COMPLICATIONS OF CHRONIC KIDNEY DISEASE

CO-MANAGEMENT OF CKD
Module 3 | Course Notes

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MALAYSIAN SOCIETY OF NEPHROLOGY
Academy of Family Physicians of Malaysia
Malaysian Family Medicine Specialist Association
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Renal Anemia

Anemia is an expected feature of chronic kidney disease (CKD) once the glomerular filtration rate (GFR) drops below 60 mL/minute. The relation of anemia to CKD is due to the production of erythropoietin (EPO) by the kidneys. EPO is the hormone that stimulates blood cell production in the bone marrow. In CKD, the production of EPO is below the normal levels. The severity of anemia in patients with CKD is related to both the degree of loss of GFR and the cause of kidney disease.

Criteria for anemia

The World Health Organization (WHO) criteria for hemoglobin (Hb) and hematocrit (Hct) levels (sea level) corresponding to anemia is shown in Table 1 below. They also provide corresponding levels for those who live at higher altitudes generally, Hb concentration can be expected to increase by about 0.6 g/dL in women and 0.9 g/dL in men for each 1,000 m of altitude above sea level.

<table>
<thead>
<tr>
<th>Age or gender group</th>
<th>Hemoglobin g/dL</th>
<th>Hematocrit mmol/l</th>
<th>l/l</th>
</tr>
</thead>
<tbody>
<tr>
<td>Children 6–59 months</td>
<td>110</td>
<td>6.83</td>
<td>0.33</td>
</tr>
<tr>
<td>Children 5–11 years</td>
<td>115</td>
<td>7.13</td>
<td>0.34</td>
</tr>
<tr>
<td>Children 12–14 years</td>
<td>120</td>
<td>7.45</td>
<td>0.36</td>
</tr>
<tr>
<td>Non-pregnant women</td>
<td>120</td>
<td>7.45</td>
<td>0.36</td>
</tr>
<tr>
<td>(above 15 years of age)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pregnant women</td>
<td>110</td>
<td>6.83</td>
<td>0.33</td>
</tr>
<tr>
<td>Men (above 15 years of age)</td>
<td>130</td>
<td>8.07</td>
<td>0.39</td>
</tr>
</tbody>
</table>

* Conventional conversion factors: 100 g hemoglobin = 6.2 mmol hemoglobin = 0.30 l/l hematocrit.

The kidney disease outcomes quality initiative (KDOQI) Clinical Practice Guidelines state that a diagnosis of anemia should be made and further evaluation should be undertaken at Hb concentrations less than 13.5 g/dL in adult males and less than 12.0 g/dL in adult females.

Differences between the KDOQI recommendation and the WHO definition arise from differences in the data source for the general population: the WHO definition is based on sparse data obtained prior to 1968, whereas the definition proposed in the current guidelines is based on the more recent national health and nutrition examination survey (NHANES) III data.

There are several reasons why Hb is a more accurate, and hence a better measure of anemia than Hct:

1. Measurement of hemoglobin gives an absolute value and, unlike hematocrit, is not affected greatly by shifts in plasma water
2. Hemoglobin levels are directly affected by lack of erythropoietin production from the kidney and thus serve as a more precise measurement of erythropoiesis.
Prevalence

The reported prevalence of anemia by CKD stage depends largely on the size of the study; whether study participants are selected from the general population, are at high risk for CKD, or are patients already under a physician’s care; what level of Hb is defined as constituting anemia; and whether patients do or do not have diabetes.\(^3\)

A comparison of the results from NHANES III with NHANES IV shows a lower prevalence of anemia for each CKD stage [Figure 1]. In this analysis, anemia was defined by WHO criteria (Hb level <12 g/dL in women and <13 g/dL in men).\(^3\)

