During the 1980s and 1990s, the focus of dealing with disorders of bone and mineral metabolism was predominantly “bone centric,” with parathyroid hormone (PTH) the main culprit and calcium the primary regulator of PTH. The term “renal osteodystrophy” was generally used to encompass these disorders. The focus of therapy was to maintain relatively high serum calcium concentrations in order to suppress PTH, which would presumably result in normal bone. This strategy did result in decreased PTH concentrations with the use of relatively high dialysate calcium baths, calcium-based phosphate binders and calcitriol; however, this practice resulted in hypercalcemia. As a result, non-calcium–containing phosphate binders and less-calcemic vitamin D receptor activators (VDRAs) were developed. During this time, there was also an increased awareness of the importance of phosphate, and more recently a better understanding of the hormonal regulation of phosphate metabolism with the identification of phosphatonin, predominantly fibroblastic growth factor 23 (FGF23). In addition, a greater appreciation of the role of extraskeletal calcification, predominantly vascular, and the prevalence and severity of fractures in the CKD population became apparent.

In 2003, clinical practice guidelines for bone and mineral metabolism were published by the Kidney Disease Outcomes Quality Initiative (KDOQI). The guidelines were largely based on evidence from the following studies:

**Study 1**—in patients with progressing TMA

- Soliris treatment resulted in sustained improvement in renal function
- 80% (4/5) of patients eliminated dialysis

**Study 2**—in patients with long duration of disease

- Patients eliminated PE/PI and did not require new dialysis
- Soliris maintained renal function in patients with significant renal damage

**Important Safety Information**

**Contraindications**

- Patients with unresolved serious *Neisseria meningitidis* infection
- Patients who are not currently vaccinated against *Neisseria meningitidis*, unless the risks of delaying Soliris treatment outweigh the risks of developing a meningococcal infection

Please see brief summary of full Prescribing Information for Soliris, including boxed WARNING regarding serious meningococcal infection on following pages.
pert opinion rather than evidence, and were ‘phosphorus and PTH centric.’ Since these guidelines were released significant progress has been made in understanding the roles of VDRAs, the calcimimetic agent cinacalcet, FGF23, and possibly alkaline phosphatase. It has become apparent that mineral disorders of CKD were not solely a problem of bone disease.

In 2006, KDOQI created a consensus group to better define the diseases associated with altered mineral metabolism in CKD, which they termed chronic kidney disease-mineral and bone disorder (CKD-MBD). It is a systemic disorder of mineral and bone metabolism found in patients with CKD manifested by either one or a combination of the following:

- Abnormalities of calcium, phosphorus, PTH, or vitamin D metabolism
- Abnormalities in bone turnover, mineralization, volume, linear growth, or strength
- Vascular or soft tissue calcification

It is important to note that this list was not intended to be all encompassing and could expand as our understanding of disordered mineral metabolism evolves. The term renal osteodystrophy should now be limited to pathologic changes of bone morphology related to progressive CKD; and is quantifiable by histomorphometry based on bone biopsy (1). It is characterized by alterations in bone turnover, mineralization, and volume and includes the following qualitative disorders of bone: osteitis fibrosis cystica, adynamic bone disease, osteomalacia, and mixed uremic osteodystrophy (2).

In 2008, Kidney Disease: Improving Global Outcomes (KDIGO) presented a preliminary draft of the guidelines for CKD-MBD for public review. The KDIGO Work Group took a more conservative approach and refrained from making specific guidelines on treatment due to lack of high-quality evidence. This was a dramatic shift from the previous 2003 KDOQI guidelines, which had recommended specific targets for calcium, phosphorus, and PTH. Reviewers of the preliminary draft and the KDOGO board...
asked that the Work Group provide recommendations even if these were based largely on expert judgment, as long as the Work Group could achieve consensus.

Consequently, in 2009 KDIGO presented the final clinical practice guidelines for the management of CKD-MBD (3). The major difference between the KDOQI and KDIGO guidelines (Table 1) was that the KDIGO followed more stringent criteria for including studies to grade the evidence.

