Chapter Two
Overview of Chronic Kidney Disease

Role Of The Kidneys

The kidneys are two bean-shaped, fist-sized organs located near the middle of the back below the rib cage. Daily, these small organs filter approximately 200 quarts of blood to remove 2 quarts of waste products and extra water.[1] The waste that is removed is what remains after the body processes food and liquids for energy and repair. Extra water and waste products from the blood become urine, which flows through tubes called ureters into the bladder for storage. Ineffective removal of waste products can lead to waste product build-up in the blood and cause damage to the kidneys and other organs. The kidneys also produce hormones that help make red blood cells, regulate blood pressure, maintain calcium for bones, and regulate normal chemical balance in the body.

The ability of the kidneys to perform their work is referred to as *kidney function*.[1] Most people are born with two healthy kidneys; however, people do not need two healthy kidneys to lead normal lives. Some people are born with only one kidney and live normal lives. Others donate a kidney to a person in need and still have adequate kidney function. A small decrease in kidney function may not cause a problem. A more significant decline in kidney function, however, can lead to serious consequences.

Some people develop acute kidney diseases that can be cured with their kidneys returning to normal function. Others develop chronic kidney disease (CKD), which persists and worsens over time. Serious medical problems arise when kidney function falls below 25% of normal kidney functioning.[1] People with less than 15% of function are considered to have kidney failure and need therapy to sustain their lives. This therapy may be in the form of dialysis or kidney transplant.

Risk Factors

Some people have clinical or sociodemographic risks that increase their likelihood of developing CKD.[2] For example, people with diabetes, high blood pressure (hypertension), cardiovascular disease, an autoimmune disease (eg, lupus), systemic infections, urinary

tract infections, urinary stones, lower urinary tract obstruction, cancer, a family history of CKD, a history of acute kidney failure, decreased kidney size, exposure to drugs toxic to the kidneys, or low birth weight are at increased risk of developing CKD.[2,3] Similarly, people who are older adults, have low incomes or low educational achievement, or have had exposure to certain chemical and environmental conditions are in higher risk categories. Although some studies indicate certain racial and ethnic minorities (African American, Native American, Hispanic/Latino, and Asian or Pacific Islander) have a higher prevalence of CKD, other studies suggest otherwise.[4-6] One study reported "metabolic abnormalities were more common in minority populations, and low GFR appeared to have a multiplicative effect. Defining CKD using a single GFR threshold may be disadvantageous for minority populations because metabolic abnormalities are present at higher levels of GFR."[7] Other risk factors for CKD include male gender, obesity, high protein intake, anemia, and dyslipidemia (abnormal levels of cholesterol, LDL, and triglycerides).[3] Large numbers of people have one or more of these risk factors, placing them at greater risk of developing chronic kidney disease. In the 2006 Behavioral Risk Factor Surveillance Survey, 9.1% of North Carolina adults reported being told they had diabetes, and 9.3% had a history of cardiovascular disease.[8] Of these different risk factors, diabetes, hypertension, and cardiovascular diseases are considered to be the primary risk factors that increase a person's likelihood of developing CKD.

Measuring, Defining, and Staging Of Chronic Kidney Disease

There are several tests that may be performed to measure kidney function. A health care professional may use a urine dipstick to test for protein in the urine, referred to as proteinuria, that may result from decreased kidney function.[9] Proteinuria, however, can also be caused by other conditions such as cardiovascular disease, diabetes, hypertension, and other forms of kidney disease, so the urine dipstick is not considered the best test of kidney function.[10] Albumin is the protein most likely to be found in the urine if there is a problem with kidney function, and a very small amount of this protein in the urine, called microalbuminuria, is one of the first signs of kidney disease.[11] A urine test for this protein may be performed on people with an increased risk for CKD.

A more specific test for kidney function is measurement of creatinine. Creatinine is a waste product in the blood that comes from muscle activity. It is normally removed by the kidneys, but people have increased creatinine levels when kidney function declines. The glomerular filtration rate (GFR), a calculation of how efficiently the kidneys filter waste from the blood, can be calculated by analyzing all of a person's urine over a 24-hour period. An *estimated* glomerular filtration rate (eGFR) can be calculated by analyzing a person's blood for serum creatinine.[10] The blood is tested in a laboratory to determine how many milligrams of creatinine are in one deciliter of blood

(mg/dL). The creatinine measure is then converted to an estimated glomerular filtration rate using age, gender, and race.[a] Given the relative convenience of the blood test approach and the reliability of the eGFR, this test is widely accepted as the best overall measure of kidney function.

