Managing Anemia and Metabolic Bone Disease in Dialysis Patients

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7.1 Anemia

Anemia occurs over 95% of patients with end-stage renal disease requiring dialysis [1]. The three most important causes of anemia in dialysis patients are: erythropoietin deficiency, because the kidney is the exclusive producer of erythropoietin; iron deficiency, because patients on dialysis have both reduced intestinal absorption of iron and some degree of blood loss during dialysis from frequent blood draws and loss of blood in the dialysis tubing and filter; and inflammation, which is almost ubiquitous among dialysis patients [1].

In most patients on dialysis, the assumption should be that erythropoietin deficiency, iron deficiency, and inflammation combine to varying degrees in determining the degree of anemia [1–3]. Understanding this balance is key to effectively managing anemia in dialysis patients. Figure 7.1a provides a practical alogrithm for managing patients. At various points, iron deficiency may be a dominant issue—for example, early in the initiation of erythropoiesis-stimulating agent (ESA) where a burst of erythropoiesis may consume available iron and exacerbate iron deficiency, which if uncorrected leads to a state of iron-restricted erythropoiesis. At other times, with a smoldering infection or a rejected allograft in place, an inflammatory mileau may induce a profound state of erythropoietin resistance where the anemia persists despite large doses of both ESA and intravenous iron [1].

Understanding the differential contribution of each of the three major causes of anemia requires work-up of patients for anemia, with a particular focus on excluding the possibility of iron deficiency, and for inflammation. Kidney Disease—Improving Global Outcomes (KDIGO) recommendations on how frequently to measure hemoglobin (Hb) and iron parameters are listed in Tables 7.1 and 7.2, respectively [1]. Although assessment of iron by a bone marrow biopsy may represent the gold standard in assessing iron stores, it is clinically impractical and measurement of serum ferritin and transferrin saturation provides the best indicators of iron stores [4, 5]. The serum ferritin is an "acute phase reactant" and is affected by inflammation. Thus, ferritin values are of greatest predictive value when low (< 100 ng/mL), but of limited value when elevated. In this setting, a transferrin saturation (TSAT; serum iron × 100 divided by total iron-binding capacity) measures circulating iron that is available for erythropoiesis, and may provide actionable information on body iron stores.

The observation that there is sluggish or suboptimal correction of anemia despite treating with ESA and iron should prompt a search for an inflammatory source [6]. There are more precise definitions of ESA resistance [1]. One definition that remains in use is from the National Kidney Foundation, which defines ESA resistance as the failure to achieve the target Hb in the presence of adequate iron stores with epoetin at doses of 450 IU/kg/week intravenously or 300 IU/kg/week subcutaneously within 4–6 months of treatment initiation, or a failure to maintain the target Hb subsequently at these doses [7]. The most common laboratory indicators of ESA resistance are two acute phase reactants—ferritin and albumin—the ferritin is usually markedly elevated with a normal or low transferrin saturation, and the albumin is low despite an absence of weight loss. A CRP can also be measured and is markedly elevated in the context of inflammation.

7.1.1 The Target Hb in Patients with CKD Anemia

Four large randomized control trials (RCTs) have explored the effect of anemia correction on clinical outcomes [8–11]. These studies have examined both non-dialysis and dialysis patients.

