Chronic Kidney Disease Continuum and Markers

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Introduction

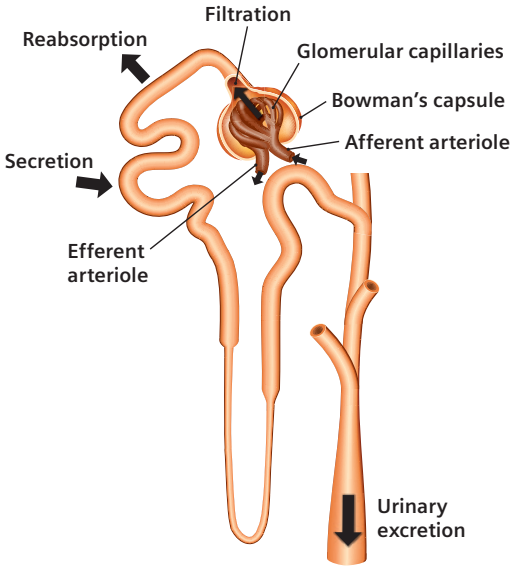
The prevalence of chronic kidney disease (CKD) continues to rise globally, currently estimated at 10 to 16% of the world's population.[1] Chronic kidney disease is defined as longstanding (greater than three months) damage to kidney structure or function that poses a threat to well-being.[2] Kidney damage may be caused by physical injury, the presence of disease, or environmental insult. Diabetes, hypertension, and glomerulonephritis (inflammation) are the leading causes of CKD. Alarmingly, the growing number of people with diabetes worldwide will place even more individuals at risk for developing the disease.[2] Left untreated, complications may affect the proper functioning of all organ systems, increasing the likelihood for progressive kidney failure, cardiovascular disease (CVD), and premature mortality. Kidney failure, or end-stage renal disease (ESRD), is characterized by a severe decline in the filtering capacity of kidneys, resulting in the accumulation of wastes to toxic levels in blood and the need for kidney transplantation or dialysis.[2]

Proper kidney function is essential for good health

The kidneys filter byproducts of metabolism and maintain electrolyte, acid-base balance in the body, and blood pressure (by maintaining salt and water volume balance). Kidneys also produce erythropoietin essential for red blood cell production and convert vitamin D into its active form. Each kidney contains approximately one million nephrons through which blood is filtered to remove wastes (such as urea and creatinine), water, glucose, and amino acids. Nephrons also control electrolyte and fluid balance. Larger molecules such as hemoglobin and albumin cannot pass through the filter unless the filter is damaged. Kidney damage can lead to accumulation of wastes in blood to toxic concentrations, resulting in various complications (Table 1).

How is kidney function measured?

Measurement of plasma concentrations of waste substances such as creatinine, urea, and electrolytes can be used to evaluate renal function. However, blood urea nitrogen (BUN) and creatinine will not increase above normal values until 50–60% of total kidney function is lost.[2] Glomerular filtration rate (GFR), which measures the flow rate of filtered blood through the kidney (blood volume filtered per unit time), is a more accurate measurement of kidney function.



Excretion = Filtration – Reabsorption + Secretion

Figure 1. Structure and function of the nephron.

Creatinine, a breakdown product of creatine phosphate in muscle, is freely filtered by the glomerulus and used as a marker of GFR. Thus, GFR is approximated or represented by the creatinine clearance rate (CCr or CrCl), which is the volume of blood plasma cleared of creatinine per unit of time, usually per minute. To determine the Ccr rate, the volume of urine excreted in 24 hours is collected. However, because 24-hour urine collection is cumbersome, Ccr or estimates of Ccr currently are based on formulae that use serum creatinine concentrations as a measure of GFR (estimated GFR, or eGFR).

