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Chronic Kidney Disease

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Continuing Education Activity

Chronic kidney disease (CKD) is characterized by the presence of kidney damage or an estimated glomerular filtration rate (eGFR) of less than 60 mL/min/1.73 m², persisting for 3 months or more. CKD involves a progressive loss of kidney function, often leading to the need for renal replacement therapy, such as dialysis or transplantation. The 2012 KDIGO CKD classification considers the underlying cause and categorizes CKD into 6 stages of progression and 3 stages of proteinuria based on glomerular filtration rate and levels of albuminuria. Although the causes of CKD vary, certain disease processes exhibit similar patterns.

The implications of CKD are extensive—it emerges from various disease processes and affects cardiovascular health, cognitive function, bone metabolism, anemia, blood pressure, and many other health indicators. Early recognition of CKD is the first step in treating it, and various methods for measuring eGFR have been described. Both modifiable and non-modifiable risk factors influence the progression of CKD. Management of CKD involves adjusting medication dosages according to the patient's eGFR, preparing for renal replacement therapies, and addressing reversible causes to slow disease progression. This activity reviews the etiology, evaluation, and management of CKD, emphasizing the crucial role of an interprofessional healthcare team in providing comprehensive care. An interprofessional approach focuses on both modifiable and non-modifiable risk factors to manage and mitigate the progression of the disease.

Objectives:

- Identify the early signs and symptoms of chronic kidney disease to facilitate prompt diagnosis and intervention.
- Implement evidence-based guidelines for managing chronic kidney disease, including lifestyle modifications, medication adjustments, and monitoring of disease progression.
- Select appropriate treatment options and renal replacement therapies based on individual patient needs and chronic kidney disease stage.
- Collaborate with an interprofessional team, including nephrologists, dietitians, nurses, and pharmacists, to provide comprehensive care for chronic kidney disease patients.

Access free multiple choice questions on this topic.

Introduction

Chronic kidney disease (CKD) is characterized by the presence of kidney damage or an estimated glomerular filtration rate (eGFR) of less than 60 mL/min/1.73 m², persisting for 3 months or more, irrespective of the cause. [1] CKD is a state of progressive loss of kidney function, ultimately resulting in the need for renal replacement

therapy, such as dialysis or transplantation. Kidney damage refers to pathologic abnormalities suggested by imaging studies or renal biopsy, abnormalities in urinary sediment, or increased urinary albumin excretion rates.

The 2012 Kidney Disease Improving Global Outcomes (KDIGO) CKD classification recommends specifying the cause of CKD and classifies the condition into 6 categories based on GFR (G1 to G5, with G3 split into 3a and 3b). In addition, it also includes staging based on 3 levels of albuminuria (A1, A2, and A3), with each stage of CKD subcategorized according to the urinary albumin-creatinine ratio (ACR; mg/g or mg/mmol) in an early morning "spot" urine sample.[2]

The 6 CKD categories, known as stages 1 through 5, are described below (stage 3 is separated into 3a and 3b):

- G1: GFR 90 mL/min/1.73 m^2 and above with evidence of kidney disease, such as hematuria or proteinuria
- G2: GFR 60 to 89 mL/min/1.73 m^2
- G3a: GFR 45 to 59 mL/min/1.73 m^2
- G3b: GFR 30 to 44 mL/min/1.73 m^2
- G4: GFR 15 to 29 mL/min/1.73 m^2
- G5: GFR less than 15 mL/min/1.73 m^2 or treatment by dialysis

The 3 levels of albuminuria include an ACR:

- A1: ACR less than 30 mg/g (<3.4 mg/mmol)
- A2: ACR 30 to 299 mg/g (3.4-34 mg/mmol)
- A3: ACR greater than 300 mg/g (>34 mg/mmol)

The improved classification of CKD has been beneficial in identifying prognostic indicators related to decreased kidney function and increased albuminuria. However, a downside of this classification system is the potential for overdiagnosis of CKD, particularly in older individuals.

Etiology

The causes of CKD vary globally, with the most common primary diseases leading to CKD and, ultimately, end-stage renal disease (ESRD) being:[3]

- Type 2 diabetes (30%-50%)
- Type 1 diabetes (3.9%)
- Hypertension (27.2%)
- Primary glomerulonephritis (8.2%)
- Chronic tubulointerstitial nephritis (3.6%)
- Hereditary or cystic diseases (3.1%)
- Secondary glomerulonephritis or vasculitis (2.1%)
- Plasma cell dyscrasias or neoplasm (2.1%)
- Sickle cell nephropathy, which accounts for less than 1% of ESRD patients in the United States. Please see StatPearls' companion resource, "Sickle Cell Nephropathy," for more information.

