REVIEW ARTICLE

Chronic Kidney Disease: Detection and Evaluation

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ABSTRACT: Chronic kidney disease (CKD) is a prevalent disease that continues to affect more than one-tenth of the American population. Early detection is essential to slow the natural progression of CKD. This can be accomplished by urine and blood screening tests, which are analyzed for creatinine, urine albumin, and urine protein. Screening is often indicated for individuals with known comorbidities such as cardiovascular disease, mineral and bone disorders, and diabetes. Asymptomatic patients with early renal disease can make detection problematic, requiring clinicians to recognize risk factors that may warrant further testing. When symptoms do appear, the renal manifestations are often broad, including changes in kidney size, electrolyte abnormalities, and proteinuria. Changes in biomarkers may be evaluated in the early stages of CKD before significant kidney damage. The current, most accurate determination of renal function is the estimated glomerular filtration rate (GFR), which must be less than 60 mL/min to prompt further testing for CKD. Novel biomarkers may allow for earlier diagnosis of CKD as they can be detected at lower levels than standard biomarkers. Biomarkers such as homocysteine, cystatin C, and kidney injury molecule-1 are predicted to become more prevalent in a clinical setting. The current gold standard for diagnosis of CKD is a renal biopsy, but MRI is a less invasive alternative. Proper staging of CKD allows for appropriate evaluation and treatment of the patient. The early stages of CKD should be treated to limit complications and to prolong the life and health of patients.

INTRODUCTION

Chronic kidney disease (CKD) is among the most prevalent chronic diseases in the United States, affecting approximately 11% of the adult population.[1] It results from disease pathways that persistently change the structure and function of the kidneys.[1] The presence of CKD has been associated with chronic comorbidities such as hypertension, diabetes, cardiovascular disease, and anemia. Complications frequently arise in CKD management due to low detection rates and comorbidities. As a result, renal disease often goes undetected until the damage has become symptomatic or has progressed to end-stage renal disease.

Chronic kidney disease is defined as the progressive loss of kidney function, causing a decrease in glomerular filtration rate (GFR) of less than 60 mL/min or producing biomarkers of kidney damage, which persist for a minimum of three months.[1] GFR remains the best indicator currently available to determine overall kidney function. This criterion can be used to further subdivide CKD into five stages.

Chronic kidney disease is a significant health care burden for the US population. According to the most recent annual data report from the US Renal Data System, Medicare expenses for chronic kidney disease were 79 billion dollars.[2] As CKD progresses, treatment expenses increase, especially in stages 3-5[3]. The average patient with end-stage renal disease is admitted to the hospital twice a year, with 30% of patients readmitted within 30 days of discharge. Inpatient treatment of these patients accounts for 40% of total yearly Medicare expenses for patients on dialysis.[4] Additionally, in 2016, 83,000 deaths occurred due to CKD in the United States alone.[5]

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The growing knowledge and proper management of comorbidities have caused the incidence rate of CKD to stabilize since 2004. Specifically, improved protocols for the management of hypertension, cholesterol levels, and obesity contribute to the incidence rate stability. Nevertheless, continuously increasing prevalence and disease progression may test the capacity to treat and bear the economic burden of the late stages of CKD. By detecting CKD earlier, prompt and effective preventive treatment can slow the progression of the disease. Opportunities for clinical planning, resource allocation, and patient outcomes can also be improved with early detection.[3]

DETECTION

Early detection of CKD is imperative due to the potential of progression to end-stage renal disease and death.[6] With early detection, therapeutic measures can reduce nephrotoxicity and prevent decreases in glomerular filtration rate, thus inhibiting CKD progression in an attempt to prevent future need for kidney transplantation or dialysis.[6,7] Screening tests are regularly employed for patients with diabetes, hypertension, and other CKD risk factors to ensure that treatment is initiated promptly.[6] Blood work or a urine sample should be used to screen anyone suspected of kidney dysfunction who presents with clinical manifestations of CKD.[7] It can be noted that when a patient does not have hypertension or diabetes mellitus, random measurement of blood glucose and blood pressure can serve as useful tools to identify patients who need further screening for CKD.[7]

COMORBIDITIES

Among the most strongly associated CKD comorbidities is cardiovascular disease. CKD is a known complication of uncontrolled hypertension.8 Inadequacy to control blood pressure among hypertensive diabetic patients with CKD is common and may be attributable to unawareness of target levels and effective management approaches.[9]