In a study done in CKD patients in Saudi Arabia who had not undergone dialysis, the prevalence of anemia in the different stages of CKD was 42%, 33%, 48%, 71%, and 82% in stages 1 to 5, respectively. The prevalence was also elevated for hemoglobin levels below 11 g/dL (the minimum hemoglobin level at which therapy should be initiated with EPO), which is, 21%, 17%, 31%, 49%, and 72%, respectively for stages 1 to 5.\(^4\)

The purpose of specifying Hb level thresholds to define anemia is to identify patients who are most likely to show pathological processes contributing to a low Hb level and who therefore are most likely to benefit from further anemia evaluation. This recommendation is made after analysis of patients with CKD before dialysis therapy, those with kidney transplants and those on dialysis therapy. The reviewed literature spanned close to 40 years of investigation up to the year 2000 and described clinical findings on relationships between Hb or Hct level and kidney function.

The majority of available data were derived from studies of small sample size, most of which are cross-sectional studies, or baseline data from clinical trials of variable size and robustness. In 12 of the 21 studies reviewed, there was an association between level of Hb or Hct and the selected measure of kidney function. These studies also demonstrate variability in levels of Hb or Hct at each stage of kidney function, whether assessed by using serum creatinine (SCr) concentration, creatinine clearance (CCr) or estimated GFR (eGFR). However, the consistency of the information provided indicates a trend toward lower Hb levels at lower levels of GFR and variability in Hb levels across GFR levels. The relationship between GFR and prevalence of anemia is determined mostly by the Hb concentration used to define anemia.
Causes of anemia in CKD

There are several likely factors contributing to anemia in CKD. Unfortunately, little is known about the relative contributions of the different factors and conditions in the early stages of CKD.

- **Blood loss**
  - Patients with CKD are at risk of blood loss due to platelet dysfunction. The main cause of blood loss is dialysis, especially hemodialysis. This loss results in absolute iron deficiency.

- **Erythropoietin (EPO) deficiency**
  - Considered the most important cause of anemia in CKD

- **Shortened red blood cell life span**
  - The life span of red blood cells is reduced by approximately one third in hemodialysis patients.

- **Iron deficiency**
  - Iron homeostasis appears to be altered in CKD. For reasons not yet known (perhaps malnutrition), transferrin levels in CKD are one half to one third of normal levels, diminishing the capacity of the iron-transporting system. This situation is then aggravated by the well known inability to release stored iron from macrophages and hepatocytes in CKD.

- **Vitamin deficiencies**
  - Difficult to determine if this plays a role as most CKD patients are on a multivitamin supplement.

- **Inflammation**
  - CKD shares several features of the inflammatory state. The anemia of inflammation is also characterized by low serum iron, low transferrin saturation, and impaired release of stored iron, manifested as high serum ferritin.

- **The “uremic milieu”**
  - An overused term that tries to explain the multiple organ dysfunction of CKD.

Investigations for anemia in CKD

Because little is known about the natural history of anemia in patients with CKD, precise information is unavailable to determine the optimum frequency of Hb testing in patients with CKD. The KDOQI Guidelines and Clinical Practice Recommendations for Anemia in Chronic Kidney Disease recommend measurement of Hb at least annually in patients with CKD.

The importance of identifying patients with anemia in the presence of CKD is 2-fold:

- A Hb value in the lowest fifth percentile of the general population may signify the presence of significant nutritional deficits, systemic illness or other disorders that warrant attention.

- Anemia in patients with CKD is a known risk factor for a number of significant adverse patient outcomes, including hospitalizations, cardiovascular disease (CVD), cognitive impairment and mortality.²

While measuring Hb and diagnosing anemia, care must be taken to assess the normal ranges of the person with respect to factors like altitude, age, race and smoking which have an impact on the Hb values. Anemia in chronic kidney disease should be evaluated and treated (Figure 2).³
Figure 2. Anemia work-up for CKD patients

