Anemia and Bone Disease of Chronic Kidney Disease: Pathogenesis, Diagnosis, and Management

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ABSTRACT

Anemia and metabolic bone disease accompany chronic kidney disease (CKD), and worsen as CKD progresses. It is likely that both processes contribute to the increased morbidity and mortality seen in CKD. This paper briefly reviews the pathogenesis and diagnosis of anemia and bone disease in CKD, and summarizes recent consensus guidelines for treatment.

KEYWORDS: Chronic kidney disease, anemia, hyperparathyroidism

INTRODUCTION

Chronic kidney disease (CKD) affects 10–15% of adults in the United States, is a group of disorders characterized by a progressive decline in the glomerular filtration and renal excretion of low molecular weight solutes. The severity of CKD is measured by the estimated glomerular filtration rate (eGFR), derived from the serum creatinine (SCr) level, and demographic criteria: age, sex, and ethnicity. The normal eGFR is over 120 ml/min; as CKD worsens, the eGFR declines. The current classification of CKD was introduced in 2002 by the National Kidney Foundation (NKF) and subsequently adopted by the international group, Kidney Disease Improving Global Outcomes (KDIGO). The cause of CKD may be diabetes mellitus, hypertension, polycystic disease, chronic glomerulonephritis or other causes, but regardless of diagnosis, the NKF/KDIGO classification defines stage III as an eGFR of 30–60 ml/min, stage IV as an eGFR of 15–30 ml/min, and stage V CKD as an eGFR below 15 ml/min.

Many large observational studies demonstrate that cardiovascular morbidity and mortality increase as the stage advances. Recently, it has been shown that albuminuria ( > 30 mg/gram creatinine/24 hour urine), independently of the eGFR predicts morbidity and mortality. Patients with CKD are at highest risk of all cause mortality if their eGFR is < 15 ml/min and urinary albumin excretion is > 300 mg/gram creatinine, but in all age groups, mortality risk increases below an eGFR of 60 ml/min.

CKD involves many pathophysiologic abnormalities: fluid overload, hypertension, accelerated atherosclerosis, inflammation, malnutrition, metabolic acidosis, hyperkalemia, anemia, and metabolic bone disease and it is difficult to ascribe the increased mortality risk to one or even a few causes. As part of a broad approach, these abnormalities can be evaluated and treated, thereby potentially decreasing the mortality risk. Reviewing the treatment of all of these processes is beyond the scope of a short paper. But two abnormalities associated with the decreased renal synthetic function of CKD: anemia, due to decreased production of erythropoietin, and bone disease, due to decreased production of calcitriol, decreased excretion of phosphorus, and increased synthesis of parathyroid hormone (PTH), may present early in CKD. They are relatively easy to diagnose and treat, and provide an opportunity to the primary care provider to potentially decrease some risks associated with CKD. This paper will review the diagnosis and management of anemia and bone disease due to CKD.

Anemia

Anemia, defined as a Hgb < 11.0 g/dL, is common in CKD and worsens as the CKD stage increases: data from a large observational study showed an anemia prevalence of 1.3% in stage III, 5.2% in stage IV, and 44.1% in stage V CKD; once patients progress to dialysis, it exceeds 90%. The cause of anemia is multifactorial, including deficiencies of vitamin B12 or folate, defective intestinal absorption of iron due to the presence of hepcidin, occult bleeding due to a qualitative defect in platelet function, hemolysis, or bone marrow disease. But the likely greatest contributor relates to CKD itself: a defect in erythropoietin (EPO) production.

EPO is a 165 amino acid protein, which stimulates bone marrow receptors to produce red cell precursors and promote their differentiation into mature erythrocytes. EPO is primarily synthesized in kidney cells, so progressive loss of kidney function leads to decreased EPO production. EPO production normally can be increased thousandfold in response to tissue hypoxia in a process mediated by hypoxia inducible factor 1, and loss of this augmentation occurs in CKD. These abnormalities are present in all causes of CKD, with some exceptions: polycystic disease, for example, may be associated with normal or high EPO production.

