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**Management of
Chronic Kidney Disease and
Secondary Complications:
An Update on Available Guidelines**

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LEARNING OBJECTIVES

1. Define the stages of chronic kidney disease based on glomerular filtration rate and pathologic findings and identify populations at risk of developing the disease.
2. Determine appropriate nonpharmacologic and pharmacotherapeutic regimens for patients with chronic kidney disease to delay progression.
3. Describe the common secondary complications and comorbid conditions observed in patients with kidney disease, including their etiology and clinical presentation.
4. Apply the guidelines available from the National Kidney Foundation's Kidney Disease Outcomes Quality Initiative (NKF-K/DOQI), where applicable, to develop a therapeutic plan for management of chronic kidney disease and the associated complications.

ABSTRACT: Chronic kidney disease (CKD) is a progressive disease that without appropriate intervention ultimately leads to end-stage kidney disease (ESKD) and the requirement for renal replacement therapy. The growing number of patients with CKD and the projected increase over the next decade have prompted efforts to detect the disease at an earlier stage and initiate therapy targeted at delaying progression. Such therapy includes aggressive blood pressure control, management of hyperglycemia, and initiation of angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs), as appropriate. Paramount to management of CKD is recognition and treatment of the secondary complications, among which are fluid and electrolyte disorders, metabolic acidosis, anemia, secondary hyperparathyroidism, dyslipidemias, malnutrition, and cardiovascular disease (CVD). These secondary complications, in particular, cardiovascular events, increase morbidity and mortality in the CKD population. In general, the likelihood of developing the associated secondary complications and comorbidities increases as kidney function declines. Guidelines that address identification and management of CKD and common secondary complications have been adopted through efforts of the National Kidney Foundation (NKF), known as the NKF-Kidney Disease Outcomes Quality Initiative (NKF-K/DOQI) Guidelines. Despite the availability of these guidelines, secondary complications in patients with CKD often go unrecognized or have been poorly managed by the time a patient develops ESKD. Improved management of CKD and its associated complications may be

realized using the NKF-K/DOQI Guidelines as a basis for therapy, while considering modifications as new information is made available. A multidisciplinary approach is also necessary for appropriate diagnosis, selection of drug therapy, dietary intervention, patient education, and assessment of outcomes.

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Narrative

Given the increase in the number of patients with chronic kidney disease (CKD) and at risk of developing this disorder, practitioners need to be aware of management strategies to delay progression of the disease and address secondary complications. This review describes the staging system used to classify CKD, interventions to delay progression to end-stage kidney disease (ESKD), and management of the associated secondary complications. Guidelines developed by the National Kidney Foundation's (NKF's) Kidney Disease Outcomes Quality Initiative (NKF-K/DOQI) are also reviewed.

Introduction

CKD is characterized by a progressive deterioration in kidney function that

ultimately leads to ESKD, the point at which renal replacement therapy (dialysis or transplantation) is required to sustain life. There are multiple etiologies of CKD; however, diabetes and hypertension are the two leading causes of ESKD in the United States (U.S.).¹ CKD is considered a worldwide health problem based on the number of individuals with or at risk for developing this disease. An estimated 20 million people in the U.S. have CKD, 8 million of whom are classified at Stage-3 CKD or higher (glomerular filtration rate (GFR) $<60 \text{ mL/min/1.73 m}^2$).^{2,3} Comorbidities such as cardiovascular disease (CVD) are also prevalent in patients with CKD and require early and aggressive intervention.⁴

Secondary complications of CKD develop early in the course of the disease, yet are often unrecognized or are inappropriately managed, leading to premature mortality or a poor prognosis by the time the patient reaches ESKD.^{5,6} Based on such information, the NKF has developed guidelines known as the NKF-K/DOQI Guidelines in an effort to increase recognition of CKD and the associated complications and to promote early and more consistent delivery of care. Current guidelines based on evidence, when available, and opinion address evaluation and classification of CKD, as well as management of secondary complications including anemia, bone and metabolic disorders, malnutrition, dyslipidemias, and hypertension. Current and forthcoming Guidelines are listed in Table 1. CKD has also been identified as one of the focus areas for the Healthy People 2010 National Health Initiative.⁷ Specific objectives of this initiative are to reduce

the number of new cases of ESKD and to promote better management.

In general, the goals of management for patients with CKD are to:

1. Prevent or slow the progression of kidney disease.
2. Evaluate and manage comorbid conditions.
3. Prevent and treat CVD.
4. Prevent and treat secondary complications of decreased kidney function.
5. Prepare for renal replacement therapy, as needed.
6. Replace kidney function by dialysis and transplantation if signs and symptoms of uremia are present.

This review discusses recommendations for delaying progression of CKD and treating secondary complications and comorbid conditions of the disease. Complications for which Guidelines from the NKF-K/DOQI are available will be emphasized. Preparation for renal replacement therapy must also be considered, but is not covered in this review. The reader is referred to the NKF-K/DOQI Guidelines (<http://www.kidney.org/professionals/kdoqi/guidelines.cfm>) for more detailed information.

Definition and Staging of Chronic Kidney Disease

As part of the NKF-K/DOQI Guidelines on evaluation, classification, and stratification of CKD, a staging system has been developed to promote more uniform terminology and specific information about the extent of kidney dysfunction when referring to patients

with CKD (Table 2). This staging system is based on the presence of kidney damage and the level of kidney function. Specifically CKD is defined as:

1. Kidney damage for ≥ 3 months, as indicated by structural or functional abnormalities of the kidney with or without decreased GFR, manifested by either pathologic abnormalities or markers of kidney damage, including abnormalities in the composition of the blood or urine, or abnormalities in image testing; or
2. A GFR < 60 mL/min/1.73m² for ≥ 3 months, regardless of identifiable kidney damage.