- Serum creatinine ≥2 mg/dL?
  - Yes: Check Hb
  - No: No Work-up

- ≤12.5 (f), Post-menopausal (f) ≤11.0 (f/prepubertal) Hb?
  - Yes: Work-up
    - CBC, Indices, Retics: Iron: TIBC, Fe, TSAT, Ferritin, Stool Guaiac
    - Normal?
      - Yes: Refer for hematology work-up
      - No: Fe deficiency?
      - Yes: Treat with iron
        - Anemia corrected: periodic follow-up
        - Anemia not corrected
      - No: Treat with Epoetin if indicated

* indicates that laboratory values are consistent with uncomplicated iron deficiency
Anemia in patients with CKD is not always caused by EPO deficiency alone. Initial laboratory evaluation therefore is aimed at identifying other factors that may cause or contribute to anemia or lead to erythropoiesis-stimulating agent (ESA) hyporesponsiveness. ESA applies to all agents that augment erythropoiesis through direct or indirect action on the erythropoietin receptor. Some of the ESAs available include epoetin alfa, epoetin beta, and darbepoetin alfa.

Although erythropoietin deficiency is common among patients with anemia and CKD, other potential causes and potentially contributing disorders should be identified or excluded. The recommended laboratory evaluation provides information regarding the degree and cause of anemia, activity of the erythroid and non-erythroid marrow, as well as assessment of iron stores and iron availability for erythropoiesis.

In particular, clinicians should consider causes of anemia other than erythropoietin deficiency when:
1. severity of the anemia is disproportionate to the deficit in renal function;
2. there is evidence of iron deficiency, or
3. there is evidence of leukopenia or thrombocytopenia.

An evaluation of the cause of anemia should precede initiation of ESA therapy.

In addition to Hb, other reported results of the complete blood count (CBC) may convey important clinical information. Deficiency of folate or vitamin B12 may lead to macrocytosis, whereas iron deficiency or inherited disorders of Hb formation (α- or β-thalassemia) may produce microcytosis. Macrocytosis with leukopenia or thrombocytopenia suggests a generalized disorder of hematopoiesis caused by toxins (eg, alcohol), nutritional deficit (vitamin B12 or folate deficiency), or myelodysplasia.

In general, the anemia of CKD is normochromic and normocytic; that is, morphologically indistinguishable from the anemia of chronic disease. It is characteristically hypoproliferative: erythropoietic activity is low, consistent with insufficient erythropoietin stimulation. While considering this type of anemia, the other types must be ruled out especially those involving the bone marrow diseases and liver and endocrine functions.

The other differential diagnosis for this condition are
• Aplastic anemia
• Myelophthisic anemia
• Myeloid metaplasia
• Liver disease – Cirrhosis
• Endocrine disorders – Hyperthyroidism, hypothyroidism, hypoadrenalism, panhypopituitarism, primary and secondary hyperparathyroidism.
Management of Anemia in CKD

Table 2 provides an outline of the key stages of managing anemia of CKD (as mentioned in the 2011 NICE guidelines).

