Conceptual Model of CKD: Applications and Implications

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The conceptual model of chronic kidney disease (CKD) was developed by the National Kidney Foundation's Kidney Disease Quality Outcome Initiative (NKF-KDOQI) in 2002 and subsequently revised and adopted by an international consensus under the auspices of KDIGO (Kidney Disease: Improving Global Outcomes) in 2005. This model includes concepts of definition, staging, outcomes, and treatment, as well as risk factors for the development, progression, and complications of CKD. Treatments are available for patients with risk factors and for each stage of CKD; these include slowing the progression of kidney disease, preventing and treating the complications of decreased glomerular filtration rate, and reducing cardiovascular disease risk factors and treating cardiovascular disease. In principle, measures to improve the prevention, detection, and treatment could reduce adverse outcomes, improve the quality of life, and prolong the survival of individuals with CKD. The conceptual model for CKD is now being applied to a public health approach for the prevention of the development, progression, and complications of CKD. Primary prevention is defined as prevention of CKD; secondary and tertiary prevention are defined as improving outcomes of patients with CKD stages 1 to 4 and kidney failure (CKD stage 5), respectively. The conceptual model has also fostered debate about important questions: Is CKD a disease or a cardiovascular disease risk-factor condition? Do all patients with CKD need to be referred to a nephrologist? What does CKD care include? Should the classification be modified to include cause of disease and prognosis? Can CKD evolve from acute kidney disease, and is CKD reversible? Is albuminuria a manifestation of a kidney disease or systemic endothelial dysfunction? Is the age-related decrease in glomerular filtration rate normal or abnormal, and should we change the definition of CKD in the elderly? A combination of immediate action, data gathering, and research to establish the efficacy, effectiveness, and costs related to CKD are needed to respond to CKD as a public health problem.

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The conceptual model of chronic kidney disease (CKD) currently in use was first detailed by the National Kidney Foundation's Kidney Disease Outcomes Quality Initiative (NKF-KDOQI) in 2002 and subsequently revised and adopted by international consensus under the auspices of KDIGO (Kidney Disease: Improving Global Outcomes) in 2005.[1-3] The Centers for Disease Control and Prevention is now applying this model in the public health approach for the prevention of the development, progression, and complications of CKD.[4] The purpose of this article is to review the conceptual model, including the definition, staging, outcomes, and treatment of patients with CKD, as well as risk factors for the development, progression, and complications of CKD. We also highlight the historical perspective of the conceptual model and some of the recent debate about the implications of these concepts for clinical practice, research, and public health. Some material in this article is reprinted from previous reports.[1-3]

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HISTORICAL PERSPECTIVE

The introduction of improved techniques for clinical chemistry and pathology in the mid-20th century dramatically expanded knowledge of the clinical characteristics, pathogenesis, natural history, diagnosis, and treatment of many types of CKD. At the same time, the development of dialysis and transplantation offered life-saving treatment to patients with kidney failure, irrespective of the cause of the disease, but were too expensive to be widely applied. The 1967 report by the Committee on Chronic Kidney Diseases, convened by the federal government and chaired by Carl Gottschalk, opens with the letter in Box 1.[5] The Gottschalk report suggested a federal system of care, paving the way for the 1972 legislation creating the end-stage renal disease program in

Box 1. Excerpt From Cover Letter From the Committee on Chronic Kidney Disease

"You charged the Committee with the responsibility of considering all aspects of the problems posed by chronic kidney disease and of making recommendations directed towards meeting these problems. . . . Prevention is obviously preferable to treatment of disease. Unfortunately, knowledge concerning the causes and prevention of end-stage kidney disease is limited and this is an area in which an expanded research effort is required. Furthermore, even if a completely successful method of prevention is developed it will have no significant impact on the numbers of people dying from end-stage kidney disease for many years. Therefore, the Committee recommends a national treatment program aimed at providing chronic dialysis and/or transplantation for all of the American population for whom it is medically indicated . . ."

Note: Text from 1967 letter from Carl W. Gottschalk, MD, to Charles L. Schultze, Director of the US Bureau of the Budget.[5]

the United States by enabling Medicare coverage for dialysis and transplantation for patients with chronic kidney failure regardless of age.[6]

In the following decades, Brenner et al,[7] investigating animal models of CKD, formulated a hypothesis for the progressive nature of kidney disease irrespective of cause, including the potential for treatment to ameliorate progression. Their hypothesis stimulated additional laboratory and clinical investigation and eventual large clinical trials. At the same time, new treatments became available for patients with some of the most important complications of kidney failure and earlier stages of CKD, including anemia and bone and mineral disorders.[8] The high burden of cardiovascular disease in patients with CKD was recognized, and CKD was identified as a new risk factor for cardiovascular disease.[9]

