

Guidelines for the management of chronic kidney disease-mineral and bone disorder (CKD-MBD)

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Summary

These guidelines are aimed at providing the doctors managing a child with chronic kidney disease (CKD) with information about interventions to minimise the effects on calcium and phosphate metabolism and the associated vascular and bone pathologies.

Introduction

The term chronic kidney disease-mineral and bone disorder (CKD-MBD) has been coined to describe the effects of renal dysfunction on calcium and phosphate homeostasis and the resultant detrimental effects on a number of systems, particularly bones and blood vessels.

This guideline outlines the measures available to reduce the effects of reduced renal function on these systems and the impact they have on long term cardiovascular and bone health. These interventions may also slow down the progression of renal dysfunction.

The primary source for this guideline is the document: KDIGO 2016 clinical practice guideline update on diagnosis, evaluation, prevention and treatment of CKD-MBD which included paediatric membership of the working group. This document is available at http://www.kdigo.org/clinical_practice_guidelines/CKD-MBD%20Update/KDIGO%20CKD-MBD%20Update_Public%20Review_Final.pdf

This is an update of a 2009 guideline.

Definitions

Definition of CKD–MBD

A systemic disorder of mineral and bone metabolism due to CKD manifested by either one or a combination of the following:

- Abnormalities of calcium, phosphorus, parathyroid hormone (PTH), or vitamin D metabolism.
- Abnormalities in bone turnover, mineralization, volume, linear growth, or strength.
- Vascular or other soft-tissue calcification.

Definition of renal osteodystrophy

- Renal osteodystrophy is an alteration of bone morphology in patients with CKD.
- It is one measure of the skeletal component of the systemic disorder of CKD–MBD that is quantifiable by histomorphometry of bone biopsy.

Background

The kidneys play a number of key roles in calcium and phosphate homeostasis:

- Excretion of phosphate
- Conversion of 25-hydroxycholecalciferol (25(OH)D) to 1,25-dihydroxycholecalciferol (1,25(OH)₂D)

The rise in serum phosphate concentration is key to the development of secondary hyperparathyroidism, acting independently of serum calcium and 1,25-dihydroxycholecalciferol. Hyperparathyroidism leads to stimulation of osteoclasts and bone resorption.

CKD-MBD is exacerbated by acidosis and therefore correction of acidosis is an important part of treatment.

The treatment of CKD-MBD is aimed at preventing the development of:

- bone resorption and renal osteodystrophy
- increased fracture risk
- vascular calcification
- cardiovascular disease

The important factors involved in CKD-MBD are:

- Phosphate
- Calcium
- Vitamin D
- PTH
- FGF-23

Monitoring

The tests we currently have available give only indirect evidence of bone health and CKD-MBD and therefore have to be interpreted with caution. The most accurate investigation is bone biopsy but this is not performed routinely. The tests available include:

- Serum calcium
- Ionized calcium (use iStat)
- Bicarbonate (serum sample must be processed quickly otherwise do gas, or use iStat)
- Serum phosphate
- Alkaline phosphatase
- PTH
- 25(OH)D
- 1,25(OH)₂D
- X ray
- DEXA scan

Target levels

- Serum calcium

This result tells us the concentration of total calcium in the serum. The calcium in the serum consists of the free, active, ionized calcium and that bound to proteins, mainly albumin. The laboratory gives two results:

1. Calcium – the total measured calcium in the serum
2. Adjusted calcium – this figure makes an adjustment based on the serum albumin. In cases of hypoalbuminaemia the result will be higher than the “calcium” figure reflecting that lower total calcium levels are needed to maintain the ionized calcium.

In CKD the effects of hyperphosphataemia and reduced 1,25(OH)₂D lead to hypocalcaemia. Hypocalcaemia leads to the increased stability of PTH mRNA, which increases the secretion of PTH and parathyroid cell proliferation. Calcium

levels are monitored via the calcium sensing receptor (CSR) on the parathyroid glands.