CKD may result from disease processes in any of the 3 categories, including prerenal (decreased renal perfusion pressure), intrinsic renal (pathology of the vessels, glomeruli, or tubules-interstitium), or postrenal (obstructive).

Prerenal Disease

Chronic prerenal disease occurs in patients with chronic heart failure or cirrhosis, where persistently decreased renal perfusion increases the risk of intrinsic kidney injury, such as acute tubular necrosis. Over time, this can lead to a progressive loss of renal function.

Intrinsic Renal Disease

Intrinsic renal vascular disease: The most common chronic renal vascular disease is nephrosclerosis, which causes ongoing damage to blood vessels, glomeruli, and the tubulointerstitium. Other renal vascular diseases include renal artery stenosis due to atherosclerosis or fibromuscular dysplasia, which, over months or years, can lead to ischemic nephropathy. This condition is characterized by glomerulosclerosis and tubulointerstitial.[4]

Intrinsic glomerular disease (nephritic or nephrotic): A nephritic pattern is indicated by abnormal urine microscopy showing red blood cell (RBC) casts, dysmorphic red cells, and occasionally white blood cells (WBCs), along with a variable degree of proteinuria.[5] The most common causes are post-infectious glomerulonephritis, infective endocarditis, IgA nephropathy, lupus nephritis, Goodpasture syndrome, and vasculitis.[6]

A nephrotic pattern is associated with proteinuria, usually in the nephrotic range (>3.5 g/24 h), and an inactive urine microscopic analysis with few cells or casts. Common causes include minimal change disease, focal segmental glomerulosclerosis, membranous glomerulonephritis, diabetic nephropathy, and amyloidosis.

Intrinsic tubular and interstitial disease: The most common chronic tubulointerstitial disease is polycystic kidney disease (PKD). Other etiologies include nephrocalcinosis (often due to hypercalcemia and hypercalciuria), sarcoidosis, Sjögren syndrome, and reflux nephropathy in children and young adults.[7]

There is increasing recognition of a relatively high prevalence of CKD of unknown cause among agricultural workers from Central America and parts of Southeast Asia, known as MesoAmerican nephropathy or chronic interstitial nephritis in agricultural communities. Please see StatPearls' companion resources, "Chronic Interstitial Nephritis in Agricultural Communities (CINAC)" and "Reflux Nephropathy," for more information.

Postrenal (Obstructive Nephropathy)

Chronic obstruction may result from prostatic disease, nephrolithiasis, or an abdominal/pelvic tumor exerting a mass effect on the ureter(s). Congenital abnormalities causing obstruction at the ureteropelvic or ureterovesical junctions are also common. Rare causes of chronic ureteral obstruction include retroperitoneal fibrosis or neurogenic bladder.[8][9] Please see StatPearls' companion resource, "Obstructive Uropathy," for further information.

Epidemiology

The true incidence and prevalence of CKD are challenging to determine due to the asymptomatic nature of early to moderate stages. The prevalence of CKD in the general population is estimated to be around 10% to 14%. Specifically, albuminuria and an eGFR less than 60 mL/min/1.73 m^2 have prevalences of about 7% and 4%, respectively.[10]

Worldwide, CKD accounted for 2,968,600 (1%) of disability-adjusted life-years and 2,546,700 (1%-3%) life-years lost in 2012.[3] In the United States, CKD affected an estimated 26 million people in 2016.[11] The Kidney Disease Outcomes Quality Initiative (KDOQI) recommends that for diagnosing chronicity and CKD, patients should be tested on 3 separate occasions over a 3-month period, with at least 2 of the 3 results being positive.[12]

Natural History and Progression of Chronic Kidney Disease

CKD diagnosed in the general population (community CKD) typically has a different natural history and progression compared to CKD in patients referred to nephrology practices (referred CKD).