The presence of protein in the urine (defined as *proteinuria*, *albuminuria*, or *microalbuminuria* based on protein type and amount) is an early and sensitive marker of kidney damage.

Assessment of Kidney Function

Estimation of GFR in conjunction with identification of early markers of disease (e.g. proteinuria) is the most reliable and practical means available to evaluate kidney function and monitor disease progression. Creatinine is an endogenous substance excreted primarily by glomerular filtration; therefore, estimation of creatinine clearance (CL_{Cr}) is a reasonable surrogate for GFR. A consideration when using serum creatinine (SCr) to estimate GFR is that creatinine is eliminated not only through glomerular filtration but also via tubular secretion. Tubular secretion of creatinine contributes more substantially to overall elimination of creatinine as kidney

function declines such that CL_{Cr} overestimates true GFR. Administration of cimetidine to patients prior to measurement of CL_{Cr} has been used as a means of obtaining a more accurate assessment of true filtration, since cimetidine blocks tubular secretion of creatinine. Averaging CL_{Cr} and clearance of urea (a substance that undergoes tubular reabsorption), is another method used clinically to estimate glomerular filtration.

Although SCr can provide a rough estimate of kidney function, using this test as the sole means of assessment is not recommended for several reasons:

- SCr may be relatively insensitive in detecting early kidney disease and is not accurate for estimating the progression of the disease.
- Creatinine generation is proportional to total muscle mass and is affected by diet, notably by the ingestion of meats.
- Use of SCr to assess kidney function in patients with liver disease may also lead to overestimation of GFR.
- Substantial variation in the calibration of SCr among laboratories also results in differences in measured SCr.

The Cockcroft-Gault equation is the most commonly used equation to estimate CL_{Cr} in adult patients with stable kidney function.⁸ Although using ideal body weight is recommended in this calculation, it is important to realize the weight discrepancies used in clinical practice (e.g., use of total body weight vs. ideal body weight) and the variability in the resulting estimates of CL_{Cr} .

More recently, a prediction equation was developed using data from the Modification of Diet in Renal Disease (MDRD) study.⁹ This equation, referred to as the MDRD equation, was derived using GFR measured directly by urinary clearance of a radio-labeled marker (¹²⁵I-Iothalamate). The MDRD equation is advocated as a method to estimate GFR in adults.³ The abbreviated MDRD equation⁹ is as follows:

$$\begin{aligned} \text{Estimated GFR (mL/min/1.73m}^2\text{)} \\ &= 186 \times (\text{SCr})^{-1.154} \times (\text{Age})^{-0.203} \\ &\times (0.742 \text{ if female}) \times (1.21 \text{ if} \\ &\text{African-American}) \end{aligned}$$

The expanded version of this equation also includes blood urea nitrogen and serum albumin; however, this version does not substantially improve accuracy when compared with the abbreviated version. According to the NKF-K/DOQI Guidelines, either the Cockcroft-Gault or MDRD equation may be used to estimate GFR.³ It is important to consider that the MDRD equation has only been validated in patients with a $GFR < 90 \text{ mL/min/1.73 m}^2$.

In the pediatric population, the Schwartz equation¹⁰ is used to assess GFR as follows:

$$\begin{aligned} \text{Creatinine clearance (mL/min)} = \\ \text{[k X length (in cm)]/SCr, where} \\ \text{k is dependent on age: infant (1} \\ \text{to 52 weeks) k = 0.45; child (1} \\ \text{to 13 years) k = 0.55; adolescent} \\ \text{male k = 0.7; and adolescent} \\ \text{female k = 0.55} \end{aligned}$$

Estimation of CL_{Cr} using 24-hour urine collection methods has not been proven more reliable than the prediction equations presented to assess kidney

function. Problems with urine collection methods include incomplete urine collection, diurnal variation in GFR, and variation in creatinine excretion. Populations in whom estimation of GFR using a 24-hour urine collection is more reasonable include patients with variation in dietary intake of creatine sources, such as vegetarians, or persons with poor muscle mass (e.g., malnourished individuals or amputees).³

Estimates of kidney function are also important when determining the appropriate doses of drugs that are eliminated by the kidney. Of note, recommendations for drug dosing are generally based on estimates of kidney function derived using the Cockcroft-Gault equation. Frequent assessment of drug selection and dosage regimen design should be integral to the evaluation of a patient with progressive kidney disease.

Proteinuria

Additional assessment of kidney function should include evaluation of urinary protein excretion. Proteinuria may precede a decline in GFR and should be considered as an early marker of kidney damage. *Microalbuminuria* is defined as an albumin excretion rate of 20 to 200 mcg/minute or 30 to 300 mg/24 hours. Specific assays with increased sensitivity relative to standard assays are required for detecting quantities of protein in the range defined as microalbuminuria. *Proteinuria* is defined as a total protein excretion rate exceeding 200 mcg/minute or >300 mg/24 hours (referred to as *albuminuria* if albumin is the only protein measured). Total protein includes albumin and other proteins such as low-molecular-weight globulins and apoproteins. Assessment

of albuminuria is a better indicator of early kidney disease, since it is primarily indicative of glomerular damage, as opposed to total protein, which is not as specific for glomerular damage. Other tests, including urinalysis, radiographic procedures, and biopsy, may also be of value in further assessing kidney function.

