Chronic Kidney Disease - Mineral Bone Disease (CKD-MBD) in Adults
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Learning outcomes
1. To understand the mechanisms of the homeostatic control of Calcium, Phosphate, Vitamin D and Parathyroid hormone (PTH)
2. To gain knowledge of the disparate consequences of CKD-MBD and understand the spectrum of disease states in CKD-MBD with the KDIGO turnover, mineralisation and volume or TMV system
3. To understand the therapeutic options for improving CKD-MBD parameters with drugs, diet, dialysis prescription and surgery with knowledge of international guidelines
4. To gain knowledge of the post-transplant considerations in CKD-MBD

Introduction
Chronic kidney disease mineral bone disease (CKD-MBD) is a universal consequence of advanced kidney failure and emphasises the kidneys’ central role in the complex homeostatic process of calcium and phosphate. CKD-MBD is defined as a systemic disorder of mineral and bone metabolism due to CKD by either one or a combination of the following:1
1. Abnormalities of calcium, phosphorous or vitamin D metabolism
2. Abnormalities in bone turnover, mineralisation, volume, linear growth or strength
3. Vascular or other soft tissue calcification

Poor CKD-MBD control leads to vascular calcification, left ventricular hypertrophy and is an independent risk factor for all-cause mortality.

Mechanisms of Homeostatic Processes
The kidney, skeleton and parathyroid gland are the principle organs involved in calcium and phosphate homeostasis. The skeleton houses rich sources of calcium and phosphate. Activated vitamin D in conjunction with the parathyroid hormone (PTH) can mobilise these stores if required. Various feedback mechanisms try and maintain a physiological balance but with advancing renal failure the system struggles and the biochemical and clinical consequences of CKD-MBD ensue. The main hormones involved are activated vitamin D₃, PTH and fibroblast growth factor 23 (FGF-23). These are discussed in more detail in Figure 1. Vitamin D has various forms or ‘vitamers’ and this can make the nomenclature confusing.

There are two major forms, vitamin D₂ (ergocalciferol) and vitamin D₃ (cholecalciferol). Combined they are called calciferol. Dropping the numerical subscript refers to these two main forms. Figure 1 details the names.

Figure 1: Different names and hydroxylation of Vitamin D

<table>
<thead>
<tr>
<th>Collective Term</th>
<th>Vitamin D₂</th>
<th>Vitamin D₃</th>
</tr>
</thead>
<tbody>
<tr>
<td>LIVER (after 1st Hydroxylation)</td>
<td>25-hydroxyvitamin D₂ or 25(OH)D₂</td>
<td>25-hydroxyvitamin D₃ or 25(OH)D₃</td>
</tr>
<tr>
<td>LIVER (after 1st Hydroxylation)</td>
<td>25(OH)D₂</td>
<td>25(OH)D₃</td>
</tr>
<tr>
<td>KIDNEY (after 2nd Hydroxylation)</td>
<td>1,25 Di-hydroxyvitamin D₂ or 1,25(OH)₂D₂</td>
<td>1,25 Di-hydroxyvitamin D₃ or 1,25(OH)₂D₃ or Activated vitamin D₃</td>
</tr>
<tr>
<td>KIDNEY (after 2nd Hydroxylation)</td>
<td>Eralciodiol</td>
<td>Calcitriol</td>
</tr>
<tr>
<td>KIDNEY (after 2nd Hydroxylation)</td>
<td>Calciol</td>
<td>Ercalcitriol</td>
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</tbody>
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Serum 25(OH)D₃ is considered the best form of vitamin D to measure as it measures both nutritional and dietary intakes and has a long half-life of ~3 weeks. It informs clinicians whether patients have vitamin D deficiency or not. The recognised classification is as follows:
- >75nmol/l = Replete
- 37.5 - 75nmol/l = Insufficiency
- <37.5nmol/l = Deficient
Since Hollick et al estimated that vitamin D insufficiency or deficiency affected 1 billion people worldwide, fervent work has been conducted on the disparate roles, outside bone metabolism, that vitamin D plays. This includes endocrine, immunological and endothelial functions. Increased knowledge gained from this basic science and epidemiological data, better informs the renal community of the merits of adequate vitamin D replacement.

