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Editorial Review

Endorsement of the Kidney Disease Improving Global Outcomes (KDIGO) Chronic Kidney Disease–Mineral and Bone Disorder (CKD-MBD) Guidelines: a European Renal Best Practice (ERBP) commentary statement

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Abstract

Under the auspices of the European Renal Best Practice, a group of European nephrologists, not serving on the Kidney Disease Improving Global Outcomes (KDIGO) working group, but with significant clinical and research interests and expertise in these areas, was invited to examine and critique the Chronic Kidney Disease–Mineral and Bone Disorder KDIGO document published in August 2009. The final form of this paper in *Nephrology Dialysis Transplantation*, as a commentary, not as a position statement, reflects the fact that we have had no more evidence to review, discuss and debate available to us than was available to the KDIGO working group. However, we have felt that we were able to comment on specific areas where we feel that further clinical guidance would be helpful, thereby going beyond the KDIGO position as reflected in their document. This present paper, we hope, will be of most use to the practising kidney specialist and those allied to the clinical team.

Keywords: calcium; chronic kidney disease mineral and bone disorder; colecalciferol; phosphate; vitamin D

Rationale for, and reflections on, the KDIGO CKD-MBD guidelines document

KDIGO 2009

Last year, the Kidney Disease Improving Global Outcomes (KDIGO) initiative published a guideline document covering chronic kidney disease–mineral and bone disorder (CKD–MBD) [1], as a follow-up to a prior KDIGO consensus conference [2].

A group of experts (the 'working party') was commissioned by the KDIGO board of directors to undertake to develop KDIGO guidelines, based on the Grades of Recommendation, Assessment, Development and Evaluation (GRADE) approach now widely understood and accepted [3]. In the three-stage compilation and review phases, prominent European nephrologists were involved.

Advanced CKD is a powerful risk factor for all-cause and cardiovascular (CV) mortality [4]. A recent systematic review was conducted to assess methodological and clinical heterogeneity across 35 studies chosen from Medline, EMBASE and Cochrane databases featuring publications between January 1980 and December 2007 [5]. A significant risk of mortality (all-cause and CV) and of CV events was observed with mineral disturbances. The data supported a greater mortality risk with elevated phosphorus, followed by calcium and parathyroid hormone (PTH).

Though there are clearly serious limitations in relying extensively, if not exclusively, on epidemiological associations rather than randomised controlled studies (RCT), there is a consistent message that a significant mortality risk was observed with mineral disturbances especially in dialysis patients [1,5]. There is an almost complete lack of high-quality hard-end point clinical interventional studies with skeletal or CV end points in stages 3–4 CKD, dialysis and transplantation.

In promoting this view, and that of the CKD–MBD concept itself, we must not lose sight of the fact that, historically, the reason for interest in measuring and manipulating serum levels of calcium, phosphate, PTH and vitamin D arose from concerns for bone, not cardiovascular, health and for preventing skeletal morbidity (e.g. bone loss and fractures).

Many of the potential interventions, which may impact on plasma phosphate, calcium and PTH, such as diet, dialysis, vitamin D, phosphate binders, calcimimetics and bisphosphonates, themselves alter the concentrations of the bone and mineral metabolism parameters, but how these alterations brought about by these treatments actually alter morbidity and mortality is not completely understood. Clinical practice pattern surveys and indicators clearly show that over the period 2001–07 for example, there have been major shifts in the achieved serum calcium, phosphate and PTH levels in dialysis patients around the world, driven at least in part by the response of the nephrological community to guideline and position statements [6–8]. Linking these changes to clinical outcomes must be a priority.

Given the importance of attempting to reduce morbidity and mortality in CKD patients, it is not surprising that guidelines for best clinical practice have been urgently needed in this area. The previous guidance, which was used by most nephrologists, was produced by Kidney Disease Outcomes Quality Initiative in 2003 [9]. While helpful in places, many authorities considered this to be an incomplete and over-opinionated document, though it probably had a documentable impact on clinical practice [10,11]. It was for this, and other reasons, that KDIGO attempted to provide guidance in CKD–MBD relatively early in their cycle of guideline projects.