Quantification of albumin may be done using timed urine samples (e.g., a 24-hour collection period) or “spot” urine samples for measurement of protein- or albumin-to-creatinine ratios. This “spot” method corrects for variations in hydration status and may be more accurate because protein excretion is normalized to glomerular filtration. Screening for albuminuria may also be done using urine dipstick testing of a spot urine sample. Several reagent strips are available that differ with regard to the specified testing procedure and the sensitivity and specificity for detecting albuminuria. Patients with a positive dipstick screening test should have a subsequent quantitative assessment of the protein- or albumin-to-creatinine ratio to confirm proteinuria. The NKF-K/DOQI Guidelines for evaluation of CKD provide criteria for diagnosis of proteinuria and albuminuria based on testing method and sex (Table 3).³

Delaying Progression of Chronic Kidney Disease

As the leading causes of kidney disease in the U.S., diabetes and hypertension are conditions that require aggressive management in an effort to prevent development and delay progression of CKD. Guidelines from the American Diabetic Association provide target glucose levels (e.g., glycosylated hemoglobin <7%.) and strategies to

achieve those targets to reduce the risk of diabetic nephropathy.^{11,12} Guidelines from the NKF-K/DOQI on diabetes in CKD are forthcoming. The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC-7) and the NKF-K/DOQI Guidelines on hypertension recommend a blood pressure <130/80 mm Hg in patients with diabetes and/or CKD.¹³ This target blood pressure to delay progression of early-stage CKD is also recommended in the NKF-K/DOQI Guidelines on hypertension and use of antihypertensive agents.¹⁴

Goals of antihypertensive therapy in CKD patients are to lower blood pressure, reduce the risk of CVD, and slow progression of CKD. Control of blood pressure is paramount to delaying progression of CKD, and often multiple antihypertensive agents are required to achieve the blood pressure goal of <130/80 mm Hg. Clinicians should apply criteria specified in JNC-7 when selecting antihypertensive therapy.¹³ Specific agents advocated to delay progression include ACE inhibitors or ARBs. Benefits are derived from a reduction in blood pressure and intraglomerular pressure and from effects independent of lowering blood pressure.¹⁵ ACE inhibitors and ARBs have been shown to prevent progression of micro- to macroalbuminuria and also have cardiovascular benefits.¹⁴ These agents are advocated in patients with diabetic kidney disease and in patients with non-diabetic kidney disease who also have proteinuria.¹⁴ Monitoring of potassium levels is necessary because of the risk of hyperkalemia, particularly in Stage-4 CKD. The non-dihydropyridine calcium channel blockers (e.g.,

verapamil, diltiazem) also have shown antiproteinuric effects.¹⁴ Other antihypertensive agents (e.g., diuretics, β -blockers, dihydropyridine calcium channel blockers) should be considered based on indications as stated in JNC-7 and the goal of reducing CVD in the population with CKD.

Protein restriction (0.6 to 0.8 g/kg per day) and lipid-lowering therapy (e.g., statins) may also be beneficial in delaying disease progression, although consistent beneficial effects from these interventions are not as well documented.^{3,16} Protein restriction introduces the risk of malnutrition, which is associated with poor outcomes by the time a patient progresses to ESKD. As the pleiotropic (i.e., non-lipid-dependent) effects are being recognized, more attention is being given to using statins to treat CKD.¹⁷ Smoking cessation is also recommended in an attempt to prevent the potential increase in proteinuria associated with tobacco use.¹⁸ Other etiologies of CKD, such as glomerulonephritis, require a complete work-up to determine appropriate management (e.g., immunosuppressant therapy) and expected outcomes.

Secondary Complications

CKD affects every major organ system, particularly once patients develop ESKD. Among the common complications of CKD are fluid and electrolyte abnormalities, metabolic acidosis, anemia, secondary hyperparathyroidism and renal osteodystrophy, malnutrition, and lipid abnormalities. CVD in patients with CKD is prevalent and has become a primary focus of intervention. Mortality secondary to CVD is 10 to 30 times

greater in patients on dialysis than in the general population.¹⁹ In addition to traditional cardiac risk factors (e.g., diabetes, hypertension, hyperlipidemia, tobacco use, and physical inactivity), patients with kidney disease have risk factors that are unique: uremia or those altered by this condition, including hyperhomocysteinemia, elevated levels of C-reactive protein, increased oxidant stress, and hemodynamic overload.²⁰ Other complications of CKD such as anemia and metabolic disorders of CKD are also contributory to CVD. Early and aggressive efforts to address common secondary complications of CKD are warranted.

Anemia of CKD

Anemia is a secondary complication that occurs in the majority of patients with CKD. The primary etiology is a deficiency in the production of erythropoietin (EPO), which becomes more severe as kidney disease progresses.²¹ This results in a decreased rate of red blood cell (RBC) production (or erythropoiesis) and subsequent anemia, which manifests as a normochromic, normocytic anemia. Contributing factors include the following:

- Iron deficiency
- Reduced RBC life span in the presence of uremia (to approximately 60 days)
- Blood loss from frequent phlebotomy and dialysis (in patients with ESKD on hemodialysis)
- Gastrointestinal (GI) bleeding
- Severe hyperparathyroidism
- Protein malnutrition
- Inflammatory conditions.²²

Beyond the characteristic symptoms of anemia such as fatigue and weakness, anemia of CKD is associated with decreased quality of life, impaired cognitive function, increased hospitalization and cost, and increased mortality.^{23,24} Development of left ventricular hypertrophy has also been linked to severity of anemia; a particular concern given the prevalence of CVD in patients with CKD.^{25,26} Although the adverse consequences of untreated anemia of CKD are well documented, anemia is often unrecognized and/or untreated in the earlier stages of CKD leading to more severe anemia by the time patients reach ESKD.

