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Chronic Kidney Disease and Its Complications

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Chronic kidney disease (CKD) is recognized as a major health problem affecting approximately 13% of the US population [1]. Numbers of prevalent CKD patients will continue to rise, reflecting the growing elderly population and increasing numbers of patients with diabetes and hypertension. As numbers of CKD patients increase, primary care practitioners will be confronted with management of the complex medical problems unique to patients with chronic renal impairment. As well documented in the literature, the nephrologist rarely manages the medical needs of CKD patients until renal replacement therapy is required. In this article, we define CKD staging and discuss five complications associated with CKD: anemia, hyperlipidemia, nutrition, osteodystrophy, and cardiovascular risk.

CKD classification/staging

CKD is defined as the presence of kidney damage, manifested by abnormal albumin excretion or decreased kidney function, quantified by measured or estimated glomerular filtration rate (GFR), that persists for more than 3 months [2,3]. Although creatinine clearances can be calculated from urine creatinine concentration measured in a 24-hour urine collection and

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a concomitant serum creatinine concentration, a more practical approach in the office is to estimate GFR (estimated GFR or eGFR) from the serum creatinine concentration, using either the Cockcroft-Gault or the Modification of Diet in Renal Disease (MDRD) Study estimating equations. Web-based tools are available for both estimating equations (MDRD eGFR: http://www.nkdep.nih.gov/professionals/gfr_calculators/index.htm; Cockcroft-Gault eGFR: http://www.mdcalc.com/cockcroftgault). Both complications and likelihood of progression to end-stage renal disease requiring renal replacement therapy are more likely to occur in patients with severe CKD. In addition, early intervention will more commonly reduce serious CKD sequelae and slow CKD progression. To facilitate assessment of CKD severity, the National Kidney Foundation developed criteria as part of its Kidney Disease Outcomes Quality Initiative (NKF K/DOQI) to stratify CKD patients [4]:

- Stage 1: normal eGFR $\geq$ 90 mL/min per 1.73 m^2 and persistent albuminuria
- Stage 2: eGFR between 60 to 89 mL/min per 1.73 m^2
- Stage 3: eGFR between 30 to 59 mL/min per 1.73 m^2
- Stage 4: eGFR between 15 to 29 mL/min per 1.73 m^2
- Stage 5: eGFR $<$ 15 mL/min per 1.73 m^2 or end-stage renal disease

The prevalence of these stages of CKD in the US population is as follows: 1.8% for stage 1, 3.2% for stage 2, 7.7% for stage 3, and 0.35 % for stages 4 and 5. Patients with stage 3 or 4 disease progress to end-stage renal disease or stage 5 at a rate of 1.5% per year. Stage 1 or 2 CKD patients progress to more advanced stages at approximately 0.5% per year [5]. In addition, the NKF K/DOQI provides evidence-based, clinical practice guidelines for all stages of chronic kidney disease to optimize management of related complications. Twelve sets of guidelines have been published and are available on the NKF Web site (http://www.kidney.org/professionals/KDOQI/). Each of the complications discussed in this article is addressed by the NKF K/DOQI guidelines.

Chronic kidney disease–associated anemia

Anemia is defined as a reduction in one or more of the major red blood cell measurements: hemoglobin concentration, hematocrit, or red blood cell count. The World Health Organization defines anemia as a hemoglobin level less than 13 g/dL in men and postmenopausal women, and less than 12 g/dL in premenopausal women [6]. The NKF defines anemia as a hemoglobin of less than 13.5 g/dL in men and less than 12.0 g/dL in women [2].

A normochromic, normocytic anemia usually accompanies progressive CKD [7], and the overall prevalence of CKD-associated anemia is approximately 50% [8]. Although anemia may be diagnosed in patients at any stage of CKD, there is a strong correlation between the prevalence of anemia and

the severity of CKD. One quarter of stage 1 CKD patients; half of those stratified to CKD stages 2, 3, and 4; and three quarters of CKD patients starting dialysis suffer from anemia [8]. Therefore, primary care providers play an important role in diagnosing and managing anemia in CKD patients.

