**Review Article**

**KDIGO clinical practice guidelines for the diagnosis, evaluation, prevention, and treatment of mineral and bone disorders in chronic kidney disease**

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**Keywords**  
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**Abstract**  
Kidney Disease: Improving Global Outcomes (KDIGO) is an international nonprofit foundation established in 2003 to improve the care and outcomes of kidney disease patients worldwide through coordination of different initiatives to develop and implement clinical practice guidelines. After almost 4 years of intensive work, the mineral and bone disorder of chronic kidney disease guidelines were presented during the American Society of Nephrology Renal Week at the end of 2008, to be finally published in *Kidney International*, August 2009. In this paper, the main points of the guidelines are discussed: the diagnosis of biochemical, bone, and vascular abnormalities, the treatment targeted at lowering high serum phosphorus, the normalization of serum calcium, and, in dialysis patients, maintaining parathormone levels in the range of 2 to 9 times exceeding the normal limit. Because there are no randomized clinical trials that compare the efficacy and toxicity of different phosphate binders, vitamin D analogs, and calcimimetics, and there is no evidence that these drugs decrease mortality, the KDIGO experts do not make any specific recommendation in regard to these treatments. Finally, the guidelines for treatment of osteoporosis using bisphosphonates, and for evaluation and treatment of bone disease developing after the kidney transplant are presented in this review.

**Introduction**  
Kidney Disease: Improving Global Outcomes (KDIGO) is a global nonprofit organization established in 2003 and governed by an international board consisting of representatives from 24 countries and 5 continents. It is dedicated to coordinating and integrating international collaboration initiatives aiming at improving the care and outcomes of kidney disease patients worldwide and establishing objectives for research. Among its several initiatives, KDIGO is actively involved in sponsoring the so-called Controversies Conferences, bringing together international experts in different fields of nephrology. The purpose of the Conferences is to establish a set of common international clinical guidelines, and subsequently, to introduce them into everyday clinical practice. Such coordination seems necessary, because a number of various international organizations and societies have been established recently, each publishing their own sets of rules and guidelines. Since development of high-quality guidelines requires a considerable financial and scientific effort, the KDIGO initiative offers a unique opportunity to conserve major resources.

KDIGO devoted almost 4 years of thorough research to chronic kidney disease-mineral and bone disorder (CKD-MBD). A 2005 conference entitled "Definition, Evaluation and Classification of Renal Osteodystrophy" initiated the entire process and led to the publication of a 2006 manifest, which stated the need for change in the definition of the disease as well as for the new guidelines. A task group, aided by experts from the KDIGO Evidence Review Team, spent 2 years reviewing international literature on the subject.
FIGURE  Definition of chronic kidney disease-mineral and bone disorder
Abbreviations: CKD—chronic kidney disease, PTH—parathormone

and released a preliminary report, which was then analyzed by the KDIGO Board. The final version was subsequently published on the Internet for public review. The guidelines were for the first time presented in public during the American Society of Nephrology congress in 2008, and subsequently published in the August 2009 issue of Kidney International.

Moreover, while working on the guidelines, KDIGO developed a system of rating the strength of recommendations and the underlying quality of evidence. After long debates, the modified “Grading of Recommendations Assessment, Development, and Evaluation System” was finally approved by the KDIGO Board in 2008. The system is an important key to interpret the guidelines. The authors use 2 levels of recommendations: strong (level 1) – the guidelines should be treated as recommendations, and weak (level 2) – the guidelines should be treated as suggestions.

The quality of underlying evidence was graded as: A – high, B – moderate, C – low, and D – very low. Additional personal expert opinions were presented as “not graded”. Overall, recommendations of the CKD-MBD guidelines are weak: only 10 of 58 recommendations reached level 1, and only 2 of these 10 recommendations were supported by high-quality evidence (A). The latter included human recombinant growth hormone therapy in children and youth, as well as the treatment of osteoporosis in patients with CKD stages 1–2 (see below). In the present review, the numbers and letters in parentheses will indicate the level of recommendations and quality of evidence for particular guidelines in keeping with the KDIGO classification.

