WHAT’S NEW IN THE 2017 KDIGO CKD-MBD GUIDELINE UPDATE?

David Wheeler,
University College London, UK
KDIGO Co-Chair
DISCLOSURES:

• Honoraria and/or travel support from: Akebia, Amgen, AstraZeneca, Boehringer Ingelheim, Vifor Fresenius Medical Care, and Janssen.
Improve the care and outcomes of kidney disease patients worldwide through the development and implementation of clinical practice guidelines.
Systematic review

Evidence Review Team

Guideline Writing Group

Formulate question
Select outcomes
Rate importance
Outcomes across studies
Create evidence profile
Rate quality of evidence for each outcome

P I C O

Outcome Critical
Outcome Critical
Outcome Important
Outcome Not important

Randomization increases initial quality

1. Risk of bias
2. Inconsistency
3. Indirectness
4. Imprecision
5. Publication bias

Grade down
Grade up

1. Large effect
2. Dose response
3. Confounders

Summary of findings & estimate of effect for each outcome

Grade overall quality of evidence across outcomes based on lowest quality of critical outcomes

Formulate recommendations:
• For or against (direction)
• Strong or weak/conditional (strength)

By considering:
- Quality of evidence
- Balance benefits/harms
- Values and preferences

Revise if necessary by considering:
- Resource use (cost)

• “We recommend using…”
• “We suggest using…”
• “We recommend against using…”
• “We suggest against using…”

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Defining CKD-MBD

The concept of CKD-MBD was first suggested at a KDIGO Controversies Conference on "renal osteodystrophy" held in Madrid in 2005, developed the definition of CKD-MBD.
THE CKD-MBD PARADIGM:

- Abnormal bone:
  - Turnover
  - Mineralisation
  - Volume

- LV hypertrophy
- Calcification

Cardiovascular Disease

Bone Disease

Secondary HPT

Laboratory Abnormalities

- Elevated
  - PTH
  - Phosphorus
  - FGF-23
  - Alkaline phosphatase

- Decreased
  - \(1,25(OH)_2D_3\)
  - Calcium

Adapted from KDIGO CKD-MBD Work Group. Kidney Int 2009;76(Suppl 113):S1–130
KDIGO CKD-MBD GUIDELINE UPDATE

August 2009

July 2017
Overview of proposed changes

- **Selective update in red**
- **Minor changes in dark grey**
- **No changes in black and white**
CKD-MBD GUIDELINE UPDATE 2017

Guideline Chairs
Markus Ketteler (Germany)
Mary B Leonard (USA)

Work Group
- Geoffrey A. Block (USA)
- Pieter Evenepoel (Belgium)
- Masafumi Fukagawa (Japan)
- Charles A. Herzog (USA)
- Linda McCann (USA)
- Sharon M. Moe (USA)
- Rukshana Shroff (UK)
- Marcello A. Tonelli (Canada)
- Nigel D. Toussaint (Australia)
- Marc G. Vervloet (Netherlands)
Summary and comparison of 2017 updated and 2009 KDIGO CKD-MBD recommendations

2017 revised KDIGO CKD-MBD recommendations

3.2.1. In patients with CKD G4-S5 with evidence of CKD-MBD and/or risk factors for osteoporosis, we suggest BMI testing to assess fracture risk if results will impact treatment decisions (2B).

3.2.2. In patients with CKD G4-S5, it is reasonable to perform a bone biopsy if knowledge of the specific etiology will impact treatment decisions (Not Graded).

3.2.3. In patients with CKD G4-S5, it is reasonable to perform a bone biopsy in certain settings including, but not limited to, unexplained fractures, persistent bone pain, unexplained hyperparathyroidism, unexplained hypophosphatemia, possible aluminum toxicity, and prior to therapy with bisphosphonates in patients on CKD-MBD therapy (Not Graded).

4.1. In patients with CKD G1-G3, the treatments of CKD-MBD should be based on weekly assessment of phosphorus, calcium, and PTH levels, considered together (Not Graded).

4.2. In patients with CKD G4-S5, we suggest lowering elevated phosphate levels toward the normal range (2C).

4.3. In adult patients with CKD G4-S5, we suggest avoiding hyperparathyroidism (2C).

4.4. In patients with CKD G4-S5, we suggest monitoring serum calcium in the age-appropriate normal range (2C).

4.5. In patients with CKD G5-D4, we suggest using a dialysate calcium concentration between 1.25 and 1.50 mmol/L (1.5-3.0 mEq/L) (2D).