Until the mid to late 1980s, the only therapy for the anemia of CKD was vitamin and iron supplementation and blood transfusions. Besides depleting the blood supply, over-reliance on transfusions caused increase in hepatitis B and C in CKD patients, iron overload, and development of antibodies, increasing sensitization to potential renal transplants.
The gene for EPO production was cloned in 1985; immediately, EPO production began, and soon, many clinical trials showed that administration of exogenous EPO increased the Hgb in patients at all stages of CKD, and decreased transfusion dependence. Also, most clinical trials showed that administration of EPO and its structural analogue, darbepoetin (with a longer half life) tends to improve subjective symptoms [fatigue, exercise tolerance, sexual dysfunction, cognitive function, and depression] in CKD in treated patients compared to controls⁷. These findings, along with suggestions that cardiovascular morbidity and mortality was decreased with EPO treatment, and Medicare payment for erythropoietin in dialysis patients on dialysis, led to virtually universal EPO treatment of the anemia in dialysis patients and common treatment at earlier stages of CKD.

But the Hgb target to which EPO therapy should be directed was not well established. Three large, randomized, placebo controlled trials, published between 2006 and 2009 addressed this issue. The trials all randomized anemic patients with CKD to either a high or low Hgb target by varying the dose of EPO or darbepoetin. The Correction of Hemoglobin and Outcomes in Renal Insufficiency (CHOIR) study randomized patients to Hgb normalization [mean achieved Hgb 13.5 g/dL] or partial correction [mean achieved Hgb 11.3] and found that normalization of the Hgb was associated with a statistically greater rate of a composite outcome of cardiovascular death or morbidity.⁸ The Cardiovascular Risk Reduction by Early Anemia treatment with Epoetin beta (CREATE) trial randomized patients to full anemia correction [target Hgb 13 -15 g/dL] or partial correction [target Hgb 10.5-11.5 g/dL]. There was a non-statistically significant trend towards a higher incidence of cardiovascular events in the full correction group.⁹ Finally, the Trial to Reduce Cardiovascular Events with Aranesp Therapy (TREAT) trial compared targeting a Hgb of 13 g/dL with darbepoetin to placebo in CKD patients with diabetes, and found treatment to a higher Hgb target was not associated with a cardiovascular benefit, and was associated with a higher risk of stroke, and cancer associated mortality.¹⁰

The results of these trials have greatly influenced treatment of CKD associated anemia with EPO or darbepoetin. In 2011, The Food and Drug Administration [FDA] released an advisory statement that the target Hgb level in CKD patients should no longer be 10–12 g/dL, but should be replaced by a program of using the lowest possible EPO or darbepoetin dose necessary to avoid transfusions.¹¹ The FDA later specified that although that treatment of CKD associated anemia should be individualized, dosing of EPO or darbepoetin in an anemic patient with CKD should be decreased once the Hgb level exceeds 11.0. The FDA guidelines were endorsed by the KDIGO advisory group in 2012 and the American advisory group KDOQI (Kidney Disease Outcomes Quality Initiative) in 2013.¹²,¹³

Bone Disease

Bone disease in CKD results from abnormalities of metabolism of two ions: phosphorus and calcium, and two hormones: 1,25 vitamin D [calcitriol] and PTH. Phosphorus in the diet is absorbed in the gastrointestinal tract, has a molecular weight of 31 daltons and is water soluble, is filtered by the kidney and its excretion decreases, and the serum level rises, as the eGFR decreases in CKD. The increase in the phosphorus level decreases the concentration of ionized and albumin bound calcium, as a greater proportion of calcium is bound to phosphorus. Renal hydroxylation of 25-vitamin D to its active form [calcitriol] also decreases as a result of progressive CKD. The presence of calcitriol is necessary for absorption of dietary calcium, and decreasing calcitriol, in addition to the high phosphorus level, leads to a drop in the serum calcium concentration.¹⁴

The decrease in the serum calcium level stimulates calcium sensing receptors in the parathyroid gland to increase transcription and synthesis of PTH. High serum phosphorus and low calcitriol level also independently increase release of PTH. The high PTH, which may be present as early in CKD as an eGFR of 40 ml/min, increases as CKD progresses. Most laboratories in the United States use an intact PTH [i-PTH] assay, which measures both the biologically active PTH molecule and renally excreted inactive fragments, so as GFR worsens, the high intact PTH is due, in part, to this artifactual effect.¹⁵ In a patient with normal renal function, the elevated PTH would correct the low calcium and high phosphorus levels by increasing renal tubular reabsorption of calcium and decreasing reabsorption of phosphorus, but this fails to occur as CKD progresses. So the metabolic bone abnormalities of CKD include hyperphosphatemia [phosphorous level > 5.5 mg/dL], hypocalcemia, a low circulating calcitriol level, and a high level of PTH.