The KDIGO document is an exhaustive text, containing one of the most thorough and in-depth reviews of the available literature for CKD–MBD [1]. Many of the statements are remarkably balanced and well weighted. Because there are so few trials, which provide clear guidance in this complex area, it was necessary to grade all evidence rigorously and, as a result, to represent the guidance mostly as suggested actions, or recommendations, and not instructions.

Chapter 1 and 2 illustrate how carefully all arguments were considered and translated into recommendations. Chapter 3, 4 and 5 deal with the recommendations/statements themselves of which a total of 49 are made. A substantial majority of the statements presented have an evidence level C (low) or D (very low) or even no gradation. Likewise, level 1 'strong' recommendations are in a small minority, and only two of the 10 level-one recommendations have an evidence level A (high). In other words, the authors were not able to generate many true 'guidelines' in an area where there is a great need for 'guidance'.

ERBP commentary on KDIGO CKD-MBD guidelines

The reader should be aware that these are not always real 'guidelines', as defined by European Renal Best Practice (ERBP) [3,11]. In many places, a very limited guidance is offered, since caution and circumspection, and many iterations, as the text was reviewed by more than 170 nephrologists external to the working group, tended to overrule didactic aspiration. So, this scholarly text may be more useful to the expert, who often is already aware of much of the baseline information, rather than to the student, trainee or starting practitioner, who may feel not much more certain how to act after reading these 'guidelines' than they felt before.

Under the auspices of the ERBP, a group of European nephrologists, not serving on the KDIGO working group but with significant clinical and research interests and expertise in these areas, was invited to examine and to critique the CKD–MBD KDIGO document. It should be noted that there was a wide range of opinions even within this smaller group currently generating this commentary and much discussion about the correct way forwards. The final form of this paper, as a commentary, not as a position statement, reflects the fact that we have no more evidence available to us than was available to the KDIGO Working Group. However, we can and have been able to comment on specific areas where we feel further guidance would be helpful, going beyond the KDIGO position as reflected in their document. The reader is also drawn to recent commentaries on this same KDIGO guidelines document by the Canadian Society [12] and by KDOQI [13].

This commentary reflects the consensus position on the KDIGO document arrived at by this European group, in line with previous position statement documents generated by ERBP on anaemia [14], hepatitis C [15] and choice of dialyser membranes [16].

In the following section, the ERBP group comments on each of the two main CKD 'therapeutic' chapters from the KDIGO document (Chapter 3 and 4). We will not add any comments to the KDIGO recommendations with which the ERBP work group agrees without any reflection or amendment.

KDIGO document—Chapter 3: ERBP-commentary

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 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 levels 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 1–3 months. In CKD stages 4–5D: for alkaline phosphatase activity, every 12 months or more frequently in the presence of in-

creased PTH levels (see Chapter 3.2 KDIGO). 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).

Although there is much emphasis rightly placed on 'rate of progression' and 'trends', these are not clearly defined. In addition, this does seem to imply that for the same absolute value of PTH, or phosphate, the therapeutic approach or prognosis should be different with or without progression of renal failure, or with or without a change in concentration over time. If this is correct, a careful scrutiny of not only the plasma or serum values but also the clinical context of the subject will be mandatory.

The analysis of trends with repeated measurements of biochemical parameters, now promoted by KDIGO as being more likely to smooth out fluctuations in these parameters, is timely as some of these might be iatrogenically driven. As with other clinical situations, it is expected that trends even within the normal range (say of iPTH) would prompt adjustments in therapies in advance of the values departing from the normal range (as intelligent anticipated action). This is not clearly specified in the rationale, so that it leaves much uncertainty but also allows some flexibility in the decision making for the practicing clinician or member of the multi-professional team caring for patients as to how approach this problem in clinical practice.