In the past 20 years, evidence from many sources indicated that CKD had become a public health problem in the United States and around the world. There was an increasing incidence and prevalence of kidney failure, with poor outcomes and high cost. There was an even greater prevalence of earlier stages of CKD. It became appreciated that CKD was under-diagnosed and undertreated, resulting in lost opportunities for prevention. The NKF convened a work group, chaired by 2 of the authors of this article, to develop clinical practice guidelines for CKD concerning evaluation, classification, and stratification of risk. KDOQI co-chairs Eknoyan and Levin wrote in the preface to the KDOQI CKD guidelines, "Thus, while dialysis has made it possible to prolong the lives of patients with ESRD, today it is also possible to retard the course of progression of kidney disease, to treat accompanying comorbidity earlier, and to improve the outcomes and quality of life of all individuals afflicted with kidney disease, well before replacement therapy becomes necessary. Yet, the application of these advances remains inconsistent, resulting in variation in clinical practice and, sadly, in avoidable differences in patient outcomes".[1]

One reason for poor outcomes was believed to be the lack of agreement about a definition and classification of stages in the progression of CKD. As stated in the introduction to the executive summary of the guidelines, "A clinically applicable classification would be based on laboratory evaluation of the severity of kidney disease, association of level of kidney function with complications, and stratification of risks for loss of kidney function and development of cardiovascular disease."[1]

CONCEPTUAL MODEL

Figure 1 shows the KDOQI conceptual model for the development, progression, and complications of CKD with modifications relevant to a public health approach.[1,4] The conceptual model identifies kidney failure as the end stage of CKD and links it to earlier stages. According to this concept, kidney failure is preceded by a decrease in glomerular filtration rate (GFR), which is preceded by kidney damage. CKD typically evolves over a long time, beginning with a lengthy latency period when the disease may go undetected, followed by late onset of symptoms caused by complications of decreased kidney function. Thus, it should be possible to detect CKD before kidney failure by testing for markers of kidney damage and/or estimating GFR. The horizontal arrows in Fig 1 pointing from left to right emphasize the progressive nature of CKD. However, the rate of progression is variable, and not all patients progress; thus, a diagnosis of CKD does not equate with eventual development of kidney failure. Interventions in earlier stages may slow or prevent the progression to later stages.

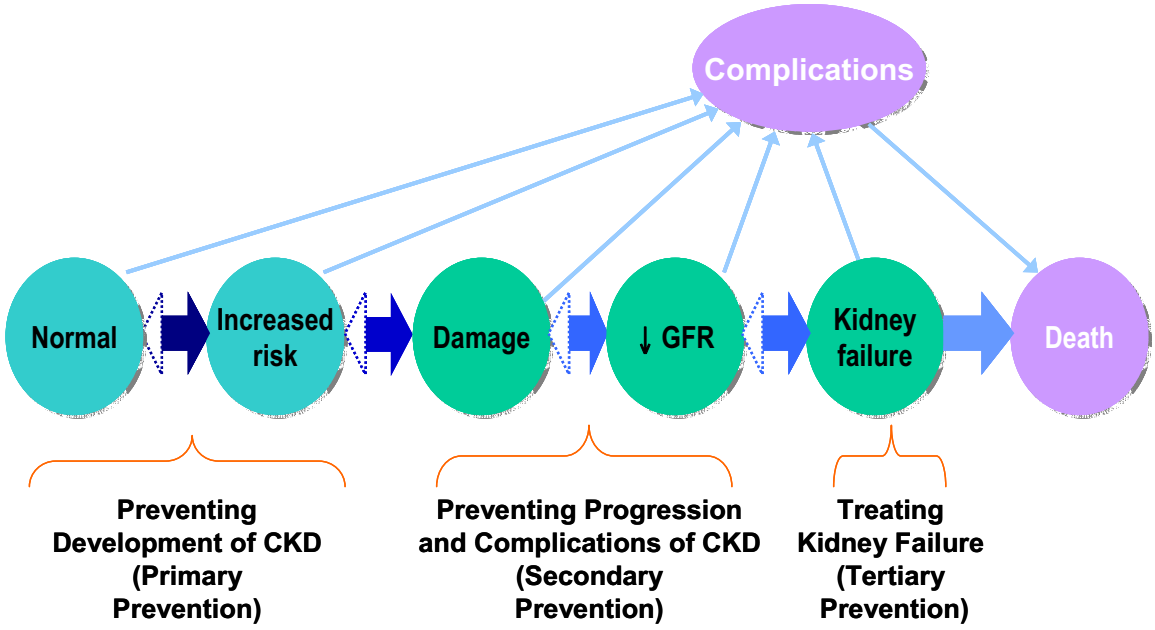

Figure 1. Conceptual model of chronic kidney disease (CKD). Overall, this diagram presents the continuum of the development, progression, and complications of CKD. Green circles, stages of CKD; aqua circles, potential antecedents of CKD; lavender circles, consequences of CKD; thick arrows between ellipses, risk factors associated with the development and progression and remission of CKD. "Complications" refers to all complications of CKD and its treatment, including complications of decreased glomerular filtration rate (GFR) and cardiovascular disease. Stages of prevention are shown along the continuum. Modified and reprinted with permission from the National Kidney Foundation.[1]

Early stages of kidney disease may be reversible, and individuals with kidney failure can revert to earlier stages through kidney transplantation, shown as dashed arrowheads pointing from right to left, signifying that remission is less frequent than progression, as discussed next.