The National Kidney Foundation (NKF) convened panels of experts to review the current evidence on kidney disease and dialysis in adult patients.[12] A separate workgroup was convened to study pediatric kidney disease and dialysis. In 1997, the workgroups published the Dialysis Outcomes Quality Initiative (DOQI) guidelines. In 1999, the NKF focused its attention on earlier kidney disease and developed staging of chronic kidney disease as well as clinical treatment guidelines. The Kidney Disease Outcomes Quality Initiative (KDOQI) was the product of their work.

The KDOQI guidelines define chronic kidney disease as either kidney damage or glomerular filtration rates less than 60 for more than 3 months.[2] Based on glomerular filtration rates (GFR), KDOQI guidelines classify people into one of five stages of CKD that range from kidney damage with normal or elevated GFR to kidney failure.[b] People with increased risk for CKD who have GFR values greater than 90 can be classified as pre-CKD. Stage 1 CKD is described as kidney damage with GFR values greater than or equal to 90. Kidney function steadily declines until Stage 5, kidney failure. Kidney failure includes patients who may or may not be treated with dialysis or transplantation.[13] In contrast, the term "end-stage kidney disease" (ESKD) includes only those individuals with kidney failure who have had a kidney transplant or who are undergoing dialysis.

Using the national prevalence estimates of kidney functioning, the University of North Carolina at Chapel Hill (UNC) Kidney Center was able to estimate the number of people in North Carolina at each stage of CKD.[14] In total, UNC estimated that there were 941,770 North Carolinians with non-ESKD CKD (Stages 1 – 4). According to the United States Renal Data System (USRDS), more than 11 000 people in North Carolina suffer from ESKD. The numbers of new cases and people living with ESKD have steadily increased since 1994, and the state is higher than the national average. Table 2.1 lists the different stages of chronic kidney disease, the estimated national prevalence of the disease, and the estimated number of people in North Carolina at each stage of the disease.

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a The most commonly used equations to estimate glomerular filtration rate are the Modification of Diet in Renal Disease (MDRD) study equation and the Cockcroft-Gault (CG) equation. The MDRD equation estimates eGFR using creatinine value, age, race, and gender, while the CG equation uses creatinine value, age, gender, and weight. The MDRD equation is validated for values <60 in adults. [22]

b The level of GFR may vary by patient. Some progress through stages more quickly while others never move past an intermediate stage. The health care provider will consider the specific risk factors of each patient to determine a treatment plan.

