CONTENTS

SECTION IV Transplantation

SECTION V Acute Kidney Injury

1

Chronic Kidney Disease: Definition, Epidemiology, Cost, and Outcomes

Tariq Shafi, MBBS, MHS, and Josef Coresh, MD, MHS, PhD

OUTLINE

Chronic kidney disease (CKD) is a global public health problem. CKD is defined based on the presence of kidney damage or reduced glomerular filtration rate (GFR), which is considered the best overall index of kidney function.[1,2] CKD staging is based on its cause, the GFR level, and degree of albuminuria. The past 20 years have seen significant improvement in recognition of the incidence, prevalence, and complications of CKD due in major part to the standardized definition and staging of CKD in 2002. The global adoption of this approach to CKD, with its emphasis on routine and automated estimation of GFR (eGFR) from serum creatinine, has improved recognition of CKD in many populations and settings where it was previously underrecognized. Increased awareness of CKD and uniform classification criteria also has led to a better understanding of the burden of illnesses that accompany CKD, an increased focus on developing methods to slow CKD progression, and a stronger emphasis on early recognition and prevention of complications associated with CKD. Fig. 1.1 shows a conceptual diagram emphasizing the importance of looking at both progression of CKD itself, from normal to damaged without reduced GFR, to reduced GFR, to kidney failure and death (horizontal progression), as well as risk for complications that can lead to mortality. Complications outside the kidney, particularly cardiac and metabolic complications are important as they often lead to death before the onset of kidney replacement therapy (KRT) with dialysis or transplantation.

Acknowledgment: The authors thank Eugenia Shing Yu Wong, BSc, for assistance with making figures and editing the chapter.

In the following sections, we will review the epidemiology, cost, and outcomes of CKD, emphasizing advances in knowledge over the past decade.

DEFINITION AND STAGING OF CHRONIC KIDNEY DISEASE

CKD is a general term for a number of heterogeneous disorders that result in sustained kidney damage with implications for the health of the individual. The initial decline of kidney function is asymptomatic and clinical manifestations of kidney failure occur late in the course of the disease. Definitions of kidney disease therefore include measures of function (e.g., GFR) and measures of damage (e.g., proteinuria, anatomical abnormalities).

Definition

Before the Kidney Disease Outcomes Quality Index (KDOQI) guidelines in 2002, there were numerous definitions of CKD in use. Many of these definitions were not well understood by patients and the lay public due to the use of word *renal* and its Latin and Greek roots. Hsu and Chertow enumerated the different names used for CKD from abstracts submitted to the American Society of Nephrology (ASN) meetings in 1998 and 1999 as well as from articles indexed in Medline.[3] They noted 23 different terms used to describe states of reduced GFR along with a number of different and overlapping definitions of kidney failure using serum creatinine, creatinine clearance, or GFR. Considering these and other factors, the 2002 KDOQI working group decided on using the word *kidney* instead of *renal* and developed an operational uniform

FIG. 1.1 Conceptual model of renal decline. (From Levey AS, de Jong PE, Coresh J, et al. The definition, classification, and prognosis of chronic kidney disease: a KDIGO Controversies Conference report. *Kidney Int.* 2011;80(1):17-28.)

TABLE 1.1A Definition of Chronic Kidney Disease

Criteria (either one of the following for > 3 months)
1. Markers of Kidney Damage (One or More):
• Albuminuria (AER ≥30 mg/24 h; ACR ≥30 mg/g [≥3 mg/mmol])
• Urine sediment abnormalities
• Electrolyte and other abnormalities due to tubular disorders
• Abnormalities detected by histology
• Structural abnormalities detected by imaging
• History of kidney transplantation
2. Decreased GFR
• GFR <60 mL/min/1.73 m^2 (GFR categories G3a-G5)

ACR, Albumin-to-creatinine ratio; *AER,* albumin excretion rate; *GFR,* glomerular filtration rate.
From Kidney Disease: Improving Global Outcomes (KDIGO) CKD Work Group. *KDIGO 2012 Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease;* 2013.

definition of CKD that was endorsed by multiple subsequent workgroups, including the KDIGO 2012 workgroup[4] despite some challenges.[5,6]