While anemia in CKD can result from multiple mechanisms (iron, folate, or vitamin B12 deficiency; gastrointestinal bleeding; severe hyperparathyroidism; systemic inflammation; and shortened red blood cell survival), decreased erythropoietin synthesis is the most important and specific etiology causing CKD-associated anemia. Erythropoietin is a glycoprotein secreted by the kidney interstitial fibroblasts [9] and is essential for the growth and differentiation of red blood cells in the bone marrow. In CKD, tubular atrophy generates tubulointerstitial fibrosis, which compromises renal erythropoietin synthetic capacity and results in anemia.

The anemia of CKD increases morbidity and mortality from cardiovascular complications (angina, left ventricular hypertrophy [LVH], and worsening heart failure) [7], which may lead to further deterioration of renal function and the establishment of a vicious cycle termed the ''cardiorenal anemia syndrome.'' The presence of LVH is associated with decreased survival of patients on dialysis. In fact, end-stage renal disease patients with LVH have a 30% lower 5-year survival rate than individuals lacking LVH [10]. In addition, anemia is an independent predictor of death in stable coronary artery disease patients with CKD [11].

The anemia of CKD is treated via recombinant human erythropoietin (epo). This intervention has replaced transfusions as the mainstay of treatment and improved the survival of anemic CKD patients [12]. The target level of Hgb in patients with CKD has changed as more studies have been reported. Normalization of hemoglobin levels is no longer considered the goal of therapy since these target levels have been associated with higher mortality [13]. The Correction of Hemoglobin and Outcomes In Renal Insufficiency (CHOIR) trial studied the outcomes of anemia treatment in over 1400 CKD patients (MDRD eGFR between 15 to 50 mL/min per 1.73 m^2), who had a hemoglobin less than 11 g/dL at entry. Enrolled subjects were randomly assigned to epo therapy treatment protocols designed to achieve a target hemoglobin level of either 13.5 (n = 715) or 11.3 g/dL (n = 717). The study was terminated prematurely because of higher mortality rates and adverse events in the group with higher targeted Hgb levels [14]. Consequently, the US Food and Drug Administration (FDA) issued an alert recommending a target Hgb level between 11 and 12 g/dL in CKD patients, although more data will be needed to determine the optimal Hgb level to maximize quality of life and reduce excess mortality from anemia-related complications. In summary, despite the clear benefit from treatment of anemia on morbidity and mortality in CKD patients, a significant proportion of anemic CKD patients do not receive adequate treatment before dialysis to achieve current FDA-recommended targets [15], and half of all CKD patients with anemia do not receive treatment with erythropoietin [16]. The precise target level for Hgb

has not been definitively determined, but following FDA recommendations is prudent.

CKD-associated mineral and bone disorders

The term "CKD-associated mineral and bone disorders" comprises abnormalities in bone and mineral metabolism and/or extraskeletal calcification secondary to CKD pathophysiology [17,18]. Renal osteodystrophy is the spectrum of histologic changes that occur in bone architecture of patients with CKD. The kidney is the primary site for phosphate excretion and 1-α-hydroxylation of vitamin D. CKD patients develop hyperphosphatemia as a result of inadequate 1,25 dihydroxy-vitamin D levels that reflect reduced synthesis from parenchymal scarring. In addition, renal phosphate excretion is reduced. Together, both processes cause serum calcium levels to fall resulting in increased secretion of parathyroid hormone (secondary hyperparathyroidism). Parathyroid hormone has a phosphaturic effect. It also increases the calcium levels by increasing bone resorption and promoting 1-α-hydroxylation of 25-hydroxy vitamin D synthesized by the liver (limited effect because of reduced kidney reserve from scarring). Rising phosphorus levels are almost universally observed in stage 3 CKD patients. However, secondary hyperparathyroidism often begins to distort bone architecture earlier before serum phosphorus is noted to be abnormal, indicating that phosphate binder therapy needs to be initiated when eGFRs have declined below 50 mL/min per 1.73 m^2.

Changes in bone architecture can be caused by either a high bone turnover state or a low bone turnover state. Four types of bone phenotypes (renal osteodystrophy) can be diagnosed in CKD patients: osteitis fibrosa cystica (high bone turnover with secondary hyperparathyroidism), osteomalacia (low bone turnover and inadequate mineralization, primarily related to diminished vitamin D synthesis), adynamic bone disorder (low bone turnover from excessive suppression of the parathyroid glands), and mixed osteodystrophy (with elements of both high and low bone turnover). The predominant type of renal osteodystrophy and CKD-mineral and bone disorder differs between predialysis and endstage renal disease patients. In predialysis patients, high bone turnover bone disease is most prevalent. In contrast, low bone turnover predominates in dialysis patients. Patients with low turnover disease represent most cases of renal osteodystrophy [19]. The cause of this prevalent bone phenotype results from oversuppression of parathyroid hormone and high calcium dialysate concentrations [20]. Acidosis, the suppressive effect of phosphate retention on renal synthesis of 1,25 dihydroxy-vitamin D synthesis, and absence of the physiologic inhibitory effect of vitamin D on parathormone secretion are also minor factors that contribute to the low turnover bone disease in CKD patients [21].