Table 2.1.
Five Stages of Chronic Kidney Disease

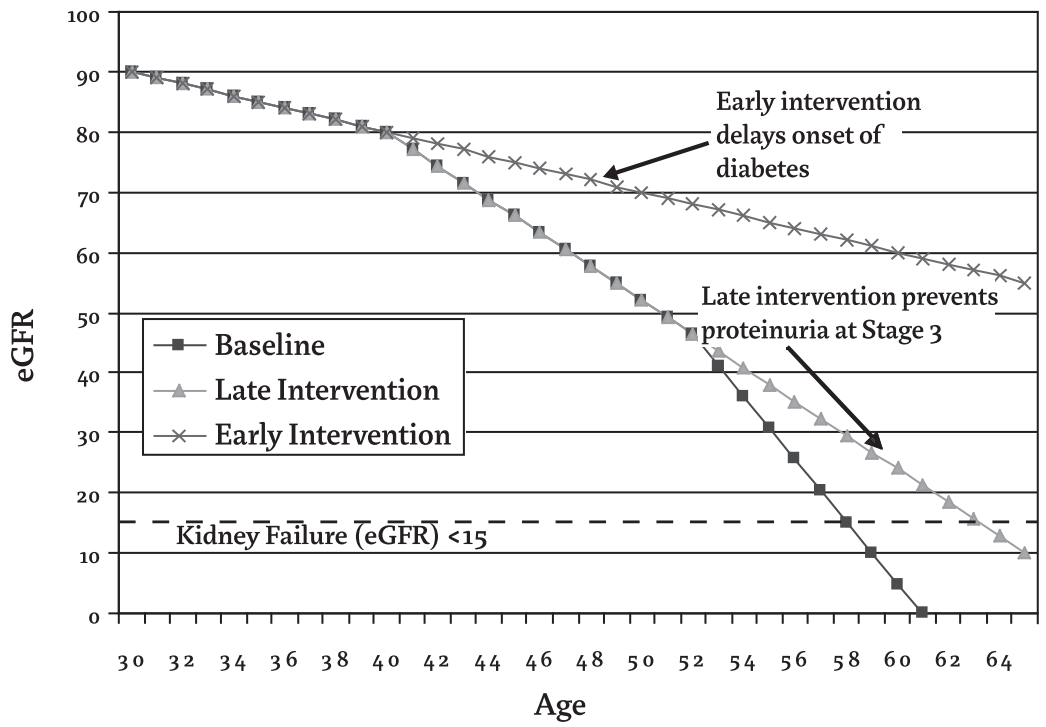
Stage	Description	GFR (mL per minute per 1.73 m^2)	US prevalence, percentage of affected patients (%)[4]	Estimated NC prevalence (see Appendix A)	Estimated number of North Carolinians with CKD by stage
—	At increased risk for chronic kidney disease	No CKD via KDOQI staging, but with risk factors for chronic kidney disease	Unknown	25.3%	1,636,629
1	Kidney damage with normal or elevated GFR	≥90	1.8%	1.8%	110,000
2	Kidney damage with mildly decreased GFR	60 to 89	3.2%	3.4%	208,000
3	Moderately decreased GFR	30 to 59	7.7%	8.1%	503,000
4	Severely decreased GFR	15 to 29	0.4%	0.4%	27,000
5	Kidney failure	<15 (or dialysis)	0.1%	—	>11,000

Despite the large number of people living with CKD, there is an overall lack of knowledge about the disease even among people who have CKD. Nationally, only about 25% of Americans diagnosed with CKD reported awareness about weak or failing kidneys.[5] Among the general population, there is even less awareness. Preliminary data from a UNC Kidney Center study shows that people do not know the risk factors for CKD and associate the factors with unrelated behaviors.[15] A telephone survey was conducted among North Carolina citizens in three counties targeted by the UNC Kidney Education Outreach Program (KEOP). Respondents were provided a list of several items and were asked whether each was a risk factor for kidney disease. The most popular responses for risk factors were not drinking enough water and drinking dark sodas, although neither is directly related to CKD. In addition, many people in the state who have CKD do not receive treatment for the condition until the disease is in the advanced stages. According to 2003 North Carolina Medicaid data, only 30% of Medicaid recipients who presented in the emergency department with acute kidney episodes had received kidney-related treatment from a health care professional within the past 60 days.[16] Furthermore, nationally over one-quarter of patients admitted to the hospital for dialysis enter through the emergency department, suggesting that the patient may not have been seeing a health care provider regularly.[17]

Complications

If not controlled, CKD can lead to rapidly deteriorating kidney function. As kidney function declines, patients develop complications related to fluid overload, chemical imbalance, and waste buildup.[18] These problems may lead to high blood pressure, high blood sugar, high lipid levels, anemia, and bone disease. Patients with CKD should receive evaluation and treatment for these complications including routine blood sugar and blood pressure testing. Figure 2.1 shows a sample of GFR decline based on published estimates of average decline and two theoretical interventions including an early intervention that prevents diabetes and a late intervention that prevents proteinuria.