Community CKD primarily affects the older population, who have had lifelong exposure to cardiovascular risk factors, hypertension, and diabetes, all of which can impact kidney function. The average rate of GFR decline in this population is approximately 0.75 to 1 mL/min/year after age 40 to 50.[13] In a large study of community-based CKD by Kshirsagar et al, only 1% and 20% of patients with CKD stages 3 and 4, respectively, required renal replacement therapy. However, 24% and 45% of patients with stages 3 and 4, respectively, died predominantly from cardiovascular disease (CVD), suggesting that cardiac events rather than ESRD are the predominant outcomes in community-based CKD.[14]

In contrast to community CKD, patients with referred CKD often present at an earlier age due to hereditary conditions (eg, autosomal-dominant polycystic kidney disease or ADPKD) or acquired nephropathies (eg, glomerulonephritis, diabetic nephropathy, and tubulointerstitial disease) that cause progressive renal damage and loss of function. The rate of progression in referred CKD varies depending on the specific disease process. Diabetic nephropathy typically shows a rapid decline in GFR, averaging around 10 mL/min/year. In nondiabetic nephropathies, progression is generally faster in patients with chronic proteinuric glomerulonephritis compared to those with lower levels of proteinuria. Patients with ADPKD and CKD stage G3b or higher may experience a faster rate of progression than those with other nephropathies. In patients with hypertensive nephrosclerosis, well-controlled blood pressure and minimal proteinuria are associated with very slow progression.

Risk Factors for Progression of Chronic Kidney Disease

Non-modifiable CKD risk factors: Older age, male gender, and non-White ethnicity, including Black Americans, Afro-Caribbean individuals, Hispanics, and Asians (South Asians and Pacific Asians), all adversely affect CKD progression.

Genetic factors that affect CKD progression have been identified across various kidney diseases. A population-based cohort study found that single nucleotide polymorphisms in the genes *TCF7L2* and *MTHFS* were associated with diabetic nephropathy and CKD progression. The same study also highlighted that polymorphisms in genes involved in renal scarring and the renin-angiotensin-aldosterone system (RAAS) affect CKD progression.[15]

Modifiable CKD risk factors: These include systemic hypertension, proteinuria, and metabolic factors.[16]

Systemic hypertension is a major cause of ESRD worldwide and the second leading cause in the United States, following diabetes. The transmission of systemic hypertension into glomerular capillary beds and the resulting glomerular hypertension is believed to contribute to the progression of glomerulosclerosis.[17] Night-time and 24-hour blood pressure measurements (such as ambulatory blood pressure monitoring or ABPM) are more strongly correlated with CKD progression than standard measurements. Systolic blood pressure, in particular, is a crucial predictor of CKD progression and is associated with complications in CKD.

Multiple studies have demonstrated that significant proteinuria (albuminuria A3) is linked to a faster rate of CKD progression in both diabetic and nondiabetic kidney diseases. Reducing significant proteinuria through RAS blockade or dietary modifications is associated with better renal outcomes. However, large intervention studies, such as the Avoiding Cardiovascular Events Through Combination Therapy in Patients Living with Systolic Hypertension (ACCOMPLISH) and the Ongoing Telmisartan Alone and in Combination with Ramipril Global End Point Trial (ONTARGET), observed notable declines in GFR despite substantial reductions in albuminuria.[18][19] Therefore, moderate-level albuminuria (A2) is not a reliable surrogate marker for CKD progression.

Multiple studies have linked the RAAS system to the development of hypertension, proteinuria, and renal fibrosis throughout CKD. Consequently, interventions targeting the RAAS have been effective in slowing CKD progression, leading to the widespread use of RAAS blockers in managing proteinuric and diabetic kidney diseases. Obesity and

smoking have been associated with the development and progression of CKD. Additionally, metabolic factors such as insulin resistance, dyslipidemia, and hyperuricemia have also been implicated in CKD development and progression.[20][21]

Recommendations for Chronic Kidney Disease Screening

Screening, primarily targeting high-risk individuals, is being implemented worldwide. The KDOQI guidelines recommend screening high-risk populations, including those with hypertension, diabetes mellitus, and individuals older than 65. Screening should involve urinalysis, measurement of urine ACR, serum creatinine levels, and estimation of GFR, preferably using the CKD Epidemiology Collaboration (CKD-EPI) equation. Currently, evidence to support screening asymptomatic individuals from the general population for CKD does not exist.

Pathophysiology

Unlike acute kidney injury (AKI), which often results in complete functional recovery, chronic and sustained insults from progressive nephropathies lead to ongoing kidney fibrosis and destruction of normal kidney architecture. This process affects all three compartments of the kidney: the glomeruli, tubules and interstitium, and vessels. Histologically, it manifests as glomerulosclerosis, tubulointerstitial fibrosis, and vascular sclerosis.