CKD is defined as abnormalities of kidney structure of function, present for >3 months, with implications for health. The 2012 Kidney Disease: Improving Global Outcomes (KDIGO) group provides a clear CKD definition (Table 1.1A) and its operational criteria (Table 1.1B).[2,7] The key elements of this definition include chronicity (>3 months), presence of kidney damage, decreased GFR, and implications for health. The chronicity component of the definition (>3 months) is arbitrarily defined to distinguish CKD from acute kidney injury (AKI). The chronicity component, implies but does not necessitate, irreversibility. Presence of kidney damage can be inferred by the presence of albuminuria, abnormal urinary sediment such as hematuria or casts, functional disorders such renal tubular acidosis or nephrogenic diabetes insipidus, pathological abnormalities detected on kidney biopsy such as immunoglobulin (Ig)A nepthropathy, or structural abnormalities of the kidney such as polycystic kidney disease. Decreased GFR is a manifestation of kidney damage from underlying renal pathology. The KDIGO 2012 guidelines kept the GFR at the <60 mL/min/1.73 m^2 threshold for definition of CKD. The threshold of <60 mL/min/1.73 m^2 was selected as it can be reliably assessed by eGFR from serum creatinine and is also a threshold below which the risk for complications of CKD increases. The CKD definition component for implications on health emphasizes that presence of CKD associates with the risk for a number of outcomes including some that were not recognized as CKD complications before the 2002 KDOQI guidelines.

Staging

The 2002 KDOQI guidelines defined a five-stage system for classification of CKD based on GFR and the 2012 KDIGO guidelines updated this staging to include the cause of CKD and the degree of albuminuria (staging by cause, GFR, and albuminuria [CGA]). The guidelines reemphasized staging by cause of CKD to remind clinicians that CKD is not a diagnosis in itself and that determination of cause is important for prognosis and treatment. The cause of the kidney disease can be assigned based on known anatomical of pathological abnormalities such as IgA nephropathy, polycystic kidney disease, vasculitis, and so on. The GFR and albuminuria categories are described in Fig. 1.2. Note that a low GFR in the G2 category, without evidence of kidney damage, is not considered CKD. KDIGO guidelines also subdivided CKD stage 3 into two categories, a and b, recognizing that the risk for complications and death in G3b CKD (eGFR 30 to 44 mL/min/1.73 m^2) is markedly higher than in G3a CKD (eGFR 45 to 59 mL/min/1.73 m^2) with the same level of albuminuria.[8,9] The guidelines also emphasize the use of albuminuria over proteinuria. Urinary protein comprises of numerous proteins including albumin, light chains, and other proteins. The concentration of these proteins can vary and standardization of measuring urine protein is difficult as there is always a variable mixture of proteins being measured. Urine albumin measurement also is difficult to standardize; however, efforts are ongoing to improve its standardization.[10-12] The guidelines suggest that urinary albumin excretion >2200 mg/day (>2200 mg/g creatinine) should be considered as nephrotic-range proteinuria, roughly corresponding to urinary protein excretion >3500 mg/day. The guidelines recognized that the use of only three categories for albuminuria

TABLE 1.1B Criteria for Definition of Chronic Kidney Disease.