CKD is associated with an increased risk for the development of normochromic, normocytic anemia.[10] Kidneys produce erythropoietin, which is key to red blood cell development. Due to the role of the kidney in erythropoietin synthesis, anemia is frequently observed in patients with kidney dysfunction.[10]

Studies have indicated a correlation between mineral and bone disorders and CKD. Patients with early CKD, as defined by a GFR no less than 45 mL/min, who have not previously been diagnosed with a mineral and bone disorder, can be screened for osteoporosis using the standard of care methods for the general population.[11] For patients with CKD and a GFR less than 45 mL/min, bone densitometry is less accurate for determining fracture risk prediction. Metabolic bone diseases, such as renal osteodystrophy, are not detectable by densitometry.[11] A bone biopsy is necessary to evaluate for such diseases in patients with advanced CKD. Serum calcium, phosphorus, 25-hydroxyvitamin D, parathyroid hormone, and alkaline phosphatase levels should be checked regularly in patients in CKD stages 3 to 5 in order to monitor the possibility of mineral kidney disease.[11]

A positive correlation between kidney disease prevalence in diabetic patients has been proven.[12] Diabetic nephropathy accounts for 40% of CKD and 50% of end-stage renal disease cases.[13] Patients with diabetes and CKD face higher risks of morbidity and mortality, making detection of CKD even more critical among these patients.

CLINICAL MANIFESTATIONS

Patients with early renal disease often do not experience symptoms, thus increasing the diagnostic challenge.[7] Many early cases of CKD are diagnosed as incidental findings during routine visits. Without proper screenings, such as urine and blood testing, early detection of CKD may be problematic.[7] Clinicians often use risk factors such as hypertension, diabetes, obesity, cigarette smoking, ethnicity, age, family history, and socioeconomic status to influence the chosen screening modalities.[7]

Since the body is interconnected and the kidney interacts closely with numerous organ systems, several characteristics can be assessed to support a diagnosis of CKD. The first objective manifestation of kidney disease is the basic decline of kidney function. Uremic retention solutes accumulate as a complication of CKD and contribute to inflammation, immune dysfunction, vascular disease, platelet dysfunction with increased bleeding risk, dysbiosis in the gut, and altered drug metabolism.[1] Uremic toxins result from these solutes causing immediate adverse biochemical or physiological effects. These effects can be systemic and often vague.[1] The mechanisms affecting the integumentary system are not fully understood, but it is suggested that the symptoms are results of the deregulation of immune responses and opioid receptors caused by advanced-stage renal disease.[1] Hypoalbuminemia in CKD causes nephrotic syndrome, which increases sodium retention and perpetuates cardiopulmonary deficits by causing edema. These cardiopulmonary symptoms can be further amplified by a decreased oncotic gradient.[1]

Renal manifestations of CKD are broad. Evaluation of kidney size from imaging studies can prove useful for determining the underlying cause of disease. Bilateral small kidneys can indicate intrinsic disease, whereas a unilateral small kidney is suggestive of renal arterial disease.[1] In addition, clubbed calyces and cortical scarring point to reflux, infection, or ischemia, while an overall enlarged cystic kidney suggests cystic kidney disease.[1] Impairment of solute diuresis or edema can lead to damaged tubular concentration ability within the kidney and is indicated by persistent frothy, proteinated urine.[1] Immune-mediated damage to the capillary walls within the kidney can also lead to hematuria from glomerular bleeding.

CKD can also affect the nervous system by increasing the risk of cognitive impairment by 65%. CKD-induced cognitive impairments often present as language and attention deficits.[1] A summary of systemic manifestations is shown in *Table 1*.

LAB AND BIOMARKERS

Standard and novel biomarkers found in urine and plasma are used to screen for fluctuations in kidney function, as summarized

TABLE 1 :

Systemic Manifestations of CKD [1,4,14]

System	Manifestations
Integumentary	Pallor, Unexplained pruritus
Cardiopulmonary	Primary or secondary hypertension, Shortness of breath, Ischemic heart disease, Anemia, Cardiomyopathy, Peripheral edema
Renal	Polyuria, Oliguria, Nocturia, Proteinuria, Hematuria
Muscular	Cramps (typically at night)
Nervous	Cognitive deficits
Gastrointestinal	Anorexia, Vomiting, Taste disturbances, Uremic odor in breath

in *Table 2*. When compared to standard CKD evaluation, novel biomarkers suggest earlier detection of renal pathology with future tests promising higher specificity in diagnosis and prognosis of CKD.

