKD G4–G5 with severe and progressive hyperparathyroidism (Not Graded).

In children, calcitriol and vitamin D analogsmay be considered to maintain serum calcium levels in the age-appropriate normal range(Not Graded).

Commentary:

The PRIMO (Paracalcitol Capsule Benefits in Renal Failure Induced Cardiac Morbidity)[24] and OPERA (Oral Paracalcitol in Stage 3-5 Chronic Kidney Disease)[25] randomized control trials failed to demonstrate improvement in cardiac structure or function with paricalcitol supplementation (2 µg and 1 µg PO once daily over 48 and 52 weeks respectively), despite a decrease in iPTH levels. On the contrary, an increased risk of hypercalcemia was seen (22.6% in PRIMO had 2 consecutive serum calcium readings > 10.5 mg/dL, 43.3% in OPERA had a single reading > 10.2 mg/dL). These studies formed the basis for the KDIGO update suggesting that calcitriol and vitamin D analogs be reserved for patients with severe and progressive parathyroidism. However, several important observations regarding these RCTs need to be made. At baseline, the median iPTH level was 1.5-2 times the upper limit of the assay (100 pg/ml in PRIMO and 156 pg/ml in OPERA) and neither study included patients with iPTH levels > 300 pg/ml. Mean serum calcium concentration at baseline was 9.2-9.6 mg/dL and there was high concomitant use of calcium based phosphate binders (70% of those who developed hypercalcemia in the OPERA study; the PRIMO study did not report calcium supplement usage). By study end, median iPTH level in the treatment arms was 51 pg/ml. OPERA, which was carried out in Chinese patients, used a lower paricalcitol dose than PRIMO (which was a multicenter study but enrolled only 12% Asian patients) and was still able to demonstrate significant iPTH (over)suppression, indicating that racial differences in response to vitamin D analogs need to be taken into consideration. Although not a primary endpoint, the intervention arm in both studies had fewer cardiovascular related hospitalizations.

In India, dietary intake of calcium is poor and influenced by socioeconomic status. [13] Vitamin D deficiency is widespread due to low dietary intake, lack of a vitamin D food fortification

programme, darker skin pigmentation and lower sunlight exposure owing to sedentary habits and atmospheric pollution[26]. As a result, nutritional bone disease is ubiquitous even in healthy adults [27]. In incident CKD Stage G4-5 patients, upto 60% have biochemical features consistent with high turnover bone disease with osteopenia and osteoporosis present in 37% and 12%[19]. Osteoporosis was also linked to elevated iPTH. A small RCT in 30 Indian adult CKD patients (20 in the intervention arm, 10 in the control arm) with iPTH > 180 pg/ml (mean iPTH was 549 pg/ml) and eGFR < 30 ml/min studied the effect of calcitriol 0.5 µg PO administered daily for 12 weeks on left ventricular systolic and diastolic function. While systolic function was not different between the two arms, diastolic function, in the form of A velocity and E/A ratio, improved significantly in the intervention arm [28]. Notably, the mean serum calcium at baseline in this study was 8.8 mg/dL and rose to 9.3 mg/dL by study end. Although the study duration was short and the sample size small, we believe this provides preliminary evidence that vitamin D analogs may still have a role in the Indian CKD population. The 2009 KDIGO guidelines recommended that calcitriol and vitamin D analogs should only be considered if hyperparathyroidism persists despite correction of modifiable risk factors. This suggests that vitamin D analog therapy should be initiated when serum calcium levels are in the normal range, the unintended consequence being a higher incidence of hypercalcemia.

Between 20-39% of Indian Stage G3-5 CKD patients are on calcitriol at the time of presentation to a tertiary care hospital[7,20], most commonly in a fixed dose combination with calcium. While the prevalence of hypercalcemia at baseline in incident patients is low (1.9 – 8.8%)[7,18,20,21], in prevalent CKD Stage 5D patients, this figure is 15%[18], reflecting the impact of unmonitored calcium and vitamin D analog supplementation. The OPERA trial showed that hypercalcemia with paricalcitol therapy was easily managed by discontinuation of calcium containing phosphate binders. In the light of these observations, we believe that vitamin D analog therapy should not be withheld from patients with persistently rising or elevated iPTH after correction of modifiable factors, and that the dose of calcium containing phosphate binder should be reduced, or patients shifted to a non-calcium containing phosphate binder when doing so. We agree with the KDIGO recommendation to initiate calcitriol and vitamin D analog therapy to maintain serum calcium in the age appropriate range in children.

Points that need further clarification:

The 2017 KDIGO update does not explicitly define "severe and progressive hyperparathyroidism". Since the recommendation was based on findings from the PRIMO and OPERA trials, neither of which enrolled patients with iPTH > 300 pg/ml, it is reasonable to assume this value as the cut off for initiating calcitriol and vitamin D analog therapy.