Activated vitamin D$_3$ (1,25-dihydroxyvitamin D$_3$) or calcitriol is predominantly formed from UV light. The skin after being exposed to UV light converts 7-dehydrocholesterol to previtamin D$_2$. This then undergoes rapid conversion and isomerisation to vitamin D$_2$ and vitamin D$_3$ account for ~10% of the total intake with UV light dominating at 90%. After the skin and gastrointestinal vitamin D combine, they firstly go to the liver where a hydroxyl side group at position 25 (25-OH) is added. The kidney adds another hydroxyl group at position 1, with the enzyme 1a-hydroxylase. 1a-hydroxylase conversion is the rate limiting final step before calcitriol or activated vitamin D$_3$ is produced. (See Figure 2).

Calcitriol increases serum calcium levels by increasing calcium uptake from the gut, mobilising calcium from bone and increasing the reabsorption of calcium in the tubular structures of the kidney. Calcitriol works in conjunction with PTH to raise serum calcium levels. See Figure 3.

**Figure 2: Synthesis of Activated Vitamin D3**

![Diagram of the synthesis of activated vitamin D3](image)

In patients with CKD the ability of 1a-hydroxylase to continue its addition of a side group is reduced. This is combined with the increasingly scarred kidneys becoming less able to excrete enough phosphate in the urine, causing the serum levels to climb. The metabolic milieu of uraemia impacts other parts of vitamin D production. The ability of the skin to convert 7-dehydrocholesterol to cholecalciferol is impaired. Urinary loss of vitamin D binding protein, (the protein that carries 25, vitamin D to the kidney) is compounded in heavily proteinuric states.

**Parathyroid Hormone**

Parathyroid hormone (PTH) is an 84 amino acid which is secreted from the chief cells of the parathyroid gland generally situated behind the thyroid gland in the neck. In response to low serum calcium, through its calcium sensing receptors, it increases the production and secretion rate of PTH. Secondary hyperparathyroidism (SPTH) is a common and early consequence of progressive CKD with guidelines suggesting that it should be tested and managed from an early as an eGFR <60ml/min.

PTH enhances the release of calcium from the bone stores, feeds back to the kidney to reabsorb more calcium in its tubular structures and increases urinary phosphate loss. It also up regulates the actions of 1a-hydroxylase to help increase calcium, via vitamin D, absorption from the intestine.

**Fibroblast Growth Factor-23**

Fibroblast growth factor 23 (FGF-23) is the main regulator of phosphate metabolism whose impact and influence in the overall homeostatic control of phosphate has only relatively recently been recognised. The majority of FGF-23 is derived from the bone. It has a co-factor, Klotho, which is expressed on the parathyroid glands and the distal tubules of the kidney. Even in the infancy stages of CKD significant increases of FGF-23 are observed. FGF-23 rise well before calcium and phosphate levels change. FGF-23 acts on the kidney to produce a net urinary phosphate excretion. This is achieved by down regulating the activity of 1a-hydroxylase. This tends to aggravate SPTH. In CKD patients high FGF-23 levels has been associated with progressive renal disease and altered skeletal mineralisation of bone. It is also another independent risk factor for mortality in CKD patients.

The interaction of PTH, vitamin D and FGF-23 is summarised in Figure 3.

**Figure 3: Summary Actions of main regulators of the serum calcium/phosphate**

![Summary actions of main regulators of serum calcium/phosphate](image)
**Bone Components**

Mature osteoblasts secrete collagen and bone matrix proteins which fill the bone trabecular. They are bone formers. They mature from mesenchymal stem cells in the bone marrow under the control of a various transcription and growth factors.\(^{12}\) Osteoclasts are bone absorbers. They originate from blood based, haematopoietic stem cells and are from different lineage from osteoblasts. Excessive bone resorption leads to osteoporosis. Bisphosphonates are the most common drug which inhibit osteoclasts and are most commonly used in preventing fractures but they are unfortunately contraindicated in patients with an eGFR of <30ml/min. When osteoclasts are underactive and not resorbing enough bone then patients can develop osteopetrosis, from relatively unopposed osteoblastic activity.