Criteria	Comment
1. Duration >3 months, based on documentation or inference	**Duration is necessary to distinguish chronic from acute kidney diseases** • Clinical evaluation will often enable documentation or inference of duration • Documentation of duration is usually not declared in epidemiologic studies
2. GFR <60 mL/min/1.73 m² (GFR categories G3a-G5)	**GFR is the best overall index of kidney function in health and disease** • The normal GFR in young adults is approximately 125 mL/min/1.73m²; GFR <15 mL/min/1.73 m² (GFR category G5) is defined as kidney failure • Decreased GFR can be detected by current estimating equations for GFR based on SCr or cystatin C but not by SCr or cystatin C alone • Decreased eGFR can be confirmed by measured GFR, if required **Albuminuria as a marker of kidney damage [increased glomerular permeability], urine AER ≥30 mg/24 h, approximately equivalent to urine ACR ≥30 mg/g (≥3 mg/mmol)** • The normal urine ACR in young adults is >10 mg/g (>1 mg/mmol) • Urine ACR 30-300 mg/g (3–30 mg/mmol; category A2) generally corresponds to "microalbuminuria," now referred to as "moderately increased" • Urine ACR ≥300 mg/g (≥30 mg/mmol; category A3) generally corresponds to "macroalbuminuria," now termed "severely increased" • Urine ACR <2200 mg/g (220 mg/mmol) may be accompanied by signs and symptoms of nephrotic syndrome (e.g., low serum albumin, edema, and high serum cholesterol) • Threshold value corresponds approximately to urine reagent strip values of trace or +, depending on urine concentration. • High urine ACR can be confirmed by urine albumin excretion in a timed urine collection expressed as AER **Urinary sediment abnormalities as markers of kidney damage** • Isolated nonvisible (microscopic) hematuria with abnormal RBC morphology (anisocytosis) in GBM disorders • RBC casts in proliferative glomerulonephritis • WBC casts in pyelonephritis or interstitial nephritis • Oval fat bodies or fatty casts in diseases with proteinuria • Granular casts and renal tubular epithelial cells in many parenchymal diseases (nonspecific) **Renal tubular disorders** • Renal tubular acidosis • Nephrogenic diabetes insipidus • Renal potassium wasting • Renal magnesium wasting • Fanconi syndrome • Non-albumin proteinuria • Cystinuria **Pathologic abnormalities detected by histology or inferred (examples of causes)** • Glomerular diseases (diabetes, autoimmune diseases, systemic infections, drugs, neoplasia) • Vascular diseases (atherosclerosis, hypertension, ischemia, vasculitis, thrombotic microangiopathy) • Tubulointerstitial diseases (urinary tract infections, stones, obstruction, drug toxicity) • Cystic and congenital diseases **Structural abnormalities as markers of kidney damage detected by imaging (ultrasound, computed tomography and magnetic resonance with or without contrast, isotope scans, angiography)** • Polycystic kidneys • Dysplastic kidneys • Hydronephrosis due to obstruction • Cortical scarring due to infarcts, pyelonephritis, or associated with vesicoureteral reflux • Renal masses or enlarged kidneys due to infiltrative diseases • Renal artery stenosis • Small and hyperechoic kidneys (common in more severe CKD due to many **History of kidney transplantation** • Kidney biopsies in most kidney transplant recipients have histopathologic abnormalities even if GFR is >60 mL/min/1.73 m² (GFR categories G1-G2) and ACR is <30 mg/g (<3 mg/mmol) • Kidney transplant recipients have an increased risk for mortality and kidney failure compared to populations without kidney disease • Kidney transplant recipients routinely receive subspecialty care

ACR, Albumin-to-creatinine ratio; *AER*, albumin excretion rate; *CKD*, chronic kidney disease; *eGFR*, estimated glomerular filtration rate; *GBM*, glomerular basement membrane; *GFR*, glomerular filtration rate; *RBC*, red blood cell; *SCr*, serum creatinine; *WBC*, white blood cell.
From Kidney Disease: Improving Global Outcomes (KDIGO) CKD Work Group. *KDIGO 2012 Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease*; 2013.

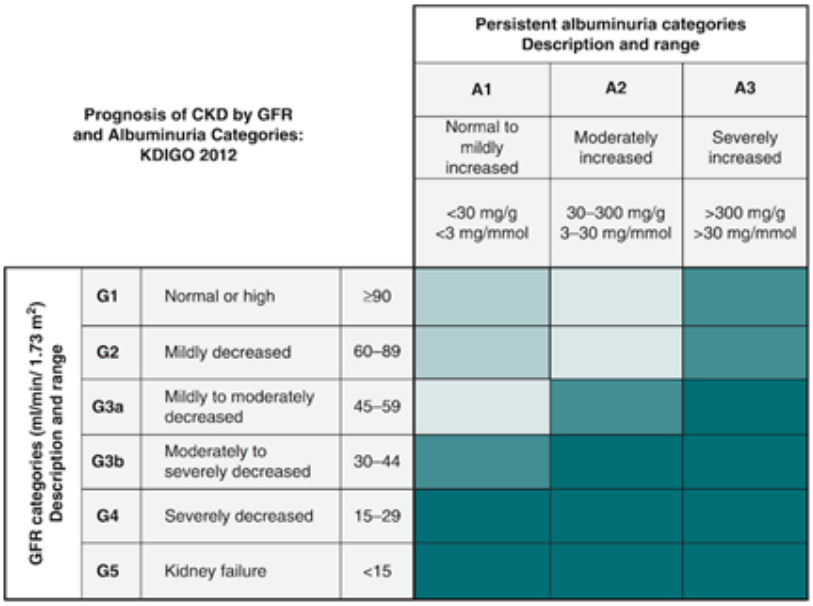

FIG. 1.2 Chronic kidney disease staging. *Dark gray,* low risk (if no other markers of kidney disease, no CKD); *light gray,* moderately increased risk; *light green,* high risk; *dark green,* very high risk. Protein to creatinine ratio (PCR) categories of <150 mg/g, 150-500mg/g, >500 mg/g are approximately equivalent to the albuminuria categories of A1-A3. (From Kidney Disease: Improving Global Outcomes (KDIGO) CKD Work Group. *KDIGO 2012 Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease*; 2013.)