4.6. In patients with CKD G4-S5, we suggest deciding on adequacy of treatment on non-anionic fraction of iPTH (2C).

2009 KDIGO CKD-MBD recommendations

Brief rationales for updating

Multiple new prospective studies have documented that low iCaBMD predicts incident fractures in patients with CKD G1-G3. The order of these first 2 recommendations was changed because a DRA BMD might impact the decision to perform a bone biopsy.

The primary motivation for this revision was the growing experience with osteoporosis medications in patients with CKD G1-G3, and a high risk of fracture. The inability to perform a bone biopsy may not justly withhold osteoporosis therapy from patients at high-risk of fracture.

This new recommendation was in order to emphasize the complexity and interaction of CKD-MBD laboratory parameters.

There is an absence of data supporting that the fracture risk is directly related to the PTH level. In this context, the serum PTH is not the major contributor to the serum calcium.

In normal circumstances, treatment is recommended to adjust the serum calcium level. In the context of renal hyperparathyroidism, mild and asymptomatic hyperparathyroidism (e.g., in the context of calcium-sensing receptor) can be tolerated in order to avoid inappropriate calcium loading in adults.

Additional studies of better quality are available; however, these do not allow for the distinction of benefits and harms between calcium dialysate concentrations of 1.25 and 1.50 mmol/L (1.5-3.0 mEq/L). Hence, the wording is unchanged, but the evidence-grade is updated to 2C.

Emphasizes the perception that early treatment with phosphate-lowering treatment is currently not supported by data (see Recommendation 4.2). It is reasonable to consider the choice of phosphate-binding agents based on the risk of fracture (see above). The broad term "phosphate-lowering therapy" should be used to include calcium-based phosphate binders and vitamin D analogs as well as other classes of phosphate binders (2C).

(Continued on next page)

2017 revised KDIGO CKD-MBD recommendations

4.1.6. In adult patients with CKD G4-S5 undergoing phosphate-lowering treatment, we suggest restricting the dose of calcium-based phosphate binder (UB) in patients with CKD G4-S5; it is reasonable to base the choice of phosphate-lowering treatment on serum calcium levels (Not Graded).

4.1.7. In patients with CKD G4-S5 and hyperparathyroidism, we suggest restricting the dose of calcium-based phosphate binder in the presence of intact PTH (2C) and/or alkaline phosphatase (2C) and/or if serum PTH levels are persistently low (2C).

4.2.1. In patients with CKD G3-S5 not on dialysis, the optimal PTH level is not known. However, we suggest that patients with levels of intact PTH progressively rising or persistently above the upper normal limit for the assay be evaluated for modification factors, including hyperparathyroidism, vitamin D insufficiency, and other modifiable factors (GFR, calcium intake, vitamin D intake) (GFR).

4.2.2. In adult patients with CKD G4-S5 not on dialysis, we suggest that calcium and vitamin D analogs not be used in patients with levels of intact PTH persistently above the upper limit of normal for the assay despite correction of modifiable factors, we suggest treatment with calcium carbonate or vitamin D analogs (U).

4.2.3. In patients with CKD G3-S5 not on dialysis, we suggest that calcitriol and vitamin D analogs be used in patients with levels of intact PTH persistently below the lower normal limit for the assay despite correction of modifiable factors, we suggest treatment with calcitriol or vitamin D analogs (U).

4.4. In patients with CKD G4-S5 requiring PTH-lowering therapy, we suggest calcimimetics, calcium carbonate, or calcium acetate or a combination of calcium-based phosphate binders with calcitriol or vitamin D analogs (UB).

4.4.1. In patients with CKD G3-S5 and elevated or rising PTH, we suggest calcitriol or vitamin D analogs, unless calcium phosphate binders have been shown to be effective in lowering PTH in CKD patients (UB).

4.4.2. In patients with CKD G4-S5 and elevated or rising PTH, we suggest calcitriol or vitamin D analogs, unless calcium phosphate binders have been shown to be effective in lowering PTH in CKD patients (UB).