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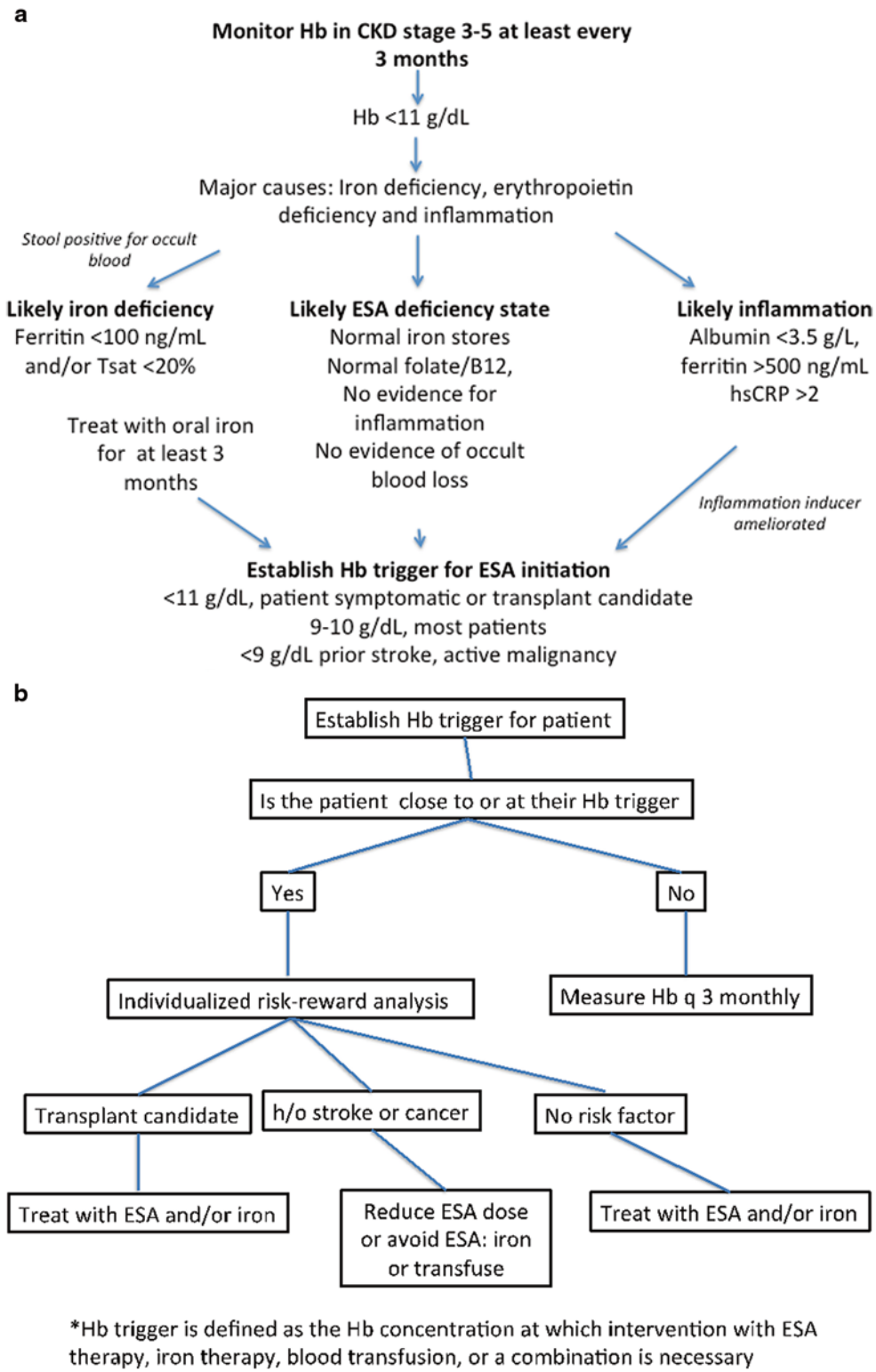

Fig. 7.1a Algorithm for managing anemia in dialysis patients. **b** An alternative approach for identifying an individualized hemoglobin (Hb) concentration

The Normal Hematocrit study evaluated symptomatic dialysis patients and tested the hypothesis that the correction of anemia with epogen in hemodialysis patients with clinical evidence of congestive heart failure or ischemic heart disease would result in improved outcomes (Fig. 7.2). The primary endpoint was the length of time to death or a first nonfatal myocardial infarction. Patients were randomized to either a higher Hb concentration of 13–15 g/dL or a lower Hb arm of

Table 7.1 Testing for anemia and investigation of anemia

For CKD patients without anemia, measure Hb concentration when clinically indicated and
At least annually in patients with CKD 3
At least twice per year in patients with CKD 4–5 ND
At least every 3 months in patients with CKD 5HD and 5PD
For CKD patients with anemia not being treated with an ESA, measure Hb concentration when clinically indicated and
At least every 3 months in patients with CKD 3–5 ND and 5PD
At least monthly in patients with CKD 5HD

CKD chronic kidney disease, *Hb* hemoglobin, *ND* not on dialysis, *HD* on hemodialysis, *PD* on peritoneal dialysis, *ESA* erythropoiesis-stimulating agent

Table 7.2 Use of iron to treat anemia in chronic kidney disease (CKD)

Evaluate iron status (TSAT and ferritin) at least every 3 months during ESA therapy, including the decision to start or continue iron therapy
Test iron status (TSAT and ferritin) more frequently when initiating or increasing ESA dose, when there is blood loss, when monitoring response after a course of IV iron, and in other circumstances where iron stores may become depleted