The following events leading to scarring and fibrosis are complex, overlapping, and multistage phenomena:

- Infiltration of damaged kidneys with extrinsic inflammatory cells.
- Activation, proliferation, and loss of intrinsic renal cells (through apoptosis, necrosis, mesangiolysis, and podocytopenia).
- Activation and proliferation of extracellular matrix producing cells, including myofibroblasts and fibroblasts.
- Deposition of extracellular matrix, replacing the normal architecture.

Mechanisms of Accelerated Progression of Chronic Kidney Disease

- Systemic and intraglomerular hypertension
- Glomerular hypertrophy
- Intrarenal precipitation of calcium phosphate
- Altered prostanoid metabolism

All these mechanisms lead to a histological entity called glomerulosclerosis.[22]

Clinical risk factors for the accelerated progression of CKD include proteinuria, hypertension, Black race, and hyperglycemia. Environmental exposures, such as lead, smoking, metabolic syndrome, certain analgesic agents, and obesity, have also been linked to the accelerated progression of CKD.[23]

History and Physical

Early CKD stages are asymptomatic, and symptoms manifest in stages 4 or 5. Some common symptoms and signs at these stages of CKD include:

- Nausea
- Vomiting
- Loss of appetite

- Fatigue and weakness
- Sleep disturbance
- Oliguria
- Decreased mental sharpness
- Muscle cramps
- Swelling of feet and ankles
- Persistent pruritus
- Chest pain due to uremic pericarditis
- Shortness of breath due to pulmonary edema from fluid overload
- Hypertension

Physical examination is often not helpful, but patients may demonstrate the following symptoms:

- Skin pigmentation
- Scratch marks from pruritus
- Pericardial friction rub due to uremic pericarditis
- Uremic frost, where high levels of blood urea nitrogen (BUN) cause urea in sweat to crystallize into fine, white powder on the skin
- Hyperreflexia or muscle twitches
- Hypertensive fundal changes suggesting chronicity

Evaluation

Establishing Chronicity

When a patient's eGFR is less than 60 mL/min/1.73m^2, attention must be paid to the previous blood and urine test results and clinical history to determine whether this is a result of AKI or previously undiagnosed CKD. The following factors can help distinguish this:

- A history of long-standing chronic hypertension, proteinuria, microhematuria, or symptoms of prostatic disease can point toward chronicity.
- Physical findings such as skin pigmentation, scratch marks, left ventricular hypertrophy, and hypertensive fundal changes suggest chronicity.
- Blood test results indicating other conditions, such as multiple myeloma and systemic vasculitis, can help aid in diagnosis.
- While low serum calcium and high phosphorus levels have little discriminatory value, normal parathyroid hormone (PTH) levels suggest AKI rather than CKD.
- Patients who suddenly develop AKI are usually symptomatic at similarly elevated BUN/creatinine levels compared to those with CKD.

Assessment of Glomerular Filtration Rate

Kidney function tests should be repeated within 2 weeks of the initial finding of decreased eGFR for patients in whom the distinction between AKI and CKD is unclear. The gold standard for calculating creatinine is measuring the clearance of inulin. However, this is not readily available; therefore, creatinine clearance is used as a surrogate to calculate GFR. Please see StatPearls' companion resources, "Renal Function Tests" and "Creatinine Clearance," for more information.

Many other compounds are also being examined for use as markers of acute kidney disease and CKD, including cystatin C, kidney injury molecule 1 (KIM-1), soluble urokinase-type plasminogen activator receptor, urinary epithelial growth factor, beta-2 microglobulin, retinol-binding protein, serum neutrophil gelatinase-associated lipocalin (NGAL), L-type fatty acid-binding protein (L-FABP), fibroblast growth factor 23 (FGF23), and beta-trace protein.[24] In addition, the Chronic Renal Insufficiency Cohort (CRIC) study demonstrated that markers such as certain cardiac markers (high-sensitivity troponin T and NTproBNP), the plasma chemokine CXCL12, and urine NGAL were highly associated with the progression of CKD.[25]

Assessment of Proteinuria

The KDIGO guidelines recommend assessing proteinuria by obtaining an early morning urine sample and quantifying the ACR. The degree of albuminuria is graded from A1 to A3, replacing previous terms such as microalbuminuria.