The full document has 130 pages and contains the guidelines along with detailed commentaries, tables, and literature references. The chapters discuss the following: 1) definition of CKD-MBD, 2) diagnosis of biochemical abnormalities, various types of bone disorders, and vascular calcification, 3) treatment of calcium-phosphorus disturbances and abnormal levels of parathormone (PTH), 4) treatment of bone disorders with bisphosphonates, other osteoporosis medications, and growth hormone, 5) evaluation and treatment of kidney transplant bone disease. Finally, future research directions are presented.

Definition  The traditional term “renal osteodystrophy”, which has been used until recently, failed to encompass the entire spectrum of bone and mineral abnormalities, because the dramatic effect of mineral disorder on cardiovascular system in uremia had not been fully known at the time. As the clinical evidence grew, the need for change of the definition became more apparent, “bone and vascular disease” being one of the possible options. Eventually, the term CKD-MBD was introduced to describe a broader clinical syndrome that included mineral disturbance and abnormal metabolism of bone-regulating hormones, as well as various bone disorders and calcification of soft tissues (FIGURE). All these types of pathologies are interrelated and together account for unfavorable prognosis in CKD. Therefore, the term “renal osteodystrophy” as a part of the above-mentioned syndrome is to be used only with respect to pathological changes within the bone. The precise diagnosis and classification of these pathologies requires bone biopsy and a thorough histomorphometric examination.

Diagnosis of CKD-MBD: biochemical abnormalities
Biochemical abnormalities play a central role in the diagnostic and therapeutic approach in CKD-MBD. The earliest detectable changes affect the levels of bone-regulating hormones. Increased PTH levels and decreased 25(OH)D3 (calcidiol) and 1,25(OH)2D3 levels are observed already in stage 3 of CKD, while calcium and phosphorus levels are usually normal until more advanced stages of the disease. Therefore, biochemical parameters should be closely monitored already in stage 3 CKD (1C), while in children such monitoring is suggested already in stage 2 due to the risk of growth disturbance and cardiac dysfunction (2D).

The authors of the guidelines suggest using individual values of calcium and phosphorus levels rather than the mathematical calculation of calcium-phosphorus product (Ca × P), which is mostly reflecting the phosphorus level, and as such it has no major significance in the diagnostic process (2D). At the same time, they stress the importance of methodology and interpretation of the results, stating that laboratories should inform clinicians about the applied measurement methods, as well as proper blood sampling and handling protocols (1B), since any misinformation in that matter can lead to inconsistencies or distortion of the results. Decisions regarding introduction of therapeutic modalities should rely on serial measurements of a given parameter rather than individual values (1C). For example, an increase in
PTH levels observed in a series of measurements, rather than a single measurement, should indicate a change of approach, even if the observed values are within the normal range.

### Diagnosis of CKD-MBD: bone disease
Diagnosis of bone disease is challenging, mainly because bone biopsy is still a rare test for various reasons. Moreover, attempts to find a reliable and easily available biochemical marker of bone disease have not been successful so far. Several proposed markers, such as the products of collagen synthesis (procollagen type I C-terminal propeptide) and breakdown (C-telopeptide type I collagen, N-telopeptide type I collagen, pyridinoline or deoxypyridinoline), did not prove better than the traditionally measured serum PTH; therefore, the recommendation for their routine use in clinical practice is weak (2C). Simultaneous measurement of serum PTH and alkaline phosphatase (ALP) levels has proved to be the most reliable tool to date. However, it should be noted that type of osteodystrophy can be predicted only when these levels are significantly elevated or decreased (2B). The diagnostic value of densitometry is also relatively low, because it does not allow for differentiating between various types of bone pathologies, and bone mineral density (BMD) is not a reliable predictor of bone fractures in CKD patients (2B). Nevertheless, children should be carefully monitored with respect to their linear growth: infants should be assessed at least quarterly (1B), children at least annually (1B).