### Table 2. Overview of Anemia Management in CKD

<table>
<thead>
<tr>
<th>Stage</th>
<th>Activity</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Diagnosis</strong></td>
<td>Is anemia due to CKD?</td>
</tr>
<tr>
<td></td>
<td>Consider other causes if eGFR &lt; 60 ml/min/1.73 m²</td>
</tr>
<tr>
<td></td>
<td>Consider investigating and treating anemia if:</td>
</tr>
<tr>
<td></td>
<td>- Hb &lt; 11 g/dL</td>
</tr>
<tr>
<td></td>
<td>- Hb &lt; 10.5 g/dL in children under 2 years</td>
</tr>
<tr>
<td></td>
<td>- Symptoms attributable to anemia develop</td>
</tr>
<tr>
<td><strong>Determination of anemia type</strong></td>
<td>Iron status:</td>
</tr>
<tr>
<td></td>
<td>Iron deficiency anemia:</td>
</tr>
<tr>
<td></td>
<td>- Diagnosed when serum ferritin &lt; 100 μg/l in stage 5 CKD</td>
</tr>
<tr>
<td></td>
<td>- Considered when serum ferritin &lt; 100 μg/l in stage 3 and 4 CKD</td>
</tr>
<tr>
<td></td>
<td>Functional iron deficiency defined by:</td>
</tr>
<tr>
<td></td>
<td>- Serum ferritin &gt; 100 μg/l and either</td>
</tr>
<tr>
<td></td>
<td>- % HRC &gt; 6% (if test available), or TSAT &lt; 20%</td>
</tr>
<tr>
<td></td>
<td>Serum ferritin is often raised in CKD; interpret diagnostic cut-off value differently than in non-CKD patients</td>
</tr>
<tr>
<td><strong>Treatment</strong></td>
<td>Optimize iron status:</td>
</tr>
<tr>
<td></td>
<td>- Before or when starting ESAs</td>
</tr>
<tr>
<td></td>
<td>- Before deciding whether to use ESAs in non-dialysis patients</td>
</tr>
<tr>
<td></td>
<td>Iron correction should maintain:</td>
</tr>
<tr>
<td></td>
<td>- Serum ferritin &gt; 200 μg/l</td>
</tr>
<tr>
<td></td>
<td>- TSAT &gt; 20% (unless ferritin &gt; 800 μg/l)</td>
</tr>
<tr>
<td></td>
<td>- % HRC &lt; 6% (if test available)</td>
</tr>
<tr>
<td></td>
<td>Review iron dose:</td>
</tr>
<tr>
<td></td>
<td>- When serum ferritin reaches 500 μg/l (should not rise above 800 μg/l)</td>
</tr>
<tr>
<td><strong>Maintenance</strong></td>
<td>Maintain iron levels:</td>
</tr>
<tr>
<td></td>
<td>- Serum ferritin 200–500 μg/l in both hemodialysis and non-hemodialysis patients and either</td>
</tr>
<tr>
<td></td>
<td>- TSAT &gt; 20% (unless ferritin &gt; 800 μg/l), or</td>
</tr>
<tr>
<td></td>
<td>- % HRC &lt; 6% (if test available)</td>
</tr>
<tr>
<td><strong>MONITOR</strong></td>
<td>Iron status monitored:</td>
</tr>
<tr>
<td></td>
<td>- No earlier than 1 week after receiving i.v. iron and at intervals of 4 weeks to 3 months routinely</td>
</tr>
<tr>
<td></td>
<td>- Hb every 2–4 weeks (induction phase) or 1–3 months (maintenance phase) during ESA therapy</td>
</tr>
<tr>
<td></td>
<td>- Hb more actively after adjusting ESA dose</td>
</tr>
</tbody>
</table>

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**Correction:** Usually 600-1000 mg for adults or equivalent doses for children, given orally depending on the preparation. (For children, the equivalent oral dose is 1 mg/kg/week.)
Management of anemia in CKD starts with the cause for the condition. If all other causes are excluded, treatment of the condition can be initiated with an ESA. The pharmacological agent is usually injected subcutaneously two or three times a week. Patients on hemodialysis who cannot tolerate ESA injections may receive the hormone intravenously during treatment. The intravenous method, however, requires a larger, more expensive dose and may not be as effective. There are several different types of ESAs as shown in Table 2.7

**Table 2. Currently available erythropoietin stimulating agents (ESAs)**

<table>
<thead>
<tr>
<th>Type of ESA</th>
<th>Company</th>
</tr>
</thead>
<tbody>
<tr>
<td>1(^{st}) generation</td>
<td></td>
</tr>
<tr>
<td>• Epoetin alfa (Eprex)</td>
<td>Janssen-Cilag</td>
</tr>
<tr>
<td>• Epoetin beta (Recormon)</td>
<td>Roche</td>
</tr>
<tr>
<td>2(^{nd}) generation</td>
<td></td>
</tr>
<tr>
<td>• Darbepoetin alfa (Aranesp)</td>
<td>Amgen (not available in Malaysia)</td>
</tr>
<tr>
<td>3(^{rd}) generation</td>
<td></td>
</tr>
<tr>
<td>• Continuous erythropoietin receptor activator (Mircera)</td>
<td>Roche</td>
</tr>
</tbody>
</table>