may represent oversimplification and specialized clinical nephrology settings may need to further subdivide A3 albuminuria (>300 mg/d) into further subcategories. The use of the term *microalbuminuria* was discouraged as it implies that the size of albumin molecules rather than the rate of excretion is smaller, which is misleading.

Strengths and Limitations of the Current Chronic Kidney Disease Classification System

Strengths

The KDOQI classification system for CKD has been widely adopted. Its operational simplicity of allowing CKD to be defined based on serum creatinine or proteinuria even when the cause of CKD or its full characterization are uncertain enabled a great expansion of CKD research leading to increased recognition of CKD as a major health issue. Using eGFR and albuminuria as central CKD markers allowed for the use of much larger data sets demonstrating a wide range of complications and risks associated with CKD. Early work focused on cross-sectional complications[1] and cardiovascular risk.[13,14] Later, global collaborations, partly formed in response to challenges to the staging system, allowed for recognition of the broad validity of the independent contributions of GFR and albuminuria levels to risk.[8,15] This in turn suggested a risk-based staging system with GFR and albuminuria as two key markers.[15] Risk algorithms have been developed and validated globally for incidence of KRT (also called end-stage renal replacement therapy [RRT]) in CKD and potential kidney donors.[16,17] The definition and staging are based on GFR, determined in any method including measurement or estimation from creatinine, cystatin C, or other markers. This has allowed clinical practice to easily incorporate improvements including the global standardization of serum creatinine measurements to gold standard traceable methods and the improved GFR estimation formulas from serum creatinine and cystatin C. This eased the incorporation of a growing literature showing that eGFR by cystatin C is an even stronger risk predictor for cardiovascular disease (CVD) and mortality, but not KRT, than estimates from serum creatinine.[18,19] The KDIGO guidelines[2] recommend that evaluation of eGFR, in addition to cause and albuminuria, include evaluation of chronicity by repeat testing, use of serum creatinine, and a GFR estimating equation for an initial assessment with additional tests, such as cystatin C or a clearance measurement, for confirmatory testing in specific circumstances where GFR estimation based on serum creatinine is less accurate. They recommend that clinical laboratories use assays with calibration traceable to international standard reference materials and specify the equation used to estimate GFR. In adults, the 2009 CKD Epidemiologic Prognosis Initiative (CKD-EPI) creatinine equation is recommended but an alternative equation is acceptable if it has been

shown to improve accuracy of GFR estimates. It is also recommended that serum creatinine concentrations be reported to the nearest 100th of a whole number when expressed in mg/dL. They suggest using cystatin C in adults with estimated GFR from creatinine of 45 to 59 mL/min/1.73 m^2 who do not have other markers of kidney damage when confirmation of CKD is required. Thus overall the guidelines provide a clear methodology for uniform evaluation and staging of CKD.

Automated reporting of eGFR with serum creatinine greatly increased the recognition of CKD and facilitated addressing it clinically. Serum creatinine is tested widely. Arguably, the only reason to measure serum creatinine is to assess GFR.[20] Automated reporting of estimated GFR overcomes the difficulty of determining the severity of kidney disease with serum creatinine due to the log-linear relationship between serum creatinine levels and measured GFR and multiple non-GFR determinants of serum creatinine concentration. There is widespread agreement that CKD classification has raised awareness of the full spectrum of CKD and its wide range of complications. The challenge and controversy is that increased awareness is also pointing a brighter spotlight on gaps in the knowledge base, particularly with regard to efficacy, cost-effectiveness, and thresholds for interventions. Changing the practice from excluding severe CKD patients from trials to including CKD patients and focusing on testing efficacy in this high-risk population may be one of the most important outcomes of a clear and simple classification system centered on uniform reporting of the key markers of kidney damage (albuminuria) and function (eGFR). Finally, kidney disease has evolved from being viewed as a subspecialty issue to a global health issue,[21] including a roadmap for closing the gaps in care, research, and policy.[22]