TSAT transferrin saturation, *ESA* erythropoiesis-stimulating agent

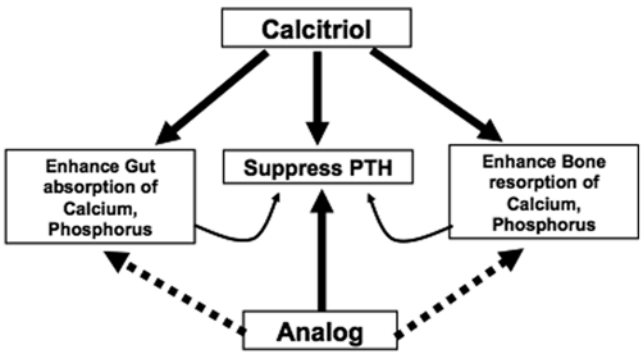

Fig. 7.2 Vitamin D action

9–11 g/dL. Patients were treated with a mean epoetin dosage of 460 U/kg/week in the high Hb arm and 160 U/kg/week in the low Hb arm. The study was halted at the third interim analysis on the recommendation of the Data Safety Monitoring Board. At 29 months, there were 183 deaths and 19 first nonfatal myocardial infarctions in the group with a normal hematocrit and 150 deaths and 14 nonfatal myocardial infarctions in the low hematocrit group (risk ratio (RR), 1.3; 95% confidence interval (CI), 0.9–1.9). There was also a higher rate of vascular thrombosis and strokes in patients in the higher Hb arm as compared to patients randomized to the lower Hb arm [8].

Three RCTs have evaluated non-dialysis chronic kidney disease (CKD) patients—Cardiovascular Reduction Early Anemia Treatment Epoetin beta (CREATE), Correction of Hemoglobin and Outcomes in Renal Insufficiency (CHOIR), Trial to Reduce Cardiovascular Events with Aranesp Therapy (TREAT) [9–11]. In all three studies, no improvement with anemia correction but instead harm with respect to a composite mortality and cardiovascular endpoint or components of the composite endpoint was observed. Taken collectively, the Normal Hematocrit, CREATE, CHOIR, and TREAT demonstrate that there is increased risk for either death or cardiovascular disease (CVD) outcomes or renal outcomes with targeting a higher Hb with higher doses of ESA. Recent meta-analyses have also reached similar conclusions. In the meta-analysis by Phrommintikul et al. [12] nine RCTs were selected on the basis of quality, sample size, and follow-up, and lumped together for a total sample of 5143 patients. Both dialysis and non-dialysis CKD trials were included. There was a higher risk of all-cause mortality (RR, 1.17; 95% CI, 1.01–1.35; $p=0.031$) and arteriovenous access thrombosis (RR, 1.34; 95% CI, 1.16–1.54; $p=0.0001$) in the higher Hb target group compared to the lower Hb target group. However, it remains uncertain whether normalization of anemia versus treatment with an ESA explains the higher risk of CVD. Synthesizing secondary analyses of the randomized trials and taking the results of the observational studies into account, the preponderance of evidence suggests that a relationship between ESA exposure and adverse outcomes is plausible—a conclusion that is also supported by evidence of adverse outcomes in non-renal populations. The US Food and Drug Administration (FDA) now recommends more conservative dosing guidelines for ESAs commensurate with these concerns.

The US FDA has also provided guidelines on the target Hb level when treating dialysis (and non-dialysis) patients with an ESA [13] (Table 7.3). While emphasizing the importance of individualizing therapy, the FDA recommends a narrow Hb "window" for treatment: initiating ESA therapy when the Hb level is <10 g/dL and interrupting or reducing ESA dose when the Hb level approaches or exceeds 11 g/dL.

The Hb targets recommended by the FDA are reasonable in a stable chronic dialysis patient, although these recommendations have generated much controversy [1, 13, 14]. However, when a dialysis patient has an acute illness and becomes more severely anemic, it becomes very challenging to manage anemia. In these circumstances, an alternative approach should be considered for identifying an individualized Hb concentration at which to intervene—identifying, if you will, the patient's "Hb trigger" (Fig. 7.1b).

The Hb trigger is the Hb level at which the patient becomes symptomatic and an intervention should be considered. For

Table 7.3 FDA recommendations for anemia treatment with an erythropoiesis-stimulating agent

Individualize therapy using the lowest ESA dose possible to reduce the need for red blood cell transfusions, and weighing the possible benefits of using ESAs to decrease the need for red blood cell transfusions against the increased risks for serious adverse cardiovascular events
For patients with CKD who have anemia and are receiving dialysis, ESA should be started when the hemoglobin level is less than 10 g/dL, and the dose should be reduced or interrupted if the hemoglobin level approaches or exceeds 11 g/dL

ESA erythropoiesis-stimulating agent, *CDK* chronic kidney disease

each patient this may be different. Generally, increasing the ESA dose or treating the patient with iron is not required because the patient is already on an optimal ESA dose or already iron replete. Here, the acute illness has created a state of heightened inflammation, and either treatment of the underlying acute problem is necessary or a blood transfusion is indicated because of patient-related factors. For a young dialysis patient, an Hb of 8 g/dL may necessitate treatment for symptoms of fatigue. In contrast, for a frail patient with underlying CVD, the Hb trigger might be 10 or 11 g/dL. How high or low one lets the Hb drift has generated much controversy [15, 16], but in general needs to be individualized. Transfusing blood might be a reasonable strategy to maintain the patient above his or her individualized Hb trigger [17, 18].