CKD-associated mineral bone disorders significantly increase mortality in CKD patients. In fact, hyperphosphatemia is one of the most important

risk factors associated with cardiovascular disease in CKD patients [22]. The exact mechanism underlying this association remains unclear. It is believed to be related to hyperparathyroidism [23] and vascular calcification, which results from high phosphorus levels [24]. Use of calcium-based binders and excessive vitamin D therapy [25] may also contribute to the vascular calcification and its attendant cardiovascular mortality. Patients on hemodialysis who have a plasma phosphorus level above the K/DOQI guideline target levels have a 40% higher mortality rate when compared with those having target levels [26].

The principal goal of the treatment of CKD-associated bone and mineral disorders is phosphorous level reduction [1]. Initial treatment restricts dietary phosphorus intake when phosphate or parathyroid hormone levels begin to rise. According to K/DOQI guidelines (http://www.kidney.org/professionals/KDOQI/guidelines_bone/index.htm), serum phosphorus levels should be maintained between 2.7 and 4.6 mg/dL in patients with stages 3 and 4 CKD, and between 3.5 and 5.5 mg/dL in individuals with stage 5 CKD. Different classes of phosphate binders can be used to accomplish this goal. For chronic therapy, calcium-based formulations for management of CKD-associated hyperphosphatemia are the most widely used class of phosphate binders and have supplanted aluminum-based phosphate binders since aluminum-associated toxicities have been recognized. However, calcium-based phosphate binders can induce hypercalcemia, which increases the tissue calcium deposition, especially in the presence of hyperphosphatemia. If indicated (eg, a CKD patient with hypercalcemia), short-term usage of aluminum-based phosphate binders remains appropriate, although alternative calcium-free, phosphates have been developed, such as the nonabsorbable agent sevelamer. This agent has the advantage of lacking calcium or aluminum.

In addition to phosphate binders, several other classes of drugs have been developed to manage CKD-associated mineral disorder. Given the reduced 1-hydroxylation of vitamin D by the failing kidney, vitamin D and its related compounds may be needed to raise the serum calcium concentration sufficiently to suppress parathyroid hormone secretion. Patients can also be given calcimimetics, agents that increase the calcium sensitivity of the calcium-sensing receptor expressed by the parathyroid gland, down-regulating parathyroid hormone secretion and reducing hyperplasia of the parathyroid gland. The K/DOQI guidelines provide specific management recommendations for use of these agents and the interested reader is referred to the Web link provided for details.

Cardiovascular risk

The increased cardiovascular risk associated with end-stage renal disease has been well established, and estimated cardiovascular mortality rates are 10- to 100-fold higher among dialysis patients than age- and sex-matched

individuals in the general population [27]. The cardiovascular risk associated with renal impairment increases earlier in the course of kidney disease progression than was initially hypothesized. More specifically, there is evidence that even mild to moderate degrees of renal impairment are associated with increased cardiovascular risk. Many traditional cardiovascular risk factors, documented in the general population, contribute to cardiovascular risk in CKD patients. In fact, many Framingham risk factors are more prevalent among individuals with CKD than among those with normal renal function. In addition, nontraditional risk factors, specific to CKD patients, also contribute to the burden of cardiovascular disease (discussed later in this article).