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).

A recommendation is made to consider measuring 25-OH vitamin D levels, in CKD stages 3–5D and 5T. There is an excellent section in the KDIGO guidelines ([1] Chapter 3 pages S28–S31) which deals in great detail with the biological source of vitamin D, and the many problems in its measurement. This should be required reading by all interested in this most important and rapidly changing area.

The ERBP working group acknowledges that the desirable ranges for plasma 25-OH vitamin D levels in CKD are not known, nor is the effect of physiological supplementation clearly established on important end points such as bone quality (density and microarchitecture), fracture rates, cardiovascular calcifications, and cardiovascular and overall mortality rates.

However, providing vitamin D therapy as repletion of 25-OH vitamin D is not expensive (though its laboratory measurement may be), and as it also has a large therapeutic range, this allows for some pragmatic recommendations. Evidence for a patient survival benefit for increasing deficient or insufficient levels of 25-OH vitamin D in chronic kidney disease have not yet definitively been demonstrated, but in view of the low cost, the relative safety of repletion and the therapeutic potential, there should not be much objection to its use either.

Which vitamin D product to use, how best to administer this (oral repletion seems more favoured than does the intramuscular route [17], and this is of course more practical for CKD 5D patients), how often to monitor levels and which will fluctuate with seasons—all of these practical questions are not yet answered. Nor yet is known the target post-repletion vitamin D concentrations to be pursued, though obtaining normal [>75 nmol/L (30 ng/mL)] 25-OH vitamin D levels does not appear to be associated with short-term harm (expressed as biochemical end points only) [17]. Obviously, access to laboratories, which can measure 25(OH)D (calcidiol), is essential.

The ERBP work group considers that it might be useful for the nephrological community to formulate some exact targets, and therefore considers that it is valid to measure 25-OH vitamin D levels in all CKD stages 3–4 patients at least once. If the 25-OH vitamin D levels are >75 nmol/L (30 ng/mL), then this is in the 'normal' or healthy range, and further measurement is not needed. 25-OH vitamin D values <30 nmol/L (<12.5 ng/mL) (deficiency) require supplementation using cholecalciferol (or another analogue of 25-OH vitamin D), and remeasurement after 6 months of oral vitamin D supplementation. How best to respond to 25-OH vitamin D plasma levels between 30 and 75 nmol/L (12.5–30 ng/mL) (insufficiency) is not known. A case can be made for repletion here too. The rationale behind this recommendation is the pleiotropic effects that have been attributed to this moiety in the setting of cardiovascular disease, cardiometabolic syndrome, cancer and other chronic conditions [18–22]. However, ERBP readily admits that there is no hard evidence for the benefit of vitamin D supplementation, nor for the vitamin D concentration thresholds mentioned above. It is of great importance that all of these suggestions and recommendations are tested prospectively, so any recommendations made should not in any way stand in the way of potential RCTs with hard patient-level outcomes being undertaken. Plasma calcium, phosphate and PTH should be monitored during 25-OH vitamin D repletion, and the repletion should be temporarily discontinued or abandoned if hypercalcaemia or hyperphosphataemia ensues.

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 changes in methods, sample source (plasma or) serum, and handling specifications to facilitate the appropriate interpretation of biochemistry data (1B).

The inter-laboratory differences in iPTH assays in particular serve to confuse national or regional audit where patients are being treated in hospitals where the measurement techniques differ. Some moves to promote analytical harmonization or standardization would then facilitate comparisons between renal units, and facilitate regional and international comparisons. Until then, one has to deal in 'upper limit of normal' constructs. Some useful advances in understanding and implications for practice using

commercially available PTH assays have been made by Souberbielle [23].

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 hypercalcaemia, unexplained hypophosphataemia, possible aluminium toxicity, before treatment with bisphosphonates in patients with CKD–MBD (not graded).