Figure 2.1.
Sample eGFR Decline



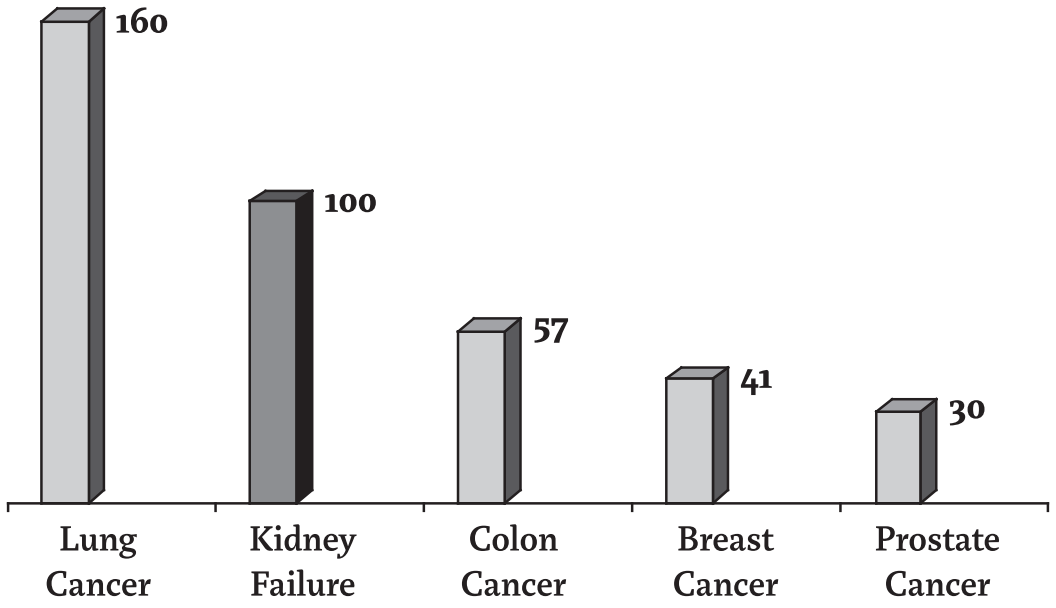
Source: NC Institute of Medicine calculations based on sample GFR decline values presented in Table 3 of Boulware et al, *JAMA*, 2003. Assumptions: Early intervention prevents onset of diabetes at age 40, patient would develop proteinuria at onset of Stage 3 unless he receives late intervention.

Most patients with CKD do not die from kidney failure. Rather, the decreased kidney function leads to failure of other organs. CKD patients are more likely to die from comorbidities of kidney disease than to progress to ESKD.[19] As GFR decreases, the rates of cardiovascular events, hospitalizations, and death increase substantially.[20] Dialysis patients are 5 to 30 times more likely to die from cardiovascular disease than are people from the general population who are the same age, race, and gender. Cardiovascular disease is the leading cause of death both for patients on

dialysis and people with chronic kidney disease. The risk of death increases sharply as estimated GFR declines even after adjusting for differences in socioeconomic status, prior cardiovascular disease, prior hospitalization, diabetes, hypertension, abnormal lipid levels, lung or liver disease, cancer, dementia, proteinuria, and dialysis.[21]

Although kidney failure is not the most common cause of death for people with CKD, it is nonetheless a common cause of death. Death from kidney failure occurs more frequently than death from many of the most prevalent forms of cancer. (See figure 2.2.)

Figure 2.2.
Sample eGFR Decline



Data taken from 2004 update to Gloeckler Ries GA, Reichman ME, Riedel Lewis D, Hankey BF, Edwards BK. Cancer survival and incidence from the Surveillance, Epidemiology, and End Results (SEER) Program. *The Oncologist*. 2003;8:541-552.

Clinical Guidelines

Evidence-based clinical guidelines are established to provide standards to treat patients with different health conditions. These guidelines change over time, and new ones are developed as health professionals gather new evidence about what treatments work best for different conditions. The *KDOQI Clinical Practice Guidelines for Chronic Kidney Disease: Evaluation, Classification and Stratification* provides 15 recommendations for early identification and appropriate treatment to improve patient outcomes.[2] The KDOQI guidelines focus on assessment and classification of CKD, associations between level of kidney function and complications, and risk for progression of the disease. Guidelines 1-15 cover the following: (1) the definition and stages of chronic kidney disease; (2) evaluation

and treatment; (3) individuals with increased risk for chronic kidney disease; (4) estimation of GFR; (5) assessment of proteinuria; (6) markers of kidney damage other than proteinuria; (7) high blood pressure; (8) anemia; (9) malnutrition; (10) bone diseases and disorders of calcium and phosphorus metabolism; (11) neuropathy; (12) functioning and well-being; (13) loss of kidney function; (14) diabetic complications; and (15) cardiovascular disease. (See Appendix B for complete KDOQI guidelines.)