Hypertension is a traditional cardiovascular risk factor that contributes to the cardiovascular risk associated with CKD. Muntner and colleagues demonstrated that patients with hypertension are at increased risk for new or recurrent cardiovascular events in individuals with stage 2-3 CKD [28]. Systolic blood pressure is more strongly associated with cardiovascular death in dialysis patients than either pulse or diastolic pressure [29]. However, a U-shaped relationship exists between systolic blood pressure and mortality in which high or low systolic blood pressures appear to be associated with increased mortality rates in stage 5 CKD patients. Low systolic pressures may identify a sicker group of patients rather than being an etiology for excess mortality. K/DOQI guidelines recommend target blood pressure less than 130/85 mm Hg for all patients with kidney disease and less than 125/75 mm Hg for patients with urinary protein excretion greater than 1 g/24 h. Detailed treatment recommendations are beyond the scope of this review. Angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor blockers, given their renal protective effects, are optimal first-line agents in patients with proteinuric ($>$ 1 g/24 h), progressive diabetic and nondiabetic renal disease.

Diabetes is associated with adverse outcomes in all stages of CKD [30]. Moreover, lower fasting plasma glucose and/or glycated hemoglobin levels are associated with lower risk of all-cause mortality and reduced cardiovascular death of borderline significance in patients with moderate to severe renal impairment. The presence of LVH, a complication that increases in relation to progressively lower levels of eGFR, is also a cardiovascular risk determinant in CKD patients. Anemia and hypertension are two CKD-associated complications hypothesized to play a role in the development of LVH [10]. In a prospective cohort of 2423 patients with stage 3 to 4 CKD, investigators noted an independent risk of LVH for the composite end point of myocardial infarction and fatal coronary heart disease (CHD). Patients were followed over a period of 102 months. In adjusted analysis, LVH was associated with increased risk for composite and cardiac outcomes hazard ratio (HR 1.67; 95% CI 1.34 to 2. 07). Tobacco use is also associated with increased mortality and incidence of heart failure among patients with stage 5 CKD [31].

Several cardiovascular risk factors associated with CKD are unique to patients with this disease (nontraditional risk factors). Anemia, which was discussed earlier, is a risk factor for adverse cardiovascular outcomes in CKD patients. Abnormal serum phosphate levels, calcium-phosphate ion product, and parathyroid hormone levels are independent cardiovascular risk factors in the setting of stage 5 CKD [32]. Higher calcium-phosphate products and the cumulative dose of oral calcium-based phosphate binders correlate with the extent and progression of arterial calcification in dialysis [33] and stage 3 or 4 CKD patients. Interestingly, serum phosphate levels were associated with increased rates of death and myocardial infarction in patients with stage 3 or 4 CKD [34,35]. This suggests that arterial calcification results in clinical morbidity and mortality in this patient population. Poorly controlled metabolic bone disease contributes to vascular calcification, which promotes arteriolosclerosis and increases vascular wall stiffness. Aortic stiffness is an independent predictor of total and cardiovascular mortality, coronary artery disease (CAD), and fatal stroke in patients with hypertension. One study of 96 patients, aged 18 to 70 with a creatinine clearances ranging from 15 to 90 mL/min per 1.73 m^2, found coronary calcification in 64%, and severe calcification present in 23% of patients [36].

Inflammation is a nontraditional risk factor believed to play a role in mediating cardiovascular risk in CKD. Markers of inflammation are often elevated in CKD patients and are predictive of cardiovascular risk in this population. Some, but not all studies, have found that serum C-reactive protein (CRP) levels predict cardiovascular outcomes in CKD patients. Menon and Sarnak [37] analyzed samples obtained from the Modification of Diet in Renal Disease study patients (all had stage 3, 4, or 5 CKD at enrollment), measuring CRP concentration and analyzing its relationship to long-term outcomes. With a 10-year median follow-up period, all-cause mortality was 20% and cardiovascular mortality was 10%. High CRP was an independent predictor of all-cause and cardiovascular mortality after investigators adjusted for confounding variables. The authors concluded that elevated CRP is useful for predicting outcomes in CKD patients.

Proteinuria, a hallmark of renal impairment, is associated with an increased risk for cardiovascular disease and early cardiovascular mortality in patients with and without diabetes and hypertension [38,39]. This association was first demonstrated by the Framingham Heart Study investigators. More recently, Gerstein and colleagues [40], in a cohort of more than 9000 individuals enrolled in the Heart Outcomes Prevention Evaluation (HOPE) trial, noted an increased relative risk in the primary aggregate outcome of myocardial infarction, stroke, and cardiovascular death in microalbuminuric (urine albumin excretion 30 mg/24 h) subjects with and without diabetes (1.97 and 1.61, respectively). The risk associated with the presence of microalbuminuria increased progressively with increasing absolute levels of microalbuminuria.