Healthy individuals secrete thousands of different proteins in their urine. The most significant of these are uromodulin (Tamm-Horsfall protein, comprising around 50% of total protein), albumin (comprising about 20%), and immunoglobulins (comprising about 5%). Various quantification and characterization methods, such as chromatography, immunoassays, electrophoresis, mass spectrometry, fluorescence spectroscopy, infrared spectroscopy, and Raman spectroscopy, may be useful. Protein-specific dipstick and immunochemical methods are the fastest and cheapest methods. The most commonly used urine dipstick protein segment measures albumin only because albuminuria is often increased out of proportion to other urine proteins in common proteinuric diseases, but this may not quantify other elevated urine protein levels such as Bence Jones proteins.[26][27][28]

If more accurate proteinuria measurements are not available, the KDIGO guidelines suggest estimation: Dipstick protein values of "trace to +" and "+ or greater" can be assigned to albuminuria categories of 30 to 299 mg/g and more than 300 mg/g, respectively.[28]

Imaging of Kidneys

If an ultrasound examination of the kidneys shows small kidneys with reduced cortical thickness, increased echogenicity, scarring, or multiple cysts, this suggests a chronic process. This may also be helpful in diagnosing chronic hydronephrosis from obstructive uropathy and cystic enlargement of the kidney in ADPKD. Renal ultrasound Doppler can be used in suspected renal artery stenosis to evaluate the renal vascular flow.

Computerized tomography can be used to further image kidney size, echogenicity, the collecting duct system, and any possible obstruction. Renal angiography has its role in diagnosing systemic vasculitis or renal artery stenosis, where multiple aneurysms and irregular areas of constriction are seen. Voiding cystourethrography is mainly used when chronic vesicourethral reflux is suspected of causing CKD,[7] which confirms the diagnosis and estimates the severity of reflux.

Renal scans can provide sufficient information about kidney anatomy and function. They are used predominantly in children as they are associated with less radiation exposure compared to CT scans. Radionuclide renal scans can also measure differences in kidney function.

Establishing an Accurate Diagnosis

An accurate diagnosis of CKD is essential, particularly when an underlying treatable condition, such as lupus nephritis or ANCA vasculitis, requires specific management. Certain diseases may have a higher recurrence rate in the

kidney after transplantation, and an accurate diagnosis can guide future management. A kidney biopsy is the gold standard for diagnosing the cause of CKD and provides information about the extent of kidney fibrosis.

Treatment / Management

General Management

- Drug dosages should be adjusted based on the patient's eGFR levels.
- Preparation for renal replacement therapy should include making surgical referrals for the placement of hemodialysis or peritoneal dialysis access and for transplantation when appropriate.

Treatment of Reversible Causes of Renal Failure

Potentially reversible causes of AKI, such as infection, drugs, hypotension, and hypovolemia, should be identified and addressed. Patients with CKD should be carefully evaluated before undergoing intravenous contrast studies, and alternatives should be considered first. Additionally, nephrotoxic agents, including aminoglycoside antibiotics and nonsteroidal anti-inflammatory drugs (NSAIDs), should be avoided.

Slowing the Progression of Chronic Kidney Disease

Factors contributing to the progression of CKD, including hypertension, proteinuria, metabolic acidosis, and hyperlipidemia, should be addressed. Hypertension should be managed according to established blood pressure goals, while proteinuria should be reduced to less than 1 g/d if possible.[29]

Multiple studies have shown that smoking is associated with an increased risk of developing nephrosclerosis, and smoking cessation retards the progression of CKD.[30] Protein restriction has also been shown to slow CKD progression. However, patients with advanced CKD are at risk of malnutrition, making dietician input crucial.

Bicarbonate supplementation for treating chronic metabolic acidosis has been demonstrated to delay CKD progression.[31] Additionally, intensive glucose control in individuals with diabetes has been effective in delaying the onset of albuminuria and preventing the progression from albuminuria to overt proteinuria.[32]

Preparation and Initiation of Renal Replacement Therapy

Once stage 4 CKD progression is noted, patients should be presented with various options for renal replacement therapy, as mentioned below.