Limitations

The current classification system also has its limitations and these have been actively debated.[5,23-25] There is inherent error and variability in the measurement of GFR and albuminuria. In addition, there are limitations in the accuracy and precision of the estimating equations used to predict GFR. The creatinine estimating equations suffer the limitations imposed by serum creatinine as an endogenous marker of GFR and are not reliable at extremes of body weight as well as when patients' creatinine metabolism is not in steady state, such as in AKI. There has been criticism of estimating GFR; suggestions for using different equations to estimate GFR; concerns about defining CKD based on a single eGFR cutoff rather than age-specific cutoffs; and defining CKD stages 1 and 2 based on persistent microalbuminuria without significant proteinuria as having a "disease."[26] Application of the CKD definitions to the population provides a useful indicator of the implications of the definition. However, it has also clearly pointed out that a large number of individuals meeting the CKD definition, particularly among many older individuals, will never require dialysis or transplantation. Some fear that these individuals may undergo unnecessary diagnostic testing,[23] whereas others suggest the potential benefit of alerting physicians to optimize existing therapies and avoiding nephrotoxic medications.[24] General screening for CKD using eGFR has not been directly demonstrated to be cost-effective.[27] The National Kidney Foundation's Kidney Early Evaluation Program (KEEP) uses a targeted screening protocol based on the presence of hypertension, diabetes, CVD, and first-degree relatives on KRT based on cost-effectiveness in high-risk groups.[28-30] Finally, the presence of CKD has been misinterpreted as indicating a need for referral to a nephrologist despite guideline suggestions that only a subset of patients require specialty care. The 2012 KDIGO guidelines clarify nephrology referral is only needed for progressive disease, GFR <30 mL/min/1.73 m^2, albuminuria >300 mg/g, or other refractory conditions.[2,31]

Future Directions

The concept of defining and classifying CKD based on estimated GFR, albuminuria, and cause of CKD when known has been transformative in the field. However, an imprecise understanding of the cause of CKD and its progression in the majority of patients is a chief limitation. The current classification system addresses major common pathways in CKD. One of its strengths has been not requiring a precise knowledge of CKD etiology. However, efforts to better understand CKD etiology at the molecular and genetic basis could lead to new effective treatments possibly targeted to specific subpopulations of patients. This can be complementary, rather than competitive with the integrative approach of the current CKD definition and staging. Finally, there is still a paucity of clinical trials for CKD prevention and treatment. The current staging system and increased recognition of the importance of CKD is helping with the design of new trials. Developing more powerful biomarkers and surrogate measures of CKD outcomes and integrating them into CKD staging would lead to further progress.

EPIDEMIOLOGY OF CHRONIC KIDNEY DISEASE

Epidemiological descriptions of CKD have advanced greatly over the past decade. Prevalence estimates are becoming more widespread globally, although the methodological rigor of studies varies. Incidence studies have described a range of risk factors but use a range of definitions of CKD progression and incidence. Substantial progress has been made in studying risks associated with CKD through global consortia. In addition, registries of the incidence and prevalence of kidney failure treated with KRT and associated complications and costs have been in existence for decades in most developed countries. The United States Renal Data System (USRDS) now provides comprehensive descriptions of both end-stage renal disease (ESRD) and CKD incidence and prevalence. In addition, the system has expanded to cover treatment and outcomes in the administrative data.[32] The Centers for Disease Control and Prevention (CDC) also has developed a project to provide surveillance for CKD using a wide range of parameters and data sources that will be tracked continuously (https://nccd.cdc.gov/ckd/). Finally, the Global Burden

of Disease Study examines CKD as a cause of death, low GFR, and recently added albuminuria as a risk factor for death and disability.[33]

Etiology of Chronic Kidney Disease

CKD can result from a variety of different pathological processes that are discussed in detail elsewhere in this book. From an epidemiological perspective, it is important to recognize that etiologies of CKD as determined by ESRD registries are limited for a number of reasons. First and foremost, in the vast majority of patients with CKD and ESRD, tissue diagnosis by kidney biopsy is not available and the cause is assumed based on the presence and severity of comorbidities, such as diabetes and hypertension. Second, ESRD patients are disease "survivors" who initiate KRT and thus reflect the slowly progressive forms of CKD. Initiation of KRTs is also determined by physician practice characteristics, availability of resources, and societal and cultural norms. Finally, registry data are dependent on completion of regulatory forms such as Form 2728 in the United States. Exact cause of CKD, even if known, may not be captured on these forms. Finally, efforts to better understand CKD etiology at the molecular and genetic basis could be transformative if they led to new effective treatments possibly targeted to specific subpopulations of patients.