The U.S. Food and Drug Administration (FDA) recommends that patients treated with ESA therapy should achieve a target Hb between 10 and 12 g/dL. Recent studies have shown that raising the Hb above 12 g/dL in people who have kidney disease increases the risk of myocardial infarctions, heart failure, and stroke. People who take ESA injections should have regular tests to monitor their Hb. Any rise in Hb level above 12 g/dL should prompt adjustment of the ESA dose.

**Complications of Anemia on CKD**

In a normal person, hypoxia serves as a stimulus for the kidneys to produce EPO which in turn stimulates the bone marrow to produce more RBCs and relieves hypoxia. In people with CKD the derangement of this mechanism results in hypoxia and its effects. Another complication is secondary hyperparathyroidism and the development of renal osteodystrophy.

Apart from the CV risk factors induced by CKD, anemia in CKD independently contributes to cardiac disease risk.

- **In a study using data from the North American study of etanercept in chronic heart failure, it was shown that 12% of these subjects had anemia, with a Hb ≤ 12 g/dL, and that anemia correlated directly with greater risk of hospitalization and mortality.**
- **There was a similar “dose-response” relationship in a large single-center study of 2281 subjects admitted to a hospital with heart failure, of which almost half had a Hct less than 37%. In that study, it was shown that each 1% drop in Hct was associated with a 2% rise in mortality.** There was a 40% greater mortality in subjects with a Hct of 27% compared with a hct of 42%, an increased risk comparable to that of having a left ventricular ejection fraction of 20%.
- **The community-based study of McClellan and colleagues showed that 14% of hospitalized subjects with heart failure had a Hct ≤ 30%, and 45% had a Hct ≤ 35%.** In this study, a 1% lesser Hct corresponded to a 1.6% increase in mortality.
Anemia is now confirmed as a risk factor for left ventricular hypertrophy (LVH) in patients on chronic dialysis and patients with chronic renal failure not yet on dialysis.\textsuperscript{11,12} LVH, in turn, is a risk factor for symptomatic heart disease, including heart failure and sudden death. Thus, heart failure can worsen the kidney function, anemia can result from those two conditions and this in turn stresses the heart, thus forming a vicious cycle.

**Malnutrition**

Protein-energy malnutrition (PEM) is very common among patients with advanced CKD and those undergoing maintenance dialysis (MD) therapy worldwide. Different reports suggest that the prevalence of this condition varies from roughly 18\% to 70\% of adult MD patients.\textsuperscript{13} In adults, the presence of PEM is one of the strongest predictors of morbidity and mortality.

There are many causes of PEM in patients with advanced CKD. These include:

- **inadequate food intake secondary to:**
  - anorexia caused by the uremic state
  - altered taste sensation
  - intercurrent illness
  - emotional distress or illness
  - impaired ability to procure, prepare or mechanically ingest foods
  - unpalatable prescribed diets
- **catabolic response to superimposed illnesses**
- **the dialysis procedure itself, which may promote wasting by removing such nutrients as amino acids, peptides, protein, glucose, water-soluble vitamins and other bioactive compounds, and may promote protein catabolism, due to bioincompatibility.**
- **conditions associated with CKD that may induce a chronic inflammatory state and may promote hypercatabolism and anorexia**
- **loss of blood due to:**
  - gastrointestinal bleeding
  - frequent blood sampling
  - blood sequestered in the hemodialyzer and tubing
- **endocrine disorders of uremia (resistance to the actions of insulin and IGF-I, hyperglucagonemia, and hyperparathyroidism)**
- **possibly the accumulation of endogenously formed uremic toxins or the ingestion of exogenous toxins.**

Notwithstanding the many causes of PEM in patients with CKD, provision of adequate nutrition is a key component of the prevention and treatment of PEM in adults and children receiving MD.