CKD patients are more likely to develop congestive heart failure (CHF). Bibbins-Domingo and colleagues [41] evaluated the association between

CKD and new-onset CHF in African and Caucasians Americans. In the study, enrollees were stratified by cystatin C- and serum creatinine-based measurements of renal function. Investigators noted that risk for developing CHF correlated with the degree of renal impairment. A meta-analysis (16 studies, which included 80,098 hospitalized and nonhospitalized patients with CHF) evaluated the prevalence and mortality risk associated with the presence of CKD in patients with CHF [42]. The eGFR was less than 90 mL/min in 63% of patients included in the analysis. Approximately 30% of these patients were found to have moderate to severe renal impairment. In 11 of the 16 studies reporting all-cause mortality rates for follow-up after 1 year or more (range 1.0–11.7 years), 26% of patients without renal impairment, 42% with any renal impairment, and 51% with moderate to severe impairment died. A combined unadjusted mortality risk of relative risk (RR) = 1.48, 95% confidence interval (CI) 1.45 to 1.52, $P < .001$ was noted in patients with any renal impairment and RR = 1.81, 95% CI 1.76 to 1.86, $P < .001$ in patients with moderate to severe impairment. The authors concluded that renal impairment confers a clinically significant risk for excess mortality in patients with heart failure and the magnitude of the increased mortality risk is comparable to that associated with traditional prognostic indicators in heart failure such as ejection fraction.

Progression of CKD is associated with a number of serious health complications, including increased incidence of cardiovascular disease (Fig. 1). Treating both traditional and nontraditional cardiovascular risk factors in individuals with CKD involves a multidisciplinary approach to care. Involvement of nurses, dieticians, educators, and surgeons increases optimization of care. Controlling blood pressure using K/DOQI guidelines (BP goal <130/85, <125/75 with proteinuria, <130/85 in the setting of diabetes), use of ACE inhibitor and/or angiotensin receptor blockers to reduce proteinuria, titrating insulin, and statin therapy to achieve appropriate glycated hemoglobin and serum cholesterol levels (<100 mg/dL), respectively, will reduce cardiovascular risk and prevent or slow the progression of kidney failure. Additional randomized trials are needed to establish treatment goals for cardioprotective therapies in this population of patients.

Dyslipidemia

Dyslipidemia is a major risk factor for cardiovascular morbidity and mortality and is common among patients with CKD. Lipid profiles vary widely in these patients, reflecting the level of kidney function and the degree of proteinuria [43]. In general, the prevalence of hyperlipidemia increases as renal function declines, with the degree of hypertriglyceridemia and elevation of LDL cholesterol being proportional to the severity of renal impairment.

Several factors contribute to the development dyslipidemia associated with chronic renal impairment. Patients with CKD have a reduction in the activity of lipoprotein lipase and hepatic triglyceride lipase. This