- Hemodialysis (home or in-center).
- Peritoneal dialysis (continuous or intermittent).
- Kidney transplantation (living or deceased donor): This is the treatment of choice for ESRD due to its superior long-term outcomes.
- For patients who decline renal replacement therapy, information about conservative and palliative care management should be provided.
- Hemodialysis is performed after establishing stable vascular access in the nondominant arm. Intravenous cannulas should be avoided to preserve the veins in this arm. The preferred vascular access is an AV fistula. Other hemodialysis access options include AV grafts and tunneled hemodialysis catheters. AV fistulas are preferred due to their good patency rates and infrequent infections. They also allow for higher blood flow rates and have a lower risk of recirculation.
- Peritoneal dialysis is performed after placing a peritoneal catheter.[33]

Indications for Renal Replacement Therapy

- Pericarditis or pleuritis (emergent indication).
- Progressive uremic encephalopathy or neuropathy, with signs such as confusion, asterixis, myoclonus, and seizures (emergent indication).
- Clinically significant bleeding diathesis attributable to uremia (emergent indication).
- Hypertension is poorly responsive to antihypertensive medications.
- Fluid overload refractory to diuretics.
- Metabolic disorders that are refractory to medical therapy, such as hyperkalemia, hyponatremia, metabolic acidosis, hypercalcemia, hypocalcemia, and hyperphosphatemia.
- Persistent nausea and vomiting.
- Evidence of malnutrition.
- Any other uremic sign or symptom.

Renal transplantation is the preferred treatment option for ESRD due to its survival benefit compared to long-term dialysis therapy. Patients with CKD are typically eligible for renal transplant evaluation when the eGFR falls below 20 mL/min/1.73 m². If a patient has a living donor who may be able to donate a kidney, referral to a transplant center can be considered even earlier.

Conservative management of ESRD is an option for patients who choose not to pursue renal replacement therapy. This approach includes symptom management, advance care planning, and appropriate palliative care. This strategy is often underutilized and should be considered, particularly for frail patients with poor functional status. To facilitate this discussion, a 6-month mortality score calculator is used, incorporating variables such as age, serum albumin levels, presence of dementia, peripheral vascular disease, and a subjective assessment (a yes/no answer to a question) by the treating nephrologist, "Would I be surprised if this patient died in the next year?"

When to Refer to a Nephrologist

Patients should be referred to a nephrologist at any stage of CKD or for urinary abnormalities, especially when the eGFR falls below 60 mL/min/1.73m^2. An early referral ensures optimal management. When the eGFR is less than 20 mL/min/1.73 m², preparations for renal replacement therapy should be initiated, including placement of a peritoneal dialysis catheter, establishment of vascular access for hemodialysis, and referral for renal transplantation.

Differential Diagnosis

When evaluating a patient for CKD, it is crucial to consider other potential diagnoses that may present with similar symptoms and clinical findings. The differential diagnoses include:

- Acute kidney injury
- Alport syndrome
- Antigiomerular basement membrane disease
- Diabetic nephropathy
- Multiple myeloma

- Nephrolithiasis
- Rapidly progressive glomerulonephritis
- Renal artery stenosis

Staging

The 6 categories of CKD staging include:

- G1: GFR 90 mL/min/1.73 m^2 and above with urinary abnormalities suggesting kidney disease such as hematuria or proteinuria
- G2: GFR 60 to 89 mL/min/1.73 m^2
- G3a: GFR 45 to 59 mL/min/1.73 m^2
- G3b: GFR 30 to 44 mL/min/1.73 m^2
- G4: GFR 15 to 29 mL/min/1.73 m^2
- G5: GFR less than 15 mL/min/1.73 m^2 or ESRD

The 3 levels of albuminuria include ACR:

- A1: ACR less than 30 mg/g (<3.4 mg/mmol)
- A2: ACR 30 to 299 mg/g (3.4-34 mg/mmol)
- A3: ACR greater than 300 mg/g (>34 mg/mmol)

Prognosis

The CRIC study is an observational study that began in 2001 and is still ongoing in the fifth and final phase. The CRIC study examined risk factors for the progression of CKD and CVD among nearly 5500 patients. The study enrolled adults aged 21 to 74 with a broad range of renal disease severity and eGFR between 20 and 70 mL/min/1.73 m^2. About half the patients had concurrent diabetes. Measures of kidney function and occurrence of new and worsening CVD were primary endpoints, and they have yielded valuable data on a variety of other significant associations.[34][35]

The CRIC study showed that CKD progression was correlated with cognitive decline, cardiovascular mortality, left ventricular hypertrophy, coronary artery calcification, and clinical depression, among other associations.[35]

Complications

Systemic Complications of Chronic Kidney Disease

Salt/fluid balance: Salt and fluid balance abnormalities are common in CKD, becoming more apparent in stages 4 and 5. These patients often respond to sodium restriction and loop diuretics. The 2012 KDIGO guidelines recommend sodium intake be restricted to less than 2 g/d for all CKD patients.

