Value of the New Bone Classification System for Pediatric Patients with Chronic Kidney Disease

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The 2009 clinical practice guideline for the diagnosis, evaluation, prevention, and treatment of chronic kidney disease–mineral and bone disorder (CKD-MBD) issued by the global organization Kidney Disease: Improving Global Outcomes (KDIGO) (1) has adopted the previous proposal to use a new definition for the skeletal component of this disorder, namely renal osteodystrophy (2). The new definition emphasizes the usefulness of assessing not only bone turnover (T) but also mineralization (M) and volume (V), the two other key histologic descriptors of bone disease. This more complete evaluation system (TMV system) (Table 1) has been recommended in the interpretation of bone biopsies for all patients with CKD.

KDIGO guidelines are meant to be applicable worldwide. From a clinical perspective, it is important to test whether the recommendations made in a global guideline are effectively applicable to different patient populations with CKD, including children, adults, and elderly individuals; to both genders; to patients with variable kidney diseases and disease courses; and to patients on differing treatment modalities, such as conservative management, dialysis, or kidney transplantation and to which extent they are applicable in various parts of the world. Note that each KDIGO global guideline is designed to provide information and assist decision-making. It is not intended to define a standard of care and should not be construed as one; neither should it be interpreted as prescribing an exclusive course of treatment (1).

In this issue of CJASN, Bakkaloglu et al. (3) report the results of a study of pediatric patients with ESRD to characterize the spectrum of renal osteodystrophy on the basis of the TMV classification system (Table 1). They included in this retrospective, cross-sectional study 161 patients who were on peritoneal dialysis (age 0.7 to 20.0 years) and had undergone bone biopsies for various clinical investigations between 1990 and 2005. This is an extremely large number of bone biopsies, especially considering that bone histomorphometry is only rarely done in children with CKD and that this represents more than 50% of the number of bone biopsies evaluated by the KDIGO CKD-MBD work group (1). Moreover, bone biopsy findings from children who did not have uremia and were of comparable age and ethnic background were available for the sake of comparison. Other positive aspects of the study are that all serum biochemistry measurements were done at the time of bone biopsy sampling, and care was taken to avoid, at least to some degree, interference with previous treatments that might have altered bone histomorphometry findings. Thus, treatment with active vitamin D derivatives was interrupted at least 4 weeks before bone biopsy, and none of the patients had undergone parathyroectomy within the year before bone biopsy.

The main finding of the report by Bakkaloglu et al. (3) is the demonstration, using classification and regression treat analysis, that both bone turnover and mineralization status can be predicted on the basis of serum intact parathyroid hormone (iPTH), total calcium, and alkaline phosphatase values. Thus, serum iPTH levels of <400 pg/ml, in combination with total alkaline phosphatase values of <400 IU/L, provided the highest correct prediction rate for patients with both normal bone turnover and normal mineralization. Levels of PTH were higher and serum calcium levels lower in patients with defective mineralization, irrespective of bone turnover. Of note, the authors identified a large prevalence of previously underecognized mineralization defects in this pediatric dialysis patient cohort.

The question that immediately arises is whether, on the basis of these findings, combinations of serum biochemistry values can provide clinically satisfactory information on bone turnover, mineralization, and volume in the individual patient with CKD. Unfortunately, we are still not there.

The consideration of only four biochemical variables in the study by Bakkaloglu et al. (3) (serum calcium, phosphorus, PTH, and total alkaline phosphatases) may be insufficient for a noninvasive assessment of the TMV system in patients with CKD. No information was available on vitamin D status or serum fibroblast growth factor 23 levels. Total alkaline phosphatase was the only bone-derived parameter measured, with possible limitations as compared with bone-specific alkaline phosphatase. The assay used for the measurement of serum iPTH (IRMA; Nichols Institute Diagnostics, San Clemente, CA) is no longer on the market. Using classification and regression treat analysis, usually a minimum of 80% of correctly identified patients is needed to reach biologic and statistical significance. The levels achieved in this study for correctly identified patients with both normal turnover and mineralization did
not exceed 72%, and for those with normal bone turnover and de¬
fective mineralization, they did not exceed 65%. The long period
during which the bone biopsies were taken may have contributed to
some heterogeneity in the histomorphometric findings, considering
marked changes in treatment strategies over time. It is possible that
combining a larger number and/or more specific markers of CKD-
MBD will allow better discrimination.

Bone volume was not predicted by any of the circulating
markers determined by Bakkaloglu et al. (3). This failure may be
explained by the limited number of biochemical variables at
hand; that none of the pediatric patients with ESRD had low
bone volume; and the inclusion of patients with an extremely
wide life span, from 1 to 20 years of age. Noninvasive measure-
ments of bone mineral density or volume were not available.
The absence of low bone volume and the only exceptional
presence of adynamic bone disease is in contrast to previous
bone biopsy findings by the same authors of children and
adolescents who were on hemodialysis (4) and in stark contrast
to reports of adult patients with ESRD (5,6).