Definitive diagnosis of renal osteodystrophy relies on a comprehensive histomorphometric analysis. Until recently, such analysis has been based mainly on determining the rate of bone turnover and proper mineralization. During the 2005 Controversies Conference, where the guidelines discussed here were initiated, an introduction of the TMV (Turnover, Mineralization, Volume) classification to the diagnosis of renal osteodystrophy was proposed. It has been used by the American Society for Bone and Mineral Research since 1987. The classification introduces the third parameter that describes bone changes, namely the bone volume. It affects bone fragility and is a result of equilibrium that exists between bone formation and resorption rates: if such balance is positive, the bone volume increases, and, at a constant rate of mineralization, an increase in BMD is usually observed.

The KDIGO experts did not formulate any guidelines concerning bone biopsy, because it is rare in clinical practice, and there are not many anatomical pathologists with relevant experience. However, the experts state that bone biopsy may be justified in some cases in CKD stages 3–5, including patients on dialysis (5D). These include unexplained bone fractures, unrelenting bone pain, unexplained hypophosphatemia or hypercalcemia, rare cases of aluminum osteopathy; it may also be used prior to the administration of bisphosphonates to exclude adynamic bone disease, which is a contraindication for such therapy.

### Diagnosis of CKD-MBD: soft tissue calcification
Multislice computed tomography, which allows to determine coronary calcification, is an expensive method and is not neutral for the patient; therefore, it should be treated merely as a reference method. In a clinical setting, diagnosis of cardiovascular calcifications in CKD stages 3–5D should be thus based on a much more broadly available lateral abdominal radiograph to detect aortic calcifications (2C), and echocardiogram to detect valvular calcifications (2C).

Tests detecting cardiovascular calcifications in patients with CKD may become a part of routine screening in the future. However, the data are insufficient to justify such an approach at present. While cardiovascular calcification is strongly predictive of cardiovascular events and death in patients with CKD, the introduction of anticalcification therapies has not been shown to improve the long-term prognosis. An effective therapeutic modality has not been established for such patients yet, and the role of calcimimetics or statins in their treatment remains elusive.

Nevertheless, a thorough diagnostic evaluation of possible cardiovascular calcifications is justified in some circumstances, e.g., in patients with significant hyperphosphatemia who require a complex therapeutic intervention, in prospective transplant recipients, and in patients whose therapy could be directly influenced by the detection of calcifications (e.g., patients on hemodialysis who would therefore become eligible for hemodiafiltration). The KDIGO experts suggest that patients with calcification should

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### Table: Suggested frequencies of serum calcium, phosphorus, parathormone, alkaline phosphatase, and calcidiol monitoring in chronic kidney disease stages 3–5D and after renal transplantation

<table>
<thead>
<tr>
<th>Table</th>
<th>Progressive CKD (stage 3 or stages 1–3 post-Tx)</th>
<th>CKD (stage 4 or stage 4 post-Tx)</th>
<th>CKD (stage 5 and patients on dialysis – 5D or stage 5 post-Tx)</th>
</tr>
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<tbody>
<tr>
<td>serum calcium and phosphorus levels</td>
<td>every 6–12 months</td>
<td>every 3–6 months</td>
<td>every 1–3 months</td>
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<tr>
<td>serum PTH and ALP levels</td>
<td>baseline</td>
<td>every 6–12 months</td>
<td>every 3–6 months</td>
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<td>25(OH)D₃</td>
<td>baseline</td>
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Abbreviations: ALP – alkaline phosphatase, Tx – kidney transplant, others – see figure.
considered at the highest cardiovascular risk (2A), and therefore, any existing atherosclerosis risk factors should be eliminated, and a meticulous control of biochemical parameters of calcium-phosphorus homeostasis ensured. Although there is no evidence to support this, the experts consider it reasonable to limit the use of calcium-based phosphate binders in such patients.

**Treatment of CKD-MBD: calcium-phosphorus homeostasis** Phosphorus levels in patients in predialysis stages of CKD should be maintained within the normal range (2C). In dialyzed patients, such strict management protocol may be particularly difficult. Although we should certainly aim at achieving normal phosphorus levels in this group, in some patients it may simply be impossible or may lead to lowering their quality of life, undernourishment (too restrictive diet), or side effects when too strong doses of intestinal phosphate binders are administered. Therefore, the KDIGO Workgroup allowed for certain flexibility in this respect and identified their recommendation as weak (2C).