The NKF-K/DOQI Guidelines recommend that a thorough evaluation for anemia be done, including assessment of iron status, for all patients with a SCr >2 mg/dL (approximate GFR <60 mL/min/1.73 m² or Stage-3 CKD). Once anemia is diagnosed and causes other than EPO deficiency are ruled out (e.g., folate and vitamin B₁₂ deficiency), patients should receive appropriate therapy, including erythropoietic agents (e.g., epoetin alfa, darbepoetin alfa), and iron supplementation, as indicated based on achievement of target parameters (Table 4).²²

Iron deficiency contributes substantially to the development of anemia of CKD; therefore, assessment of iron status and iron supplementation, if indicated, based on the transferrin saturation and ferritin, should occur prior to initiation of erythropoietic therapy. Oral iron supplements are available as ferrous salts (ferrous sulfate, ferrous fumarate, and ferrous gluconate), iron polysaccharide, and heme iron. The recommended dose of oral iron is based

on the elemental iron component; recommended dose of 200 mg of elemental iron per day. The number of tablets or capsules and frequency of administration vary depending on the content of elemental iron in each formulation. Barriers to success of oral iron supplementation include its poor bioavailability and the side effects (primarily GI related), which contribute to patient noncompliance. For these reasons, oral iron supplementation is usually inadequate for repletion of iron in patients on hemodialysis who experience chronic blood loss, and intravenous (IV) iron supplementation is necessary. For the population in the earlier stages of CKD (Stages 3 and 4) and for patients on peritoneal dialysis (PD), an initial trial of oral iron may correct the deficiency, since these patients do not have the same degree of blood loss. Oral iron also is more convenient for these patients who do not have regular IV access. For many of these patients, however, IV iron therapy will be required to replete iron and meet the increased iron demands that result from stimulation of erythropoiesis with erythropoietic therapy.

The IV iron preparations currently available are iron dextran (InFeD[®], DexFerrum[®]), sodium ferric gluconate complex in sucrose (Ferrlecit[®]), and iron sucrose (Venofer[®]). Iron dextran is no longer considered the IV iron product of choice because of the risk of anaphylactic reactions (see the black box warning). If an iron dextran product is administered, a one-time, 25-mg test dose is recommended, followed by a 1-hour observation period, before the remainder of the dose is infused to minimize the risk of reactions.²² Sodium ferric gluconate and iron sucrose do not

have the black box warning and are advocated as safer IV iron preparations for the CKD population.²⁷ Both agents can be administered without a test dose and by slow IV push (125 mg over 10 minutes for sodium ferric gluconate and 100 mg over 5 minutes for iron sucrose).^{28,29} The dose of IV iron recommended to correct absolute iron deficiency (transferrin saturation <20%, serum ferritin <100 ng/mL) in patients on hemodialysis is a total dose of 1 gm, administered in divided doses of 100 to 125 mg, depending on the formulation used. Iron status should be assessed at least 7 days following the last dose to provide a more accurate assessment of storage iron (serum ferritin) and iron immediately available for use in RBC production (as indicated by the transferrin saturation). Maintenance iron supplementation (e.g., doses ranging from 25 to 125 mg) administered weekly or monthly is recommended to prevent iron deficiency. Maintenance therapy should provide 250 to 1000 mg of iron within 12 weeks, with an assessment of iron status every 3 months.²²

The hemodialysis procedure does not remove the available IV iron preparations; therefore, they can be administered at any time during the session. Side effects to consider with IV iron include the risk of anaphylactic reactions (although less than with iron dextran), iron overload, and infection. The safety and efficacy of higher dose IV iron regimens have been evaluated to determine other more practical dosing strategies, particularly for patients who are seen less frequently in the clinic setting (e.g., patients on PD and patients with Stages 3 and 4 CKD). Iron dextran has been safely administered in total dose infusions ranging from 400 mg to 2

grams to patients on dialysis.³⁰ Similar high-dose regimens of 500 mg have also been given to patients with Stages 3 and 4 CKD.³¹ Larger doses of sodium ferric gluconate (250 mg infused over 1 hour) and iron sucrose (200 to 300 mg over 2 hours) have been safely administered.^{32,33} Doses in these higher ranges for the newer IV iron preparations, however, are not approved and should not be adopted as standard of care until further safety data become available.

Once iron deficiency is corrected the hemoglobin and hematocrit should be reassessed. If patients remain anemic despite correction of iron status, then erythropoietic therapy should be initiated. Available erythropoietic agents include epoetin alfa (Epogen[®], Procrit[®]) and darbepoetin alfa (Aranesp[®]). Subcutaneous (SC) administration of epoetin alfa is preferred based on efficacy in improving erythropoiesis and reduced dose requirements, when compared with IV administration.²² This route of administration is also more convenient for patients with early CKD (Stages 3 and 4) and for patients undergoing PD who do not have regular IV access. Starting doses of epoetin alfa are 80 to 120 Units/kg per week SC or 120 to 180 Units/kg per week IV administered in 1 to 3 divided doses. The starting dose of darbepoetin alfa is 0.45 mcg/kg SC or IV administered once weekly. A conversion chart is available for patients receiving epoetin alfa who are being switched to darbepoetin (Table 5). Dose adjustments of erythropoietic agents are based on the hemoglobin/hematocrit response and should not be made more frequently than every 4 to 6 weeks based on the time required for production of

mature RBCs (i.e., the pharmacodynamic response). Failure to respond to erythropoietic therapy requires evaluation of factors causing resistance, such as iron deficiency (primary cause), infection, inflammation, chronic blood loss, aluminum toxicity, hemoglobinopathies, malnutrition, and hyperparathyroidism. Erythropoietic therapy with epoetin or darbepoetin generally is well tolerated, and most adverse events reported are frequent sequelae of CKD and not necessarily attributable to therapy. Hypertension is the most common adverse event reported. The NKF-K/DOQI Guidelines for anemia recommend withholding erythropoietic therapy only when hypertension is refractory to aggressive blood pressure management approaches, such as pharmacologic therapy and dialysis.²²

Secondary Hyperparathyroidism and Renal Osteodystrophy

Secondary hyperparathyroidism (sHPT) is another common complication of CKD, which occurs as early as Stage 3 CKD. Metabolic abnormalities in CKD that contribute to development of this disorder include hyperphosphatemia, hypocalcemia (in the early stages of CKD), vitamin D deficiency, and resistance to vitamin D therapy. If unmanaged, sHPT leads to renal osteodystrophy (ROD). Collectively, ROD refers to specific bone abnormalities that include osteitis fibrosa or high-turnover bone disease (most common pattern), osteomalacia, osteosclerosis, and osteopenia.