New data on phosphate sources were deemed not sufficient to prompt major updates to the previous recommendation.

4.4.3. In patients with CKD G4-S5 and hyperparathyroidism, we suggest restricting the dose of calcium-based phosphate binders in order to reduce serum calcium levels (2C) and/or if serum PTH levels are persistently low (2C).

4.4.4. In patients with CKD G4-S5 and hyperparathyroidism, we suggest restricting the dose of calcium-based phosphate binders in order to reduce serum calcium levels (2C) and/or if serum PTH levels are persistently low (2C).

The Work Group felt that modest increases in PTH may represent an appropriate adaptive response to declining kidney function and has revised this statement to include "persistent" above the upper normal PTH level as well as "progressively rising" PTH levels, rather than "above the upper normal limit." That treatment should not be based on a single elevated value.

Recent ICHs of vitamin D analogs failed to demonstrate improvements in clinically relevant outcomes and potentially increased risk of hypercalcemia.

4.4.5. In patients with CKD G4-S5 requiring PTH-lowering therapy, we suggest calcimimetics, calcium carbonate, or calcium acetate or a combination of calcium-based phosphate binders with calcitriol or vitamin D analogs (UB).

4.4.6. In patients with CKD G3-S5 and elevated or rising PTH, we suggest calcitriol or vitamin D analogs, unless calcium phosphate binders have been shown to be effective in lowering PTH in CKD patients (UB).

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This recommendation originated not having been suggested for updating by the KDIGO Compilations Committee in 2013. However, due to a subsequent series of secondary and post hoc publications of the EKOS trial, the Work Group decided to reevaluate the recommendation. 24.4.2 as an update. Although EKOS did not meet its primary endpoint, the majority of the Work Group members were reluctant to exclude potential benefits of calcimimetics for CKD patients based on subsequent prespecified analyses. The Work Group, however, decided not to prioritize any PTH-lowering treatment at this time because calcimimetics, calcium carbonate, or vitamin D analogs are all acceptable first-line options in CKD patients.

Recent data on phosphate sources were deemed not sufficient to prompt major updates to the previous recommendation.
GUIDELINE TOPICS

Topic 1: Bone Quality
Topic 2: Serum phosphate
**Topic 3:** Serum calcium
Topic 4: Dialysate calcium
Topic 5: Phosphate binders
Topic 6: Dietary phosphate intake
**Topic 7:** Vitamin D and PTH
Topic 8: Vascular calcification
Topic 9: Parathyroid hormone range
OLD 4.1.2: In patients with CKD G3a–G5D, we suggest maintaining serum calcium in the normal range (2D).

NEW 4.1.3: In adult patients with CKD G3a–G5D, we suggest avoiding hypercalcemia (2C).

In children with CKD G3a–G5D, we suggest maintaining serum calcium in the age-appropriate normal range (2C).
**Primary endpoint**

Time to the primary composite endpoint comprising: all-cause mortality or nonfatal CV events (myocardial infarction, hospitalisation for unstable angina, heart failure or peripheral vascular event)

**Secondary endpoints**

Fracture, PTX, CV death, stroke; components of primary composite endpoint
EVOLVE*: BIOCHEMICAL PARAMETERS (ITT)

*EVOLVE did not meet its primary end point
OLD: 4.1.3 In patients with CKD G5D, we suggest using a dialysate calcium concentration between 1.25 and 1.50 mmol/l (2.5 and 3.0 mEq/l) (2D).

NEW: 4.1.4: In patients with CKD G5D, we suggest using a dialysate calcium concentration between 1.25 and 1.50 mmol/l (2.5 and 3.0 mEq/l) (2C).
## Grading System

<table>
<thead>
<tr>
<th>Descriptor</th>
<th>Recommendation grading</th>
<th>Quality of evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Level 1</td>
<td>“We recommend”</td>
<td></td>
</tr>
<tr>
<td>Level 2</td>
<td>“We suggest”</td>
<td></td>
</tr>
<tr>
<td>Not graded</td>
<td>Based on common sense</td>
<td></td>
</tr>
<tr>
<td>A</td>
<td></td>
<td>High</td>
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<tr>
<td>B</td>
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<td>Moderate</td>
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<tr>
<td>C</td>
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<td>Low</td>
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<tr>
<td>D</td>
<td></td>
<td>Very Low</td>
</tr>
</tbody>
</table>
TRIAL OF 2 DIALYSIS CALCIUM CONCENTRATIONS

Population: 431 HD patients with PTH < 300 pg/ml
Intervention: 1.25 mmol/l calcium bath vs. 1.75 mmol/l calcium bath
Primary Outcome: Coronary calcification (CAC) scores
Secondary Outcome: Bone histomorphometry
Follow-up: 24 months

“At 24 months, bone formation rate, trabecular thickness, and bone volume were higher in the 1.25 Calcium group than in the 1.75 Calcium group.”