The 2012 Kidney Disease Improving Global Outcomes (KDIGO) guidelines recommend using the 2009 CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration) serum creatinine equation for measuring eGFR in adults.[2] Cystatin C is an alternative serum marker used in equations for eGFR and should be used in clinical settings where eGFR based on serum creatinine is less accurate.[2] Equations for children differ from those used for adults.[2] Elevated protein levels in urine provide another marker for CKD. The most sensitive marker of proteinuria is elevated urine albumin.[2]

Table 1. Chronic kidney disease complications and their serum and urine markers.

Chronic Kidney Disease Complications	Serum and Urine Markers
Cardiovascular disease	Cardiac troponin BNP* NT-proBNP†
Malnutrition and hypoalbuminemia	Albumin
Anemia	Hemoglobin Erythropoietin Soluble transferrin receptor
CKD-mineral and bone disorder • Secondary hyperparathyroidism • Bone disease (renal osteodystrophy) • Vascular calcification	Phosphorus Calcium 25(OH)D Parathyroid hormone Fibroblast growth factor 23
Acute kidney injury	Creatinine Urine volume
Hyperkalemia	Potassium
Metabolic acidosis	CO_2

**B-type natriuretic peptide.*
†N-terminal pro-brain natriuretic peptide.

Table 2. Risk factors for CKD.[2]

Non-modifiable Risk Factors	Modifiable Risk Factors	CKD High-risk Definition
• Age: >60 years • Family history of CKD • Hereditary CKD • Race: – African-Americans – Hispanics – Pacific Islanders – Native Americans	• Obstruction • Use of painkillers Antibiotic effects • Drug abuse (e.g., heroin, cocaine) • Inflammation (e.g., inherited or acquired glomerulonephritis) • Infectious diseases	• Existing CKD • Diabetes • Hypertension • Family history of CKD • Hereditary CKD • AKI • CVD

Table 3. Risk assessment for early detection.

Parameters Measured	Markers
Blood pressure	
Estimated glomerular filtration rate (eGFR)‡	Serum creatinine and/or cystatin C
Albumin-to-creatinine ratio (ACR)	Urine albumin
Glucose	Serum glucose
HbA1c§ and estimated average glucose	Whole-blood HbA1c

‡Approximated by creatinine clearance rate.
§Glycated hemoglobin.

Definition of CKD and categories of eGFR and albuminuria

Chronic kidney disease is defined as abnormalities in kidney structure or function of greater than three months.[2] The KDIGO guidelines recommend classifying CKD by cause, GFR category, and albuminuria category (CGA).[2] A CKD diagnosis is made when one or both of the following are present for greater than three months:[2]

- A decline in kidney function as defined by eGFR <60 mL/min/1.73 m^2 (normal is >90 mL/min/1.73 m^2)
- Kidney damage [albuminuria: >30 milligram (mg) urine albumin per gram (gm) of urine creatinine (urine albumin to creatinine ratio, ACR); imaging abnormalities, genetic, or renal transplant history]

Kidney failure, or ESRD, refers to an eGFR <15 mL/min/1.73 m^2 and typically requires dialysis or a transplant.[2]

Symptoms of CKD

People with CKD may lose 90% of their kidney function over several years before clinical symptoms appear. Awareness is less than 10% for those with CKD stages G1–G3.[2] By CKD stages G4–G5 (<30 mL/min/1.73 m^2), symptoms include those associated with the kidney's inability to filter wastes, metabolic acidosis, and anemia.

Symptoms of severe CKD include fatigue, trouble concentrating, general ill-feeling, headache, nausea, loss of appetite, loss of lean body mass, muscle weakness, vomiting, trouble sleeping, swelling of legs, frequent urination, itchy skin, swollen eyes, and muscle cramps. Predictors of progression or risk factors for CKD are listed in Table 2, and risk assessment parameters and markers are listed in Table 3.