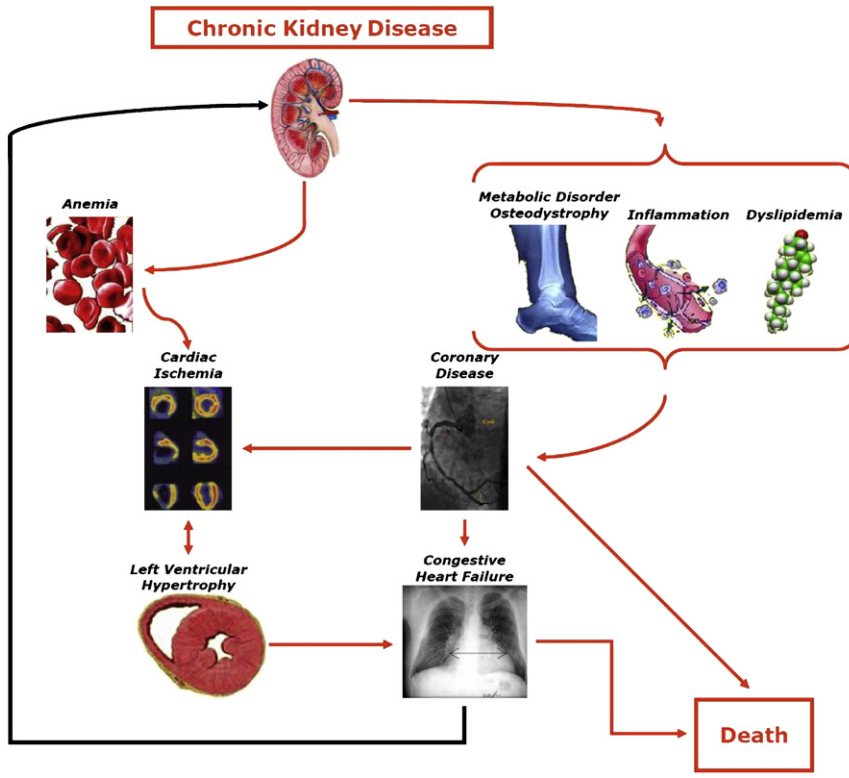

Fig. 1. Interplay of processes secondary to chronic kidney disease leading to cardiovascular disease and death. *Red arrows:* Pathogenetic pathways; *black arrow:* feedback loop; kidney disease worsened by heart failure.

interferes with uptake of triglyceride-rich, apolipoprotein B–containing lipoproteins by the liver and in peripheral tissue, yielding increased circulation of these atherogenic lipoproteins. Hypercholesterolemia in nephrotic syndrome is thought to be a result of increased production and decreased catabolism of lipoproteins. The degree of lipoprotein abnormality is roughly proportional to the amount of proteinuria and inversely proportional to serum albumin levels. However, infusions of albumin or dextran both normalize lipoprotein concentrations, suggesting that oncotic pressure changes rather than hypoalbuminemia signals increased lipoprotein synthesis by the liver. Additional data supporting this hypothesis is derived from in vitro experiments demonstrating direct stimulation of increased hepatic apolipoprotein-B gene transcription in cells exposed to reduced oncotic pressure [44]. Studies also suggest that hyperparathyroidism and the accumulation of calcium in pancreatic islet cells likely contribute to dyslipidemia of CKD as well [45].

Clinical trials in the general population have demonstrated that CHD mortality decreases proportional to LDL-cholesterol level reduction. Evidence for benefit of statins in reducing cardiovascular risk (ie, composite outcomes) in CKD patients is less definitive. Recently, the largest clinical trial of statins in patients with stage 5 CKD (4D trial) was conducted in Germany. In this study, atorvastatin did not to reduce death from fatal stroke, nonfatal myocardial infarction, or nonfatal stroke in 200 patients with diabetes and stage 5 CKD [46]. The results of the Study of Heart and Renal Protection (SHARP) will be available in 2008 and should provide further insight into the role of cholesterol-lowering therapy in reducing cardiovascular events in kidney disease patients. SHARP is a prospective, randomized trial in which 9000 patients with CKD and 3000 dialysis patients without coronary artery disease have been enrolled to assess the effects of lowering LDL-cholesterol with the combination of simvastatin and ezetimibe, with the primary outcome measure being the time to a first ''major vascular event'' defined as nonfatal myocardial infarction or cardiac death, nonfatal or fatal stroke, or an arterial revascularization procedure.

A relationship between total cholesterol levels and CHD mortality as the primary outcome also has not been clearly established. In fact, several observational studies of stage 5 kidney disease patients suggest that lower total cholesterol levels are associated with higher mortality rate. For example, in a recent 10-year prospective study, the importance of total cholesterol levels on mortality was evaluated in 1167 stage 5 kidney disease patients [47]. Hypercholesterolemia (total cholesterol levels >200) was associated with increased all-cause mortality rate. Further studies are needed to evaluate whether low cholesterol identifies a subgroup of more severely ill patients or whether inflammation and/or malnutrition were confounding variables in these studies.

A complete fasting lipid profile with assessment of total, LDL and HDL cholesterol, and triglyceride levels should be included in the evaluation of patients with CKD and hyperlipidemia. Individuals with elevated cholesterol or other forms of hyperlipidemia should undergo evaluation for secondary dyslipidemias before initiation of lipid-lowering therapy [48]. K/DOQI guidelines recommend that all stages of CKD be considered a CHD-risk equivalent. Thus, patients with CKD are viewed as being in the highest risk group for CHD and LDL-cholesterol levels should be lowered below 100 mg/dL (2.6 mmol/L). CKD patients may achieve LDL goals via implementation of lifestyle modification (dietary modification with dietitian consultation, increased physical activity, moderate alcohol intake, and smoking cessation). All adults with CKD should be evaluated for lipid abnormalities. In CKD patients with nephrotic syndrome, the primary goal is to induce remission of the disease [49]. When this is not possible, any reduction in urinary protein excretion will be beneficial. In addition, nephrotic patients with elevated lipid levels should be treated with a lipid-lowering diet, which may aid in reducing total cholesterol and LDL cholesterol levels.