The conceptual model also identifies a population at increased risk of developing CKD. Attributes that differentiate the population at greater risk from the population at lower risk are defined as risk factors for the development of CKD. Some risk factors may be modifiable, and in principle, the detection and modification of these risk factors could delay or prevent the development of CKD.

The model highlights the possibility of complications of earlier stages of CKD, often leading to death, without progression to kidney failure. Strategies for the prevention, early detection, and treatment of CKD complications may prolong survival and improve quality of life even if there is no effect on kidney disease progression.

DEFINITION, STAGES, OUTCOMES, AND TREATMENTS FOR CKD

CKD is defined as the presence of kidney damage or GFR less than 60 mL/min/1.73 m^2 for 3 months or longer, irrespective of cause.[1-3] Table 1 lists the rationale for each criterion. An important aspect of the definition is that the criteria are objective and can be ascertained by means of simple laboratory tests.[10,11] Markers of kidney damage include abnormalities in serum or urine or on imaging studies and generally reflect the underlying pathological state. Albuminuria reflects increased glomerular permeability to macromolecules. Although a number of definitions have been proposed for albuminuria, in this classification, the accepted threshold for albumin-creatinine ratio in an untimed spot urine sample is greater than 30 mg/g; sex- and race-specific ratios have been proposed because of variation in creatinine excretion, but are more difficult to implement. GFR generally is considered to be the best index of overall kidney function in patients in health and with disease. Because GFR is difficult to measure, it is estimated

Table 1. Criteria and Rationale for the Definition of CKD

Criteria	Rationale or Comment
Duration ≥ 3 mo based on documentation or inference	Duration is necessary to distinguish chronic from acute kidney diseases Inference of chronicity allows clinical judgment in the absence of documentation of past history
Kidney damage, defined as structural or functional abnormalities of the kidneys	Pathological abnormalities Markers, including: Urine abnormalities (eg, albuminuria) Blood abnormalities (eg, renal tubular syndromes) Imaging abnormalities (eg, polycystic kidneys, hydronephrosis, small and echogenic kidneys) History of kidney transplantation
Albuminuria as a marker of kidney damage (spot urine albumin-creatinine ratio > 30 mg/g)	Albuminuria reflects increased glomerular permeability Threshold level is 2-3 times greater than normal value Higher levels are infrequent in young individuals (<40 y) Higher levels are the earliest marker of kidney damage due to diabetes, glomerular disease, and hypertension Higher levels are associated with adverse outcomes, including progression of kidney and cardiovascular disease in individuals with or without diabetes mellitus Therapies that reduce albuminuria are associated with slowing the progression of diabetic and nondiabetic kidney disease
GFR < 60 mL/min/1.73 m^2	GFR is the best overall index of kidney function in health and disease Threshold level is substantially greater than the level associated with kidney failure Threshold level is approximately half the normal adult level Lower levels are rare in young individuals (<40 y) Lower levels are associated with increasing complications of CKD Lower levels are associated with adverse outcomes, including cardiovascular disease morbidity and mortality in individuals with or without diabetes Threshold and lower levels can be detected by current estimating equations for GFR based on serum creatinine, but not by serum creatinine alone

Note: Conversion factor for units: GFR in mL/min/1.73 m^2 to mL/s/1.73 m^2, ×0.01667.
Abbreviations: CKD, chronic kidney disease; GFR, glomerular filtration rate.

from serum creatinine concentration in clinical settings. Currently available estimating equations are reasonably accurate at estimated GFRs (eGFRs) less than 60 mL/min/1.73 m^2; however, bias and precision are worse at greater levels of eGFR. Like all diagnostic tests, interpretation is influenced by the prior probability of disease. Isolated abnormalities in otherwise healthy individuals should be confirmed before definitive diagnosis or action is taken. Although confirmation with GFR measurement may be helpful when decisions depend on a precise knowledge of GFR (for example, when evaluating a potential kidney donor), in most cases, eGFR is appropriate for diagnosis, staging, and tracking the progression of CKD.