Another scenario in which individualization may be necessary is when there is a need to use ESAs sparingly. For example, the KDIGO guidelines recommend caution in using ESAs in patients with a history of a stroke or in patients actively being treated with chemotherapy for a curable cancer [1]. Here, especially in a patient with cancer, a dialysis patient may be managed on a low dose or even no ESA, and decisions around transfusion will depend on the patient's individualized Hb trigger [19] .

7.1.2 Erythropoiesis-Stimulating Agents

In the era prior to the discovery of epoetin alfa (Epo), that is, before 1989, the treatment of CKD anemia consisted largely of blood transfusion and anabolic steroids. With the introduction of Epo, a transformation occurred in the management of anemia. By the 1990s, almost all patients on dialysis were receiving Epo therapy. At least initially, normalization of the Hb level in dialysis patients was recommended because observational studies, dating back to the 1990s, suggested an association between better outcomes and higher levels of Hb—lower rate of cardiovascular complications, lower mortality risk, and higher health-related quality of life. However, in 1998 with the publication of the Normal Hematocrit trial in hemodialysis patients, and in 2006 and 2009 with the publication of the CHOIR and TREAT studies in non-dialysis patients, respectively, it became clear that treatment of mild anemia with normalization of the Hb was not associated with clinically meaningful benefits. Rather, there was an increased risk of cardiovascular complications and kidney disease progression without clinically meaningful improvement in quality of life in patients assigned to a higher Hb target level. Based on these studies, the US FDA has recommended that end-stage renal disease (ESRD) patients should be treated to Hb target less than 11 g/dL.

The 2012 KDIGO Anemia guidelines backed this up by recommending against normalization of the Hb concentration and advocated for a target Hb of 9.0–11.5 g/dL [1]. The guidelines emphasized that ESAs should be used "cautiously, if at all, in patients with a prior history of a stroke or a history of cancer." The KDIGO guidelines recommend that anemia treatment in dialysis patients should be individualized based on the rate of fall of Hb concentration, prior response to iron therapy, the risk of needing a transfusion, and the risks attributable to anemia as well as those related to ESA therapy.

7.1.3 ESA Therapeutic Options

There are many ESAs currently in the market, but only two currently in the USA (Table 7.4) [19–24]. Available ESAs can be broadly divided into short- and long-acting agents. The very first ESA was Epo, marketed in the USA as Epogen and approved in 1989 by the US FDA, which is short-acting (half-life ($t_{1/2}$) of approximately 8.5 h). Epo can be administered subcutaneously or intravenously. Epo is the only short-acting ESA available currently in the USA. There are three other short-acting ESAs available in non-US markets: epoetin-beta, epoetin-omega (Repotin®, South Africa), epoetin-theta (Biopoin®, Eporatio®, Ratioepo®, Europe). Differences exist in potency, safety, tolerability, and immunogenicity among these various forms of epoetin. In addition, to different classes of short-acting Epos, Epo biosimilars are also widely available. Biosimilars are "copy-cat" agents to the innovator or originally developed ESA. Currently, no Epo biosimilar has received approval from the US FDA, although the emergence of biosimilar agents in the USA is imminent [25].

The most commonly used long-acting Epo is darbepoetin alfa (Aranesp®, Amgen, Thousand Oaks, CA, USA). Darbepoetin alfa is a hyperglycosylated Epo analogue designed for prolonged survival in the circulation and with consequent greater bioavailability than the shorter-acting epoetins (darbepoietin has a three-fold longer $t_{1/2}$ than Epo: 25.3 vs. 8.5 h) [26]. Although darbepoietin alfa was approved by the US FDA and the European Medicines Agency (EMA) in 2001, it is currently used mostly in non-dialysis CKD patients, even though it has a much longer half-life than epoetin and can

Table 7.4 Types of ESAs currently available

Available in the USA	
Type of ESA	*Duration of action*
Epoetin alfa (Epogen®/Procrit®)	Short acting
Darbepoetin-alfa (Aranesp®)	Longer acting
Not available in the USA	
Epoetin omega (Epomax)	Short acting
Epoetin delta (Dynepo)	Short acting
Epoetin beta (NeoRecormon®)	Short acting
CERA (Mircera®)	Longer acting

ESA erythropoiesis-stimulating agent

therefore be dosed less frequently ($t_{1/2}$ of darbepoetin-alfa compared with Epo is 54 vs. 16–24 h in dialysis patients).