The Task Force is supportive of all KDOQI guidelines but focused on those guidelines that assisted in developing recommendations for identification and screening of people at risk for CKD (Guidelines 3, 4, 5) and recommendations for appropriate treatment plans for the primary health problems that exacerbate CKD (Guidelines 7, 14, 15). The KDOQI evidence-based guidelines that the Task Force focused on can be summarized into the following categories.

- ***Testing.*** Some individuals without kidney damage and with normal or elevated GFR are at increased risk for development of chronic kidney disease. All individuals at increased risk for CKD should be assessed using a spot urine sample as part of routine health encounters to determine whether they are at increased risk of developing chronic kidney disease.[c] The recommended urine test varies based on clinical and sociodemographic factors.[d] Individuals at increased risk of developing chronic kidney disease should undergo testing to estimate kidney function. Individuals found to have chronic kidney disease should be evaluated and treated. Individuals at increased risk but not found to have chronic kidney disease, should be advised to follow a program of risk factor reduction, if appropriate, and undergo repeat periodic evaluation.

- ***Measuring kidney function.*** Estimates of GFR are the best overall indices of the level of kidney function. The level of GFR should be estimated from prediction equations that take into account the serum creatinine concentration and some or all of the following variables: age, gender, race, and body size.[e] The serum creatinine concentration alone should not be used to assess the level of kidney function. Clinical laboratories should report an estimate of GFR using a prediction equation in addition to reporting the serum creatinine measurement.[f]

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c The 1996 release of the United States Preventive Services Task Force recommended urinalysis only for individuals with hypertension or diabetes but no longer has any recommendations related to proteinuria screening. KDOQI recommendations acknowledge this difference but point out that broader screenings will detect CKD earlier. [Guide to Clinical Preventive Services, 2nd ed, 1996. Report of the US Preventive Services Task Force. Alexandria, VA: International Medical Publishing; 1996. Accessed at http://www.ahrq.gov/clinic/cpsix.htm on 19 May 2003])

d It is usually not necessary to obtain a timed urine collection (overnight or 24-hour) for these evaluations.

e The following equations provide useful estimates of GFR: In adults, the Modification of Diet in Renal Disease (MDRD) Study and Cockcroft-Gault equations, and in children, the Schwartz and Counahan-Barratt equations.

f Autoanalyzer manufacturers and clinical laboratories should calibrate serum creatinine assays using an international standard. Measurement of creatinine clearance using timed (for example, 24-hour) urine collections does not improve the estimate of GFR over that provided by prediction equations. A 24-hour urine sample provides useful information for estimation of GFR in individuals with exceptional dietary intake (eg, vegetarian diet, creatinine supplements) or muscle mass (eg, amputation, malnutrition, muscle wasting), assessment of diet and nutritional status, and the need to start dialysis.

- ***Treatment of patients with high blood pressure.*** High blood pressure is both a cause and a complication of chronic kidney disease. As a complication, high blood pressure may develop early during the course of chronic kidney disease and is associated with adverse outcomes—in particular, faster loss of kidney function. In addition, patients with chronic kidney disease—irrespective of diagnosis—have a high risk of developing cardiovascular disease (CVD) including coronary heart disease, cerebrovascular disease, peripheral vascular disease, and heart failure. Blood pressure should be closely monitored in all patients with chronic kidney disease. Treatment of high blood pressure in chronic kidney disease should include a multifaceted approach. Target blood pressure levels should be specified. Antihypertensive medicines should be given to prevent the progression of kidney disease and the development of cardiovascular disease. Specific examples of these medications include angiotensin-converting enzyme (ACE) inhibitors and angiotensin-2 receptor blockers (ARB). Finally, in addition to medication, other therapeutic interventions should be used.

- ***Treatment of patients with diabetes.*** The risk of cardiovascular disease, retinopathy, and other diabetic complications is higher in diabetic patients with kidney disease than in diabetic patients without kidney disease. Prevention, detection, evaluation, and treatment of diabetic complications in patients with chronic kidney disease should follow published guidelines and position statements including strict glucose control in diabetes. Guidelines regarding angiotensin-converting enzyme inhibitors or angiotensin receptor blockers and strict blood pressure control are particularly important since these agents may prevent or delay some of the adverse outcomes of both kidney and cardiovascular disease.

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