CKD is a heterogeneous condition with varying expression among individual patients, in part related to the cause and pathological characteristics of kidney disease, rate of progression, and presence of comorbid conditions. Because of the central importance of level of kidney function in the care of patients with CKD, stage of CKD is defined by level of GFR. Table 2 lists the 5-stage classification of CKD, associated *International Classification of Diseases, Ninth Revision* codes, and links to the KDOQI clinical action plan for each stage.[1-3] The action plan is cumulative; the plan for each stage includes actions from previous stages. Although strong evidence is available to justify action related to some interventions, many of the other recommendations are based on weak evidence or opinion. To highlight the specialized care required for dialysis and transplantation, patients receiving treatment with dialysis

Table 2. Stages, Description, and Clinical Action Plan for CKD and Individuals at Increased Risk of CKD

Stage	Description	GFR (mL/min/1.73 m^2)	*ICD 9* Code	Clinical Action Plan
—	At increased risk	≥60 (with CKD risk factors)	—	Screening CKD Risk Reduction
1	Kidney damage with normal or ↑ GFR	≥90	*585.1*	Diagnosis and treatment Treatment of comorbid conditions Evaluation of risk Slowing progression CVD risk reduction
2	Kidney damage with mild ↓ GFR	60-89	*585.2*	Estimating progression
3	Moderate ↓ GFR	30-59	*585.3*	Evaluating and treating complications
4	Severe ↓ GFR	15-29	*585.4*	Preparing for kidney replacement therapy
5	Kidney failure	<15 (or dialysis)	*585.5* *585.6 (if ESRD)* *V codes for dialysis or transplantation*	Replacement (if uremia present)

Note: Patients treated with dialysis are classified as CKD stage 5D, and patients in all CKD stages with a functioning transplant are designated with a T. Conversion factor for units: GFR in mL/min/1.73 m^2 to mL/s/1.73 m^2, ×0.01667.

Abbreviations: CKD, chronic kidney disease; CVD, cardiovascular disease; *ICD 9*, *International Classification of Diseases, Ninth Revision*; ESRD, end-stage renal disease; GFR, glomerular filtration rate.

are subclassified as CKD stage 5D, and patients in all stages with a functioning transplant are designated with a T.

Major outcomes of CKD include loss of kidney function possibly leading to kidney failure, complications of decreased GFR, and increased risk of cardiovascular disease. The rate of decrease in kidney function varies among individuals, with fast progression defined as a GFR decrease greater than 4 mL/min/1.73 m^2/y. At this rate, the interval from onset of CKD stage 3 (GFR < 60 mL/min/1.73 m^2) to kidney failure (15 mL/min/1.73 m^2) would be approximately 10 years or less. Patients with uncontrolled hypertension, proteinuria, and diabetes, as well as members of US racial and ethnic minority groups, appear to have faster rates of kidney disease progression. Treatments to slow progression are now available. The most dramatic results are appreciated with strict blood pressure control and use of antihypertensive agents that inhibit the renin-angiotensin system in patients with more rapidly decreasing GFR (as seen in patients with diabetic kidney disease, those with nondiabetic kidney disease with proteinuria, or African Americans).[12] Recent data from the US Renal Data System suggest a decreasing incidence of kidney failure in some groups, perhaps reflecting beneficial effects of early detection and improved treatment.[13]

Complications of decreased GFR include hypertension, anemia, malnutrition, bone and mineral disorders, neuropathy, and decreased quality of life.[1] As shown in Fig 2, the burden of complications is especially high in patients with CKD stages 4 to 5 (GFR < 30 mL/min/1.73 m^2). Therapeutic interventions at earlier stages can prevent or ameliorate many of the complications of decreased GFR.[12,14-17] In addition, susceptibility to acute kidney injury (AKI) and other side effects of medications or diagnostic and therapeutic procedures, such as imaging studies, are increased at decreased GFRs.

Cardiovascular disease is considered separately because cardiovascular events occur more frequently than kidney failure in patients with CKD, CKD appears to be an independent risk factor for cardiovascular disease, and cardiovascular disease in patients with CKD is treatable and potentially preventable. The 1998 Report of the NKF Task Force on Cardiovascular Disease in Chronic Renal Disease recommended that patients with CKD be considered in the highest risk group for subsequent cardiovascular disease events, and that most interventions effective in the general population should also be applied to