Treatment is aimed at maintain serum calcium in the upper half of the normal range (see below). There is a balance between the need to minimise the risks of long term complications of vascular calcification with the need to maintain a positive calcium balance to support the growing skeleton. Hypercalcaemia should be avoided.

Ionized calcium

As described above, the active calcium in the serum is in the free ionized form and this is therefore a better measure of calcium status. It is not routinely measured in the laboratory but can be requested or obtained using the iStat facility.

- Serum phosphate

Control of serum phosphate is key to management of CKD-MBD. CKD leads to hyperphosphataemia which in turn causes:

- Vascular calcification and cardiovascular disease
- Elevated PTH levels
- Skeletal resistance to PTH
- Reduced 1,25(OH)₂D
- Resistance of parathroids to 1,25(OD)₂D
- Parathyroid hyperplasia

Looking at adult data, the 2016 KDOQI update made the following comments:

- The association between serum phosphorus and clinical outcome is not monotonic there being a U-curve relationship between serum phosphorus and mortality
- There is a lack of demonstrated efficacy of phosphate binders for lowering serum phosphorus in people with CKD stages 3-4
- The safety of phosphate binders in this population is unproven

As a result of these statements, the Work Group abandoned the previous suggestion to maintain phosphorus in the normal range and has instead suggested to focus treatment on patients with hyperphosphatemia. They do recognize that preventing, rather than treating, hyperphosphatemia may be of value in patients with CKD 3-5D, but acknowledges that current data are inadequate to support the safety or efficacy of such an approach and encourages research in this specific area.

The recommendation they have produced is:

In patients with CKD Stages 3a-5D, we suggest lowering elevated phosphorus levels towards the normal range. (2C)

Without a strong evidence base it would seem sensible to keep control of serum phosphate, particularly in the face of rising serum PTH levels.

It is importnat to recognise that the normal levels of phosphate vary with age (see appendix 1).

- Serum PTH

The hallmark of CKD is secondary hyperparathyroidism. It results from a combination of:

- Hyperphosphataemia
- Hypocalcaemia
- Increased calcium phosphate (Ca × P) product
- Reduced synthesis of vitamin D

Raised serum PTH levels lead to:

- Reduced fractional excretion of calcium
- Mobilization of calcium from skeleton and soft tissues
- Increased 1 α -hydroxylase activity

There has been debate over what the target level of PTH should be in CKD as over treatment can lead to adynamic bone disease and this is only diagnosed with the use of bone biopsy. The optimum PTH level remains unclear and this is reiterated in the 2016 KDOQI guidelines which state:

In patients with CKD Stages 3a-5 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 modifiable factors, including hyperphosphatemia, hypocalcemia, high phosphate intake, and vitamin D deficiency (2C).

The KDOQI recommendations for patients on dialysis differ, although again the evidence base, particularly in children is poor:

In patients with CKD stage 5D, we suggest maintaining iPTH levels in the range of approximately two to nine times the upper normal limit for the assay (2C).

The 2015 version of the Renal Association guideline on this subject just quotes these recommendations:

Recent data from large registries suggest an optimal PTH target range of 1.7–3 times the ULN in pediatric PD patients to avoid CKD-MBD-associated complications, such as growth failure (Haffner & Schaefer, 2013).

- Vitamin D

With increased awareness of the problem of vitamin D deficiency in our general population it is sensible to monitor 25(OH)D levels in children with CKD who are at risk of bone disease, irrespective of the debate about optimum management of this problem in otherwise well children. Management of 25(OH)D deficiency is dealt with in a separate guideline. It is advised to check 25(OH)D levels at least 6 monthly and it will need to be done more frequently in patients receiving treatment. Calcium levels should be checked every 2 weeks when starting treatment.

CKD leads to reduced activity of 1α -hydroxylase which converts 25(OH)D to 1,25(OH) $_2$ D.