OLD 4.1.7: In patients with CKD G3a–G5D, we suggest limiting dietary phosphate intake in the treatment of hyperphosphatemia alone or in combination with other treatments (2D).

NEW 4.1.8: In patients with CKD G3a–G5D, we suggest limiting dietary phosphate intake in the treatment of hyperphosphatemia alone or in combination with other treatments (2D).

It is reasonable to consider phosphate source (e.g., animal, vegetable, additives) in making dietary recommendations. (Not Graded)
**TOPIC 6: DIETARY PHOSPHATE INTAKE**

9 patients, eGFR 30 ml/min/1.73 m²
7-day crossover trial\(^1\)

<table>
<thead>
<tr>
<th>Measurement</th>
<th>Meat (casein) diet</th>
<th>Vegetarian (grain) diet</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Before</td>
<td>After</td>
<td>Before</td>
</tr>
<tr>
<td>Daily PO(_4) (mg/day)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>810 ± 27</td>
<td>795 ± 51</td>
<td>NS</td>
</tr>
<tr>
<td>Plasma PO(_4) (mg/day)</td>
<td>3.5 ± 0.6</td>
<td>3.7 ± 0.6</td>
<td>3.5 ± 0.6</td>
</tr>
<tr>
<td>Plasma iPTH (pg/ml)</td>
<td>58 ± 31</td>
<td>46 ± 29</td>
<td>58 ± 39</td>
</tr>
<tr>
<td>Plasma FGF23 (pg/ml)</td>
<td>72 ± 39</td>
<td>101 ± 83</td>
<td>84 ± 65</td>
</tr>
<tr>
<td>Plasma Ca (mg/dl)</td>
<td>9.2 ± 0.4</td>
<td>9.4 ± 0.7</td>
<td>9.3 ± 0.4</td>
</tr>
<tr>
<td>Urine CA exc. (mg/day)</td>
<td>66 ± 69</td>
<td>77 ± 48</td>
<td>60 ± 59</td>
</tr>
<tr>
<td>Urine PO(_4) exc. (mg/day)</td>
<td>836 ± 187</td>
<td>583 ± 216</td>
<td>778 ± 190</td>
</tr>
</tbody>
</table>

Phosphate/protein ratio (mg/g) in processed vs unprocessed meat products\(^2\)

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

NEW 4.2.4: In patients with CKD G5D requiring PTH-lowering therapy, we suggest calcimimetics, calcitriol, or vitamin D analogs, or a combination of calcimimetics with calcitriol or vitamin D analogs (2B).
EVOLVE STUDY: PRIMARY OUTCOME (ITT ANALYSIS)

Hazard ratio: 0.93 (95% CI: 0.85–1.02)
Log-rank, p=0.112

The EVOLVE trial Investigators NEJM 2012;367:2482-94
After adjustment for baseline characteristics, the relative hazard for the primary composite end point was 0.88 (95% CI, 0.79 to 0.97; \( P = 0.008 \)).

When censored after kidney transplantation, parathyroidectomy, or use of commercially available cinacalcet, relative hazards for the primary composite end point was 0.90 (95% CI, 0.82 to 0.99; \( P = 0.03 \)).
1. In the context of calcimimetic therapy, hypocalcaemia may be difficult to avoid and does not seem to be associated with harm.

2. In a small randomized controlled trial, a dialysate calcium of 1.25 mmol/l (as compared to 1.75 mmol/l) was associated with better bone formation and less arterial calcification.

3. Plant-based foods are less likely than meat-based foods to contribute to hyperphosphataemia. Food additives may contain large amounts phosphate.

4. In a randomized controlled trial, cinaclacet did not show superiority over placebo in terms of death and CV events.