**Consequences of CKD-MBD**

CKD-MBD is generally an asymptomatic condition with only the extremes of its disease spectrum causing frank symptoms. General aches and pains are common and rather non-specific and typically occur in weight bearing areas. Patients’ CKD-MBD parameters are in constant flux and should not be seen as a static entity.

**Hyperparathyroidism**

The classical biochemical consequence of CKD-MBD is SPTH, where there is low calcium, high phosphate and high PTH levels. This is typically managed by calcium containing phosphate binders and vitamin D replacement. The four glands of the parathyroid respond by growing in size (hypertrophy) with increasing density (hyperplasia) and producing more PTH.\(^{13}\) Tertiary hyperparathyroidism (3ohPTH) occurs when the parathyroid gland loses the feedback mechanisms and moves into a state where despite normal or high normal calcium levels, which would ordinarily slow or stop the production, it continues to produce PTH unabated. This generally results in hypercalcemia, hyperphosphatemia and a high alkaline phosphatase (ALP) reflecting the high bone turnover.

As severe hyperparathyroidism ensues, bone deformities can develop and lead to fractures with impaired healing; impacting on patients’ level of function and mobility. Ostetitis fibrosa is characterised by both over active osteoclasts and osteoblasts and gives rise to sub periosteal erosion and variable degrees of peri-trabecular fibrosis.

The parathyroid gland, (generally 4 glands) is located behind the thyroid gland in the neck. It recognises hypocalcaemia via its calcium sensing receptors (CaSR) which promotes a complex process of PTH gene expression and synthesis inside the gland. PTH secretion rises in response to low serum calcium, high phosphate and ineffectual or low vitamin D levels. In CKD, patients who are by definition also partially uraemic the whole regulatory system is changed and the normal feedback loops are lost\(^{14}\). The regulatory feedback loops are depicted below:

**Skeletal and Extra-skeletal Calcification**

Peri-articular deposition of calcium and phosphate gives rise to arthritic symptoms. Other extra-skeletal calcifications can occur in any organ or tissue but the deposition on heart valves and within the vasculature seem to be of particular significance\(^{15,16}\). Deposition within the peripheral vasculature reduces the compliance of the arteries and speeds up atherosclerosis, aggravating the cardiovascular risk burden of people with CKD\(^ {17}\). Vitamin K’s role in the calcification of the arterial media is now well established but its precise interplay with CKD-MBD remains unclear.\(^ {18}\)

Figure 5 illustrates the extra-skeletal calcium deposition which is often visible on plain X-rays.

![Figure: 5: Florid Soft tissue calcification. Note the numerous calcified small and large vessels to the skin in this thigh. This predisposed to calciphylaxis. Note the hemiarthroplasty from a previous hip fracture.](image)
**Calciphylaxis**, otherwise known as calcific uraemic arteriolopathy (CUA) deserves a particular mention. When calcium deposits in smaller vessels it can cause critical ischaemia of the distal tissues, known as ischaemic vasculopathy. When this tissue is the skin, CUA can develop. Patients develop severe pain, from the ischaemic tissue which quickly forms an eschar. It is a devastating condition, with up to 50% with a one year mortality and significant morbidity. Treatment of established CUA is limited but is centred on reducing a positive calcium load and the total Calcium x Phosphate product. This is generally achieved by with non-calcium phosphate binders, cinacalcet and good quality low calcium haemodialysis. Sodium thiosulphate, a chelating agent is an option occasionally used as is hyperbarbic oxygen. There is an international registry whose aims is to retrospectively analyse the natural history of the condition, identify risk factors and clarify the best treatments.

**TMV KDGIO Classification**

The international consortium, KDIGO has classified the various forms of CKD-MBD into the following categories on the definition of CKD-MBD. It emphasises abnormalities of bone Turnover, Mineralization and bone Volume and is known as the TMV classification.

Turnover reflects the speed of bone remodelling and is characterised by high osteoclast and osteoblast activity. Histomorphometry is required for its proper assessment.

Mineralisation reflects how well the bone and collagen becomes calcified as it remodels.

Bone Volume reflects the amount of bone per unit volume.

With this classification the typical clinical manifestations of CKD-MBD can more easily be appreciated. Patients can and do move between the following labels:

- **Osteitis Fibrosa (OF) /Hyperparathyroid related bone disease**
  This reflects high bone turnover with high bone volume and normal bone mineralisation.