EVALUATION

In 2016, the Evidence Based Practice Project implemented a clinical decision tool for CKD into the electronic medical record system of primary care physicians, physician assistants, and nurse practitioners.[21] One of the goals of this program is to educate providers on the risk factors, staging, management, and outcomes of their patients with CKD in order to improve early detection rates and long term management.[21] As a result of this project, more patients were correctly diagnosed with CKD, detection rates improved, and appropriate referrals to nephrologists increased. This showed that evidence-based medicine is a valuable tool for primary care providers, especially when implemented into electronic medical record systems.[21]

While the current gold standard for diagnosis of CKD is a renal biopsy, recent studies present magnetic resonance imaging (MRI) as a less invasive alternative.[22] Implementation of a non-invasive modality, such as MRI, is proposed to decrease the number of undiagnosed cases of CKD in the population.[22] The magnetic resonance (MR) technique provides broad spatial coverage compared to traditional tissue biopsy and allows for detailed analysis of atherosclerosis associated with CKD.[22] By applying image restoration to dynamic T1-weighted images, MRI researchers were able to match MR biomarkers to those from tissue biopsy samples. Significant correlations were also found between deformation, volume change, and pressure gradient in atherosclerotic kidneys.[22] Staging is required for appropriate diagnosis, evaluation, and treatment of CKD. *(Table 3)*

The 2017 Kidney Disease Improving Global Outcomes (KDIGO) Guidelines contain a framework for the classification of CKD using albuminuria. They address prognosis as well as follow-up frequency and referral recommendations.[6,23] KDIGO recommends that primary care providers use GFR and urine albumin levels to appropriately stage CKD and use albuminuria, urine sediment changes, electrolyte abnormalities, tubular disorders, histologic changes, structural deficiencies, and history of transplantation as a means for assessing subjects with CKD.[7,11,23] Renal fibrosis is the final histologic indication of CKD and presents when the kidneys become unable to properly heal from injury, leaving behind scarred kidney tissue. In the early stages, renal fibrosis contributes to the development of interstitial fibrosis, tubular atrophy, and glomerulosclerosis. Proliferating smooth muscle cells, endothelial damage, and podocyte effacement prompt the development of glomerulosclerosis. Such conditions are often caused by smoking, dyslipidemia, and hypertension.

If a CKD diagnosis is found in the early stages (stages 1-3), the progression and complications of CKD can be altered with proper intervention.[27] Once CKD has reached stage 4, renal replacement therapy should be considered, which includes methods such as dialysis or renal transplant.[18,27] Stage 5 CKD is also referred to as end-stage renal disease as the kidneys are no longer functioning adequately to support life.[1] Although small fluctuations in GFR are common and generally unalarming, higher frequency monitoring is suggested for those at risk of disease progression. Progression is defined as a decline in GFR ≥ 25% from baseline.[1]

Once a patient is diagnosed with CKD and staged using biomarkers or GFR, the next step is to evaluate disease progression. If the GFR remains abnormal or worsens over the subsequent three months, then it is necessary for physicians to further evaluate for potential causes. Common etiologies of CKD include hypertensive kidney disease, diabetic nephropathy, and primary or secondary glomerulonephritis.[1] Minimal change disease or focal point glomerulonephritis should also be considered. Exposure to potential nephrotoxins, current and historical blood pressures, family history of CKD, dietary history, and weight measurements should all be investigated during a full medical history, followed by a complete physical exam.[1]

TREATMENT AND REFERRAL

The Cockcroft-Gault equation is used only to estimate GFR and determine dosing of medications for first line therapy and management in a primary care setting.[6] Clinical practice guidelines

TABLE 2 :

Biomarkers of CKD [6,7,12-20,24-26]

STANDARD		
Marker	**Application**	**Measurement**
Albumin/ Creatinine Ratio	First line CKD screen	Mild: <30 mg/g, Moderate: 30-300 mg/g , Severe: >300 mg/g Assessed in early morning urine sample
Proteinuria	Indicative of renal injury at any GFR	Urinary protein levels exceeding 300 mg are considered clinically significant
Glomerular Filtration Rate (GFR)	Most accurate determination of renal function	Mild: 60-89 mL/min, Mild-Moderate: 45-59 mL/min, Moderate-Severe: 30-44 mL/min, Severe: 15-20 mL:/min, Failure: <15 mL/min Estimated from serum creatinine levels, with adjustments for age, BUN, gender, and race
Serum Creatinine	Lacks predictive value when assessed alone	Used with serum assessment of electrolytes, fasting lipids, A1C, and albumin/creatinine ratio
Urinalysis and Microscopy	Adjunct for diagnosis Can be indicative of kidney dysfunction	Determines presence of increased or abnormal sedimentation, hematuria, chronic pyuria, cellular casts, urine concentration, and urine acidification Assessed in early morning urine sample