Specific K/DOQI guidelines on the management of hyperlipidemia include the following:

1. For patients with LDL cholesterol levels between 100 and 129 mg/dL (2.57 to 3.34 mmol/L), lifestyle changes may be the initial therapy. If target LDL levels are not achieved (LDL $<$ 100 mg/dL [2.57 mmol/L]), low-dose statin therapy can be instituted.
2. For patients with LDL $\geq$ 130 mg/dL (3.36 mmol/L), lifestyle changes alone are likely to be ineffective. Statins can used as initial therapy and the dose titrated to achieve target LDL $<$ 100 mg/dL (2.57 mmol/L).
3. For patients with triglyceride (TG) $\geq$ 200 mg/dL (3.36 mmol/L), the goal is to achieve non-HDL cholesterol $\leq$ 130 mg/dL. Initial treatment comprises lifestyle changes plus a low-dose statin, which is increased as needed to achieve target levels.

In summary, patients with CKD have a higher burden of dyslipidemia in comparison with the general population and are at increased risk for cardiovascular morbidity and mortality. This disproportionate cardiovascular disease burden places CKD patients in the highest risk category, as defined by the Adult Treatment Panel III (ATPIII) treatment guidelines. Identification of these patients and intervention via lifestyle and/or pharmacologic therapy is a sound, initial clinical approach. Ongoing randomized trials will provide more definitive data on the risk and benefits of lipid-lowering therapy in this population of patients.

Nutritional issues

As patients progress through the stages of CKD, nutritional requirements are altered and metabolism of protein, water, salt, potassium, and phosphorus are affected [50]. These changes lead to ineffective energy generation despite adequate intake of protein and carbohydrate substrates. In more extreme manifestations, these alterations in nutrient use cause ''uremic malnutrition,'' a syndrome that is distinct from malnutrition caused by inadequate nutrient intake. Both inadequate nutrient intake and ineffective nutrient use can contribute to nutritional disorders in CKD patients and we will not distinguish between these etiologies in our discussion. The association between uremic malnutrition and outcomes in the early stages of CKD has not been investigated. However, there is adequate evidence to suggest that a poor predialysis, nutritional status increases patient morbidity and mortality after initiation of renal replacement therapy [51]. Maintenance of neutral nitrogen balance is important for preservation of nutritional health in patients with chronic renal impairment. Treatment goals in this setting should be to establish and maintain optimal nutritional status, minimize uremic symptoms and signs as renal impairment declines, and to establish a nutritional plan that is acceptable to the patient. To accomplish these goals, involvement of a dietician in the care of these patients is often necessary.

The ability of the generalist to assess nutritional status in the setting of CKD is important in addressing the nutritional needs of individuals with CKD. Several nutritional markers can be used to assess nutritional status. Serum albumin is the most extensively studied nutritional marker in all patient populations because of its easy availability and strong association with hospitalization and risk of death [52]. Low levels of serum albumin are highly predictive of poor clinical outcomes in all stages of CKD, and therefore, serum albumin is considered a reliable marker of general clinical status [53]. K/DOQI guidelines recommend maintenance of an albumin value of 4.0 although this has not been proven in randomized, prospective clinical trials. Non-nutritional causes of hypoalbuminemia, such as tissue injury, hepatic disease, gastrointestinal disorders, and volume overload, can affect the specificity of this marker [54]. Moreover, given that serum albumin is a negative acute-phase reactant, its levels decrease in response to inflammatory stimuli such as burns, infection, or trauma [55]. Serum prealbumin is a sensitive marker for assessing subtle changes in visceral protein stores given its low body pool and fairly rapid turnover of 2 to 3 days. Levels less than 30 mg/dL suggest protein depletion [56]. Low serum creatinine concentrations are associated with poor clinical outcome in maintenance of stage 5 CKD. Patients with serum creatinine concentration less than 10 mg/dL should be evaluated for muscle wasting as a result of poor nutrition. Serum cholesterol concentration is an independent predictor of mortality in chronic dialysis patients, and low levels can suggest low dietary and energy intake. Serum cholesterol concentrations less than 150 mg/dL also warrant careful evaluation of nutritional status. Use of Subjective Global Assessment (SGA) as a nutritional assessment tool for various stages of CKD is growing in both clinical and research settings [57]. Studies have demonstrated that SGA can adequately assess nutritional status in the setting of peritoneal and hemodialysis [58].

