Contents

Introduction

Summary of Clinical Practice Guidelines in CKD-MBD

1.1 CKD-MBD: Monitoring of biochemical parameters
2.1 CKD-MBD: Serum calcium in patients with CKD 3-5 (not on dialysis)
2.2 CKD-MBD: Serum calcium in dialysis patients (stage 5D)
3.1 CKD-MBD: Serum phosphate in patients with CKD 3-5 (not on dialysis)
3.2 CKD-MBD: Serum phosphate in dialysis patients (stage 5D)
4.1 CKD-MBD: Serum PTH in patients with CKD 3b-5 (not on dialysis)
4.2 CKD-MBD: Serum PTH in patients on dialysis (stage 5D)

Summary of Audit Measures (1-4)

Rationale for Clinical Practice Guidelines in CKD-MBD

1.1 CKD-MBD: Monitoring of biochemical parameters
2.1 CKD-MBD: Serum calcium in patients with CKD 3-5 (not on dialysis)
2.2 CKD-MBD: Serum calcium in dialysis patients (stage 5D)
3.1 CKD-MBD: Serum phosphate in patients with CKD 3-5 (not on dialysis)
3.2 CKD-MBD: Serum phosphate in dialysis patients (stage 5D)
4.1 CKD-MBD: Serum PTH in patients with CKD 3b-5 (not on dialysis)
4.2 CKD-MBD: Serum PTH in patients on dialysis (stage 5D)

Declaration of conflict interest

Dr Edward Sharples – received travel grants from Alexion and Amgen
Dr Simon Steddon- no conflicts of interests to declare
Introduction

This is a review of the 5th edition Renal Association guidelines chapter on CKD-MBD. The current guideline was published in the period following release of the KDIGO guidelines which prompted changes in guidelines around the world. For this updated version, a systematic literature review was performed using www.pubmed.gov, focusing on the topics of:

Mineral bone disorder
Renal osteodystrophy
Hyperphosphat(a)emia
Calcium
PTH
Vascular calcification
Phosphate binder

The search covered the period from Dec 2009 to October 2013. Articles not written in English were not assessed. Articles available in abstract forms; letters; case reports; editorials or review articles were also excluded. Articles were assessed for relevance to the guideline topic, eligibility for inclusion in the evidence base for that guideline and methodological quality. Articles were considered of particular relevance if they were describing:

- Meta-analysis of several trials
- Cochrane systematic reviews
- Prospective randomized trials
- NICE clinical guidelines

As with other Renal Association Clinical Practice Guidelines, the modified GRADE (Grades of recommendation, assessment, development and evaluation) system is used throughout. This system defines both the strength of the recommendations and the level of evidence upon which each is based (1). It classifies recommendations as “strong” (Grade 1) or “weak” (Grade 2) based upon benefits, risks, burden and cost. The quality or level of evidence is designated as high (Grade A), moderate (Grade B), low (Grade C) or very low (D) depending on factors such as study design, directness of evidence and consistency of results.
References


Summary of Clinical Practice Guidelines on CKD-MBD

1. CKD-Mineral and Bone Disorders (Guideline CKD-MBD 1.1)

Guideline 1.1 CKD-MBD: Monitoring of biochemical parameters

We suggest that serum levels of calcium, phosphate, alkaline phosphatase, PTH and calcidiol (25(OH) D₃) should be monitored in patients with CKD stage 3-5, and patients on dialysis, with a frequency based on stage, rate of progression and whether specific therapies have been initiated. In general, it is recommended that therapeutic decisions are based on the clinical situation, and trends in parameters, rather than a single laboratory value, as part of the entire available dataset, (not graded).

2. CKD-Mineral and Bone Disorders (Guidelines CKD-MBD 2.1-2.2)

Guideline 2.1 CKD-MBD: Serum calcium in patients with CKD stage 3-5 (not on dialysis)

We suggest that serum calcium, adjusted for albumin concentration, in patients with CKD stage 3-5 should be kept within the normal reference range for the laboratory used (2D).

Guideline 2.2 CKD-MBD: Serum calcium in dialysis patients (stage 5D)

We suggest that serum calcium, adjusted for albumin concentration, should be maintained within the normal reference range for the laboratory used, measured before a “short-gap” dialysis session in haemodialysis patients. Ideally, adjusted serum calcium should be maintained between 2.2 and 2.5 mmol/L, with avoidance of hypercalcaemic episodes (2D).