NOVEL		
Marker	**Function**	**Application**
Kidney Injury Test (KIT)	Used when concern of comorbidity is present	Performed on urine samples and requires no additional processing at the site of collection Emerging as an alternative standard of care test to monitor dysfunction burden as well as therapy efficacy
Serum Cystatin C	Used to estimate GFR in patients with no known structural kidney disease or risk factors Supplemental confirmatory test	Not reliable in patients with a high body mass index, thyroid abnormalities, acute kidney injury, or general inflammatory conditions
Homocysteine	Increased concentration predicts diminished GFR	Maintains high predictive value after adjustments for age, smoking history, and body mass index are made to GFR
Asymmetric Dimethylarginine (ADMA)	Increased levels indicates decreased renal function	Increased levels correlate to a more aggressive course of renal damage leading to glomerular hypertension, endothelial damage, cell senescence, and salt build-up
Symmetric Dimethylarginine (SDMA)	Increased levels indicates decreased renal function	Increased levels coincide with kidney dysfunction as determined by GFR and creatinine clearance
Uromodulin	Reduced level correlates with decreased number of functioning nephrons	Glycoprotein likely engaged in the defense of tubular cells from ascending urinary tract infections, chronic pyelonephritis, and urolithiasis Patients with renal interstitial fibrosis or tubular atrophy due to CKD are shown to have reduced levels
Kidney Injury Molecule 1 (KIM-1)	Upregulated after ischemic or toxic injury of proximal tubular epithelial cells	Only detectable in dysfunctional kidneys Levels seen prior to detectable changes in GFR
Neutrophil Gelatinase Associated Lipocalin (NGAL)	Associated with innate kidney dysfunction	Predictive power for patients at higher risk for faster progression of CKD Increased levels associated with damage in the loop of Henle and distal convoluted tubule

TABLE 3 :

Stages of Chronic Kidney Disease According to Current National Guidelines [12,14,24,25,26]

Stage	GFR Descriptor	GFR Range (mL/min)	Suggested Treatment
G1*	Normal or high	≥ 90	Manage comorbid conditions and reduce cardiovascular risk
G2*	Mildly decreased	60-89	Evaluate progression potential
G3a	Mild-moderately decreased	45-59	Evaluate progression and treat complications
G3b	Moderately-severely decreased	30-44	Evaluate progression and treat complications
G4	Severely Decreased	15-29	Prepare for renal replacement therapy
G5	Kidney Failure	<15 (or receiving dialysis treatment)	Renal replacement therapy if uremia is present

*(GFR= glomerular filtration rate) *= biomarkers of kidney damage such as proteinuria, albuminuria, and abnormalities in urinary sediment or electrolytes are required for a diagnosis of stage 1 or 2 CKD.*

recommend that primary care physicians discuss those patients at risk for progression of CKD with their local nephrologist. It is highly encouraged to refer a patient during and after stage 3 CKD. Absolute referral indications are summarized in *Table 4*.

CONCLUSION

CKD continues to impact the health of a significant portion of American society even with improved detection practices. Standard biomarkers are only useful to detect significant damage, but novel biomarkers have promise for earlier detection. Additionally, estimates of GFR and creatinine must be corrected for risk factors such as race, age, and gender, which may change the indications of results. Thus, the development of more efficient and sensitive methods of early detection is essential to aid primary care physicians in their key role in slowing the progression of CKD.

Studies are currently underway to identify additional sensors for key biomarkers such as cystatin C and KIM-1. As continued research uncovers more effective detection methods, patients with early CKD may be diagnosed before the presence of symptoms, promoting long-term well-being among patients.

TABLE 4 :

Absolute referral indications [1,25,26,28]

Diagnosis of CKD from AKI that is unresponsive to initial management
Diagnosis of anemia with CKD
Presence of red blood cell casts in the urine
Management of CKD when hemoglobin <10 g per dL
CKD and refractory hypertension
Mineral and bone disorders diagnosis with CKD
Persistent abnormalities in serum potassium
Persistently elevated albuminuria with the albumin/creatinine ratio >300 mg/g
Refractory proteinuria with urinary protein/creatinine ratio >500:1000 mg/g
Recurrent nephrolithiasis
Concern for nephrocalcinosis
Preparation for renal replacement therapy

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