Cause of CKD is now formally a part of the CKD staging system to acknowledge the importance of etiology in treatment. However, the most common assigned causes are diabetes and hypertension. In both conditions, the precise pathogenesis and factors leading to more rapid progression of disease are not fully understood. The discovery of the *APOL1* genetic susceptibility locus leading to much of the increased risk beyond environmental factors in kidney disease among populations of African descent provides the most dramatic example of a better etiological understanding of CKD.[34-41] Separate chapters address specific subgroups of CKD by known and presumed etiology and its implications for treatment and prevention.

Prevalence and Incidence of Chronic Kidney Disease

Prevalence estimates for CKD provide a useful measure of the burden of disease by stage. Early work on the burden of kidney failure treated with dialysis or transplantation pointed out the large costs to patients, and society of this most severe stage of CKD and its epidemic increase. Subsequent work demonstrated that the full spectrum of CKD goes well beyond "predialysis" with over 10% of the population affected with CKD based on kidney damage or decreased kidney function with adverse consequences to their health. Understanding the variation across time, geography, and risk factors is important for grasping the full implications for public health. Incidence is important to understand as it is more directly linked to changes in risk factors. Likewise, mortality and complications are important to quantify, particularly as reduction in mortality will lead to increases in prevalence through longer disease duration.

Prevalence of Chronic Kidney Disease

The most definitive prevalence estimates for CKD are based on population-based surveys with rigorous sampling and laboratory methods. The 2002 KDOQI definition of CKD was accompanied by population based estimates for the United States.[1,42] This early work struggled with and brought attention to many of the complexities needed for valid estimates, including the need for understanding creatinine and albuminuria measurement and variability. These methods have now been applied in a number of settings providing a global estimate of CKD prevalence.

United States CKD Prevalence: Estimates by guidelines working groups, the USRDS, and the CDC still center on the analysis of the National Health and Nutrition Examination Surveys (NHANES).[43-45] The NHANES are cross-sectional, multistage, stratified, clustered probability samples of the US civilian noninstitutionalized population conducted by the National Center of Health Statistics (NCHS), a branch of the CDC. The NHANES were conducted from 1988 to 1994 in two phases (1988 to 1991 and 1991 to 1994) and starting in 1999 to 2000 in 2-year phases until the present.

Initial prevalence estimates from NHANES were based on participants who were older than 20 years of age and did not have a missing serum creatinine concentration. Serum creatinine in NHANES was measured using the kinetic rate Jaffe method and the creatinine values were initially calibrated to the Cleveland Clinic Research Laboratory and subsequently to reference methods.[46–49] Albuminuria was assessed using a spot urine sample and calculation of urine albumin to creatinine ratios. Estimates of persistence of albuminuria were based on a sample of 1241 patients in NHANES 1988 to 1994 who underwent repeat measurements; this showed that although severely increased albuminuria (A3 >300 mg/g) measured on one occasion nearly always indicated persistent albuminuria, moderately increased albuminuria (A2 30 to 300 mg/g) only corresponded to an elevated level of repeat measurement in 50% to 75% of the participants. As a result, modeling the lack of persistent results in lower prevalence of albuminuria and CKD, analysis of CKD trends over time are not influenced by persistence issues since they usually assume persistence is unchanged over time. The CKD stages were based on the KDOQI classification system and showed an increase in prevalence from 1988 to 2004 (Fig. 1.3).[50]

Prevalence estimates for the US population have been updated using the CKD-EPI creatinine equation.[51] The CKD-EPI equation results in a shift to the right in GFR values at eGFR ≥45 mL/min/1.73 m^2; below that level, the GFR distribution remains largely unchanged. The overall prevalence of CKD in adults in the United States in 1996 to 2006 was 11.5% (95% confidence interval [CI], 10.6 to 12.4) which translates to 23.2 (95% CI, 21.3 to 25.) million people in the United States with CKD. This estimate is somewhat lower than the estimated 13.1% based on the MDRD (Modification of Diet in Renal Disease) study equation. The prevalence of CKD stages 1 to 4 based on the CKD-EPI equation were 2.24% (stage 1), 2.56% (stage 2), 6.32% (stage 3), and 0.4% (stage 4). Compared with the prevalence estimates based on MDRD