Optimal monitoring of protein-energy nutritional status for MD patients requires the collective evaluation of multiple parameters, particularly using measures that assess different aspects of protein-energy nutritional status.
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No single measure provides a complete overview of protein-energy nutritional status.

- Serum albumin is recommended for routine measurement because there is a large body of literature that defines the normal serum albumin values, characterizes the nutritional and clinical factors affecting serum albumin concentrations, and demonstrates the relationship between serum albumin concentrations and outcome.
- Body weight, adjusted for height, is proposed because of the clear association between body weight and body fat mass and because body weight is correlated with clinical outcome.
- Subjective global nutritional assessment (SGA) is recommended because it gives a comprehensive overview of nutritional intake and body composition, including a rough assessment of both muscle mass and fat mass, and because it is correlated with mortality rates.
  - Assessment of nutrient intake is essential for assessing the probability that a patient will develop PEM, for evaluating the contribution of inadequate nutrient intake to existing PEM, and for developing strategies to improve protein-energy nutritional status. Also, nutrient intake is correlated with clinical outcome.
  - Protein Equivalent of Total Nitrogen Appearance normalized to body weight (nPNA) provides an independent and less time-consuming assessment of dietary protein intake (DPI).
  - Dietary interviews and diaries can be used to assess intake not only of protein and energy but also of a variety of other nutrients as well as the pattern and frequency of meals (information that may aid in identifying the cause of inadequate nutrient intake).
  - A low predialysis or stabilized serum urea level may indicate a low intake of protein or amino acids.
  - Others like serum creatinine, serum cholesterol, dual energy X-ray absorptiometry are useful tests to assess protein energy nutritional status.

Cardiovascular disease in CKD

Cardiovascular Disease (CVD) and CVD seem to be lethally synergistic and both are approaching the epidemic level. Far more patients with a GFR below 60 mL/min/1.73 m² will die from CV causes than progress to end-stage renal disease. Understanding the complex mechanisms underlying the development of CVD among CKD patients is required to begin devising therapy to prevent or reverse this process. Observational studies of CVD in CKD are difficult to interpret because renal impairment is almost always accompanied by confounding factors. These include the underlying disease process itself (for example, diabetes mellitus and systemic vasculitis) and the complications of CKD, such as hypertension, anemia and inflammation.

CVD, defined as the presence of either congestive heart failure (CHF), ischemic heart disease (IHD), or LVH, is prevalent in cohorts with established CKD (8-40%). The prevalence of hypertension, a major risk factor for coronary artery disease (CAD) and LVH, is high in patients with CKD (87-90%). At least 35% of patients with CKD have evidence of an ischemic event (myocardial infarction or angina) at the time of presentation to a nephrologist. The prevalence of LVH increases at each stage of CKD, reaching 75% at the time of dialysis initiation, and the modifiable risk factors for LVH include anemia and systolic blood pressure, which are also worse at each stage of kidney disease. Even under the care of nephrologists, a change in cardiac status (worsening of heart failure or anginal symptoms)
occurs in 20% of patients. The presence of CVD predicts a faster decline of kidney function and the need for dialysis, after controlling for all other factors including GFR, age, and the presence of LVH. A study found that reduced GFR is associated with increased mortality risk in patients with heart failure. Significant correlations were observed between eGFR and systolic blood pressure, diastolic blood pressure, age, New York Heart Association class, complications of percutaneous coronary interventions, including bleeding, and major adverse cardiac events.