The other long-acting epoetin that is approved worldwide is "Continuous Erythropoietin Receptor Activator (CERA)" [27]. Notably, CERA is approved in the USA but not marketed because of patent infringement issues. CERA is a molecule that has a water-soluble polyethylene glycol (PEG) moiety added to the epoetin beta molecule. The $t_{1/2}$ after intravenous administration is approximately 134 and 139 h after subcutaneous administration, and the dose is the same by either route. Peginesatide, introduced with much excitement a few years ago [28, 29], has now been withdrawn because of a series of unexpected adverse effects, including over 50 deaths among dialysis patients.

7.1.4 Iron Supplementation to Treat Anemia in Dialysis Patients

Iron deficiency is a common finding in patients in dialysis patients. Absolute iron deficiency reflects no stores of iron, and occurs when both transferrin saturation and ferritin levels are low (<20% and 100 ng/mL, respectively; reviewed extensively in reference [1] and references [30–34]). Functional iron deficiency is the inadequate release of iron to support erythropoiesis, despite the presence of adequate stores of iron. ESA therapy can be associated with functional iron deficiency when patients are inflamed (e.g., with a coexisting smoldering infection or a failed kidney allograft still in place. Functional iron deficiency should be suspected when the serum ferritin is high but transferrin saturation is low. Iron deficiency can lead to decreased effectiveness of ESA therapy, and iron therapy without ESA therapy is usually unsuccessful in patients with CKD. Untreated iron deficiency is a major cause of hyporesponsiveness to ESA treatment.

Iron deficiency is treated with iron administered either by the oral or intravenous route. Oral iron therapy is the preferred method of treating non-dialysis CKD patients. Various oral iron agents are available (Table 7.5).

Oral iron may be tried initially, but is generally not effective in hemodialysis patients because of concerns about lack of absorption due to a hepcidin-mediated functional block in absorption of iron at the level of the enterocyte iron channel. Recently, ferric citrate was approved for the control of serum phosphorus levels in ESRD patients. In addition, ferric citrate repletes iron in dialysis patients. In the ferric citrate phase 3 trials, dialysis patients treated with ferric citrate attained a higher Hb and required less intravenous iron and ESA than control patients [35, 36].

Table 7.5 Oral iron agents and elemental iron content

Iron preparations	Number of pills required to provide ~200 mg of iron	Tablet size (mg)	Amount of elemental iron (mg)/pill
Ferrous sulfate	3	325	65
Ferrous gluconate	6	325	35
Ferrous fumarate	2	325	108
Iron polysaccharide	2	150	150

Table 7.6 Intravenous iron preparations commonly used in treating iron deficiency in dialysis patients*

Product	Indication	Warnings	Total dose infusion	Relative cost
Ferric gluconate (Ferrlecit)	HD pts receiving ESA	General	No	$$$
Iron sucrose (Venofer)	HD, PD, CKD pts	General	No	$$$
LMW iron dextran (INFeD)	Iron-deficiency anemia	Black box	Yes	$$
HMW iron dextran (DexFerrum)	Iron-deficiency anemia	Black box	Yes	$

ESA erythropoiesis-stimulating agent, *CDK* chronic kidney disease, *LMW* low molecular weight, *HMW* high molecular weight
*Ferumoxytol is approved but not commonly used

Four intravenous agents are currently used the USA: iron dextran, ferrous gluconate, and iron sucrose. These agents have low molecular weight and are safer than high molecular weight iron dextran that preceded them and was associated with a high risk of anaphylaxis (Table 7.6).

The 2012 KDIGO Anemia Clinical Practice Guidelines make several recommendations about the use of iron [1]. Most of these recommendations are based on opinion rather than evidence derived from randomized trials. The KDIGO guidelines recommend that decision-making around the route of iron therapy should be governed by the severity of iron deficiency, availability of venous access, response to prior oral or intravenous iron therapy and tolerance of side effects, patient compliance, and cost. Furthermore, KDIGO suggests that decisions to continue iron therapy may be based on recent patient responses to iron therapy, TSAT and ferritin, Hb concentration, ESA responsiveness, ESA dose, ongoing blood losses, and patient's clinical status. There is much debate about when to administer intravenous iron, particularly in relation to the TSAT and ferritin levels [37]. Table 7.7 summarizes one approach that is consistent with KDIGO.