Calcium levels in CKD stages 3–5D should be maintained within the normal range (2D). However, the experts argued that there was no sufficient evidence to support the Kidney Disease Outcomes Quality Initiative (K/DOQI) recommendation to maintain calcium levels within the lower margins of the normal range (T.B. Drüeke, personal communication). Suggested calcium dialysate level should not exceed 1.25–1.50 mmol/l (2D).

The clinical practice guidelines for patients with hyperphosphatemia have not changed for years. Low-phosphate diet is suggested, although the strength of recommendation is surprisingly weak (2D). Dialysis efficiency needs to be further increased, which is an easy and relatively inexpensive process, although not supported by strong evidence (2C). Intestinal phosphate binders, although used for years in the prevention of hyperparathyroidism and treatment of hyperphosphatemia, are only suggested as a possible regimen due to the lack of randomized studies (2B). The workgroup does not recommend any particular binding agent due to the lack of sufficient data. As a logical consequence, each treatment should be customized, i.e., adjusted individually to the patient’s clinical parameters. For example, it is strongly recommended to lower the dose or even to completely withdraw calcium-based medications and vitamin D analogs in patients with persistent or recurring hypercalcemia (1B). Lower doses of calcium-based preparations are also suggested in patients with significant vascular calcification or those who have persistently low PTH levels (2C).

**Treatment of CKD-MBD: abnormal PTH levels** Determining the optimal serum PTH level remains one of the weakest points of clinical practice. So far, it has been arbitrarily established at 150–300 pg/ml, based on a gradual increase in bone resistance to PTH in patients with progressive renal disease. However, it still remains unclear whether achieving the recommended levels of PTH correlated with the normalization of bone metabolism. This is complicated by the fact that mineral and bone abnormalities are interrelated with the cardiovascular system. Importantly, what is favorable for the former may prove detrimental for the latter. Therefore, assuming that the optimal PTH level is currently unknown, the KDIGO workgroup suggests monitoring calcium, phosphorus, and calcidiol levels in patients with CKD stages 3–5 with abnormal PTH levels (2C). An increase in PTH levels may be a possible adaptive process and can be reversed to normal values after normalizing other parameters of calcium-phosphorus homeostasis. However, if increased serum levels of PTH are maintained, treatment with calcitriol or its analogs can be considered (2C).

The KDIGO experts suggest a different approach in dialyzed patients: their PTH serum levels should be maintained within the range of approximately 2 to 9 times the upper normal limit (2C). It is one of the major changes introduced by KDIGO, since the 2003 K/DOQI guidelines suggested a range of 3 to 6 times the upper normal limit.3 Broadening the range of acceptable PTH levels is supported by evidence. First, cross-sectional studies have suggested that while CKD progresses, both the mean levels as well as the range values of PTH levels increase. As a result, the predictive value of PTH as a marker of bone disease within the 2 to 9 times normal limit is fairly low. Second, methodological difficulties concerning measurement of PTH cannot be ignored. Various tests measure varying amounts of accumulating PTH fragments, including the antagonistic fragment C7–84. As a result, high concentrations of intact PTH may coexist with a relatable hypoparathyroidism at the bone level.

KDIGO suggestion to carefully monitor trends in serial PTH measurement deserves particular attention – any definite shifts towards the upper or lower limit should be a clear signal to modify the therapy in such a way as not to exceed the acceptable range (2C). On the other hand, a general trend towards one direction observed in the majority of tested patients in one center may suggest a recent change in the methodology of PTH measurement in a given laboratory.

While reviewing the treatment of CKD-MBD, the authors of the guidelines avoid any suggestions concerning the choice of any particular medication, mainly because there is not enough evidence to support any specific selection. They only recommend the use of calcitriol or its analogs, calcimimetics, or a combination of vitamin D analogs and calcimimetic in the case of increased PTH levels. The choice of therapeutic modality should be based on the presence of possible contraindications in each individual case. For example, hypercalcemia will be a clear contraindication for administering vitamin D analogs, and
the treatment will either have to be stopped or reduced (1B); similar although much weaker recommendation was formulated for hyperphosphatemia (2D). Similarly, hypocalcemia is a clear contraindication for calcimimetics, and withdrawal or dose reduction is recommended depending on disease severity, symptoms, and the use of other medications (2D). In severe secondary hyperparathyroidism, which is resistant to pharmacological intervention, parathyroidectomy should be considered, although there is no reliable evidence for its effect on any of the hard endpoints.