The etiology of sHPT and ROD is complex and a result of metabolic changes characteristic of CKD. As kidney function declines (indicated by a

decrease in GFR), phosphorus excretion by the kidney decreases resulting in hyperphosphatemia.

Hyperphosphatemic conditions lead to a corresponding decrease in the ionized calcium concentration, a primary stimulus for release of parathyroid hormone (PTH) by the parathyroid gland. Higher concentrations of PTH decrease renal tubular reabsorption of phosphorus and increase reabsorption of calcium, at least in the earlier stages of CKD, while sufficient kidney function remains to invoke this response. PTH also mobilizes calcium from bone. These actions of PTH lead to correction of serum phosphorus and calcium concentrations; however, this occurs at the expense of an elevated PTH concentration (the “trade off” hypothesis). As kidney disease becomes more severe (GFR <30 mL/minute or Stage 4 CKD), the phosphaturic response to PTH diminishes and sustained hyperphosphatemia and hypocalcemia develop. This continued mobilization of calcium from bone ultimately leads to development of ROD. With more severe kidney dysfunction hypercalcemia becomes problematic attributable, in part, to the calcium load delivered from the use of calcium-containing phosphate binders.

Vitamin D metabolism is also altered in patients with kidney disease and is a key component to development of sHPT. As kidney disease progresses, there is loss of activity of 1- α -hydroxylase, the enzyme present in proximal tubular cells of the kidney. It is required for conversion of vitamin D in a precursor form that is produced, following the initial hydroxylation step in the liver (25-hydroxyvitamin D) to the active

form (1,25-dihydroxyvitamin D₃ or calcitriol). Vitamin D in its active form as calcitriol increases gut absorption of calcium and binds with vitamin D receptors on the parathyroid gland to suppress PTH synthesis. As a result of decreased calcitriol production, the absorption of dietary calcium in the gut is diminished, thus contributing to hypocalcemia. Decreased suppression of PTH synthesis by vitamin D in conjunction with hypocalcemia promotes continued stimulus for mobilization of calcium from bone. In early CKD deficiencies in the precursor 25-hydroxyvitamin D are also common with deficiencies observed in up to 86% of patients.³⁴

Adverse consequences of hypercalcemia (vascular calcifications), hyperphosphatemia, sHPT, and vitamin D deficiency beyond development of ROD (e.g., associations with mortality) are now recognized and a reason for more aggressive treatment. The NKF-K/DOQI Guidelines on bone metabolism and disease recommend measuring serum levels of intact plasma PTH, phosphorus, and calcium in all patients with a GFR <60 mL/min/1.73 m² (Stage-3 CKD).³⁵ The frequency of measurements and target ranges are based on the stage of disease (annually in Stage-3 CKD, every 3 months in Stage-4 CKD, and as frequently as monthly in Stage-5 CKD). Target ranges for these parameters are listed in Table 6. It is also recommended that 25-hydroxyvitamin D, the precursor to calcitriol, be measured in patients with Stages 3 or 4 CKD who have elevated PTH levels. Supplementation with a vitamin D precursor, ergocalciferol or cholcalciferol, is recommended if 25-hydroxyvitamin D levels are below 30

ng/mL.³⁵ Thus far, there is little experience in clinical practice with this supplementation strategy to determine its effectiveness in treating sHPT.

To achieve the NKF-K/DOQI goals, dietary phosphorus should be restricted to 800 to 1,000 mg/day adjusted for dietary protein needs. Unfortunately, as kidney disease progresses dietary phosphorus restriction alone cannot maintain target phosphorus levels, and phosphate binder therapy is often necessary. Available phosphate binders include products that contain calcium (calcium acetate, calcium carbonate), aluminum, magnesium, and lanthanum cations or the polymer-based agent, sevelamer hydrochloride (Table 7). When prescribing these agents, it is important to counsel patients to take them with meals and snacks. Patients in the earlier stages of CKD who have hypocalcemia may benefit from calcium supplementation and use of calcium-containing binders; however, the risk of hypercalcemia (and calcifications) must be considered as kidney disease progresses. To minimize the risk of hypercalcemia the NKF-K/DOQI Guidelines recommend restricting the total dose of elemental calcium from binders to 1500 mg per day and the total intake of elemental calcium from binders and dietary intake to 2000 mg per day in patients with Stage 5 CKD.³⁵ Calcium-based phosphate binders should not be used in patients with hypercalcemia or with severe vascular calcification. In such cases, a non-calcium-containing binder such as sevelamer or lanthanum carbonate should be used. Sevelamer (Renagel[®]) is a non-elemental phosphate binder commonly prescribed to reduce the calcium load, which also has beneficial effects in lowering LDL

levels.³⁶ Lanthanum carbonate (Fosrenol[®]) is a phosphate-binding agent recently approved and provides another alternative to calcium-containing binders. While comparison data with calcium binders are limited, one prospective trial suggests a benefit of sevelamer compared to calcium-based phosphate binders in preventing progression of aortic and coronary artery calcification.³⁷ Although an encouraging finding, studies evaluating the effects of these non-calcium binders on cardiovascular morbidity and mortality in dialysis patients are needed.