It may at first seem surprising that in 2009, the use of bone biopsy was advocated by KDIGO in several different clinical situations. This may prove to be a difficult advice to follow for many practising nephrologists without access to specialized diagnostic and histopathological support services as clinical use of bone biopsies is now unusual in most parts of the world. Subjecting patients to a potentially unpleasant, and invasive, procedure would only be justified firstly if there were no better way to obtain the same information and, secondly, if we knew that for undergoing the procedure, there was the certainty that the biopsy material so obtained would be processed and interpreted optimally. Also, there is no RCT of therapeutic strategies derived from bone biopsy information. If bone biopsy material as part of a diagnostic procedure were to be collected rigorously in all of the clinical situations suggested by KDIGO, then this might lead to a serious problem of lack of expertise in interpreting the biopsies due to a worldwide lack of suitably skilled pathologists. Against this view, however, it must also be clearly stated that the available non-invasive tests, including a wide range of PTH levels, clearly fail to provide definitive information on bone turnover and mineralization states, and may thus lead to wrongful therapeutic choices in a substantial number of patients. Therefore, besides promoting prospective clinical studies and registries, efforts should also be undertaken and supported by national societies investing in the training of skilled bone pathologists in countries with limited supply.

3.2.2. In patients with CKD stages 3–5D 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 type of renal osteodystrophy (2B).

The ERBP work group agrees, but in practice, such patients are often seen by osteoporosis specialists or rheumatologists, and such scans are performed, and sometimes, treatment (e.g. bisphosphonate therapy—see KDIGO 4.3.2 and ERBP comment) is based on them. Making formal links with rheumatologists and other clinicians to discuss cases where nephrologists would have concerns about the use of BMD scans alone to assess skeletal integrity and health may be of benefit. It should be noted that a recent publication does show a link between femoral bone BMD determined by densitometry and histologically determined cortical bone volume in CKD stage 5D patients [24].

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). Also see KDIGO 4.1.8.

The ERBP work group states that a definition of 'markedly high' is important. We suggest thresholds of iPTH <10.5 pmol/L (100 pg/mL) for low bone turnover and iPTH >85 pmol/L (800 pg/mL) for high bone turnover. Analysing trends of total, and bone-specific, alkaline phosphatase can help refine the diagnosis of bone turnover status [25].

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).

There is an agreement on behalf of the ERBP group in as far as this recommendation refers to clinical practice, but assessing and using these parameters for research, as well as other novel biomarkers, should be encouraged.

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 vavular calcification as reasonable alternatives to computerized tomography-based imaging (2C).

If it is thought necessary to look for vascular calcification, KDIGO recommend that plain X-rays and echocardiography may yield as much information as CT scanning with less radiation and cost involved. However, routine clinical screening of all CKD–MBD patients for the presence of vascular calcification is not currently recommended by KDIGO. This is not because of any failure of either simple clinical (plain X-ray, echocardiography) or more complicated research-based techniques (electron beam CT and multi-slice CT) to detect cardiovascular calcification, but on the grounds of their not being a clear-cut therapeutic option then to recommend once cardiovascular calcification is detected, at least in the opinion of the KDIGO group. In clinical practice, however, many CKD and dialysis patients will undergo radiological investigations which will lead to the serendipitous disclosure of the presence of vascular calcification. Screening for vascular calcification is especially considered by the ERBP group to be sensible for potential transplant recipients and for those having brachial artery arteriovenous fistulae formed.

The ERBP work group considered that it was justified to screen incident dialysis patients using plain lateral X-ray of the abdomen (or by echocardiography for calcified aortic or mitral valves); such calcified patients should receive little, or no, additional binder-based calcium loading. This screening has the utility, in view of the recommendation, both by KDIGO and ERBP, to permit targeted

minimization or withdrawal of calcium-containing phosphate binders in the case of vascular calcification (see KDIGO 4.1.5 and ERBP comments). Clearly, there is continued and fierce debate within the nephrological community about this [26,27].