Updates to the 2011 Indian commentary:

The 2011 Indian commentary agreed with the 2009 KDIGO recommendation to initiate vitamin D analog therapy in patients with progressively rising or persistently elevated iPTH levels despite correction of modifiable factors. We believe this is still a pragmatic approach in the Indian context, with the added observation that serum calcium and phosphate should be actively monitored while on vitamin D analogs. Because lower doses of vitamin D analogs may be effective in Asians[25], low dose (eg. 0.25 µg calcitriol) daily or intermittent vitamin D analog therapy (eg. alternate days) may be considered.

Impact on clinical practice and recommendations to Indian nephrologists:

We believe the 2009 KDIGO CKD-MBD guideline 4.2.2 is still relevant in the Indian context and make the following suggestions:

1.   In patients with rising or persistently elevated iPTH levels above 300 pg/ml, despite correction of modifiable factors such as hypocalcemia, hyperphosphatemia, high dietary phosphate intake and vitamin D deficiency, the use of calcitriol and vitamin D analogs is reasonable

2.   When initiating vitamin D analog therapy, we suggest that the dose of calcium containing phosphate binders be reduced, or the patient be shifted to a non-calcium containing phosphate binder

3.   We suggest that, to minimize risk of hypercalcemia, clinicians start with the lowest dose of vitamin D analog or consider the use of intermittent (eg. alternate day) therapy.

(KDIGO 2009. *UPDATE 2017 No change*)

4.2.3: In patients with CKD G5D, we suggest maintaining iPTH levels in the range of approximately 2 to 9 times the upper normal 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).

KDIGO 2009

4.2.4. In patients with CKD G5D and elevated or rising PTH, we suggest calcitriol, or vitamin D analogs, or calcimimetics, or a combination of calcimimetics and calcitriol or vitamin D analogs be used to lower PTH (2B).

 It is reasonable that the initial drug selection for the treatment of elevated PTH be based on serum calcium and phosphate levels and other aspects of CKD-MBD (Not Graded).

 It is reasonable that calcium or non–calcium-based phosphate binder dosage be adjusted so that treatments to control PTH do not compromise levels of phosphate 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 the intact PTH levels fall below 2 times the upper limit of normal for the assay, calcitriol, vitamin D analogs, and/or calcimimetics be reduced or stopped (2C).

UPDATE 2017

4.2.4. In patients with CKD G5D requiring PTH-lowering therapy, we suggest calcimimetics, calcitriol, or vitamin D analogs, or a combination of calcimimetics with calcitriol or vitamin D analogs (2B).

Commentary:

The Evaluation of Cinacalcet Hydrochloride Therapy to Lower Cardiovascular Events (EVOLVE) trial, in which patients with moderate to severe hyperparathyroidism on dialysis were randomized to receive cinacalcet or placebo for upto 64 weeks, failed to meet its composite primary endpoint of reduction in all-cause mortality, nonfatal myocardial infarction, hospitalization for unstable angina, peripheral vascular events and congestive heart failure [29]. The guideline summary acknowledged that cinacalcet may still be of benefit in patients aged > 65 years, in whom the primary end point was met [30] and a significant reduction in fragility fractures was seen[31]. In addition, cinacalcet use was associated with a reduction in incidence of severe unremitting hyperparathyroidism (> 1000 pg/ml), with hypercalcemia and parathyroidectomy [32]. However, owing to the negative results with respect to the primary end point in the EVOLVE study, and the results of the PARADIGM trial[33] that compared cinacalcet and active vitamin D monotherapy in dialysis patients and found them to be equally effective in lowering PTH[33], the KDIGO 2017 guidelines do not recommend the use of any one PTH lowering therapy over the other. To emphasize this, the authors have clarified that PTH lowering drugs have been mentioned *in alphabetical order*, and not in order of preference in the recommendation. In a departure from the 2009 guideline, the 2017 guideline no longer mentions the factors that need to be taken into consideration while choosing the appropriate PTH lowering therapy, nor does it specify when therapy must be discontinued.

We agree that there is currently no evidence to support the use of one PTH lowering therapy over the other, and emphasize that the clinician must choose the appropriate therapy keeping in mind the individual patient's calcium, phosphate and iPTH levels. Regular monitoring of these parameters, in keeping with KDIGO recommendations, is essential to avoid treatment related complications. In India, the cost of cinacalcet and higher propensity to develop hypocalcemia without concomitant vitamin D and/or calcium supplementation is a major consideration to be kept in mind.