When oral iron is being considered in correcting iron deficiency in a dialysis patient, it is important to dose iron adequately. In general, 200 mg of elemental iron is necessary (ferrous sulfate 325 mg three times daily). If iron supplementation with oral iron after a 1–3-month trial is ineffective (measured by no rise in Hb level and/or no fall in ESA requirement) then it is appropriate to consider intravenous iron. Intravenous iron can be administered as a single large

Table 7.7 Practical approach to repleting iron in end stage renal disease (ESRD) patients

Hb at target	Hb < target	Hb < target	Hb < target
TSAT > 20 % Ferritin 200–500	TSAT > 20 % Ferritin 200–500	TSAT > 20 % Ferritin 500–800	TSAT > 20 % Ferritin > 800
No iron	Iron	Individualize iron	Hold iron

TSAT transferrin saturation

dose or repeated smaller doses depending on the specific intravenous iron preparation used. The initial course of intravenous iron is approximately 1000 mg in divided doses, which may be repeated if there is no effect on Hb level and/or decreased ESA dose.

Iron status should be monitored every 3 months with TSAT and ferritin while on ESA therapy [1]. When initiating or increasing ESA dose, in the setting of ongoing blood loss, or in circumstances where iron store may become depleted, it is also appropriate to monitor TSAT and ferritin more frequently. A common setting in which to monitor iron status more frequently is infection or inflammation.

7.2 Metabolic Bone Disease

Disturbances in calcium and phosphorus metabolism are common in CKD patients [38–40]. The spectrum of disorders observed in CKD patients has been defined by the KDIGO guideline group (Fig. 7.3).

As glomerular filtration rate (GFR) declines, the kidney's ability to excrete phosphorus decreases as a result of lower nephron mass and the serum phosphate level rises. In order to maintain normophosphatemia there is increased secretion of fibroblast growth factor 23 (FGF23) [41, 42], the main hormonal regulator of phosphorus homeostatis. In patients with early CKD, FGF23 stimulates increased phosphate excretion in order to maintain phosphorus homeostasis. However, in more advanced CKD, FGF23 is unable to enhance renal phosphate excretion, and hyperphosphatemia results. In addition to its effects on phosphate excretion, FGF23 stimulates parathyroid hormone (PTH) production by the parathyroid glands and reduces $1,25(OH)_2D_3$ levels through inhibition of 1-alfa hydroxylase, an enzyme produced in the kidney. Advanced kidney failure independently contributes to reduced activity of 1 alfa hydroxylase [43, 44]. Reduced $1,25(OH)_2D_3$ levels result in reduced gastrointestinal (GI) calcium absorption and hypocalcemia [45].

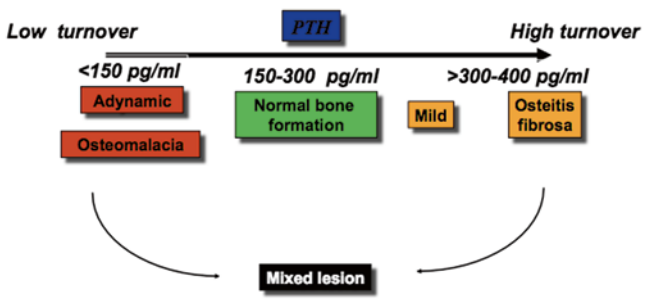

Fig. 7.3 Spectrum of mineral bone density (MBD)

The parathyroid gland is highly sensitive to even very small changes in ionized extracellular calcium and rapidly releases PTH in response to a decrease in calcium concentration. This response is mediated by the calcium-sensing receptor (CaR), the primary regulator of PTH secretion.

Calcitriol inhibits gene transcription of precursors of PTH, and therefore a decline in calcitriol leads to increased PTH production (Fig. 7.2). Decreased calcitriol has also been linked to decreased expression of vitamin D receptors (VDR) and of CaR in parathyroid tissue, which also contributes to increases in serum PTH levels.

High PTH results in osteoclast-mediated bone demineralization and in the long-term renal bone disease or osteodystrophy [43, 44].

Elevated PTH is known to contribute to pathogenesis of renal osteodystrophy and has also been implicated in damage to other systems, including cardiac, cutaneous, endocrine, immunologic, and nervous systems [45–47]. Associated imbalances in mineral homeostasis probably also contribute to organ system damage.

7.2.1 Hyperphosphatemia

In dialysis patients, the focus of management is to prevent metabolic bone disease by aiming for a serum phosphorus level within normal limits [48–51]. The normal ranges are listed in Table 7.8.

This is accomplished by controlling the serum phosphorus and PTH to normal or near-normal levels. In patients with stage 5 CKD, the target serum level of phosphorus is between 3.5 and 5.5 mg/dL [1]. To achieve these levels, a phosphate-restricted diet (800–1000 mg/day) and treatment with a phosphate binder to decrease dietary absorption of phosphate is necessary.