KDIGO document—Chapter 4: ERBP commentary

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 towards the reference range (2C).

A major change in emphasis is now given by KDIGO in terms of 'target levels'—namely that no absolute level for serum phosphate is recommended, but rather, that a reduction towards a normal level is desirable. The stated target is normal phosphate levels across the board from CKD stages 3, through 5D and 5T; for all stages except 5D, the KDIGO advice is to reach the target, and for 5D, P should be decreased as close as possible to target. This concept will soon be tested by a clinical trial in CKD [28]. It should be recognized that over the last 10 years, the average plasma phosphate levels in CKD 5D patients have fallen. Practice pattern analyses, and audits, should report proportions of patients with plasma phosphate <0.8 mmol/L (<2.4 mg/dL) (unequivocally low), 0.8–1.5 mmol/L (2.4–4.5 mg/dL) (normal), >1.5–2.0 mmol/L (>4.5–6.0 mg/dL) (mildly raised), and >2.0 mmol/L (>6.0 mg/dL) (significantly raised).

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

The ERBP work group wants to point out that the use of calcium-sensing receptor agonists (calcimimetics) is often associated with mild to moderate hypocalcaemia [29]. This is rarely symptomatic. See also KDIGO recommendation 4.2.4 and the corresponding comments of the ERBP work group. Normal serum calcium levels are recommended, without the previous KDOQI preference for the lower half of the normal range. Correction for plasma albumin is also abandoned; however, the ERBP group feels that for clinicians, knowledge of the plasma albumin level, if it is significantly low (e.g. <30 g/dL), is still potentially important in interpreting plasma calcium levels.

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 mEg/L) (2D).

The choice of dialysate calcium (or magnesium) concentrate should reflect an understanding of the likely calcium and magnesium balance, which will reflect dietary intake, oral phosphate binder usage and the usage of vitamin D analogues.

4.1.4 In patients with CKD stages 3–5 (2D) and 5D (2B), we suggest using phosphate-binding agents in the treatment of hyperphosphataemia. It is suggested 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).

Dietary phosphate assessment and restriction are the cornerstone of the management of raised phosphate. This should be done by a skilled dietician. Phosphate restriction can only safely be done if concomitant protein restriction can be avoided. Phosphate-binding agents are commonly needed in addition. The choice of which agents to use should reflect efficacy, availability, affordability, and patient perspectives and choices. See also KDIGO recommendation 4.1.7 and the corresponding comment by the ERBP work group.

4.1.5 In patients with CKD stages 3–5D and hyperphosphataemia, we recommend restricting the dose of calcium-based phosphate binders and/or the dose of calcitriol or vitamin D analogue in the presence of persistent or recurrent hypercalcaemia (1B). In patients with CKD stages 3–5D and hyperphosphataemia, 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).

The ERBP group endorses the observation that nephrologists may care to consider not using calcium-based phosphate binders in the presence of CV disease, vascular calcification, adynamic bone disease and hypercalcaemia. This reflects the perception of the KDIGO and ERBP working groups that all phosphate binders tend to reduce plasma phosphate levels if taken appropriately, and that efficacy, toxicity, affordability and patient palatability are all important considerations when determining which to use singly, or in combination.

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

The present guidelines tend to reject aluminium-based phosphate binders, on the grounds of perceived potential toxicity rather than any lack of efficacy. This statement is made more because of the fear of the consequences of prolonged or unrestricted usage of aluminium salts as oral phosphate-binding agents.

The ERBP group advises that prolonged (>3 months continuous or 6 months cumulative) use of aluminium salts as phosphate binders should be avoided. There is probably a much greater risk of aluminium accumulation and toxicity where exposure to aluminium occurs through the dialysate water (something that should of course be impossible

today). It should be recognized that toxicity of per oral aluminium has never been explored in controlled studies.