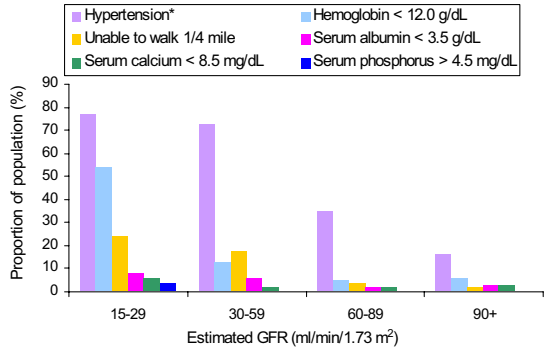

Figure 2. Estimated prevalence of complications related to chronic kidney disease (CKD) according to estimated glomerular filtration rate (GFR) in the general population. Hypertension was defined as systolic blood pressure of 140 mm Hg or higher, diastolic blood pressure of 90 mm Hg or higher, or receipt of antihypertensive medication. The study population includes participants in the Third National Health and Nutrition Evaluation Survey (1988 to 1994) aged 20 years or older. A total of 10,162 participants with a mean age of 39 years had a GFR greater than 90 mL/min/1.73 m^2; 4,404 with a mean age of 54 years had a GFR of 60 to 89 mL/min/1.73 m^2; 961 with a mean age of 72 years had a GFR of 30 to 59 mL/min/1.73 m^2; and 52 with a mean age of 75 years had a GFR of 15 to 29 mL/min/1.73 m^2. Conversion factors for units: GFR in mL/min/1.73 m^2 to mL/s/1.73 m^2, ×0.01667; serum calcium in mg/dL to mmol/L, ×0.2495; hemoglobin in g/dL to g/L, ×10; serum albumin in g/dL to g/L, ×10; serum phosphorus in mg/dL to mmol/L, ×0.3229. Modified and reprinted with permission from National Kidney Foundation.[1]

patients with CKD.[9] These conclusions were affirmed by the 2003 Statement from the American Heart Association Councils on Kidney in Cardiovascular Disease, High Blood Pressure Research, Clinical Cardiology, and Epidemiology and Prevention[18] and recent guidelines by the Joint National Committee on Prevention, Detection, Evaluation and Treatment of High Blood Pressure,[19] American Diabetes Association,[20] and NKF.[21-23] Few clinical trials have been designed to evaluate "hard" clinical outcomes, such as total mortality and kidney failure, in the CKD population. However, treatment for patients with cardiovascular disease risk factors is effective in earlier stages of CKD,[9] and the CKD subgroup in cardiovascular disease trials appears to benefit as much or more than the non-CKD subgroup from reduction in cardiovascular disease risk factors and intensive management of clinical cardiovascular disease.[24-26] Recently, it has been recognized that cardiovascular disease is a risk factor for loss of kidney function.[27] Possibly, better treatment of patients with cardiovascular disease may slow the development or progression of kidney disease.

Thus, there is now therapy to slow the progression of kidney disease, prevent and treat the complications of decreased GFR, and reduce cardiovascular disease risk factors and treat cardiovascular disease in patients with CKD. In principle, measures to improve the prevention, detection, and treatment of CKD in its earlier stages could reduce adverse outcomes, improve quality of life, and prolong the survival of individuals with CKD.

CKD RISK FACTORS AND STRATEGIES FOR PREVENTION

Risk factors are defined as attributes associated with increased risk of adverse outcomes. Table 3 lists risk factors for the development, progression, and complications of CKD and the relationship of risk factors to preventive strategies.[28] Identification of modifiable risk factors allows targeting of specific populations for diagnostic testing and therapeutic intervention at different stages in the development and progression of CKD and can be linked to preventive strategies. Primary prevention is defined as prevention of CKD and would include screening for risk factors for development of CKD in the general population. Secondary prevention is defined as improving outcomes of CKD stages 1 to 4 and would include early detection of CKD through education and CKD testing in individuals at increased risk of the development of CKD. Secondary prevention would also include evaluation and management of risk factors for the progression and complications of CKD in patients found to have CKD stages 1 to 4. Tertiary prevention is defined as improving outcomes of patients with kidney failure (CKD stage 5) and would include evaluation and management of risk factors for complications in patients with kidney failure. To date, there are few data to evaluate prevention programs for patients with earlier stages of CKD.

IMPLICATIONS

The conceptual model, definition, and staging for CKD raise many new questions. The answers will have major implications on clinical practice, research, and public health.

Table 3. Risk Factors for the Development, Progression, and Complications of CKD and Preventive Strategies

Risk Factor	Definition	Examples	Preventive Strategies
Development	Increase susceptibility to kidney damage	Older age, family history of CKD, US racial or ethnic minority status, reduced kidney mass, hyperfiltration states	Primary prevention
	Directly initiate kidney damage	Diabetes, high blood pressure, obesity, dyslipidemia, autoimmune diseases, infections, stones, obstruction	
Progression	Worsen kidney damage or accelerate GFR decrease	Higher level of proteinuria	Secondary prevention
Complications	Increase risk of complications of decreased GFR	Factors related to hypertension, anemia, malnutrition, bone and mineral disorders, neuropathy; drugs and procedures with kidney or systemic toxicity	
	Accelerate onset or recurrence of CVD	Traditional CVD risk factors; nontraditional "CKD-related" risk factors	
	Increase morbidity and mortality in kidney failure	Late referral, dialysis factors, comorbid conditions	Tertiary prevention

Note: Factors implicated at different stages in the development and progression of CKD are listed in the initial category in which they could potentially appear.

Abbreviations: CKD, chronic kidney disease; CVD, cardiovascular disease; GFR, glomerular filtration rate.

Is CKD a Disease or a Cardiovascular Disease Risk-Factor Condition?