In patients on dialysis, it is necessary to use both a calcium-containing and non-calcium-containing phosphate binder because use of only a calcium-containing binder frequently results in a positive calcium balance and a higher risk of arterial calcification. On the other hand, managing hyperphosphatemia with only non-calcium-containing binders requires large doses of the binders leading to higher risk

Table 7.8 Normal ranges for mineral bone density (MBD) biochemical parameters

Normal phosphorus	2.5–4.5 mg/dL
Normal calcium	8.5–10 mg/dL
Normal iPTH	15–65 pg/mL (varies with the assay used)

of side-effects from these agents (e.g., bloating and GI discomfort with the use of sevelemar) and greater expense.

7.2.1.1 Calcium-Containing Binders

Calcium-containing phosphate binders are available as the calcium salts of carbonate, acetate, and citrate [52]. Calcium citrate increases aluminum absorption and should be avoided. Calcium acetate is the most potent phosphate binder in this class. Although calcium-containing binders provide an effective means of controlling phosphorus, their use may not be without risk. Calcium excess induced by the prescription of large doses of calcium-containing phosphate binders has been associated with calcifications of the aorta and the carotid and coronary arteries; calcium-containing phosphate binders have been implicated in the acceleration of vascular disease that accompanies advancing CKD. Widespread use of these drugs may also play a contributory role in the development of calciphylaxis.

Calcium-containing binders should not be used if the patient has hypercalcemia (> 10.2 mg/dL), a PTH < 150 pg/mL, or evidence of severe extraskeletal calcification. The total intake of elemental calcium should not exceed 2000 mg/day, and the total dose of elemental calcium provided by calcium-based binders should not exceed 1500 mg/day.

7.2.1.2 Non-Calcium-Containing Binders

There are 4 types of non-calcium-containing phosphorus binders: Sevelamer, lanthanum, aluminum hydroxide, and ferric citrate [53–55].

Sevelamer is available as sevelemar hydrochloride (RenaGel) or sevelamer carbonate (Renvela). Both are calcium- and aluminum-free phosphate binders that control serum phosphorus and reduce PTH levels without inducing hypercalcemia. In addition, both lower serum cholesterol levels. Sevelamer hydrochloride is an exchange resin that releases chloride in exchange for phosphate. The subsequent formation of hydrochloric acid creates an acid load and may cause metabolic acidosis; sevelamer carbonate is less likely to cause acidosis.

Lanthanum carbonate (Fosrenol) is also a calcium- and aluminum-free binder that is approved for the treatment of hyperphosphatemia in patients with ESRD. The initial clinical experience has shown the drug to be both effective and well tolerated. Oral bioavailability of lanthanum is very low, and the drug is excreted largely unabsorbed in the feces. There has been concern about the long-term safety of lanthanum because of reports of tissue deposition of lanthanum in the liver, lung, and kidney in animal models exposed to lanthanum. However, no long-term toxicity has been reported in humans.

Aluminum is a powerful phosphate binder because it forms a very strong ionic bond with phosphorus. However, because of concerns about long-term toxicity, including dementia and aluminum bone disease, aluminum-containing binders have largely fallen from favor. In patients with severe hyperphosphatemia refractory to treatment, aluminum-containing compounds such as aluminum hydroxide and aluminum carbonate may be used as a short-term therapy (for up to 1 month); thereafter, they should be replaced with either lanthanum or sevelamer.

Ferric citrate is a newly approved phosphate binder, effective in both reducing hyperphosphatemia and correcting iron deficiency [56]. Ferric citrate works as well as sevelemar or calcium carbonate as a phosphate binder. Ferric citrate also effectively reduces both intravenous iron and ESA utilization and thus could become the default therapeutic agent in dialysis patients, both for phosphate control and iron repletion. A maximum of 12 tablets of ferric citrate may be given with meals. It is likely, however, that 12 tablets each day (doses as much as 12 g of ferric citrate) are unlikely to be well tolerated by patients—the most common adverse effects being GI (nausea, vomiting, diarrhea, and constipation). Each tablet of ferric citrate (1 g ferric citrate) is 210 mg of ferric iron.

7.3 Metabolic Bone Disease

There are a spectrum of metabolic bone disease abnormalities in ESRD patients [57] (Fig. 7.3). On one end of the spectrum is low turnover "adynamic bone disease" (ABD), which occurs in a minority of patients. On the other side of the spectrum is secondary and tertiary hyperparathyroidism—high-turnover bone disease osteitis fibrosa.