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

The ERBP work group takes note of the fact that in the KDIGO monograph there is little practical information about how to assess and alter dietary phosphate intake in order to curtail plasma phosphate values. We suggest that for detailed information about this important matter the interested reader should consult the recent ERBP nutrition guidelines [30]. In brief, the most important recommendations in that text refer to a maximum of 800–1000 mg (25–35 mmoL/day) daily dietary phosphate intake. Reference is also made to the need for education, for support, and for avoiding the risk of prejudicing dietary protein intake. Also see KDIGO 4.1.4.

4.1.8 In patients with CKD stage 5D, we suggest increasing dialytic phosphate removal in the treatment of persistent hyperphosphataemia (2B).

Successful management of raised plasma phosphate levels in CKD 5D patients should include examination of oral phosphate intake, evaluation of the rate of bone turnover [which would help determining the origin of hyperphosphataemia (bone resorption or gastrointestinal absorption)], and use of and compliance with oral phosphate binders. As well as these measures, careful thought about increasing the efficiency of dialytic methods to remove phosphate should be undertaken. The latter dialytic methodological options include prolonged haemodialysis [31] and convective strategies [32].

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).

The desirable range for PTH is now 2–9× the upper limit of the normal range (from 2–4× ULNR in KDOQI) as it was felt that a narrow range was difficult to target, that the evidence for outcome associations across this narrow range was modest, and that there was some evidence of adynamic bone lesion being common (and not 'normal' bone histomorphometry) despite achieving iPTH values in this range [33]. Balancing this change, with which the ERBP group agrees, it should be conceded that no RCT has proved a causative link between adynamic bone lesion and cardiovascular outcomes. This alteration in the desired PTH range may lead to a shift in therapeutic practices over the next few years; many of the recent trials of the newer therapeutic agents (synthetic vitamin D analogues and calcimimetics) had as their 'target' the 150–300 pg/mL value range.

Furthermore, to interpret these new PTH recommendations, one also needs to be mindful of how much serum phosphate has fallen in national, European and practice pattern registries over the last 5–6 years [4–6], and also by how much PTH has fallen under the previous stimulus of KDOQI guidelines.

The vexed issue of which PTH assay methodology to use is also well described, but no over-arching recommendation was suggested. See also KDIGO 3.1.6 and ERBP comment.

Using plasma bone-specific, or total, alkaline phosphatase levels can help to a small degree in the interpretation of PTH values. See also KDIGO 3.2.3 and ERBP comment.

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

Most treatment algorithms suggest starting with calcitriol, or other vitamin D analogues, with moderate rises in PTH levels. If there is no response with the PTH falling back into the normal accepted PTH range, or intolerance, or hypercalcaemia or hyperphosphataemia, switching to calcimimetics is logical, assuming these are available and affordable. Combining low doses of vitamin D and calcimimetics may be efficacious and efficient, but long-term follow-up data of such patients using hard end points such as parathyroidectomy, fracture, and especially cardiovascular morbidity and mortality are missing.

4.2.5. In patients with CKD stages 3–5D with severe hyperparathyroidism that fails to respond to medical/pharmacologic therapy, we suggest parathyroidectomy—PTX (2B).

The ERBP working group consider that parathyroidectomy should be considered the last resort for medical/secondary hyperparathyroidism (except where access to calcimimetics is limited, e.g. due to cost). In particular, in dialysis and transplant patients, the question should be asked: why should calcium-sensing receptor agonists not be used in place of surgical or ablational parathyroidectomy? Calcium-sensing receptor agonists are not ideal for use in CKD stages 2–4 for severe secondary hyperparathyroidism, so PTX may be justified here, but for patients on dialysis, or within 12–18 months of successful renal transplantation, calcium-sensing receptor agonists are, we feel, preferable to try in advance of parathyroidectomy. These drugs should be given at least 3, possibly 6 or more, months in which to be titrated up, and shown to be either successful or ineffectual, before a decision about PTX is made.