Impact on clinical practice and recommendations for Indian nephrologists:

1. We recommend that in CKD G5D patients, clinicians choose the appropriate PTH lowering therapy weighing biochemical parameters such as calcium, phosphate and iPTH levels as well as the cost of treatment
2. We recommend that once PTH lowering therapy is initiated, calcium, phosphorus and iPTH be monitored as recommended, to avoid iatrogenic complications of hypercalcemia, hypocalcemia and hyperphosphatemia.

(KDIGO 2009. *UPDATE 2017 No change*)

4.2.5: In patients with CKD G3a–G5D with severe hyperparathyroidism (HPT) who fail to respond to medical or pharmacological therapy, we suggest parathyroidectomy (2B).

Chapter 4.3: Treatment of bone with bisphosphonates, other osteoporosis medications, and growth hormone

(KDIGO 2009. *UPDATE 2017 No change*)

4.3.1: In patients with CKD G1–G2 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 G3a–G3b with PTH in the normal range and osteoporosis and/or high risk of fracture, as identified by World Health Organization criteria, we suggest treatment as for the general population (2B).

KDIGO 2009

4.3.3. In patients with CKD G3a–G3b withbiochemical abnormalities of CKD-MBD and low BMD and/or fragility fractures, we suggestthat treatment choices take into account the magnitude and reversibility of the biochemicalabnormalities and the progression of CKD, with consideration of a bone biopsy (2D).

4.3.4. In patients with CKD G4–G5D having biochemical abnormalities of CKD-MBD, and low BMD and/or fragility fractures, we suggest additional investigation with bone biopsy prior to therapy with antiresorptive agents (2C).

UPDATE 2017

4.3.3: In patients with CKD G3a–G5D 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 the progression of CKD, with consideration of a bone biopsy (2D).

Commentary:

The 2009 KDIGO CKD-MBD guidelines suggested that patients with CKD Stage G1-3 with low BMD and/or fragility fractures and iPTH in the normal range be managed with antiresorptive therapy along the same lines as the general population. In patients with CKD Stage G4-G5D with biochemical abnormalities of CKD-MBD, low BMD on DEXA and/or history of fragility fractures, bone biopsy was advised prior to antiresorptive therapy. The 2017 KDIGO CKD-MBD recommendation has broadened the consideration for anti-resorptive therapy and anabolic

therapy to include Stage G4-G5D, and bone biopsy is suggested, but no longer considered essential prior to initiating anti-resorptive therapy. This change in policy was mandated by the growing body of evidence supporting the safety and efficacy of antiresorptive agents such as bisphosphonates (alendronate, risedronate)[34-36] raloxifene,[37,38]teriparatide[39] and denosumab [40] in CKD G3a-G4, the recognition that fracture risk progressively increases with declining GFR(29), and the lack of conclusive evidence that antiresorptive therapy use in CKD causes low bone turnover over and above that seen in the general population. Moreover, facilities for performing and interpreting bone biopsies are not widely available even in the developed world, due to which patients with high fracture risk who might have benefited from antiresorptive therapy were denied it. The guideline makes note of the fact that biochemical abnormalities contribute to low BMD and increased fracture risk, and it is therefore implied that wherever these are identified, appropriate measures for their correction be implemented.

We agree with the letter and spirit of this recommendation and make two additional comments. First, Indian nephrologists need to rule out locally prevalent metabolic bone disease syndromes prior to initiating antiresorptive therapy. These include osteomalacia due to vitamin D deficiency, endemic fluorosis, and aluminum related bone disease due to antacid preparations and leaching from aluminum cooking vessels. Second, the decision to choose antiresorptive or anabolic therapy, and which agent to choose, must be based on the estimated fracture risk of the patient (eg. FRAX score[9], and side effect profile, local availability and cost of antiresorptive agents.

Impact on clinical practice and recommendations for Indian nephrologists:

We suggest that:

1. In patients with CKD Stage G3-G5D with prior history of fragility fractures or low BMD on DEXA, co-existing biochemical abnormalities of CKD-MBD be identified and corrected
2. The decision to initiate antiresorptive or anabolic therapy should be based on the patients' estimated fracture risk (eg. FRAX score), side effect profile of each agent, local availability, and cost
3. Vitamin D related osteomalacia, endemic fluorosis and aluminium related bone disease need to be ruled out prior to initiating anti resorptive therapy
4. In centers where the facility is available, consideration should be given to performing a bone biopsy to determine the type of bone disease prior to initiating antiresorptive therapy

(KDIGO 2009. *UPDATE 2017 No change*)

4.3.4: In children and adolescents with CKD G2–G5D and related height deficits, we recommend treatment with recombinanthuman growth hormone when additional growth is desired, after first addressing malnutrition andbiochemical abnormalities of CKD-MBD (1A).