Administration of active vitamin D, in conjunction with control of serum phosphorus and calcium, is necessary to control sHPT and prevent ROD. Calcitriol is available as an oral formulation (Rocaltrol[®]) or IV formulation (Calcijex[®]). Calcitriol interacts with vitamin D receptors located in the parathyroid gland, intestines, bone, and kidney. Calcitriol suppresses PTH synthesis in the parathyroid gland and stimulates calcium absorption from the GI tract. To avoid hypercalcemia, the lowest effective dose should be used and the serum calcium and calcium-phosphorus product should be closely monitored. Control of serum phosphorus is recommended before calcitriol is initiated, since this agent also increases GI phosphorus absorption. Newer vitamin D analogs are available that retain the suppressive effect on PTH release while decreasing the potential for hypercalcemia compared with calcitriol because of differences in interactions with vitamin D receptors. Currently approved agents in the U.S. are paricalcitol (Zemplar[®]), also known as 19-nor-1,25-dihydroxyvitamin D₂, and doxercalciferol (Hectorol[®]), or 1- α -

hydroxyvitamin D₂. Doxercalciferol requires conversion to the active form (1- α -25-dihydroxyvitamin D₂) by the liver. Doses of the available vitamin D products based on severity of sHPT in patients with Stage-5 CKD on hemodialysis are provided in Table 8. Active vitamin D therapy may be initiated in patients with Stage 3 or 4 CKD with elevated intact PTH levels despite normalization of 25-hydroxyvitamin D levels (>30 pg/mL). Initial recommended oral doses are calcitriol 0.25 mcg per day, doxercalciferol 2.5 mcg 3 times per week, and paricalcitol 1 mcg/day or 2 mcg 3 times/week.³⁵ It is recommended that calcium and phosphorus be less than 9.5 mg/dL and 4.6 mg/dL, respectively, prior to initiation of active vitamin D therapy in this population.³⁵ Adjustments to vitamin D therapy are based on PTH response and maintaining target calcium and phosphorus levels. Algorithms for management are available from the NKF-K/DOQI Guidelines.³⁵

Cinacalcet hydrochloride is a calcimimetic agent recently approved for treatment of sHPT in patients with Stage-5 CKD.³⁸ This compound acts on the calcium-sensing receptor on the surface of the chief cell of the parathyroid gland to “mimic” the effect of extracellular ionized calcium and increase the sensitivity of the calcium-sensing receptor to calcium, subsequently reducing PTH secretion. Cinacalcet was approved after the availability of the NKF-K/DOQI Guidelines for bone metabolism and disease. The starting dose in patients with Stage-5 disease is 30 mg once daily, with dose titrations made in approximately 30-mg increments every 2

to 4 weeks up to 180 mg per day or until the target PTH (150 to 300 mg/mL) is achieved. Cinacalcet may cause hypocalcemia and should not be started if the calcium level is <8.4 mg/dL. The potential for drug interactions should be evaluated in all patients, since cinacalcet is metabolized by cytochrome P450 enzymes CYP3A4, CYP2D6, and CYP1A1 and is a strong inhibitor of CYP2D6. This agent may be used alone or in combination with vitamin D and phosphate binders. Information on the use of cinacalcet in combination with existing vitamin D therapies will be of interest, as these agents are used together in clinical practice.

Malnutrition

Protein-energy malnutrition is very common among patients with advanced CKD (Stages 4 and 5), and is associated with mortality in patients with ESKD.¹⁶ Protein restriction, if implemented as an intervention to potentially delay progression of kidney disease in patients with Stage 3 or 4 CKD, may lead to protein malnutrition by the time a patient reaches ESKD. Other contributing factors include anorexia that develops with accumulation of uremic toxins, altered taste sensation, concomitant illnesses, hypercatabolism from inflammation, and the effect of the dialysis procedure on removal of nutrients.^{16,39}

Guidelines for nutrition in patients with ESKD address the increased nutritional needs in this population.¹⁶ The recommended dietary protein intake for patients who are on chronic hemodialysis (HD) is 1.2 g/kg body weight per day.¹⁶ The recommended intake for patients on chronic PD is greater: 1.2 to 1.3 g/kg body weight per

day, based on the increased protein loss that occurs with this dialysis modality.¹⁶ The weight recommended to determine these needs is the adjusted edema-free body weight.¹⁶ The recommended total daily energy intake in patients on both HD and PD is 35 kcal/kg body weight per day.¹⁶ The intake from both diet and glucose in the peritoneal dialysate must also be considered for patients requiring PD. Daily energy intake for patients older than 60 years of age is 30 to 35 kcal/kg/day, since older age is generally associated with reduced physical activity and lean body mass.¹⁶ Nutritional support should be considered for those patients who cannot meet these needs with oral intake alone. Interdialytic parenteral nutrition is another option for nutritional supplementation in patients on hemodialysis.