A study examined the associations between hemoglobin level, kidney function, and risks of death and hospitalization in persons with chronic heart failure between 1996 and 2002 within a large, integrated, healthcare delivery system in northern California and found that compared with those with a GFR ≥ 60 mL/min/1.73 m², persons with a GFR <45 mL/min/1.73m² had an increased mortality risk: adjusted HR, 1.39 and 95% CI, 1.34 to 1.44 for 30 to 44; HR, 2.28 and 95% CI, 2.19 to 2.39 for 15 to 29; HR, 3.26 and 95% CI, 3.05 to 3.49 for <15; and HR, 2.44 and 95% CI, 2.28 to 2.61 for those on dialysis.

**Bone disease**

Disturbances in mineral and bone metabolism are common in patients with CKD. A large body of evidence indicates that these derangements are associated with increased mortality and morbidity. These patients have bone pain, increased incidence of bone fractures, deformity, myopathy, muscle pain and ruptures of tendons. Hyperphosphatemia also appears to be associated with increased mortality, and elevated blood levels of PTH exert significant adverse effects on the function of almost every organ.

Importantly, the long-term effects of these derangements on soft tissue calcification have become an area of growing concern in the care of CKD patients.

- **Calcification of the lung leads to impaired pulmonary function, pulmonary fibrosis, pulmonary hypertension, right ventricular hypertrophy and right-side CHF.**
- **Calcification of the myocardium, coronary arteries and cardiac valves results in CHF, cardiac arrhythmias, ischemic heart disease and death.**
- **Vascular calcification leads to ischemic lesions, soft-tissue necrosis and difficulties for kidney transplantation.**

The processes causing disordered mineral metabolism and bone disease have their onset in the early stages of CKD, continue throughout the course of progressive loss of kidney function, and may be influenced beneficially or adversely by the various therapeutic approaches now used. Thus, prevention of the disturbances in mineral and bone metabolism and their management early in the course of CKD are extremely important in improving the quality of life and longevity of CKD patients. The nature and type of bone disease that develops in CKD may vary from one patient to another. Multiple reasons may account for these variations.

The two major types of bone disease that are commonly encountered in patients with CKD are:

- enhanced bone resorption (osteitis fibrosa)
- adynamic bone disease
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Some patients may have one of these types predominantly, whereas others may have a mixed type of bone disease. Mild forms of these derangements in bone metabolism may be observed in the early stages of CKD (Stage 2) and they become more severe as kidney function deteriorates. Osteosclerosis may also occur, and osteoporosis may be encountered.

### Managing bone abnormalities

<table>
<thead>
<tr>
<th>CKD STAGES 1 and 2</th>
<th>With osteoporosis and/or high risk of fracture, as identified by World Health Organization (WHO) criteria...</th>
<th>Manage as per general population.</th>
</tr>
</thead>
<tbody>
<tr>
<td>CKD STAGE 3</td>
<td>With PTH in the normal range and osteoporosis and/or high risk of fracture, as identified by WHO criteria...</td>
<td>Treat as per the general population.</td>
</tr>
<tr>
<td></td>
<td>With biochemical abnormalities of CKD-MBD and low BMD and/or fragility fractures...</td>
<td>Suggest treatment choices taking into account the magnitude and reversibility of the biochemical abnormalities and the progression of CKD, with consideration of a bone biopsy.</td>
</tr>
<tr>
<td>CKD STAGES 4–5 D</td>
<td>With biochemical abnormalities of CKD-MBD and low BMD and/or fragility fractures...</td>
<td>Perform additional investment with bone biopsy prior to therapy with antiresorptive agents.</td>
</tr>
<tr>
<td>CKD STAGES 1–3T</td>
<td>Consider treatment with vitamin D, calcitriol/alphacalcidol, or bisphosphonates in the first 12 months. Base treatment choices on presence of CKD-MBD, as indicated by abnormal levels of calcium, phosphorus, PTH, alkaline phosphatases, and 25(OH)D. Consider bone biopsy to guide treatment, specifically before the use of bisphosphonates due to the high incidence of adynamic bone disease. There are insufficient data to guide treatment after the first 12 months.</td>
<td></td>
</tr>
<tr>
<td>CKD STAGES 4–5T</td>
<td>Suggest management as for patients with CKD stages 4–5 not on dialysis.</td>
<td></td>
</tr>
</tbody>
</table>
## Managing hyperphosphatemia