Vitamin D deficiency leads to:

- Increased release of PTH
- Decreased intestinal calcium absorption
- Skeletal resistance to the calcaemic action of PTH

Routine monitoring of 1,25(OH) $_2$ D is not indicated.

- **Alkaline phosphatase**

Alkaline phosphatase is part of the bone profile. It is a hydrolase enzyme responsible for removing phosphate groups from many types of molecules, including nucleotides, proteins, and alkaloids. It is present in all tissues, but is particularly concentrated in the liver, bile duct, kidney, bone, intestinal mucosa and placenta. In the serum, two types of alkaline phosphatase isozymes predominate: skeletal and liver. It is elevated particularly in diseases involving the liver, gut or bone. The clinical state will guide which system is responsible for a rise in levels and if it is still unclear isoenzymes can be requested.

Levels of alkaline phosphatase give an approximate measure of osteoblast activity and high levels are commonly seen in hyperparathyroid bone disease, while low levels may indicate low turnover osteodystrophy. However the discriminatory power of alkaline phosphatase is poor. Serial measurements may help in assessing the progression of bone disease.

Overall the target levels are:

Serum calcium	Upper half of normal range; avoid hypercalcaemia
Serum phosphate	Normal range
Serum PTH	Normal range in CKD levels 1-4 2-3 x normal range in CKD level 5
Serum 25(OH)vitD	> 75 nanomoles/l
Alkaline phosphatase	Normal age-adjusted levels

Use of imaging

Routine X-ray examination of the skeleton is an insensitive means of diagnosing renal osteodystrophy. However subperiosteal erosions are often present in severe secondary hyperparathyroidism, detected in the hands, clavicles and pelvis. Brown tumors can also develop. These are focal collections of giant cells and are usually seen as well-demarcated radiolucent zones in long bones, clavicles and digits.

DEXA scans can be used to assess bone density. However its utility in CKD-MBD is unclear and it is unlikely to lead to a change in management.

Treatment options

The key to the management of CKD-MBD is control of serum phosphate levels. At the same time maintenance of normal 25(OH)D levels seems sensible although there is no evidence base for this. Acidosis should be corrected.

Control of hyperphosphataemia

This is achieved by step-wise introduction of therapeutic strategies:

1. Dietary phosphate restriction
 2. Use of phosphate binders
 - a. Sevelamer
 - b. Calcium carbonate
 - c. Lanthanum
 - d. Iron-based phosphate binders
 3. Increased dialysis
- Dietary phosphate
Infants can be placed on low phosphate feeds and older children given advice about controlling the intake of foods rich in phosphate. However growth should not be compromised as protein is a key source of phosphate but is required for maintaining growth. There is an absence of data showing that dietary phosphorus restriction improves clinical outcomes. Input from a specialist paediatric renal dietician is essential.
 - Phosphate binders
There is very limited data on the use of phosphate binders in CKD in children.

The first line agent should be sevelamer carbonate (Renvela®). Calcium containing phosphate binders carry an increased risk of cardiovascular disease and are only indicated in the face of low serum calcium levels or where use of sevelamer is not possible. Sevelamer carbonate (which contains bicarbonate and not carbonate) has the advantage over sevelamer HCl in helping manage acidosis.

Calcium-based phosphate binders have been used for many years and still have a role in childhood CKD where calcium levels need to be bolstered. Calcium carbonate is the main form used although calcium acetate is also an option.

Lanthanum is a resin-free, noncalcium-based binder with a high binding potential. Although lanthanum is poorly absorbed there are still concerns regarding long-term complications of low-grade accumulation. There is no paediatric data but adult studies have shown that lanthanum monotherapy is effective and well tolerated for up to 6 years with no evidence of safety concerns or increased frequency of adverse events. It is taken as a chewable preparation and a powder-based formulation is available which can be mixed with food. This appears pharmacologically equivalent to the chewable form but this still needs to be proven in patients with ESRD. Lanthanum is however expensive and it seems sensible to avoid its use in paediatric patients at the present time.