Although CKD is not as severe a condition as kidney failure, as shown, it is still a serious health concern. In describing CKD, it is important to convey an appropriate balance between the importance of diagnosis and treatment of a disease versus simple identification of a high-risk state. KDIGO considered alternative proposals, but favored retaining the term "disease."[3] The KDOQI definition of CKD as a disease is consistent with current use of this term. The Oxford English Dictionary (compact edition) defines a disease as "A disorder of structure or function in a human, animal, or plant, especially one that produces specific symptoms."[29] Evidence in support of a condition being defined as a disease includes clinical-pathological correlations (as defined by case series), associations with symptoms or findings (as defined by cross-sectional analyses), and associations with outcomes (as defined by longitudinal analyses). The use of the term disease in CKD is consistent with: (1) the need for action to improve outcomes through prevention, detection, evaluation, and treatment; (2) providing a message for public, physician, and patient education programs; (3) common use; and (4) its use in other conditions defined by findings and laboratory tests, such as hypertension, diabetes, and hyperlipidemia. As recognized by several clinical practice guidelines, more data are needed to strengthen the evidence for a number of action plans for patients with different complications of CKD, as well as referral and care practice models for patients with different stages of CKD.

Do All Patients With CKD Need to Be Referred to a Nephrologist?

CKD is common. Nephrologists cannot and do not need to care for all patients with CKD. Using the definition and classification for CKD described, it has been estimated that approximately 13% of the US adult population has CKD[30] compared with 0.2% treated by dialysis or transplantation. The number of practicing nephrologists is not sufficient to care for all patients with CKD, and the recent publication of clinical practice guidelines for many of the conditions affecting patients with early stages of CKD should

Table 4. Recommendations for Referral to Specialists for Consultation and Comanagement of CKD

Evaluation and Management of CKD as Described in KDOQI CKD Clinical Action Plan	Kidney Disease Specialist; Other Specialists as Appropriate
GFR $<$ 30 mL/min/1.73 m^2	Kidney disease specialist
Spot urine total protein–creatinine ratio $>$ 500-1,000 mg/g	Kidney disease specialist
Increased risk of progression of kidney disease	Kidney disease specialist
GFR decrease $>$30% within 4 mo without explanation	Kidney disease specialist
Hyperkalemia (serum potassium $>$ 5.5 mEq/L) (despite treatment)	Kidney disease specialist
Resistant hypertension (blood pressure $>$ 130/80 mm Hg despite adherence to a 3-drug antihypertensive regimen that includes a diuretic)	Kidney disease or hypertension specialist
Difficult-to-manage drug complications	Kidney disease or hypertension specialist
Acute presentations of cardiovascular disease	Cardiovascular disease specialist
Complex or severe chronic cardiovascular disease conditions	Cardiovascular disease specialist
Age $<$ 18 y	Pediatric kidney disease specialist

Note: Conversion factor for units: GFR in mL/min/1.73 m^2 to mL/s/1.73 m^2, $\times$0.01667. Serum potassium levels in mEq/L and mmol/L are equivalent.

Abbreviations: CKD, chronic kidney disease; GFR, glomerular filtration rate; KDOQI, Kidney Disease Outcomes Quality Initiative.

Reprinted with permission from National Kidney Foundation.[12]

facilitate the care of many of the routine problems that occur in patients with CKD by primary care physicians and other specialists.[1,12,14-23] This is similar to other common chronic diseases in older adults. Not all patients with type 2 diabetes are referred to an endocrinologist and not all patients with cardiovascular disease are referred to a cardiologist. Suggested indications for referral to nephrologists and other specialists are listed in Table 4.[12] Nephrologists and other physicians should work to refine these recommendations and develop practice models to facilitate coordination of care for patients with earlier stages of CKD. Randomized trials of care programs or components of care will provide the most rigorous basis for action.

What Does CKD Care Include?

Most patients with CKD do not develop kidney failure. We suggest that nephrologists and other physicians need to adopt a broader view of care for patients with CKD. In a large clinical population, the average age of patients with CKD was approximately 70 years, and death was approximately 25 times more common than progression to kidney failure.[31,32] Even in patients with CKD stage 4, death was 3 times more common than initiation of dialysis therapy. Cardiovascular disease is the leading cause of death in patients with CKD, and these conditions share many risk factors. Thus, appropriate CKD care extends beyond interventions to slow the decline in GFR and treat patients with the complications of decreased GFR to also include management of cardiovascular disease and its risk factors. A careful evaluation of the risks of CKD should include risks of multiple outcomes, as listed in Table 5.[33] Older age increases the risk of mortality and cardiovascular disease in absolute terms and relative to the risk of kidney failure.[34] The appropriate evaluation for treatable causes and complications of kidney disease in the elderly is not certain. As discussed next, this is an important area for research.

Should the Classification Be Modified to Include Cause of Disease and Prognosis?