In the case of 25(OH)D₃ deficiency, it should be supplemented in accordance with the guidelines concerning the general population (2C).

**Treatment of CKD-MBD: bisphosphonates and other medications** Diagnosis of osteoporosis with the use of densitometry is feasible only in stages 1 and 2 of CKD (1A), and the diagnostic process and therapeutic approaches parallel the guidelines for the general population. Low BMD is the main diagnostic feature of osteoporosis. Since defective bone quality with normal or even increased mineral parameters is a typical feature of CKD-MBD, the assessment of structural imperfections is even more complex and dependent on histomorphometric analysis.

In stage 3 of the disease diagnosing osteoporosis is possible, although much less reliable (2B), because stage 3 encompasses a very heterogeneous group of cases, as clearly reflected by a broad range of glomerular filtration rate (GFR) values characteristic for this group (30–60 ml/min/1.73 m²). There are limited data on the pathomorphological changes within the bone tissue at this stage of disease. The rare reports indicate high degree of heterogeneity in terms of both abnormal bone histology and the rate of bone turnover. Therefore, stage 3 of CKD requires introduction of individualized treatment.

The authors of the guidelines suggest that patients with low BMD and asymptomatic course of the disease, especially those with higher GFR values, can be managed using the guidelines for the treatment of osteoporosis in the general population. However, prior to establishing the diagnosis of osteoporosis, secondary hyperparathyroidism must be excluded and serum PTH measured. If PTH levels are normal, then, similarly to stages 1 and 2, stage 3 patients can be treated according to the general guidelines (2B). Nevertheless, the occurrence of CKD symptoms will require a change of therapeutic protocol and its adjustment according to the degree of disturbances, their possible reversibility, and progression of the disease. If GFR remains stable and the risk of bone fractures is higher than the risk associated with induced adynamic bone disease, administering bisphosphonates, preferably after bone biopsy, becomes a viable option (2D).

Later stages of CKD with low BMD are characterized as CKD-MBD with low BMD. Percentage of individuals with low BMD is significantly higher in CKD patients as compared with the general population. As reported by the National Health and Nutrition Survey, osteoporosis was diagnosed in 23% of adult women with CKD stages 3–4. According to recent studies in the United States, 61% of women suffering from osteoporosis were in stage 3 and 23% in stage 4 of CKD.

Increased prevalence of osteoporosis significantly increases the risk of bone fractures in patients with CKD. Nevertheless, unlike in the general population, BMD value is not an accurate predictor of bone fractures in CKD due to a considerable role of qualitative changes in the bone tissue as well as the presence of other CKD-related risk factors. Bone fractures occur in 10% to 40% of dialysis patients and in approximately 50% of patients older than 50 years. The risk of hip fracture in the population with end-stage renal disease was reported to be up to 4-fold higher than in the general reference population.

Evidence supporting the role of bisphosphonates in preventing bone fractures in patients with stage 3–5D of CKD-MBD is not conclusive (C), because it is derived from post hoc analyses of large scale trials designed to study the treatment of osteoporosis in the general population.

It is possible that some patients in stage 4–5D, especially those with low BMD and a high rate of bone turnover, after mineral disturbances and increased PTH levels are normalized, may benefit from bisphosphonate therapy, but only large, well-planned, randomized trials can provide a reliable answer to this question. Moreover, the guidelines emphasize the need for further studies that would investigate the pharmacodynamics of bisphosphonates in patients with CKD.