It has become apparent that iron also has phosphate binding properties. Two iron-based phosphate binders have been approved by the FDA: sucroferric oxyhydroxide and ferric citrate. Adult studies have demonstrated effective phosphate binding with minimal side effects. In addition there was a reduced requirement for IV iron and ESA use. There are no publications of their use in

children but there would appear to be potential benefits and they look likely to become an option.

Current recommendation:

1. Start Renvela
 - 800mg tablets or 2.4G powder sachet
 - Dissolve sachet in 60ml of warm water = 40mg/ml.
 - 1-2 tablets before meals
2. Add Calcium carbonate
 - Calcichew or Calcium-500. Tablets contain 1.25G calcium carbonate (calcium 500mg or Ca^{2+} 12.5mmol)
 - 1-2 tablets before meals
 - Calcium carbonate solution also available. Two strengths: 120mg/ml and 250mg/5ml. The 120mg/ml strength should be prescribed.

Vitamin D

There are a number of forms of vitamin D:

- 25(OH)D equivalents
 - Ergocalciferol (vitamin D2)
 - Colecalciferol (vitamin D3)
- Hydroxylated forms
 - Alfacalcidol (1 α -hydroxycholecalciferol)
- Synthetic forms with reduced hypercalcaemic actions, but which can bind to the vitamin D receptor on the parathyroid gland
 - Doxercalciferol (Hectorol®) – not available in the UK
 - Paricalcitol – recent study from Webb et al

25(OH)D levels should be maintained at 75 -120 nmol/l (see separate guideline).

Alfacalcidol should be used in response to raised PTH in the presence of low or normal serum calcium levels. Avoid hypercalcaemia. Starting dose of 20 ng/kg/day.

Vitamin D analogues are potentially helpful in patients with hyperparathyroidism in whom hypercalcaemia develops when treated with alfacalcidol.

Calcimimetics

These agents bind to the calcium-sensing receptor and are aimed primarily at the parathyroid gland.

The main agent used is cinacalcet.

Cinacalcet was licensed for use in children over 3 years of age by the EMA in 2017. There is concern about potential effects on growth in children as CaSRs are expressed on chondrocytes at the growth plates of epiphyses and have a role in the proliferation and differentiation of these cells in vitro.

Cinacalcet should be used in cases of uncontrolled hyperparathyroidism and may be helpful in avoiding parathyroidectomy (Platt et al.). Guidance on the use of cinacalcet has been produced by the ESPN ([Bacchetta et al.](#)).

Suggested starting dose: 0.2 mg/kg/day

Maximum dose: 2.5 mg/kg/day

Common side effects include: nausea and vomiting, hypocalcemia, and adynamic bone disease if intact parathyroid hormone (iPTH) levels drop below 100pg/mL (10.5 pmol/L).

Contraindications:

- Prolonged QT interval
- Drugs that increase QTc
 - Ondansetron
 - Albuterol
 - Salbutamol
- Inhibitors of CYP3A4
 - Grapefruit juice
 - Erythromycin
 - Clarithromycin
 - Ketoconazole
 - Itraconazole
- Inhibitors of CYP2D6
 - Flecanide
 - Propafenone
 - Metoprolol
 - Desipramine
 - Nortroptyline
 - Clomipramine

An ECG should be performed prior to prescribing cinacalcet.

Careful monitoring of serum calcium, is essential.

Summary of aims of management (see appendix 2):

- Maintenance of serum phosphate concentration in the normal range for age.
- Maintenance of serum PTH to less than twice the upper limit of normal.
- Avoidance of hypercalcaemia.