3. CKD-Mineral and Bone Disorders (Guidelines CKD-MBD 3.1-3.2)

Guideline 3.1 CKD-MBD: Serum phosphate in patients with CKD 3-5 (not on dialysis)

We suggest that serum phosphate in patients with CKD stage 3b-5 should be maintained between 0.9 and 1.5 mmol/L (2C).

Guideline 3.2 CKD-MBD: Serum phosphate in dialysis patients (stage 5D)

We suggest that serum phosphate in dialysis patients, measured before a “short-gap” dialysis session in haemodialysis patients, should be maintained between 1.1 and 1.7 mmol/L (2C).

4. CKD-Mineral and Bone Disorders (Guidelines CKD-MBD 4.1-4.2)

Guideline 4.1 CKD-MBD: Serum PTH in patients with CKD 3b-5 (not on dialysis)

We suggest that treatment is considered in patients with CKD stages 3b-5 not on dialysis therapy in whom serum PTH levels are progressively increasing and remain persistently higher than the upper reference limit for the assay, despite correction of modifiable factors (2C).
Guideline 4.2 CKD-MBD: Serum PTH in patients on dialysis (stage 5D)

We suggest that the target range for parathyroid hormone measured using an intact PTH assay should be between 2 and 9 times the upper limit of normal for the assay used (2C).

We suggest that marked changes in PTH levels in either direction within this range should prompt an initiation or change in therapy to avoid progression to levels outside this range (2C).

Summary of Audit Measures in CKD-MBD

Percentage of patients with all bone parameters within target range (Ca/P/PTH)

Percentage of patients CKD5D with serum PO4 <1.7 mmol/l
Rationale for Clinical Practice Guidelines in CKD-MBD

1. CKD-Mineral and Bone Disorders (Guideline CKD-MBD 1.1)

Guideline 1.1 CKD-MBD: Monitoring of biochemical parameters

We suggest that serum levels of calcium, phosphate, alkaline phosphatase, PTH and calcidiol (25(OH) D₃) in patients with CKD stage 3-5, should be monitored, with a frequency based on stage, rate of progression and whether specific therapies have been initiated. In general, it is recommended that therapeutic decisions are based on trends, rather than a single laboratory value, and that they take into account the entire available data set, rather than isolated variables (ungraded).

Rationale

Abnormal biochemical parameters of CKD-MBD can be observed relatively early in the progression of chronic kidney disease, although the rate of change and severity of abnormalities are highly variable among patients. Evidence from large observation studies, including the STEEKD (Study to Evaluate Early Kidney Disease) which included 1800 patients with CKD stages 3-5, demonstrate that although PTH may be elevated at eGFR>80 mL/min, the prevalence of hyperphosphataemia is relatively rare until eGFR falls below 30 mL/min (1). A similar prevalence of hypocalcaemia was observed.

There is still no data showing that routine measurement of bone parameters improves patient outcomes. However, it is reasonable to suggest that these parameters are measured with frequency of monitoring based on stage, rate of progression and whether specific therapies have been initiated. A suggested frequency of monitoring is suggested in table 1, but will depend on initial values, trends of change and whether there have been adjustments to treatment. Alkaline phosphatase is a useful adjunct test and may increase the predictive power of biochemical monitoring when taken into consideration concomitantly with PTH (2).

Although the prevalence of mild hyperparathyroidism in people with a reduced GFR is higher than normal kidney function, the significance of such modest elevations in PTH concentration remains unknown (3). There are also cost and logistical implications for the routine measurement of serum PTH in all CKD stage 3. This is reflected in NICE guidance not to measure unless there is another clinical indication such as hypercalcaemia, or symptoms suggestive of hyperparathyroidism (4). However, such problems often occur late or are difficult to identify. A pragmatic approach is to measure serum PTH at baseline in all those with progressive CKD stage 3b or higher, as values in need of therapeutic attention are more likely to be identified.