Calcium-sensing receptor agonists are more complex to use in CKD stages 2–4 for severe secondary hyperparathyroidism—there is a tendency to a more severe hypocalcaemia, and a rise in plasma phosphate values, with their use, so PTX may be justified here. The use of these drugs in the post-renal transplantation setting is now widespread,

Table 1. Areas where diagnostic, or therapeutic, uncertainty remains post-KDIGO CKD-MBD guidelines

(i) Whether to use bone- or total-alkaline phosphatase levels together with PTH in CKD, dialysis and transplant patients to try to assess bone turnover rates. Whether to use bone-derived collagen type I degradation product and/or TRAP5b together with PTH in CKD, dialysis and transplant patients to try to assess bone resorption rate

(ii) Whether/when (and how) to measure 25-OH vitamin D levels in CKD, dialysis and transplant patients

(iii) Whether/when (and how) to replete 25-OH vitamin D in CKD, dialysis and transplant patients

(iv) Whether/when (and how) to use synthetic analogues of vitamin D in CKD, dialysis and transplant patients

(v) Whether/when (and how) to replete physiological levels of 1,25-(OH)2 vitamin D in CKD, dialysis and transplant patients

(vi) Whether/when (and how) to choose between treatment with 1,25(OH)2 vitamin D, 25-OH Vitamin D, or both in CKD, dialysis and transplant patients

(vii) When to consider performing a bone biopsy in CKD, dialysis and transplant patients

(viii) How to interpret a bone biopsy in CKD, dialysis and transplant patients

(ix) Whether to (and when, and how) to screen for the presence of cardiovascular calcification

(x) How to interpret DEXA scan results in CKD stage 3 and 4 patients (although this procedure is not recommended by KDIGO, the reality is that they are being performed, often by non-nephrologists)

(xi) Whether to, and how to, use bisphosphonate therapy safely in CKD stage 3 and 4 and transplanted patients (there is consensus that these drugs are best avoided in CKD 5D patients [33]) as adynamic bone disease is a serious risk. This is particularly taxing for nephrologists dealing with CKD patients with bone problems, referred from osteoporosis clinics and other specialists, as we know that high (intravenous) doses of certain bisphosphonates can be nephrotoxic for CKD patients [33], while we also know that bisphosphonate therapy can protect against steroid-related bone density loss after renal transplantation [36]. How best to recommend and reconcile the appropriate use of these compounds is a major issue.

(xii) When to avoid the use of a predominantly calcium-based oral phosphate binder therapeutic strategy (and is there any evidence for a 'safe calcium load threshold'?).

(xiii) When and how to use inhibitors of the intestinal sodium-phosphate co-transporter NPT2b such as nicotinamide acid?

(xiv) When calcimimetic drugs are indicated, and in which sub-populations of CKD, dialysis, and transplanted patients, for how long, etc.

(xv) When a surgical parathyroidectomy is mandated, and whether calcimimetics should have been tried beforehand (and failed), and how to handle those in the setting of a surgical parathyroidectomy; also, what type of surgical parathyroidectomy is recommended, in different groups of patients.

(xvi) The best use of different calcium concentration dialysate baths in conjunction with vitamin D and other therapies.

(xvii) Whether to prevent the plasma phosphate level from rising out of the normal range in CKD patients (by use of phosphate restricted diet, and binders, before plasma hyperphosphataemia has been detected)?

(xviii) How best to tackle 'adynamic bone disease' once this is diagnosed (by clinical, laboratory or best by histomorphometric analysis)? Options include allowing plasma calcium to fall [37], plasma phosphate and iPTH to rise, or PTH analogue therapy (teriparatide) [38].

though it is not (yet) a licensed indication; there are for example no registration phase III trials examining outcomes and safety. Likewise, since renal transplant recipients are very likely to end up with a renal function equivalent to CKD stage 2–3a after their transplantation, any patient who can be expected to receive a renal graft in the next 24 months can also be considered as a less ideal candidate. However, dealing with the consequences of severe post-transplantation hypercalcaemia such as is seen in severe

tertiary hyperparathyroidism (for example pancreatitis, psychological disturbance, renal stones or acute kidney injury) is clinically challenging, so active management of CKD–MBD, whether by calcimimetics or parathyroidectomy, prior to transplantation is optimal practice.