Patients with ESKD may also have deficiencies in water-soluble vitamins (B₁, B₂, B₆, B₁₂, niacin, pantothenic acid, folic acid, biotin, and vitamin C) because dialysis removes many of these vitamins. The goal for vitamin supplementation in this population should be to prevent deficiency, yet avoid overdosage. Special vitamin supplements have been formulated for the dialysis population that primarily include vitamins B with C and folic acid. Supplementation with L-carnitine has also been advocated for its potential benefits in patients with ESKD, including management of hypertriglyceridemia, hypercholesterolemia, and anemia.⁴⁰ While some of these benefits have been demonstrated, the evidence is not strongly in favor of making L-carnitine supplementation a routine practice in patients with ESKD. The NKF-K/DOQI nutrition Guidelines recommend supplementation with L-carnitine only if

the disorders for which L-carnitine has shown some benefit are not responding to standard therapies.¹⁶ The suggested dose of L-carnitine is approximately 1 gram administered after dialysis.¹⁶

Hyperlipidemia

Lipoprotein metabolism is altered early in the course of kidney disease and becomes pronounced with more advanced disease. Elevated triglyceride, total cholesterol, LDL cholesterol, and decreased high-density lipoprotein (HDL) cholesterol levels are generally observed. The prevalence of atherosclerotic CVD is high in patients with CKD. Based on strong evidence of risk reduction and benefits of lipid-lowering therapy in the general population, it is recommended that patients who have CKD be treated aggressively for dyslipidemia to an LDL-C goal below 100 mg/dL.^{41,42} Management of dyslipidemia in patients with CKD is based on the report from the National Cholesterol Education Program (NCEP III) and the NKF-K/DOQI Guidelines for dyslipidemia in patients with CKD (Table 9).^{41,42} Although diet therapy is a reasonable first-step approach, it may not be successful in many patients with CKD; therefore, drug therapy is warranted. Drug classes that may prove useful in treatment of lipid disorders include the following:

- HMG-CoA reductase inhibitors (statins)
- Bile acid sequestrants
- Nicotinic acid
- Fibrates (gemfibrozil and clofibrate)

Statins are the most effective drugs for lowering LDL and total cholesterol in

patients with kidney disease (with or without nephrotic syndrome), and should generally be regarded as the drugs of first choice.^{42,43} Drug therapy for hypertriglyceridemia includes a fibrate or niacin. In general, fibrates are better tolerated than nicotinic acid. Statins are indicated to lower LDL to acceptable levels in CKD patients based on efficacy and additional benefits observed in the general population, including the reduction in cardiovascular events and all-cause mortality.⁴²

Drug-Related Problems in Chronic Kidney Disease

Given the vast number of medications required to address CKD and manage the associated complications, drug-related problems are prevalent in this population.^{44,45} Such problems include improper drug selection, subtherapeutic dosage, overdose, adverse drug reactions, drug interactions, failure to receive a drug, and inappropriate laboratory monitoring.⁴⁵ In the dialysis population, the extent of medication use, including medications administered during dialysis therapy, contributes to the potential for drug interactions, adverse reactions, and nonadherence to therapy. The effect of decreased kidney function on absorption, distribution, metabolism, and elimination of pharmacologic agents, in addition to the contribution of dialysis to drug removal, further complicates pharmacotherapy in this population. Appropriate pharmacotherapeutic management includes choice of rational agents based on the indication, a regular comprehensive review of all medications, and frequent re-evaluation to adjust regimens relative to kidney function. Another important consideration in patients with CKD is

avoiding use of nephrotoxic agents, particularly in patients with more severe disease (Stage 4 CKD).

Other Complications

Because every major organ system is affected by CKD, there are many other complications that develop. Among these complications are fluid and electrolyte abnormalities, metabolic acidosis, bleeding, GI disorders, alterations in endocrine and immune function, altered glucose and insulin metabolism, dermatologic disorders, and neurologic abnormalities. Specific guidelines for management of these complications in CKD are not available; however, they must be considered when evaluating patients with CKD.

Multidisciplinary Approach to Chronic Kidney Disease Management

Appropriate management of CKD and the associated complications must also involve a multidisciplinary approach to manage the nonpharmacologic and pharmacologic interventions required, including appropriate diagnosis, pharmacotherapy, dietary education, and financial concerns. A core team would include physicians (primary care physicians, nephrologists), nurses, pharmacists, dietitians, and social workers, similar to the existing structure in outpatient dialysis facilities. It is important for clinicians to provide education to patients with CKD, particularly in Stages 3 to 5. Historically, pharmacists have not been considered part of the team of federally mandated health care providers (e.g., nephrologists, nurses, dietitians, and social workers) for patients with ESKD; however, they serve an essential role at all stages of CKD to improve medication use and evaluation. More widespread

acceptance of pharmacists as key providers of care in the CKD setting is needed and may become more widespread as pharmacists demonstrate their knowledge of the problems and appropriate interventions in this patient population.

Conclusions

The number of patients with and at risk for CKD is increasing, with a substantial rise in the population with Stage-5 CKD expected in the next decade. Although efforts to delay progression of CKD are paramount, measures to diagnose and manage the associated secondary complications and comorbid conditions early in the course of the disease are also essential. Common complications of Stages 4 and 5 CKD include anemia,

secondary hyperparathyroidism, fluid and electrolyte abnormalities, metabolic acidosis, and malnutrition. Cardiovascular complications are also prevalent in the population with CKD and the leading cause of mortality in patients with Stage-5 disease. The NKF-K/DOQI Guidelines should be used as a basis for the work-up of CKD and the design of appropriate therapy for associated complications. Patient education plays a critical role in the appropriate management of CKD and related complications. A multidisciplinary team structure is a rationale approach to provide this education and effectively design and implement the extensive nonpharmacologic and pharmacologic interventions required.