Of note, bisphosphonates have an antiresorptive potential; they can be incorporated into the bone tissue and remain there for several years (T½ >10 years), which severely and almost permanently slows down the rate of bone turnover. Other serious side effects include mandibular osteonecrosis, arrhythmia, ulcerations of the upper part of the gastrointestinal tract, and nephritic syndrome. Therefore, the decision to administer bisphosphonates has to be supported by clinical data. Since the risk of inducing adynamic bone disease significantly increases with the progression of CKD, administering bisphosphonates in patients in stages 4–5D (especially in those already on dialysis) should be preceded by bone biopsy in order to exclude the possibility of a decrease in bone turnover rate (2D).

According to the authors of the guidelines, there is not enough data concerning other antosteoporotic medications (e.g., recombinant active PTH₁–₃₄, teriparatide, or a selective estrogen receptor modulator – raloxifene) to allow for any recommendations or even suggestions to be formulated.

In children with CKD stages 2–5D and associated height deficits, the treatment with human recombinant growth hormone is recommended, providing that the coexistent malnutrition...
and biochemical abnormalities have been normalized (1A).

Clinical management of kidney transplant patients  The pathogenesis of CKD-MBD in kidney transplant recipients is quite complex, because transplant-specific therapies, such as corticosteroids, and overall kidney dysfunction in these patients lead to the development of new bone abnormalities in addition to the previously existing ones. Directly after transplantation, patients can experience disturbances in calcium-phosphorus homeostasis with pronounced hypophosphatemia; therefore, it is necessary to closely monitor the serum levels of calcium and phosphorus. Measurement taken at least once a week until they fully stabilize (1B), which usually occurs within the first 2 months after transplantation, is strongly recommended. In the majority of patients diagnosed with secondary hyperparathyroidism, the first few months after transplantation are characterized by a slow and gradual decrease in the activity of the glands; however, PTH levels usually remain slightly elevated. Similarly, calcitriol levels, although higher than the pre-transplant values, will never be normalized.3

Later, in stable patients, monitoring and correcting biochemical abnormalities depends on their presence and intensity as well as kidney disease progression. In general, it is similar to that in patients with CKD stages 3–5D (TABLE). Calcidiol deficiencies should be treated according to the guidelines for the general population (2C), and the frequency of measurements should depend on the detected levels and possible therapeutic interventions (2C).

The treatment of osteoporosis in posttransplant patients poses a number of challenges. During the first few months after transplantation, a significant decrease in BMD, clearly correlating with corticosteroid dose, is usually observed.10,11 Subsequently, BMD continues to decrease at a much slower rate. Depletion of minerals from the bone tissue significantly increases a risk of fractures in these patients.

Therefore, it is recommended to perform densitometric bone analysis during the first 3 months after transplantation in patients with GFR >30 ml/min, patients who receive corticosteroids, or who have other osteoporosis risk factors. If BMD values in these patients are low, treatment with vitamin D, calcitriol or its analogs, or bisphosphonates is suggested. The choice of medication should be based on the biochemical abnormalities observed in a given patient, while administration of bisphosphonates should best be preceded by a bone biopsy due to an increased risk of adynamic bone disease in these patients.

Conclusions  The newest KDIGO guidelines will certainly disappoint those clinicians who expected definite answers or clear suggestions for the treatment of hyperparathyroidism in CKD patients. So, is it “much ado about nothing”? It is, if we hoped for innovative approaches or specific numbers. However, the guidelines are definitely a source of thorough and reliable analyses and commentaries, which are extremely instructive. They indicate doubts and avoid categorical statements, and as such they teach us caution and a thoughtful approach to clinical problems in question.

On the other hand, what may be disappointing is that the guidelines question even some of the most basic concepts (such as introducing low phosphorus diet or treatment with intestinal phosphorus binders) due to lack of evidence from randomized studies that will never be conducted. It only seems fair to ask whether our willingness to support the principles of evidence-based medicine did not lead us all slightly astray.

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Wytyczne KDIGO dotyczące rozpoznawania, oceny, zapobiegania i leczenia powikłań mineralno-kostnych w przewlekłej chorobie nerek

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SŁOWA KLUCZOWE
KDIGO, osteodystrofia nerkowa, powikłania mineralno-kostne, przewlekła choroba nerek, zwapnienia naczyńowe

STRESZCZENIE