Risk assessment and markers for slowing progression

Hypertension

About 20–30% of people with hypertension have CKD.[2] Blocking the renin-angiotensin-aldosterone system (RAAS) lowers blood pressure and reduces the risk of kidney disease and CVD in the presence of albuminuria.[2,3]

eGFR creatinine (eGFRcreat)-based equations. Lower eGFRcreat levels are associated with mortality;[4-6] adverse outcomes;[7] mortality and ESRD in CKD patients;[8] and, increase in hospitalizations.[4]

eGFR cystatin C (eGFRcyst)-based equations are used as an alternative or confirmatory method for the estimation of GFR for the diagnosis and treatment of renal diseases in adults.[2] Lower eGFRcyst levels correlate with complications and mortality.[9] Equations using cystatin C, alone or with creatinine, are better than equations using serum creatinine alone for associations between eGFR and mortality and ESRD.[9,10]

Albuminuria

Higher levels of urine albumin are possibly the earliest indication of diabetic and other glomerular kidney diseases and are associated with mortality,[6] adverse outcomes,[4] and mortality and ESRD in CKD patients.[8]

Diabetes and CKD

Diabetes is the leading cause of CKD,[2] which is more prevalent in diabetics than non-diabetics.[11] Uncontrolled high blood glucose and high blood pressure cause damage to small blood vessels, leading to decreased kidney function.[12] Glycated hemoglobin (HbA1c) is a representative marker for average glycemia and avoids the day-to-day variations in blood glucose concentrations.[13] HbA1c levels are used to calculate estimated average glucose concentrations (eAG).[14]

Complications of CKD

Cardiovascular disease

Guidelines recommend that all CKD patients, including children, should be considered at increased risk for CVD because lower eGFR and abnormally high levels of albumin in the urine are associated with CV mortality.[2,5,6] The most common cause of death in the dialysis population is CVD; CVD mortality is higher in dialysis patients than in the general population,[1] and increased risk for CVD is observed in the early stages of CKD.[15] Cardiovascular disease is twice as high in patients with CKD as in those without CKD.[1] Traditional risk factors include atherosclerosis, age, hypertension, diabetes, dyslipidemia, and physical inactivity. Unique CKD-related risk factors include hormonal and mineral disturbances (elevated serum phosphorus, sP, and calcium, sCa), albuminuria, and anemia. Markers to aid in the assessment of CVD include B-type natriuretic peptide (BNP), N-terminal pro-brain natriuretic peptide (NT-proBNP), and cardiac troponin (cTn).[2]

Hypoalbuminemia

Albumin is made by the liver and makes up 60% of plasma proteins. Malnutrition is a risk factor for mortality in CKD patients.[16] Hypoalbuminemia may result from several causes.[17] Higher urine ACR ratios are associated with hypoalbuminemia.[18] (Hypoalbuminemia is also seen in marked liver failure.)

Anemia

The prevalence of anemia increases as eGFR declines.[2,18] CKD-associated anemia is a result of insufficient production of erythropoietin by damaged kidney tissue.[1] Measurements of hemoglobin and erythropoietin are used to assess anemia status in CKD.[19] Other causes of anemia in CKD may include iron deficiency, detected by tests for iron, serum ferritin, transferrin saturation (TSAT), and serum soluble transferrin receptor. Other tests include folate, vitamin B12, blood smear, and blood in stools.

CKD-MBD

The term "chronic kidney disease-mineral and bone disorder (CKD-MBD)" was introduced to better define the range of bone and mineral disturbances observed in CKD patients.[20,21] The disturbances that define CKD-MBD include:[20,21]

1. Abnormalities in sCa, sP, serum vitamin D, and serum PTH concentrations
2. Defects in skeletal modeling and remodeling and bone lesions (renal osteodystrophy), which were previously defined as high and low bone turnover disease hyperparathyroid bone disease, adynamic bone disease, and osteomalacia
3. The presence of vascular and soft tissue calcifications