<table>
<thead>
<tr>
<th>DIET</th>
<th>PHOSPHATE BINDERS AND OTHER MEDICATIONS</th>
<th>DIALYTIC PHOSPHATE REMOVAL</th>
</tr>
</thead>
</table>
| CKD stages 3–5 and kidney transplant recipients (KTRs) with hyperphosphatemia | Suggest using phosphate binders, taking into account (NG):  
  • CKD Stage  
  • Presence of other components of CKD-MBD  
  • Concomitant therapies  
  • Side effect profile | N.A. |
| CKD stages 3–5 and KTRs with hyperphosphatemia and persistent or recurrent hypercalcemia | Recommend restricting dose of:  
  • Calcium-based phosphate binders and/or  
  • Calcitriol or vitamin D analogue | N.A. |
| CKD stages 3–5 and KTRs with hyperphosphatemia and arterial calcification and/or adynamic bone disease and/or persistently low PTH levels | Suggest restricting the dose of calcium-based phosphate binders | |
| CKD stage 5D | Suggest using phosphate binding agents.  
Suggest the choice of agent should take into account:  
  • CKD stage  
  • Presence of other components of CKD-MBD  
  • Concomitant therapies  
  • Side effect profile | Suggest increasing dialytic phosphate removal in the treatment of hyperphosphatemia |
# COMPLICATIONS OF CHRONIC KIDNEY DISEASE

## Treatment of abnormal parathyroid hormone

### CKD Stages 3–5 ND

<table>
<thead>
<tr>
<th>Higher PTH</th>
<th>Parathyroidectomy is suggested.</th>
</tr>
</thead>
<tbody>
<tr>
<td>If PTH is progressively increasing and remains persistently above the upper limit of assay despite correction of modifiable factors...</td>
<td>Suggest treatment with calcitriol or vitamin D analogs.</td>
</tr>
<tr>
<td>If intact PTH is above the upper normal limit of the assay, evaluate for:</td>
<td>It is reasonable to correct these abnormalities with any or all of:</td>
</tr>
<tr>
<td>• Hyperphosphatemia</td>
<td>• Reducing dietary phosphorus</td>
</tr>
<tr>
<td>• Hypocalcemia</td>
<td>• Phosphate binders</td>
</tr>
<tr>
<td>• Vitamin D deficiency</td>
<td>• Calcium supplements, and/or</td>
</tr>
<tr>
<td></td>
<td>• Native vitamin D</td>
</tr>
</tbody>
</table>

Normal PTH range varies with type of assay. The optimal PTH level is not known.

### Lower PTH

### CKD Stage 5D

**Suggestion:** Maintain PTH at approximately 2 to 9 times upper normal limit for assay, if PTH changes markedly in either direction within this range, initiate or change therapy to avoid progression to levels outside this range.

Parathyroidectomy is suggested when there is severe HPT and failure to respond to medical/pharmacologic therapy.

### Higher PTH

**IF PTH IS ELEVATED OR RISING**

Suggested treating with:

- Calcitriol, or
- Vitamin D analogs, or
- Calcimimetics, or
- Combination of calcimimetics and calcitriol or vitamin D analogs

It is reasonable to base initial drug selection on:

- Levels of serum calcium and phosphorus
- Other aspects of CKD-MBD

Adjust calcium or non-calcium-based phosphate binder so that treatments to control PTH do not compromise levels of phosphorus and calcium.

**IF PTH FALLS BELOW 2 TIMES THE UPPER LIMIT OR NORMAL**

Suggested reducing or stopping:

- Calcitriol
- Vitamin D analogs and/or
- Calcimimetics

### Lower PTH

### UPPER/LOWER LIMIT OF NORMAL

## References