CKD is a heterogeneous condition. Classification according to severity (level of eGFR) is only the first step in evaluating a patient with CKD. Clinicians must consider all relevant characteristics in estimating prognosis and formulating treatment plans, including the cause of kidney disease, comorbid conditions, complications related to level of GFR, risks of kidney disease progression, and risks of cardiovascular disease. For example, the prognosis for some people in earlier stages of CKD may be worse than for others in

Table 5. CKD Measures as Risk Factors for Outcomes of CKD

Outcome	Importance of Different CKD Measures		
	CKD Stage	Type of Kidney Disease (diagnosis)*	Proteinuria
Concurrent complications†	+++	+	+
Prognosis			
Risk of cardiovascular disease or mortality	+++	+	++
Risk of kidney failure	+++	++	+
Rate of decrease in GFR	+	+++	+++
Acute kidney injury, drug toxicity	+++	?	?

Abbreviations: CKD, chronic kidney disease; GFR, glomerular filtration rate.
Modified from Levey and Coresh.[33]
*For example, diabetic, glomerular, vascular, tubulointerstitial, and cystic diseases.
†Hypertension, anemia, malnutrition, bone disease, neuropathy, fatigue.

later stages of CKD. A child with nephrotic syndrome and normal GFR caused by focal and segmental glomerulosclerosis is more likely to progress to kidney failure than an elderly person with a moderate decrease in GFR caused by hypertensive nephrosclerosis, and evaluation and management should be appropriately tailored for this possibility. The child should be carefully evaluated for underlying causes of kidney disease; treated to induce a remission and relieve symptoms of nephrotic syndrome; frequently monitored for complications of treatment, kidney disease progression, and complications related to decreased GFR; counseled about lifestyle adjustments to cope with chronic disease; and educated about options for dialysis and transplantation if kidney disease progresses. The risk of drug toxicity and clinical cardiovascular disease is greater in the older patient than in the child. Accordingly, in the absence of risk factors for fast progression of kidney disease, intervention for the elderly patient with stage 3 CKD may differ substantially, with the greatest benefit obtained through cardiovascular disease risk reduction and prevention of AKI and other side effects of medications and procedures. These considerations are the basis of recommendations for referral, as discussed.

Some have suggested modifying the current classification according to cause of CKD or prognosis. Others have believed that the simplicity of the current classification system has been critical to its success and acceptance by nonnephrologist physicians and therefore have not been in favor of modification of the current system. We agree that adding prognosis to the classification system would have merit. Age, sex, race, diabetes, level of blood pressure, and magnitude of albuminuria are among the most important prognostic factors for kidney disease progression and cardiovascular disease; however, more research is needed to develop clinically useful predictive instruments. The goal should be to find ways to articulate the differential risks for the various outcomes of CKD (Table 5) while still maintaining its simplicity and appropriateness for use by all health care professionals.

Can CKD Evolve From Acute Kidney Disease and Is CKD Reversible?

Recent statements from the Acute Kidney Injury Network define AKI as a "an abrupt (within 48 hours) reduction in kidney function"[35] and propose a conceptual model for AKI that is analogous to the model for CKD, including identification of kidney damage, decreased GFR and kidney failure as stages within AKI, and antecedents and outcomes other than kidney disease.[36] Failure to recover within 3 months would constitute CKD. Although nomenclature for kidney disease that evolves during an interval longer than 48 hours and less than 3 months is not formally established, the term "acute kidney disease" would be reasonable.

Recovery from CKD was not formally included in the conceptual framework of CKD. There are many examples of improving GFR and remission of markers of kidney damage in patients with CKD, such as recovery from kidney failure caused by scleroderma or malignant hypertension and remission of nephrotic syndrome in patients with minimal change disease, idiopathic

membranous nephropathy, or lupus nephritis. However, until recently, later stages of most types of kidney disease had been considered "inexorably progressive."[37] Remissions of albuminuria are well documented in patients with diabetic kidney disease with glucose control or inhibition of the renin-angiotensin system and, in 1 recent study, in patients with nondiabetic kidney disease in association with weight loss.[38] Thus, we have highlighted the possibility for remission in the conceptual model shown in Fig 1.

Is Albuminuria a Manifestation of Kidney Disease or Systemic Endothelial Dysfunction?

Albuminuria indicates increased glomerular permeability to macromolecules, with the magnitude of albuminuria generally correlating with the degree of glomerular damage.[39] The kidney is a highly vascular organ; therefore, it is likely that endothelial dysfunction in the kidney is a kidney disease, even if part of a systemic process. The distinction between the early stage of a kidney disease versus generalized endothelial dysfunction is difficult because not all individuals with earlier stages of CKD progress to later stages.