KDIGO presented two levels of recommendations based on evidence. Level 1 is “we recommend,” and implies that most patients should receive the course of action. Level 2 is “we suggest,” and implies that the choices are likely debatable. Most of the guidelines (approximately 80 percent) were graded Level 2 due to the lack of evidence and/or good randomized controlled trials, and it was left up to the clinician to make a decision based on the clinical circumstances of the individual patient.

Unfortunately, the publication of these guidelines has resulted in more controversy than therapeutic guidance. A meta-analysis published in 2011 of 47 cohort studies concluded that the current guidelines for calcium, phosphorus, and PTH in CKD patients are poor. They line up with the KDIGO guidelines in that it “promotes invasive strategies without sufficient evidence” and that “high-quality evidence is required before specific treatment should be advocated strongly” (4).

A commentary response to this meta-analysis published in the same volume of Kidney International when the KDIGO Work Group does not dispute that there was insufficient data, but tries to address “what should a guideline panel do when evidence is inconclusive.” It reports that even when there is a lack of evidence, most clinicians prefer to have at least an educated opinion from a guideline committee with a transparent rationale provided as a point of reference (5).

Key questions still need to be answered regarding target phosphate and PTH levels and an optimal treatment strategy for achieving phosphate and PTH targets. These questions are urgent for well-conducted randomized control trials in the CKD and dialysis population to address these questions. However, in the interim, it seems reasonable to use the KDIGO recommendations as a guideline.

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Table 1. Guidelines for CKD-MBD(6)

<table>
<thead>
<tr>
<th>Monitoring biochemical components</th>
<th>KDIGO 2009 (3)</th>
<th>KDOQI 2003(7)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Goal Phos</strong></td>
<td>Start at CKD 3. Include Ca, Phos, PTH, ALP</td>
<td>Same but no comment on ALP</td>
</tr>
<tr>
<td><strong>Goal Ca</strong></td>
<td>Normal</td>
<td>CKD 3–4: normal</td>
</tr>
<tr>
<td><strong>Goal PTH</strong></td>
<td>CKD 3–4: unknown</td>
<td>CKD 5: 5 to 6</td>
</tr>
<tr>
<td><strong>Goal 25(OH) Vit D</strong></td>
<td>Start at CKD 3. Correct as in general population</td>
<td>CKD 3–4, measure only if PTH is above target. Replace if &lt;30 ng/mL</td>
</tr>
<tr>
<td><strong>PTH assay</strong></td>
<td>Clinical labs should report assay and handling and sampling. Recommend 2nd generation assay</td>
<td>Recommendation based on 2nd generation Nichols Allegro assay currently unavailable</td>
</tr>
<tr>
<td><strong>Bone-specific ALP</strong></td>
<td>Suggest testing bone-specific ALP in certain individuals and very high or low levels predict underlying bone turnover</td>
<td>No specific suggestions</td>
</tr>
<tr>
<td><strong>Bone biopsy</strong></td>
<td>Reasonable in various settings and prior to bisphosphonates in CKD-MBD</td>
<td>Should be considered</td>
</tr>
<tr>
<td><strong>BMD</strong></td>
<td>Not routinely in CKD 3–5 with biochemical abnormalities</td>
<td>DEXA should be measured in patients with fracture and osteoporosis risk</td>
</tr>
<tr>
<td><strong>Vascular calcification</strong></td>
<td>No recommendation for routine screening</td>
<td>Same</td>
</tr>
</tbody>
</table>

Abbreviations: ALP = alkaline phosphatase; Ca = calcium; CaPhos = product of serum calcium and phosphorus; CKD = chronic kidney disease; DEXA = dual-energy X-ray absorptiometry; KDIGO = Kidney Disease: Improving Global Outcomes; KDOQI = Kidney Disease Outcomes Quality Initiative; MBD = mineral and bone disorder; Phos = phosphorus; PTH = parathyroid hormone; Vit D = vitamin D.