Sustained elevation of the PTH causes two major problems in CKD. PTH regulates bone mineral content, and elevation of the PTH increases osteoblastic, and more importantly, osteoclastic activity, leading to decreased bone mineralization and growth, and an increased risk of fractures. In addition, release of calcium and phosphorus from bone can lead to deposition of calcium and phosphorus in soft tissue and blood vessels, contributing to accelerated atherosclerosis and arterial stiffening. There is an incremental relationship between elevation of the PTH level and cardiovascular morbidity and mortality.¹⁶ Low circulating levels of calcitriol are also associated with increased mortality.¹⁷ A high phosphorus level is clearly identified with mortality in CKD patients treated with maintenance dialysis¹⁶ and there is now new evidence suggesting a relationship between elevation of the serum phosphorus and mortality in individuals with less advanced CKD.¹⁸

Therapies for the metabolic bone abnormalities of CKD are aimed at correcting the abnormal levels of calcium, phosphorus, calcitriol, and PTH, and hopefully decreasing the effects of bone abnormalities on mortality. Unfortunately,
most of the data on these therapies are present in retrospective, observational, or short-term prospective trials. But, similar to guidelines on treatment of anemia in CKD, two main consortiums of experts, the KDIGO group, in 2009, and the KDOQI group in 2010, have established guidelines for the evaluation and treatment of metabolic bone disease in CKD, and the guidelines are largely in agreement.19,20

In stage III CKD, both groups recommend measuring the calcium and phosphorus every 6–12 months, and the PTH level once, with follow-up levels depending on the circumstance. In stage IV CKD, they recommend calcium and phosphorus levels every 3–6 months and PTH levels every 6–12 months, and in stage V CKD, calcium and phosphorus measurements every 1–3 months, and PTH levels every 3–6 months. In all CKD stages, the 25-vitamin D level should be measured at least once, with follow-up levels depending on the circumstance.

In all CKD stages, if 25–vitamin D deficiency [≤ 30 ng/ml] is detected, patients should be given nutritional vitamin D [ergocalciferol]. Because of decreased hydroxylation of 25-OH vitamin D in advanced CKD, some experts suggest administration of calcitriol instead.21 In CKD stages III–V, the calcium and the phosphorus level should be maintained in the reference range, [for phosphorus, 2.7–4.6 mg/dL in stage III–IV, and 3.5–5.5 in stage V CKD]. Although earlier position papers suggested tight control of the PTH level, KDIGO and KDOQI suggest maintaining the PTH level at 2–9 times the upper limit of normal of the reference range; this works out to be 150–600 pg/ml.

The details of achieving these targets are not specified, but usually involve a combination of vitamin D, dietary phosphorus restriction, and phosphorus binders. As above, ergocalciferol, 50,000 to 100,000 IU per week, with substitution of calcitriol, 0.25 mcg daily as renal function worsens, should be prescribed to vitamin D deficient patients; calcitriol will also independently decrease the PTH level. However vitamin D products will increase the phosphorus level, by increasing gastrointestinal phosphorus absorption. Dietary phosphorus restriction [5–10 mg/kg/day, compared to a usual phosphorus intake of 15–20 mg/kg/day] is the first step. Phosphate restriction may entail protein restriction, so this may require the involvement of a dietician to avoid malnutrition. Ingestion of plant-based proteins leads to less hyperphosphatemia than ingestion of animal based proteins.22

If dietary restriction fails to control the phosphorus level, phosphate binders, which prevent gastrointestinal phosphorus absorption, should be used, and there is some evidence that phosphorus binders improve morbidity and mortality in CKD.23 Phosphorus binders are calcium-based (calcium carbonate, calcium acetate) or non-calcium based (sevelamer, or lanthanum). All phosphorus binders will lower the serum phosphorus. There is no proven superiority of one class or agent over another.24 Calcium containing agents, have, in small observational studies, been linked with a greater degree of vascular calcification,25 and they should be avoided in patients with hypercalcemia.

CONCLUSION

Anemia and bone disease commonly occur as consequences of CKD, become more severe as CKD progresses, and contribute to the increased morbidity and mortality seen in CKD. Both abnormalities can be relatively easily diagnosed. The specifics of treatment are subject to some debate, but initial treatment, as summarized above, can readily be administered by a primary care physician.

References


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