The terms microalbuminuria and macroalbuminuria are sometimes used to designate an urine albumin excretion rate between 30 and 300 mg/d versus greater than 300 mg/d, respectively (approximately equivalent to a spot urine albumin-creatinine ratio of 30 to 300 and >300 mg/g, respectively). Microalbuminuria is widely accepted as an early sign of kidney disease in patients with diabetes. Recent data show that microalbuminuria is associated with a similar relative risk for progression to macroalbuminuria in both diabetic and nondiabetic individuals,[40] suggesting that microalbuminuria reflects a kidney disease; however, not all individuals with CKD have microalbuminuria. In the National Health and Nutrition Examination Survey (NHANES), only approximately 65% of diabetic and 30% of nondiabetic individuals with decreased GFR had a urine albumin-creatinine ratio greater than 30 mg/g.[41,42]

Lower levels of albuminuria, even less than those consistent with microalbuminuria, are associated with the subsequent development of cardiovascular disease in diabetic and nondiabetic patients.[43] Possibly, lower levels of albuminuria reflect an even earlier stage of kidney damage. Lower levels of albuminuria are associated with the subsequent development of microalbuminuria,[44] but whether lower levels of albuminuria are associated with increased risk of the subsequent development of decreased GFR has not been well studied.

Is an Age-Related Decrease in GFR Normal or Abnormal, and Should We Change the Definition of CKD in the Elderly?

GFR decreases with age (Fig 3),[45] and the prevalence of decreased GFR is greatest in the

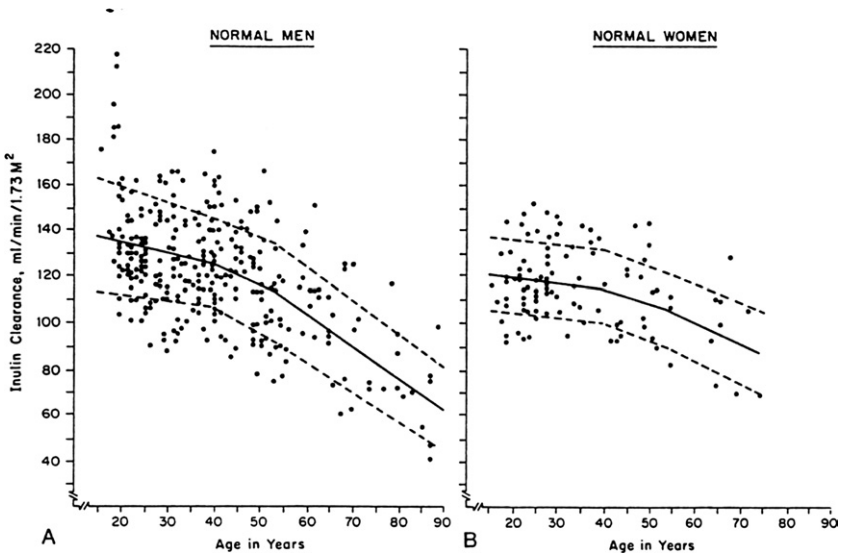

Figure 3. Glomerular filtration rate (GFR) in aging. Normal values for inulin clearance are shown for (A) men and (B) women of various ages, with GFR measured as urinary clearance of inulin. A GFR of 60 mL/min/1.73 m^2 is the threshold for the definition of chronic kidney disease; solid lines, mean GFR per decade of age; dashed lines, the value 1 SD from the mean value of GFR per decade of age. Conversion factors for units: GFR in mL/min/1.73 m^2 to mL/s/1.73 m^2, ×0.01667. Reprinted with permission from Wesson.[45]

elderly, reaching more than 35% by age 70 years.[30] The age-related decrease in GFR is associated with decreased renal blood flow; impaired maximal urine concentration; pathological findings of global glomerular sclerosis, vascular sclerosis, and tubular atrophy; and reductions in cortical thickness and overall kidney size.[46,47] All these changes are considered abnormal when observed in younger individuals. The magnitude and cause of the age-related decrease in GFR is an important area of research; however, there is already substantial evidence for health risks of decreased GFR in the elderly.[48] The elderly are the fastest growing segment of the population initiating dialysis therapy for kidney failure.[13] Many studies show an association between decreased eGFR and greater rates of cardiovascular disease and mortality and higher cost.[31,32,49] However, in some studies, increased risk of mortality in the elderly is not apparent until eGFR is less than approximately 45 mL/min/1.73 m^2.[34,50] However, adverse effects of medication and complications of procedures are more common in the elderly,[51,52] in part because of decreased GFR. Decreased GFR likely is not the only determinant of risk in the elderly (Table 5). Studies that include the combination of albuminuria and eGFR together are a first step toward this goal.[53,54] The magnitude, cause, and consequences of the age-related decrease in GFR are important areas of research; it should not be defined as normal just because it is common.

CONCLUSION

The conceptual model of CKD developed by the KDOQI and subsequently revised and adopted by KDIGO is applicable to a public health approach to preventing the development, progression, and complications of CKD. The model has stimulated debate about important topics that can be resolved only through further research. In the meantime, a combination of immediate action, data gathering, and research to establish the efficacy, effectiveness, and costs related to CKD are needed to respond to CKD as a public health problem.

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