References

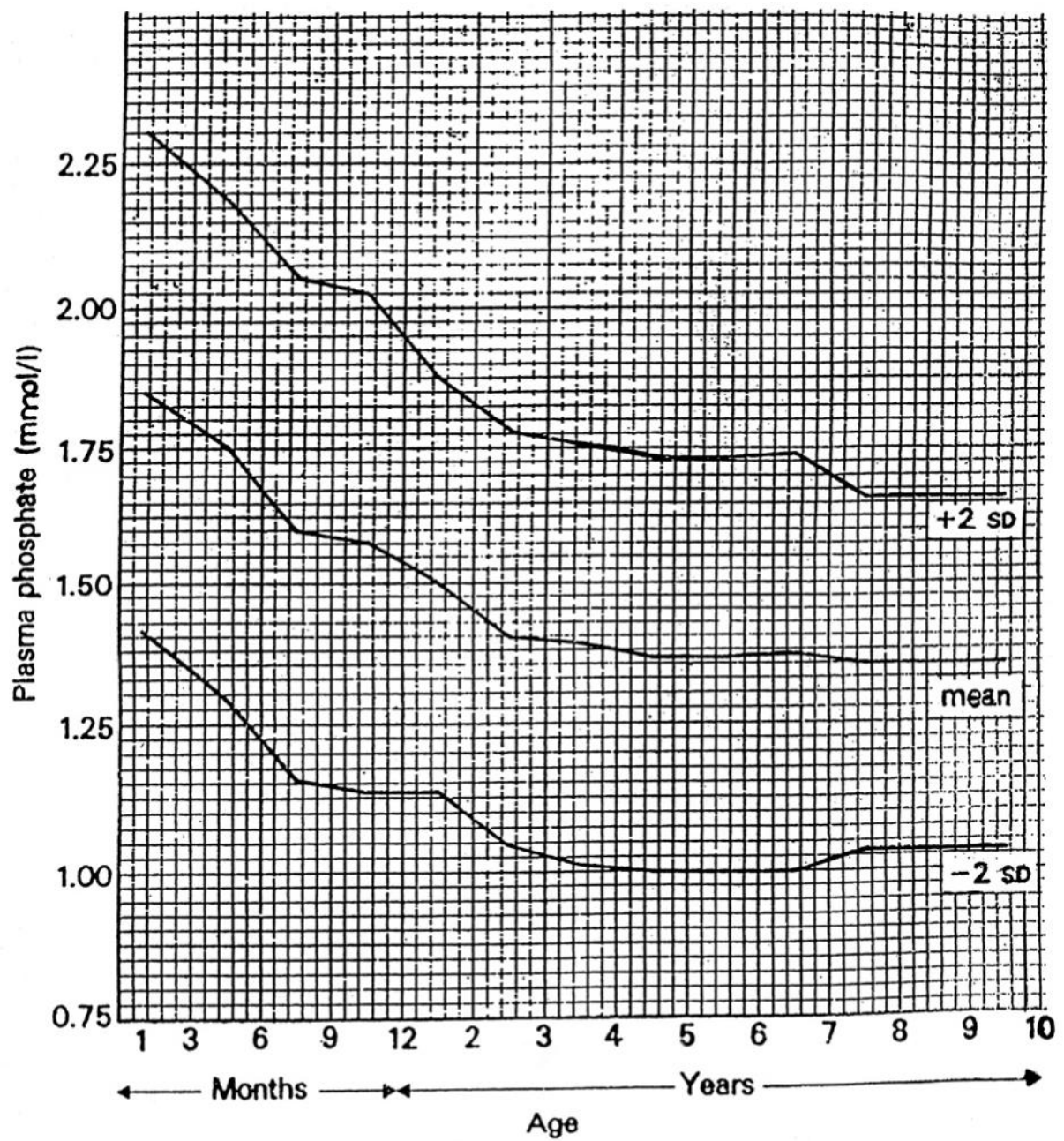
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Appendix 1. Nomogram for plasma phosphate levels.



Plasma phosphate.

Appendix 2. Algorithm for management of CKD-MBD