In early CKD, the inability of kidneys to excrete phosphate leads to hyperphosphatemia, which is exacerbated by dietary intake. Hyperphosphatemia stimulates the synthesis and secretion of PTH and fibroblast growth factor 23 (FGF23), which mediate phosphate excretion by the kidney to normalize circulating sP concentrations. In addition, activation of vitamin D that occurs in the kidney is suppressed by elevated sP and serum FGF23 concentrations; this leads to lower sCa concentrations that are sensed by the parathyroid glands.[20,21] In early CKD, the lower sCa concentrations are compensated for by elevated serum PTH.[20,21] Sustained decreases in vitamin D, hypocalcemia, and hyperphosphatemia lead to further elevation in serum PTH (secondary hyperparathyroidism, HPT), which is associated with systemic toxicities and increased risk for bone disease. Avoiding sP accumulation can avoid progression to secondary HPT, CVD, bone disease, and vascular calcification.[20,21]

Serum phosphorus

Dietary intake and inability of failing kidneys to excrete phosphorus lead to excess sP (hyperphosphatemia) in CKD patients.[2,18,20] Hyperphosphatemia is a CV risk factor in the general population and in CKD patients. In CKD patients, hyperphosphatemia is associated with progression of CKD.[2,22] In CKD patients (not on dialysis), hyperphosphatemia is associated with bone disease, CVD, vascular calcification, and mortality.[23] In CKD stages G4–G5 and in ESRD patients on dialysis, the compensatory mechanisms have failed, and hyperphosphatemia is associated with all-cause and CV mortality[24] and coronary artery calcification.[25]

Serum calcium

In CKD patients not on dialysis, deficiency of 1,25(OH)D (calcitriol) and its precursor 25(OH)D manifests early in the progression of the disease. In ESRD patients on dialysis, compensatory mechanisms to maintain sCa levels fail, increasing the prevalence of deficiencies in calcitriol, 25(OH) D, and sCa.[2,22] In CKD, hormonal and mineral disturbances are associated with end-organ resistance to PTH and calcitriol,[2] thereby altering the balance of calcium uptake into and release from bone. Further derangements in bone and mineral metabolism may occur as a result of various therapies.[2,20,21] Hypercalcemia is associated with increased risk of CKD progression,[26] mortality,[27-29] and cardiac and vascular calcifications.[25,30] A recent meta-analysis questioned the independent association of hypercalcemia with CV events and mortality.[23]

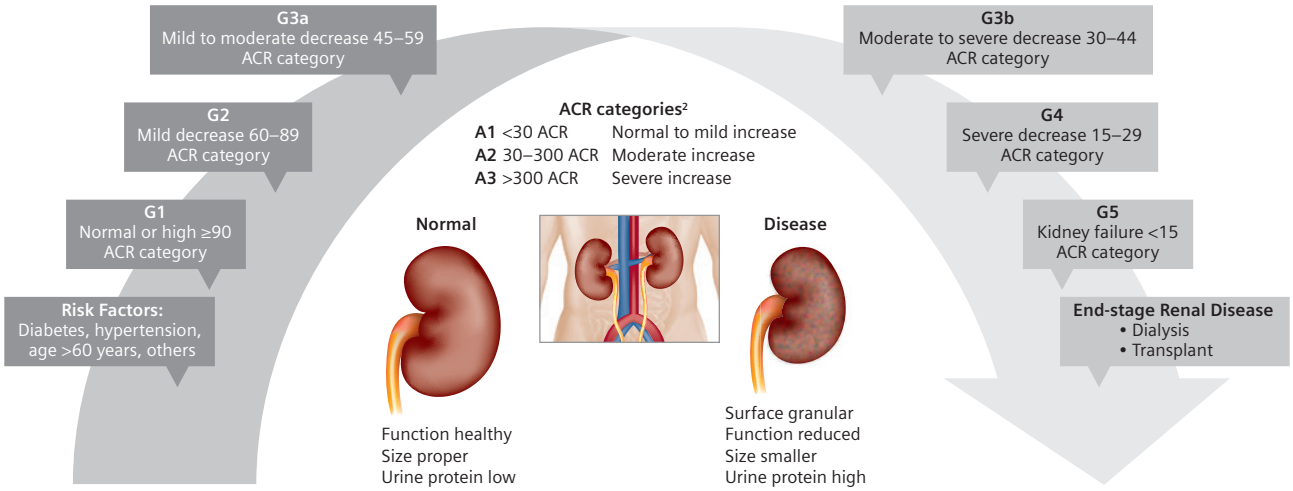


Figure 2. Estimated GFR (mL/min/1.73 m2) and ACR (mg/gm) categories.[2]