Justification for the identification and treatment of vitamin D ‘substrate’ deficiency assumes independent benefits for non-activated vitamin D (ergocalciferol, colecalciferol) through tissue conversion of 25-hydroxyvitamin D (calcidiol) to 1,25-dihydroxyvitamin D (calcitriol). Vitamin D insufficiency appears common in the CKD population, perhaps the consequence of co-
morbidity limiting access to sunlight, and may be a cause of early increases in PTH concentration (3). In addition, numerous observational studies show an association between low vitamin D levels and adverse clinical outcomes, although randomised trial evidence remains inconclusive (5). Although the benefits are unconfirmed, a reasonable case exists for the measurement of vitamin D in CKD. A pragmatic approach is to measure 25-hydroxyvitamin D at baseline in CKD stage 3b and above, with a view to correction of insufficiency or deficiency (>75nmol/L = repletion, 37.5 -75nmol/L = insufficiency, <37.5nmol/L = deficiency). Vitamin D levels need to be interpreted in the context of the patient's overall clinical condition, other biochemical abnormalities, and the pre-existing therapy. Repeat testing will be determined by baseline value and therapeutic interventions. There is insufficient evidence to suggest measurement or repletion in patients who are already receiving an active vitamin D sterol such as calcitriol, alfacalcidol, or paricalcitol, in whom the strength of the relationship with outcome is reduced. It must be pointed out, however, that repletion strategies are currently ill-defined and may actually have very little effect on vitamin D stores.

Table 1: Suggested frequency of biochemical testing in CKD-MBD.

<table>
<thead>
<tr>
<th>CKD stage</th>
<th>Calcium</th>
<th>Phosphorus</th>
<th>PTH</th>
<th>Alkaline phosphatase</th>
<th>Calcidiol (25(OH)D)</th>
</tr>
</thead>
<tbody>
<tr>
<td>3b</td>
<td>Every 6-12 months</td>
<td>Every 6-12 months</td>
<td>Baseline</td>
<td>Every 6-12 months</td>
<td>Baseline</td>
</tr>
<tr>
<td>Progressive</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>Every 3-6 months</td>
<td>Every 3-6 months</td>
<td>Every 6-12 months</td>
<td>Every 3-6 months</td>
<td>Baseline*</td>
</tr>
<tr>
<td>5</td>
<td>Every 1-3 months</td>
<td>Every 1-3 months</td>
<td>Every 3-6 months</td>
<td>Every 1-3 months</td>
<td>Baseline*</td>
</tr>
<tr>
<td>5D</td>
<td>Every 1-3 months</td>
<td>Every 1-3 months</td>
<td>Every 3-6 months</td>
<td>Every 1-3 months</td>
<td>Baseline*</td>
</tr>
</tbody>
</table>

*If not receiving an active vitamin D sterol such as calcitriol, alfacalcidol, or paricalcitol.
References


2. **CKD-Mineral and Bone Disorders (Guidelines CKD-MBD 2.1-2.2)**

**Guideline 2.1 CKD-MBD: Serum calcium in patients with CKD stage 3-5 (not on dialysis)**

We suggest that serum calcium, adjusted for albumin concentration, in patients with CKD stage 3-5 should be kept within the normal reference range for the laboratory used (2D).

**Guideline 2.2 CKD-MBD: Serum calcium in dialysis patients (stage 5D)**

We suggest that serum calcium, adjusted for albumin concentration, should be maintained within the normal reference range for the laboratory used, measured before a “short-gap” dialysis session in haemodialysis patients. Ideally, adjusted serum calcium should be maintained between 2.2 and 2.5 mmol/L, with avoidance of hypercalcaemic episodes (2D).

**Rationale (for 2.1-2.2)**

The measurement of serum calcium, adjusted for albumin concentration, is susceptible to all the problems of inter-assay variation, and in addition, there are several different formulae for corrected for albumin concentration. Calcium should be controlled to avoid symptomatic hypocalcaemia and hypocalcaemia driven stimulation of the parathyroid glands. There is some evidence that, in addition to known associations between hyperphosphataemia and mortality, calcium concentrations have an independent association with relative mortality risk (1). In a large retrospective review of over 40,000 haemodialysis patients, all-cause mortality was relatively
higher the higher the corrected calcium level, after adjustment for gender, age, dialysis vintage and diabetes (2).

Observational data from the DOPPS study (3) show a similar relationship between calcium and mortality. In 17,236 haemodialysis patients from 307 participating centres in the US, Europe and Japan, all-cause mortality was associated with an increased RR for each 0.25 mmol/L increase in calcium. There was an increased relative risk associated with calcium levels less than 2.2 mmol/L. With this observation data, and in the absence of randomised controlled trials demonstrating reduced mortality associated with corrected calcium at the lower end of the normal range, we do not recommend the serum calcium should be below 2.2 mmol/L. Cumulative time dependent analysis of the DOPPS study shows that calcium values >2.65 are associated with significant hazard ratio for all-cause mortality (1.66 (1.09-2.55)).