Hypertension: Hypertension in CKD can be a manifestation of volume expansion, although patients with CKD do not always have edema to suggest volume expansion. Many patients with CKD benefit from using a loop diuretic before escalating the doses of other antihypertensives. The KDIGO 2021 Clinical Practice Guideline for the Management of Blood Pressure in CKD recommends aiming for a systolic blood pressure below 120 mm Hg for patients not on dialysis.[36]

The 2017 ACC/AHA guidelines set the blood pressure target for patients with diabetes or CKD at less than 130/80 mm Hg.[37] However, other renal societies advocate for more patient-specific goals, suggesting that an office blood pressure between 120 and 140 mm Hg systolic and between 70 and 80 mm Hg diastolic is appropriate.[38] Despite varying guidelines, close monitoring with frequent home blood pressure readings is essential to accurately adjust medications and achieve the desired goals.

Hyperkalemia: Hyperkalemia in CKD can occur particularly in oliguric patients and those with distal renal tubular dysfunction. Contributing factors include dietary potassium intake, tissue breakdown, and aldosterone resistance. Additionally, medications such as angiotensin-converting enzyme (ACE) inhibitors and nonselective beta-blockers can also lead to hyperkalemia.

Metabolic acidosis: Metabolic acidosis is a common complication of advanced CKD due to the retention of acidic compounds. Chronic metabolic acidosis can lead to osteopenia in these patients. Treatment typically involves bicarbonate supplementation to maintain a serum bicarbonate level of 23 mEq/L.

Hyperphosphatemia: Hyperphosphatemia is a common complication of CKD due to a decreased filtered phosphorous load. This leads to increased secretion of PTH and causes secondary hyperparathyroidism. While hyperparathyroidism aims to normalize phosphorus and calcium levels, it often leads to hyperphosphatemia at the expense of bone health. Additionally, FGF23, a protein involved in calcium and phosphorus metabolism, is associated with cardiovascular mortality independently of its bone metabolic effects.[35] Please see StatPearls' companion resource, "Chronic Kidney Disease-Mineral Bone Disorder," for further information.

Anemia: Anemia of CKD is typically normocytic normochromic and results from reduced erythropoietin production due to decreased functioning renal mass, abnormal iron metabolism, and reduced red blood cell survival. Hemoglobin levels should be checked annually in stage 3 CKD, every 6 months in stages 4 and 5, and monthly in dialysis patients. Erythropoiesis-stimulating agents should be considered when hemoglobin is below 10 g/dL, with iron saturation at least 20% to 30% and ferritin greater than 200 ng/mL. For dialysis patients, the target hemoglobin concentration is 10 to 11.5 g/dL. Please see StatPearls' companion reference, "Anemia of Chronic Renal Disease," for further information.

Cardiovascular disease: The risk of CVD increases with the severity of CKD. Considerable evidence indicates a significant association between epicardial adipose tissue thickness and the incidence of CVD events in CKD patients. Therefore, assessing epicardial adipose tissue could be a reliable parameter for evaluating cardiovascular risk in CKD patients.[39]

Insulin resistance: Insulin resistance and metabolic syndrome are strongly associated with CKD and contribute to the development of atherosclerotic disease. This association is thought to be mediated by increased inflammatory markers.[11]

Treatment of Complications of End-Stage Renal Disease

Malnutrition in ESRD is often caused by anorexia and inadequate protein intake. The diet for ESRD patients should provide at least 30 to 35 kcal/kg/d. Dietitians play a crucial role in improving the nutritional status and overall health of patients with CKD and ESRD.

Uremic bleeding is a complication resulting from impaired platelet function, which leads to prolonged bleeding times. Asymptomatic patients typically do not require treatment. However, correction of uremic platelet dysfunction is necessary during active bleeding or before surgical procedures. Interventions may include desmopressin (DDAVP), cryoprecipitate, estrogen, and initiation of dialysis.

Complications of Renal Transplantation

Infectious complications are prevalent in posttransplant patients, necessitating appropriate prophylaxis and vaccinations. Other common CKD complications include hypertension, dyslipidemia, coronary artery disease from

new-onset diabetes mellitus, arrhythmias, and heart failure. Neurological complications include stroke and posterior reversible encephalopathy syndrome, central nervous system infections, neuromuscular and seizure disorders, and neoplastic disease. Gastrointestinal complications include infection, mucosal injury, mucosal ulceration, perforation, biliary tract disease, pancreatitis, and diverticular disease. Due to immunosuppression, patients with kidney transplants have an increased risk of malignancy, such as posttransplant lymphoproliferative disorder and skin cancer. [40][41]

Consultations

As mentioned below, managing CKD often requires input from various specialties to address complex issues and provide comprehensive care.