Table 1. NKF-K/DOQI Clinical Practice Guidelines

Available Guidelines
Anemia of Chronic Kidney Disease
Vascular Access
Hemodialysis Adequacy
Peritoneal Dialysis Adequacy
Nutrition in Chronic Renal Failure
Chronic Kidney Disease: Evaluation, Classification and Stratification
Managing Dyslipidemias in Chronic Kidney Disease
Bone Metabolism and Disease in Chronic Kidney Disease
Hypertension and Antihypertensive Agents in Chronic Kidney Disease
Cardiovascular Disease in Dialysis Patients
Guidelines Under Development
Diabetes and Chronic Kidney Disease

<http://www.kidney.org/professionals/kdoqi/guidelines.cfm>

Table 2. Staging of CKD Based on GFR³

Stage	Description	GFR (mL/min/1.73m²)
1	Kidney damage with normal or ↑ GFR	≥90
2	Kidney damage with mild ↓ GFR	60-90
3	Moderate ↓ GFR	30-59
4	Severe ↓ GFR	15-29
5	Kidney failure	≤15 (or dialysis)

Table 3. Diagnostic Criteria for Proteinuria and Albuminuria³

	Total Protein			Albumin		
	24-hour Collection (mg/day)	Spot Urine Dipstick (mg/dL)	Spot Urine Protein-SCr Ratio (mg/gm)	24-hour Collection (mg/day)	Spot Urine Dipstick (mg/dL)	Spot Urine Albumin-SCr Ratio (mg/gm)
Normal	<300	<30	<200	<30	<3	<17 (men) <25 (women)
Microalbuminuria	NA	NA	NA	30-300	>3	17-250 (men) 25-355 (women)
Albuminuria or Clinical Proteinuria	>300	>30	>200	>300	NA	>250 (men) >355 (women)

Table 4. Target Parameters for Anemia of CKD²²

Parameter	Target Based on NKF-K/DOQI Guidelines	Information Provided
Hemoglobin	11-12 g/dL	Concentration of hemoglobin
Hematocrit	33%-36%	% of red blood cells
Transferrin Saturation	20%-50% = $\frac{\text{serum iron}}{\text{TIBC}} \times 100$	Iron available for erythropoiesis
Ferritin	100-800 ng/mL	Storage Iron

TIBC = Total iron binding capacity

Table 5. Estimated Darbepoetin Alfa Starting Doses (mcg/wk) Based on Previous Epoetin Alfa Dose (Units/wk)⁴⁶

Previous Weekly Epoetin Alfa Dose (Units/wk)	Weekly Darbepoetin Alfa Dose (mcg/wk)
< 2500	6.25
2500-4999	12.50
5000-10,999	25.00
11,000-17,999	40.00
18,000-33,999	60.00
34,000-89,999	100.00
≥90,000	200.00

Darbepoetin alfa should be administered weekly for patients receiving epoetin alfa 2 or 3 times per week and every other week for patients receiving epoetin alfa once per week. For patients requiring darbepoetin alfa every other week, the weekly dose of epoetin alfa should be multiplied by 2 and this dose used in the conversion chart to determine the appropriate darbepoetin alfa dose.

Table 6. NKF-K/DOQI Guidelines for Calcium, Phosphorus, Ca X P, and Intact PTH³⁵

Laboratory	Stage-3 CKD	Stage-4 CKD	Stage-5 CKD
Corrected Ca (mg/dL)	“Normal”	“Normal”	8.4-9.5
Phosphorus (mg/dL)	2.7-4.6	2.7-4.6	3.5-5.5
Ca X P (mg ² /dL ²)	<55	<55	<55
Intact PTH (pg/mL)	35-70	70-110	150-300

Table 7. Phosphate-Binding Agents³⁵

Compound	Trade Names	Starting Doses
Calcium Carbonate^a (40% elemental calcium)	Tums, Oscal-500, Caltrate 600, Nephro-Calci, LiquiCal, CalciChew	0.5-1 gram (elemental calcium) tid with meals
Calcium Acetate^b (25% elemental calcium)	Phos-lo	0.5-1 gram (elemental calcium) tid with meals
Sevelamer Nonelemental (polymer based)	Renagel	800 mg tid with meals
Lanthanum carbonate	Fosrenol	750-1500 mg divided tid with meals
Aluminum Hydroxide^c	AlternaGel, Amphojel, Alu-Cap	300-600 mg tid with meals
Magnesium Carbonate^d	MagneBind	70 mg tid with meals

^aApproximately 39 mg phosphorus bound per 1 gram calcium carbonate; multiple agents available

^bApproximately 45 mg phosphorus bound per 1 gram calcium acetate.

^cNot a first-line agent, short-term use only (4 weeks or less) in patients with hyperphosphatemia not responding to other binders.

^dNot a first-line agent. Risk of hypermagnesemia, limited by side effects (diarrhea). tid = three times daily

Table 8. Dosing Recommendations for Vitamin D in Patients with Stage-5 CKD on HD³⁵

PTH (pg/mL)	IV & PO Calcitriol Dose per HD	IV Paricalcitol Dose per HD	PO & IV Doxercalciferol Dose per HD
300-600	0.5-1.5 mcg PO or IV	2.5-5.0 mcg	5 mcg PO 2 mcg IV
600-1000	1-4 mcg PO 1-3 mcg IV	6.0-10 mcg	5-10 mcg PO 2-4 mcg IV
>1000	3-7 mcg PO 3-5 mcg IV	10-15 mcg	10-20 mcg PO 4-8 mcg IV

Table 9. Management of Dyslipidemia in Patients with CKD^{41,42}

Dyslipidemia	Goal	Initial Therapy	Modification in Therapy	Alternative
TG \geq 500 mg/dL	TG <500 mg/dL	TLC	TLC + Fibrate or niacin	Fibrate or niacin
LDL 100-129 mg/dL	LDL <100 mg/dL	TLC	TLC + low-dose statin	Bile acid sequesterant or niacin
LDL \geq 130 mg/dL	LDL <100 mg/dL	TLC + low-dose statin	TLC + maximum-dose statin	Bile acid sequesterant or niacin
TG \geq 200 mg/dL and non-HDL \geq 130 mg/dL	Non-HDL <130 g/dL	TLC + low-dose statin	TLC + maximum-dose statin	Fibrate or niacin

TLC = therapeutic lifestyle changes

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