This association has been confirmed in the COSMOS study (4). This observational study of 6797 patients from 20 European countries examined the association between management of CKD-MBD and survival on dialysis. Although the primary outcome was that prescription of phosphate binders was associated with a lower relative risk of all-cause mortality, the investigators also performed an analysis of target ranges for biochemical parameters, based on the mortality risk analysis. The optimum calcium range was 7.6-9.2 mg/dl (1.80-2.35 mmol/l), lower than the ranges in the current RA guidelines and KDIGO. This suggests that a lower target range, perhaps to reduce further the incidence of hypercalcaemia, may be beneficial.

There is evidence that calcium load and episodes of hypercalcaemia are associated with a relative increase in vascular calcification and arterial stiffness, although, at present, randomised controlled trials of non-calcium binders versus calcium binders have not demonstrated a significant reduction in mortality, despite a reduction in the amount, and progression, of vascular calcification. A meta-analysis of the effect of calcium-based versus non-calcium based phosphate binders on mortality examined 18 studies (11 randomised trials) showed that patients assigned to non-calcium binders had a 22% reduction in all-cause mortality compared to those assigned to calcium based phosphate binders (5). This is a stronger negative association than a previous meta-analysis, in part due to the addition of new trials including lanthanum. A potential confounder with more recent trials is the potential effect of more widespread use of cinacalcet. This mirrors the observations in large trials in the general population where there is strong association between high-dose calcium supplementation and cardiovascular mortality, confirmed recently in a large meta-analysis (6).

References


### 3. CKD-Mineral and Bone Disorders (Guidelines CKD-MBD 3.1-3.2)

**Guideline 3.1 CKD-MBD: Serum phosphate in patients with CKD 3-5 (not on dialysis)**

We suggest that serum phosphate in CKD patients stage 3b-5 should be maintained between 0.9 and 1.5 mmol/L (2C).

**Guideline 3.2 CKD-MBD: Serum phosphate in dialysis patients (stage 5D)**

We suggest that serum phosphate in dialysis patients, measured before a “short-gap” dialysis session in haemodialysis patients, should be maintained between 1.1 and 1.7 mmol/L (2C).

**Rationale (for 3.1-3.2)**

Hyperphosphataemia is one of the commonest biochemical abnormalities through the course of CKD and poses significant challenges for management. Epidemiological and observational studies have shown an association between hyperphosphataemia and mortality in dialysis patients. A systematic review of the evidence of an association between hyperphosphataemia and mortality confirmed that, despite wide heterogeneity between studies, there was a clear association between hyperphosphataemia and mortality in both haemodialysis and peritoneal dialysis patients (3). The cut-off value for this association was between 1.5 - 2.4 mmol/L, as individual studies used different reference ranges, which limiting potential for accurate meta-analysis. The 2012 Renal Registry report shows that for haemodialysis patients median phosphate is 1.5, and there has been a progressive lowering of median concentrations over time. This epidemiological evidence is consistent with substantial laboratory data from both cell culture and animal studies that demonstrate a role for hyperphosphataemia in the induction of vessel changes contributing to vascular calcification and altered compliance.

However, recent studies have questioned the strength of this association, especially in early CKD. Mehrotra et al examined 10672 patients with early CKD in the Kidney Early Evaluation Program (KEEP) study. Over a median follow-up of 2.3 years, there was no association between quartiles of phosphate and all-cause mortality. There was a associated between higher quartiles of
phosphate and progression to ESRD, although this associated became non-significant after full adjustment for potential confounders (4).

Management remains difficult, particularly as there remain no randomised controlled trials of the benefits of phosphate lowering on patient survival. There is no specific evidence that lowering serum phosphate to a particular level leads to an improved clinical outcome in patients with CKD, so recommended treatment goals continue to be grounded on evidence from observational data. In view of this, there is no evidence to alter the current suggested upper target limit, despite the low level of evidence. In support, a retrospective US study of 13,792 patients on haemodialysis demonstrated a reduced relative risk of mortality in patients who achieved serum phosphate concentrations within the K/DOQI guideline range, when compared to patients who did not achieve target. It is worth assessing target ranges as a composite including PTH and calcium, as the hazard of mortality or cardiovascular hospitalisations is altered by interaction between these parameters (5).