**References**

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**KidGIO Glomerulonephritis Guideline**

By Daniel Cartran

Glomerulonephritis (GN)—including both primary and secondary variants in aggregate—remains one of the most common types of kidney disease that progress to end stage renal disease (ESRD). However, this fact alone seriously underestimates the extent of the problem associated with GN. Many cases of the disease begin early in life and can have a devastating effect both on the individual and their families. The disease process is often slowly progressive and therefore its devastating impact on the individual’s physical, educational, occupational, quality of life, and eventual societal productivity is rarely taken into account when assessing the impact of these disorders.

The variants of GN included in the Kidney Disease: Improving Global Outcomes (KDIGO) GN guideline are classified as orphan diseases because of their rarity. This—in combination with their long clinical course, punctuated with remissions and relapses, and very large variation in treatment responsiveness—makes tracking them difficult. A recent *Kidney International* editorial, entitled *Glomerular Disease: Why Is There a Dearth of High-quality Clinical Trials?,* further delineates these problems (1). The authors proposed that the GN guidelines developed under the auspices of a global non-profit foundation KDIGO would help by encouraging a uniform classification system of diseases and common clinical end points as well as utilizing an evidence-based review process to establish clinical practice guidelines for glomerulonephritis. These guidelines were published as a *Kidney International* supplement in June 2012 (2).

Clinical practice guidelines (CPGs) have become an important element in clinical practice and can now be found in virtually every branch of medicine. The Institute of Medicine defines CPGs as “systematically developed statements about appropriate health care for specific clinical circumstances” (3). The potential benefits of CPGs include providing clear recommendations based on currently available evidence, thereby potentially improving the quality of clinical decisions. The advantage of the physician knowing the specific circumstances surrounding the individual patient cannot be underestimated in the final judgment about treatment. Ideally, decisions take into account the physician’s expertise and acumen in addition to the underlying patient characteristics and opinion as well as the evidence. The KDIGO GN guideline was purposely developed to have potential global application. This implies that it takes into account not only the different financial situations at the individual level, but also the social and economic realities of the underlying health care system.

The development of the GN guideline was a lengthy process and took several years. The Work Group consisted of both experienced and expert clinicians and an evidence review team trained in the complex field of guideline development. The Work Group developed recommendations related to a specific question or topic with each set of recommendations followed by a rationale section summarizing the evidence and the reasoning for each recommendation, and explaining why specific wording was chosen. It is critical to understand the grading process in the KDIGO GN guideline. Each recommendation has both an alphabetical and numeric code. The alphabetical code (A, B, C, and D) indicates the quality of the evidence supporting the recommendation or suggestion, whereas the numeric grade (1 or 2) denotes the strength of the evidence. At a practice level, level 1 generally means a recommendation that this course of action should be instituted, whereas level 2 is more compatible with a suggestion that requires that each affected individual needs careful consideration and that different choices may be appropriate for different patients. This provides a range of recommendations from 1A (the highest recommendation) to 2D (the lowest), with the latter usually reflecting the considered opinion of the GN Work Group.

No matter what the grading, the ultimate physician decision always requires consideration in regards to the balance between the risks and benefits of treatment. Ideally, the chosen treatment regimen reduces the total exposure to immunosuppressive therapy yet still results in the minimization of immediate morbidity (e.g., achieving remission of nephrotic syndrome) and prevents disease progression. The total exposure risk, however, must always be balanced against the alternatives (i.e., potential progression to ESRD with its associated shortened life span, and/or a renal transplant with its absolute requirement of continuous immunosuppression). This has modified the physician stance in favor of more intensive and prolonged treatment in the more chronic GN variants—for example, lupus nephritis, vasculitis, focal segmental glomerulosclerosis (FSGS), and even membranous nephropathy—given the alternative. In addition, the recognition that the clinical equivalent of control is often as well as the individual patient characteristics and opinion as well as the evidence. The KDIGO GN guideline was purposely developed to have potential global application. This implies that it takes into account not only the different financial situations at the individual level, but also the social and economic realities of the underlying health care system.