- **Mixed Uraemic Osteodystrophy (MUA)**
  High bone turnover, abnormal mineralisation with high bone volume

- **Osteomalacia (OM)**
  This reflects low bone turnover with abnormal mineralisation

- **Adynamic Bone Disease (ADM)**
  Low Turnover of bone with relatively preserved mineralisation but of low bone volume.

Fracture Risk

People with CKD, particularly those receiving haemodialysis have a significantly increased risk of fractures as well as a higher morbidity and mortality associated with them. Repeated studies have put the magnitude of a fracture at double those of age matched individuals with a prevalence of fractures in the dialysis population of around 50% in those older than 50 years old.

**Therapeutic options:**

Management decisions for CKD-MBD should be overseen by multi-disciplinary teams including physicians, nurses, renal dietician, and renal pharmacists.

The following should inform what changes need to be made:

- Historical & current biochemical results of calcium, phosphate, 25(OH) Vitamin D, ALP, PTH levels
- Other bloods as indicated (e.g. Aluminium, Bicarbonate)
- Current drug prescription and concordance
- Patient factors
  Dialysis prescription duration on dialysis and vintage
  Diet and nutritional status
  Past medical history
  History of cardiovascular morbidity and of prior fracture history
  Smoking, Osteoporosis risk factors
- Skeletal X-Rays and other imaging as indicated by the clinical scenario

**International Guidelines**

The KDIGO, an international consortia of experts, CKD-MBD’s guidance suggests the following:

- Phosphate control
  - Dialysis patients: “suggest lowering an elevated phosphate towards normal range”
  - Non dialysis CKD patients: “maintain normal range”
- Calcium
  - All CKD patients, including dialysis patients: “maintain normal range”
- PTH
  - Dialysis patients: “maintain between 2-9 times the upper normal limit”
  - Non-dialysis CKD patients: range unknown but “correct modifiable factors and treat with calcitriol or vitamin D analogues.”

The paucity of bone biopsies that are performed in CKD-MBD patients prevents clinicians using this hard end point to accurately type the bone disease of CKD patients. Initial evaluation of CKD-MBD should be with calcium, phosphate, ALP, PTH and bicarbonate levels alongside any imaging for soft tissue calcification.
Strategies:

**Diet**

Phosphate and calcium advice may have to be balanced against the patient’s general nutritional state and other dietary goals. Low potassium, salt and/or fluid restriction may also take precedent in some circumstances. Diabetes mellitus, coeliac disease or cultural/religious diet restrictions may also be relevant to individuals. However phosphate reduction in the diet is the key component to achieving good phosphate control. Examples of low phosphate foods would include the minimisation of dairy products and avoidance of liver, kidney, pate and chocolate.

**Phosphate Binders**

- Calcium salts
  - These are cheap and are to be taken with meals to help with phosphate binding. They contain various strengths of calcium salts. Their toleration by patients is variable because of the size and taste of the tablets. They are generally used first line to correct hypocalcaemia and hyperphosphataemia. With this effect they can also suppress the SPTH. Beyond the compliance issues of the tablets, hypercalcaemia is the other limitation to its use. Calcium acetate and calcium carbonate are the most frequently used, with the former having better phosphate binding.
  - Non-calcium containing Phosphate Binders
    - Sevelamer (Renagel® or Renvela®)
    - Lanthanum/Fosrenol®
    - Aluminium/AIuCaps
    - Iron Based Phosphate binder
      - In research only
    - Sevelamer and Lanthanum have the advantage of not causing hypercalcaemia associated with calcium salts. They offer effective phosphate control but at considerable extra financial costs than calcium salts. Older non-calcium phosphate binders such as aluminium have historically been put aside because of the aluminium accumulation and toxicity. However if aluminium levels are checked, they remain a good alternative for some patients to achieve control. Sevelamer seems to offer other benefits to the metabolic environment of CKD by reducing LDL cholesterol, C-reactive protein and uric acid levels. The dangers of aluminium toxicity include encephalopathy and fractures from adynamic bone disease.