There is also insufficient data from randomised controlled trials that any specific oral phosphate binder impacts on individual patient outcome, and hence the choice of oral binders should be individualized, based on the effects of available agents on a range of clinical parameters. The largest randomised trial, the Dialysis Clinical Outcomes Revisited (DCOR) study randomised 2103 patients to either sevelamer or a calcium-based phosphate binder, with a mean follow-up of 20 months (6). There was no difference in all-cause or cardiovascular mortality between the two binders (sevelamer arm: mortality 15.0/100 patient years, calcium arm: 16.1/100 patient years, HR 0.93 (0.79-1.1) P=0.4). There are concerns, however, that high doses of calcium binders are associated with worse outcomes. A recent large meta-analysis of the effect of calcium-based versus non-calcium based phosphate binders on mortality examined 18 studies (11 randomised trials) showed that patients assigned to non-calcium binders had a 22% reduction in all-cause mortality compared to those assigned to calcium based phosphate binders (5). This is a stronger negative association than a previous meta-analysis, in part due to the addition of new trials including lanthanum. A potential confounder with more recent trials is the potential effect of more widespread use of cinacalcet. This mirrors the observations in large trials in the general population where there is strong association between high-dose calcium supplementation and worse outcome (8). It would be reasonable to minimize calcium exposure but the desperate need for large scale clinical trials to clarify best management remains.

References


4. **CKD-Mineral and Bone Disorders (Guidelines CKD-MBD 4.1-4.2)**

**Guideline 4.1 CKD-MBD: Serum PTH in patients with CKD 3b-5 (not on dialysis)**

We suggest that treatment is considered in patients with CKD stages 3b-5 not on dialysis therapy in whom serum PTH levels are progressively increasing and remain persistently higher than the upper reference limit for the assay, despite correction of modifiable factors (2C).

**Guideline 4.2 CKD-MBD: Serum PTH in patients on dialysis (stage 5D)**

We suggest that the target range for parathyroid hormone measured using an intact PTH assay should be between 2 and 9 times the upper limit of normal for the assay used (2C).

We suggest that marked changes in PTH levels in either direction within this range should prompt an initiation or change in therapy to avoid progression to levels outside this range (2C).

**Rationale (for 4.1-4.2)**

These recommendations are in concordance with KDIGO (1). To date, no randomised controlled trial has examined whether treatment to achieve a specific PTH target will improve outcomes. In the pre-dialysis setting, optimal PTH concentration is unknown and it is sensible to evaluate those with values outside the reference range for contributory factors, such as hyperphosphataemia, hypocalcaemia, and ‘nutritional’ vitamin D deficiency. Treatment of these factors may reduce
PTH levels toward the reference range, or prevent further increases. Serum alkaline phosphatase may also provide useful information on bone turnover and response to therapy. If PTH levels increase progressively and remain higher than the reference range, treatment with active vitamin D is likely to be necessary.

In the dialysis population, the PTH target focuses on avoidance of risk at extremes of PTH; i.e. at <2x or >9x the upper limit of the normal reference range. The ‘multiplication’ reference range accommodates the significant variation in PTH levels between assays and laboratories. Intact PTH levels do not consistently predict bone histology, particularly if considered in isolation. The level at which PTH becomes significantly associated with increased all-cause mortality varies among studies from 400-600pg/mL (2-6). The use of cinacalcet to control hyperparathyroidism was studied in the EVOLVE trial, although it did not reach its primary outcome to demonstrate a reduction in all-cause mortality (2). EVOLVE randomised 3883 patients on haemodialysis to either cinacalcet or placebo. There was a small difference in age between the groups which acted as a confounder, and an age-adjusted outcome did demonstrate a small but significant reduction in relative risk in those patients taking cinacalcet. What is clear from EVOLVE is that it is an extremely effective treatment to control hyperparathyroidism, with reduction in the rate of parathyroidectomies. It is not known as yet how NICE will review their cinacalcet guidance based on the results of EVOLVE.

References

1. KDIGO Clinical Practice Guideline for the Diagnosis, Evaluation, Prevention, and Treatment of Chronic Kidney Disease-Mineral and Bone Disorder (Kidney International 2009, volume 76, supplement 113, s1-132)