- Nephrology: Nephrologists should be consulted for all patients with CKD, especially once stages 3 to 5 are reached.
- Urology: A urologist is needed for obstructive uropathy to relieve obstruction using retrograde ureteral catheters or percutaneous nephrostomy.
- Interventional radiology: A consultation with an interventional radiologist can be made for the placement of permanent tunneled hemodialysis catheters.
- Surgery: A surgical consultation is recommended for placing arteriovenous fistulas (AVF) or grafts (AVG), as well as for the insertion of peritoneal dialysis catheters.

Deterrence and Patient Education

All high-risk patients, including those with diabetes or hypertension, should be screened for CKD and also receive counseling on the symptoms and signs of the condition.

Patients with CKD can benefit from the following home interventions:

- About 85% of CKD patients have hypertension. They should be advised to measure their blood pressure daily and maintain a log of their blood pressure readings and daily weights.
- Patients with hemoglobin levels below 10.0 g/dL might benefit from home administration of subcutaneous erythropoietin-stimulating agents if this is more convenient than office visits.
- Consultation with a nutritionist is recommended for optimal dietary management and to avoid high-potassium foods.
- All patients with advanced CKD should be instructed to monitor their phosphorus levels and take phosphate binders with each meal.
- CKD patients who are pregnant or planning to become pregnant should be informed that pregnancy may exacerbate CKD and that impaired kidney function can negatively impact pregnancy. They should also be made aware that some medications used in CKD, such as ACE inhibitors, are teratogenic.

Pearls and Other Issues

Key facts to keep in mind regarding CKD include:

- CKD is defined as kidney damage or an eGFR less than 60 mL/min/1.73 m^2, persisting for 3 months or more, irrespective of the cause.

- CKD is usually asymptomatic until it reaches stages 4 and 5.
- The KDOQI guidelines recommend screening high-risk populations, which include individuals with hypertension, diabetes mellitus, and those aged 65 or older. This screening should involve urinalysis, measurement of urine ACR, serum creatinine, and estimation of GFR, preferably using the CKD Epidemiology Collaboration (CKD-EPI) equation.
- Calcium and phosphorus levels are not useful in distinguishing AKI from CKD. However, normal PTH levels suggest AKI rather than CKD.
- Systemic hypertension, proteinuria, hyperlipidemia, and metabolic acidosis cause the progression of CKD and need to be treated aggressively.
- Bicarbonate supplementation to reach a serum bicarbonate target equal to 23 mEq/L can help delay the progression of CKD.
- All CKD patients need to be evaluated for anemia, hypertension, metabolic acidosis, and bone and mineral disorders.

Enhancing Healthcare Team Outcomes

CKD has a multitude of manifestations and is optimally managed by an interprofessional team of healthcare professionals. These teams should adhere to guideline-driven kidney care, address complications, recommend lifestyle modifications, and educate patients about various dialysis options. A study comparing standard care with a "healthy transitions" program—where a nurse care manager utilizes a protocol-driven informatics system to provide daily reports on incomplete steps for each patient—demonstrated notable benefits. This approach resulted in reduced hospitalizations, increased use of arteriovenous (AV) fistulas, fewer emergency dialysis procedures, and decreased catheter use, suggesting that such models could potentially lower overall healthcare costs significantly.[42]

Nephrologists play a crucial role in managing CKD by minimizing patient risk factors and optimizing goals for electrolytes and anemia. Primary care providers should focus on educating patients about the importance of quitting smoking, eating a healthy diet, maintaining a healthy weight, and addressing cardiac risk factors. Clinics should include access to a nutritionist, who assesses nutritional status and develops individualized meal plans. Additionally, pharmacists are essential for reviewing medications, screening for nephrotoxic drugs, and adjusting non-nephrotoxic medications based on the patient's renal function.

The nurse practitioner monitors blood pressure and adjusts medications as needed. The dialysis nurse is critical in educating patients on caring for dialysis catheters or AV fistulas. A vascular access nurse assesses suitable patients for hemodialysis access, whereas a renal transplantation nurse provides information on the transplantation procedure and patient selection criteria. An interprofessional approach to managing chronic renal failure reduces redundant testing, is cost-effective, minimizes patient morbidity, and leads to improved outcomes.

Review Questions

- Access free multiple choice questions on this topic.
- Comment on this article.

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