Prevention and treatment are as important as identifying inadequate nutritional status in CKD patients. Therapy varies with the severity of CKD and no single treatment approach will alleviate the adverse consequences associated with uremic malnutrition [59]. In cases in which low protein and energy intake (as noted in patients on unrestricted diets), a dietary protein intake of less than 0.75 g/kg/d is an early warning sign for the development of uremic malnutrition. For many CKD patients, poor nutrition may warrant initiation of hemodialysis or be an indication for transplantation. Several studies have suggested better outcomes with early initiation of hemodialysis in this setting. Additional signs that suggest need for early hemodialysis initiation include energy intake less than 20 kcal/kg/d, serum albumin concentration of less than 4.0 g/dL, and decrements in other nutritional indices such as transferrin, prealbumin, insulin growth factor-1, and lean body mass. Alternative interventions may be necessary in cases when dietary counseling alone fail to optimize dietary intake. Enteral delivery of nutrition may be necessary, including oral protein, amino acid, and/or

Table 1
Mainstay of treatment in chronic kidney disease complications

Complication	Treatment		
Osteodystrophy	Vitamin D supplements[a]	Calcium supplements[a]	Intestinal phosphate binder[a]
Anemia	Recombinant erythropoietin[b]		Transfusion in urgent cases[b]
Cardiovascular	Statins[c]	Blood pressure control via ACE inhibitor and/or angiotensin receptor blockers[d]	Specific CAD interventions[e]
Dyslipidemia	Statins[c]		Fibrates[c]

[a] K/DOQI Guidelines: http://www.kidney.org/professionals/kdoqi/guidelines_bone/index.htm.

[b] K/DOQI Guidelines: http://www.kidney.org/professionals/kdoqi/guidelines_anemia/index.htm.

[c] Kariske B, Cosio FG, Beto J, et al. American Journal of Transplantation 2004;4:13–53.

[d] Clinical Practice Guidelines on Hypertension and Antihypertensive Agents in Chronic Kidney Disease. K/DOQIGuidelines: http://www.kidney.org/professionals/KDOQI/guidelines_bp/index.htm.

[e] Clinical Practice Guidelines for Cardiovascular Disease in Dialysis Patients. K/DOQI-Guidelines: http://www.kidney.org/professionals/kdoqi/guidelines_cvd/index.htm.

energy supplements; feeding through nasogastric tubes or percutaneous endoscopic gastroscopy or jejunostomy tubes, or institution of intradialytic parental nutrition. Evidence supporting these approaches is limited, however. Only a few studies evaluating the efficacy of oral nutrition supplementation in stage 5 CKD patients have been published. For example, Eustace and colleagues [60] found that oral amino acid supplementation improved serum albumin concentration in stage 5 CKD patients. Caglar and colleagues [61] noted that intradialytic oral nutritional supplementation improved several nutritional parameters in a subgroup of malnourished stage 5 CKD patients. However, the role of supplemental enteral nutrition in patients with advanced CKD or in dialysis patients remains controversial, and a primary care provider should consider expert consultation before initiating any of these therapies.

In conclusion, uremic malnutrition is prevalent in CKD patients, and several studies have established a correlation between malnutrition and poor clinical outcome. Management of nutrition in CKD and dialysis patients can be difficult and involvement of dieticians with experience in the treatment of kidney disease patients is recommended.

Summary

Patients with CKD present several complex management issues to health care providers. The staging system introduced in 2002 by the National Kidney Foundation is a significant accomplishment, which stratifies patients according to disease severity. In addition, the K/DOQI guidelines are an

excellent tool for management of CKD and dialysis patients and recommend treatments according to disease stage. These interventions may reduce morbidity and mortality in these patients. With early identification and treatment of anemia, renal osteodystrophy, uremic malnutrition, hyperlipidemia, and cardiovascular disease, primary care physicians and nephrologists together are making significant strides toward extending and improving the lives of patients with chronic renal disease. Table 1 briefly summarizes current treatment and preventive measures.

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