Observations made in pediatric patients with CKD may not be
sufficient to allow immediate extrapolations to adult patients with
CKD, particularly those in the higher age range, who frequently
have systemic diseases such as diabetes and osteoporosis, which
do not exist in childhood. Of note, Bakkaloglu et al. (3) found a
50% prevalence of mineralization defect, which was higher on
average than in the adult ESRD patient population, in whom the
prevalence was found to be near 32% (combining adynamic bone
disease, osteomalacia, and mixed disease) (1).

Finally, it will also be useful for future studies to analyze cortical
bone, in addition to trabecular bone. Changes in the structure and
function of cortical bone may be of higher predictive value in
terms of fracture than those of trabecular bone (7).

Taken together, Bakkaloglu et al. (3) made the laudable at-
ttempt to improve the classification of renal osteodystrophy by
a detailed bone histomorphometry analysis that is based on the
TMV classification system and its possible prediction using
classical serum biochemistry parameters; however, the predic-
tion of TMV parameters by classical biochemistry alone re-
mains imperfect. The inclusion of more highly performing
markers of bone turnover and mineralization (8,9), together
with noninvasive skeletal imaging procedures (10), may allow
a better discrimination of the different types of renal osteodys-
trophy and their significance for patient treatment and out-
comes in the future.

Table 1. TMV classification system for renal
osteodystrophy

<table>
<thead>
<tr>
<th>Turnover</th>
<th>Mineralization</th>
<th>Volume</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low</td>
<td>Normal</td>
<td>Low</td>
</tr>
<tr>
<td>Normal</td>
<td>Abnormal</td>
<td>Normal</td>
</tr>
<tr>
<td>High</td>
<td></td>
<td>High</td>
</tr>
</tbody>
</table>

TMV, bone turnover, mineralization, and volume. Reproduced from Moe et al. (reference 2), with permission.

Disclosures

None.

References

1. Kidney Disease: Improving Global Outcomes (KDIGO)
CKD-MBD Work Group: KDIGO clinical practice guide-
line for the diagnosis, evaluation, prevention, and treat-
ment of chronic kidney disease-mineral and bone disorder
2. Moe S, Drukeke T, Cunningham J, Goodman W, Martin K,
Olgaard K, Ott S, Sprague S, Lameire N, Eknoyan G,
Kidney Disease: Improving Global Outcomes (KDIGO):
Definition, evaluation, and classification of renal osteodys-
trophy: A position statement from Kidney Disease: Im-
1953, 2006
3. Bakkaloglu SA, Wesseling-Perry K, Pereira RC, Gales B,
Wang H-J, Elashoff RM, Salusky IB: Value of the new bone
classification system in pediatric renal osteodystrophy.
Segre G, Goodman W: Renal bone disease in pediatric and
young adult patients on hemodialysis in a children’s hos-
5. Barreto FC, Barreto DV, Monier-Faugere MC, Gil C, Galvao
ME, Draibe SA, Carvalho AB: K/DOQI-recom-
mdended intact PTH levels do not prevent low-turnover
bone disease in hemodialysis patients. Kidney Int 73: 771–
777, 2008
6. Ferreira A, Frazão JM, Monier-Faugere MC, Gil C, Galvao
J, Oliveira C, Balsaia J, Rodrigues I, Santos C, Ribeiro S,
Hoenger RM, Duggal A, Malluche HH, Sevelamer Study
Group: Effects of sevelamer hydrochloride and calcium
carbonate on renal osteodystrophy in hemodialysis pa-
7. Ott SM: Review article: Bone density in patients with
chronic kidney disease stages 4–5. Nephrology (Carlton) 14:
395–403, 2009
8. Herberth J, Monier-Faugere MC, Mawad HW, Branscum
most commonly used intact parathyroid hormone assays
are useful for screening but not for diagnosing bone turn-
over abnormalities in CKD-5 patients. Clin Nephrol 72:
5–14, 2009
9. Zidehsarai MP, Moe SM: Review article: Chronic kidney
disease-mineral bone disorder: Have we got the assays
right? Nephrology (Carlton) 14: 374–382, 2009
10. Adragao T, Herberth J, Monier-Faugere MC, Branscum AJ,
Ferreira A, Frazao JM, Malluche HH: Femoral bone min-
eral density reflects histologically determined cortical bone
volume in hemodialysis patients. Osteoporos Int 21: 619–
625, 2010

See related article, “Value of the New Bone Classification System in Pediatric Renal Osteodystrophy,” on pages 1860–1866.