7.3.1 Low Turnover Adynamic Bone Disease

ABD is characterized by extremely low bone turnover with reduced synthesis of bone matrix owing to decreased osteoblastic and osteoclastic activity [58]. In association with reduced bone formation rates (BFR), there is a lack of osteoid accumulation differentiating this abnormality from osteomalacia. Whether ABD is a benign, asymptomatic condition of ESRD has been a matter of debate since its first description. The two major concerns with ABD are the frequent episodes of hypercalcemia with possible soft tissue calcification, and increased risk for fractures due to the impaired remodeling process. The most likely mechanism for the occurrence of ABD is the relative hypoparathyroidism seen in these patients. As the serum-ionized calcium level is one of the most powerful factors affecting PTH secretion, a continuously positive calcium balance associated with oral calcium carbonate ($CaCO_3$) treatment, vitamin D administration, and supraphysiological dialysate calcium may lead to oversuppression of parathyroid gland activity.

7.3.2 High Turnover Bone Disease

When PTH levels remain persistently elevated, secondary hyperparathyroidism develops. Left untreated, secondary hyperparathyroidism can progress to refractory hyperparathyroidism, a condition in which the parathyroid glands become autonomous and release high amounts of PTH out of proportion to a patient's hypocalcemia or hyperphosphatemia; this may occur in late-stage CKD or in ESRD. Secondary hyperparathyroidism is associated with effects on bone—ostitis fibrosis cystica, where osteoclasts stimulated by chronically elevated concentrations of PTH cause severe bone loss and predispose patients to fractures and bone cysts.

Monitoring and treatment of an elevated PTH level may help prevent the development of secondary hyperparathyroidism. The KDIGO guidelines recommend a PTH target in dialysis patients of 2–9 times the upper limit of the normal PTH range (the Kidney Disease Outcomes Quality Initiative (KDOQI) target is 150–300 pg/mL). The target values for PTH in patients with dialysis patients is higher than normal because higher levels are thought to be required for normal bone remodeling, and suppression of PTH to normal non-uremic values may be associated with a higher prevalence of adynamic bone disease. Monthly monitoring of PTH is necessary in order to calibrate the use of active vitamin D therapy. Monthly monitoring of serum calcium and phosphorus levels is also recommended.

In addition to vitamin D and its analogues, cinacalcet (Sensipar) is now widely used [59–61]. Cinacalcet was approved in 2004 and is a calcimimetic that binds to the calcium-sensing receptor in the parathyroid gland and leads to reductions in PTH release. However, to date, there is no definitive proof that cinacalcet improves hard outcomes in patients with CVD or bone disease. In this regard, EValuation Of Cinacalcet Hydrochloride Therapy to Lower CardioVascular Events (EVOLVE) [62–64], a double-blind randomized trial of 3883 hemodialysis patients with moderate to severe hyperparathyroidism (cinacalcet versus placebo) was null with respect to the primary composite endpoint of time to death, myocardial infarction (MI), hospitalization for unstable angina, heart failure, or a peripheral vascular event [62]. The fracture rate between the two arms of the study was not different. However, patients randomized to cinacalcet had a 50 % lower rate of parathyroidectomy, but hypocalcemia was common in the active treatment arm. Importantly, however, the trial has been criticized for the high rate of cross-overs between the two arms of the study and for imbalances in baseline characteristics [63, 64].

As with active vitamin D therapy, cinacalcet effectively lowers the circulating levels of PTH; however, it does not cause the increased GI absorption of calcium and phosphorus associated with vitamin D therapy. Hypocalcemia can occur in a small percentage of patients. In patients with ESRD, combination therapy with cinacalcet and active vitamin D is advantageous, but the optimal mix has not yet been determined.

7.3.3 Parathroidectomy in Dialysis Patients

While most dialysis patients are now managed successfully with cinacalcet, active vitamin D, and management of hyperphosphatemia, some patients become refactory to medical management. These patients are usually characterized by severe clinical, biochemical, and radiological hyperparathyroidism. The PTH levels are usually very high (8–20-fold higher than the upper limit of normal (ULN) for PTH) and resistant to high-dose vitamin D and cinacalcet therapy. The serum calcium is either normal or more commonly elevated. Morphologically, there is evidence of nodular hyperplasia in very enlarged parathyroid glands. There is also evidence of monoclonality (monoclonal proliferation) in the nodules.

While ethanol injection into the largest parathyroid glands is sometimes used to treat refractory hyperparathyroidism, the mainstay is surgical parathyroidectomy [65, 66]. There are three surgical options: subtotal parathyroidectomy, total parathyroidectomy with parathyroid autotransplantation, and total parathyroidectomy without autografting. The main disadvantage of the first two options is recurrence of hyperparathyroidism, whereas the main disadvantage of the latter approach, that is, total parathyroidectomy without autografting is the risk of adynamic bone disease and vascular calcification. Even with this approach, however, detectable PTH levels have been reported because residual tissue is left behind following surgery.

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