**Vitamin D Sterols**

There are various vitamin D analogues that are licensed in CKD-MBD. They replace vitamin D insufficiency and mimic the physiological role of active vitamin D. They suppress PTH with a consequential rise in calcium and phosphate. Alfacalcidol is most frequently prescribed and can be given IV during haemodialysis sessions or orally and observed by the dialysis nursing staff on dialysis to help with concordance. Paricalcitol was thought to be less calcaemic, and phosphataemic than vitamin D analogues but this was not borne out in a randomised control trial against alfacalcidol.

Animal models have shown a variety of renal-protective effects to vitamin D replacement, all of which appear attractive: suppression of the renin-angiotensin system, amelioration of chronic fibrosis and reducing proteinuria. However replacing vitamin D to normal levels has not been shown to improve patient survival.

KDIGO guidelines merely suggest checking for vitamin D when eGFR <60m/min levels but do not guide clinicians on the frequency of testing nor the rate of replacement.

**Calcimimetics**

Cinacalcet (Europe)/Mimpara® (North America) or Sensipar

This drug mimics the effects of calcium on tissues by binding to the calcium sensing receptor in various organs. They are used in patients with severe SHPT. Different regulators, in different countries have given guidance on its use as cost is a limiting factor. It offers an alternative to parathyroid surgery. The EVOLVE study did not show a reduction cardiovascular end points despite good reductions in PTH. Hypocalcaemia is its major drawback.

**Parathyroid Surgery**

For severe SHPT that is unresponsive to medical treatment, parathyroidectomy offers a solution. However it comes at the expense potentially of rendering the bones adynamic especially if the patient fails to take their vitamin D sterols post-operatively. Various surgical techniques have been used but total parathyroidectomy is the most common.

**Post-Transplant Bone Health**

Renal transplantation undoubtedly can have a positive effect on a patient’s bone health as once again a functioning kidney graft is able to activate vitamin D and clear excessive phosphate loads in the urine. Transplantation though brings some negative factors to bone health which are of relevance. Corticosteroids are used pre-implantation, for acute cellular rejection episodes and as maintenance immunosuppression. All these uses compound the low turnover which hugely increases fracture risk. Avascular necrosis (AVN) is a serious consequence of high dose exposure to steroids.

A study of transplanted patients hospitalised for fracture showed that renal transplant patients had an adjusted risk ratio of 4.59 and an increased mortality risk of 1.6. With the changing demographics of transplanted patients; grafts lasting longer and increasing numbers of transplants in the > 55 years old this problem is likely to increase. Olgard K et al offers
an excellent précis of the management issues in this field by
detailing the multifactorial nature of this condition and empha-
sising the complicating factors of pre-transplant bone health
and the chosen immunosuppressive regime which effects the
skeletal axis.35

Summarising Comments, Future Prospects

The main thrust of management in CKD-MBD is to try and
obtain and maintain neutral bone health. Good phosphate
control combined with dietary advice and phosphate binders
does work but requires patient motivation and ongoing clinical
vigilance. Working in partnership with patients and discussing
the importance of their CKD-MBD blood test results can aid
concordance. People with CKD relate to other aspects of their
CKD health such as understanding that if they do not keep
to their fluid restriction that they will become breathless. The
implication of not taking those ‘big horrible tablets’ is less im-
mediate and perhaps harder to comprehend. Despite the lack
of robust prospective multi-centre randomised control trials on
the merits of managing specific CKD-MBD parameters it stand
to reason to try and mitigate the morbidity it undoubtedly holds.
Health care professionals interested in this area of nephrology
need to pool their knowledge and resources to help design
good quality randomised controlled trials to update the current
evidence base.

Learning Follow Up

1. Be able to describe the physiological factors controlling calcium, phosphate and vitamin D in normal health and CKD.
2. Understand the significant morbidity that poor CKD-MBD parameters carries for patients from skeletal pathologies and the
   consequences of vascular and soft tissue calcium deposition.
3. What is the increased fracture risk for dialysis patients?
4. Understand the spectrum of CKD-MBD using the TMV classification. Know the normal ranges of calcium, phosphate and
   PTH relevant to your area of practice.
5. Outline the multidisciplinary nature of treating CKD-MBD and the main classes of medicines used.
References

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20. www.calciphylaxis.net