Chapter 5: Evaluation and treatment of kidney transplant bone disease

(KDIGO 2009. *UPDATE 2017 No change*)

5.1: In patients in the immediate post–kidney transplant period, we recommend measuring serum calcium and phosphate 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, phosphate, 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 G1T–G3bT, for serum calcium and phosphate, every 6–12 months; and for PTH, once, with subsequentintervals depending on baseline level and CKD progression.
In CKD G4T, for serum calcium and phosphate, every 3–6 months; and for PTH, every 6–12 months.
In CKD G5T, for serum calcium and phosphate, every 1–3 months; and for PTH, every 3–6 months.
In CKD G3aT–G5T, 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 G3a–G5 (see Chapters 4.1 and 4.2) (Not Graded).

5.3: In patients with CKD G1T–G5T, 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 G1T–G5T, we suggest that vitamin D deficiency and insufficiency be corrected using treatment strategies recommended for the general population (2C).

KDIGO 2009

5.5. In patients with an estimated glomerular filtration rate greater than approximately 30ml/min/1.73 m2, we suggest measuring BMD in the first 3 months after kidney transplant if they receive corticosteroids, or have risk factors for osteoporosis as in the general population (2D).

5.7. In patients with CKD G4T–G5T, 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).

UPDATE 2017(5.5 and 5.7 of KDIGO 2009 combined to form 5.5 0f 2017 UPDATE)

5.5: In patients with CKD G1T–G5T with risk factors for osteoporosis, we suggest that BMD testing be used to assess fracture risk if results will alter therapy (2C).

KDIOG 2009

5.6. In patients in the first 12 months after kidney transplant with an estimated glomerular filtration rate greater than approximately 30 ml/min/1.73 m2 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, phosphate, 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.

UPDATE 2017

5.6. In patients in the first 12 months after kidney transplant with an estimated glomerular filtration rate greater than approximately 30 ml/min/1.73 m2 and low BMD, we suggest that treatment with vitamin D, calcitriol/alfacalcidol, and/or antiresorptive agents be considered (2D).

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

 It is reasonable to consider a bone biopsy to guide treatment (Not Graded).
There are insufficient data to guide treatment after the first 12 months.

(KDIGO 2009. UPDATE 2017 No change)

5.7: In patients with CKD G4T–G5T with known low BMD, we suggest management as for patients with CKD G4–G5 not on dialysis, as detailed in Chapters 4.1 and 4.2 (2C).

Commentary

Kidney transplant recipients are at a heightened risk of developing fractures in the early part of the post-transplant period,[42] i.e. fracture rate of 3.3 per 1000-patient years, more than a third higher than in their pre-transplant period.[43] There is insufficient prospective evidence to show that Dual Energy X-ray Absorptiometry bone mineral density (DEXA BMD) scores predict the incidence of fractures. However, retrospective data suggests that fracture risks were higher in recipients who had osteopenia (HR: 2.7, 95% CI: 1.6–4.6) or osteoporosis of the hip (HR: 3.5, 95% CI: 1.8–6.4).[44] In the light of this data, the guideline recommends BMD testing of all transplant recipients.

The authors of the guideline freely admit insufficient data to contemplate treating transplant recipients beyond the first year, during which period, those with osteopenia or osteoporosis and estimated glomerular filtration rate (eGFR) more than 30 ml/min/1.73 m2 are to receive treatment. A Cochrane systematic review showed that nutritional supplementation of vitamin D, calcitriol (or vitamin D3 analogues), and antiresorptive agents (like bisphosphonates and denosumab) prevent bone loss in the early post-transplantation period.[45] However, there is as yet, no definite proof of this resulting in lower risk of fractures and remains an area of much needed research. As with other stages of chronic kidney disease, CKD-MBD markers i.e. serum levels of calcium, phosphate, PTH, alkaline phosphatases, and 25(OH)D3 are to guide definitive therapy. The optimum levels of PTH and vitamin D3 in transplant patients also need to be proven. When needed, the treating physician should consider a bone biopsy when it is vital to correctly classify the type of renal osteodystrophy to guide treatment. Its availability, though, is scarce worldwide and is likely to remain a research tool for the most part.

Impact on clinical practice and recommendations to Indian nephrologists

1. Bone mineral density estimating using Dual Energy X-ray Absorptiometry (DEXA) bone mineral density should be done at least in the first year after transplantation.

2. To prevent bone loss, supplementation of vitamin D, calcitriol (or vitamin D3 analogues), and antiresorptive agents (like bisphosphonates and denosumab) must be prescribed to prevent bone loss in the early post-transplantation period although there is no evidence of reduced fracture risk.

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