For the remaining patients, both options should be taken into account, taking into consideration whether the patient may already have undergone a previous parathyroidectomy (making the chances of success of a subsequent parathyroidectomy less likely), his/her clinical condition and surgical risks, and the cost to patient and society and complications of both strategies. If calcimimetics are prescribed, these drugs should be given at least 3, possibly 6 or more, months during which time they should to be titrated up, and shown then to be either successful or ineffectual, before the therapy as classified as inappropriate, and then a decision about parathyroidectomy be taken.

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).

The ERBP group agrees for CKD stage 3a (GFR 45–60 mL/min/BSA) as these patients are less likely to progress to CKD stage 4 or ESRF/dialysis, and their renal excretory reserve is higher (anti-resorptive therapy—bisphosphonates—is predominantly renally excreted). However, for CKD stage 3b patients (GFR 30–44 mL/min/BSA) without marked progression, consideration should be given in decreasing the dose of, or increasing the dosing interval for, bisphosphonate therapy. The risks of inappropriate or excessive use of bisphosphonate in CKD include renal toxicity from the drugs themselves (rare and usually confined to high-dose intravenous use as seen in malignancy and myeloma therapies), and accumulation in the skeleton leading to profound adynamic bone lesion and risk of subsequent fracture [34,35].

Conclusions of the ERBP group on the KDIGO guidelines document

The ERBP position is to welcome the KDIGO CKD–MBD guidelines document, while at the same time respecting the daily difficulties everyone in clinical practice faces, even after the publication of these guidelines [1]. The rigorous process involved in assembling the guidelines positions was a huge challenge to all involved, and the outcome, a readable and very useful reference text for many aspects of CKD–MBD, is a major achievement. Rather than focus excessively on the lack of direct implementability of the 49 guideline statements, the ERBP position is strongly to call for a concerted international and geographical regional response to the many key uncertainties that the KDIGO document elegantly exposes. There is now an urgent need to respond with educational, practical and investigational and audit/outcome projects to try to improve the immediate and future care of the millions of

people in the world with mineral and bone disorder abnormalities as a result of chronic kidney disease. This challenge may require new ways of thinking, acting and collaborating which would clearly need active involvement from continuous medical education providers, ERA–EDTA clinical research working group memberships, ERA–EDTA Scientific Advisory Board and ERA–EDTA ERBP members, all acting collaboratively in a coordinated fashion. It could then be possible to 'fast-track' coordinated European approaches to these many difficulties, which in time would help the next set of guidelines by providing some of the missing evidence.

All through the text, there are numerous calls for prioritized research efforts to try to bridge the huge gaps in evidence which tax epidemiologists, practising nephrologists and clinical scientists alike. The most important of these, which the ERBP group wishes to highlight, is presented in Table 1, with some commentary. These topics, the ERBP group feels, should be the subject of future research effort.

Disclaimer. The present text is based upon the information available to the work group at the moment of the preparation of this publication. It has been designed to provide information and assist decision making, but is not intended to define a standard of care or to improve an exclusive course of diagnosis, prevention or treatment. Individual decision making is essential in the approach to any disease and thus also CRBSI. Variations in practice are inevitable when physicians take into account individual patient needs, available resources, and limitations specific for a geographic area, country, institution or type of practice. In addition, evidence may change over time as new information becomes available, so that practice may be modified subsequently. Every practitioner using this text is responsible for its application to any particular clinical situation. The work group members involved in the development of the present text have disclosed all actual and potential conflicts of interest that may arise as a result of an outside relationship or a personal, professional, or business interest.

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