Vitamin D

The prevalence of vitamin D deficiency is greater in CKD patients than in individuals without CKD.[31] 25 hydroxyvitamin D 25(OH)D is the major metabolite of vitamin D in the circulation and the recommended marker of vitamin D status for those at risk for developing vitamin D deficiency.[2,22,32] In CKD patients not on dialysis, deficiency and insufficiency of 25(OH)D are common findings and correlate with eGFR category.[31,33] In patients with CKD stages G4–G5, deficiency in 25(OH)D is associated with greater serum PTH concentrations, bone disease (osteoporosis and osteopenia), and increased risk for bone fractures. Low 25(OH)D concentrations are associated with all-cause mortality,[33,34] with 33% higher risk of mortality for those with eGFR <15 ng/mL.[34] ESRD patients on dialysis have widespread 25(OH)D deficiency,[2,22] which is associated with mortality.[35]

Secondary hyperparathyroidism

Secondary HPT refers to excess serum PTH concentrations, a common complication in CKD patients associated with declining eGFR.[2,18,22] As described above, secondary HPT is induced during the early CKD stages G2–G3 to compensate for elevations in sP and reductions in sCa and serum 1,25(OH)D concentrations.[2,20,21] As kidney disease progresses, bone abnormalities result from prolonged hormonal and mineral disturbances.[20,21]

Renal osteodystrophy

"Renal osteodystrophy" describes the bone disease aspect of CKD-MBD.[21] Bone disease is more severe in CKD patients than in the general population, due to long-standing secondary HPT, vitamin D deficiency, abnormal sP and sCa concentrations, and therapies that include vitamin D, vitamin D analogs, and phosphate binders (calcium and non-calcium containing). Histology remains the gold standard for diagnosis of the type of bone lesion and involves assessment of bone turnover, mineralization, and volume.[21]

Noninvasive markers used to predict the type of bone lesion include serum PTH for bone turnover and bone-specific alkaline phosphatase for bone formation. The predictive value of serum PTH for bone disease is high at very elevated and very low serum PTH levels.[36]

Vascular calcification

There are two types of vascular calcification CKD patients:[21] Intimal layer calcification is associated with atherosclerotic lesions and inflammation, and medial layer calcification involves smooth muscle cells that transform into bone-forming (osteoblast-like) cells in the presence of high sP and sCa concentrations. The prevalence of vascular calcification in patients starting dialysis exceeds 50% and is associated with calcium-based phosphate binder therapy, high sP and serum PTH concentrations, bone disease (mainly adynamic bone that cannot take up calcium, which then deposits in vessels), and insufficient levels of mineralization inhibitors.[21] Medial vascular calcification has been associated with increased arterial stiffening, increased blood pressure, left ventricular dysfunction, and increased CV and all-cause mortality in CKD patients.[21] In addition, "calcific uremic arteriolopathy" describes calcification in small arterioles in the skin, resulting in ulceration, tissue ischemia, and increased mortality in CKD patients.[21]

Acute kidney injury

Acute kidney injury (AKI) is defined as a sudden drop in kidney function occurring within days to hours, as measured by serum creatinine or rapid drop in urine volume.[37] Patients with CKD have a higher risk for AKI due to exposure to nephrotoxic agents, which include contrast media used in some imaging techniques, NSAIDS, and some antibiotics.[38] Acute kidney injury is common among hospitalized patients and is a cause and risk factor for CKD progression in diabetic CKD patients.[39]

Table 4. Markers and complications of CKD.

Marker		Screen for CKD Risk Factors	Screen for CKD and Risk Reduction	Diagnose and Treat Comorbidities, Slow Progression	Establish Progression, Treat Complications, Prepare for Replacement	Replacement by Hemodialysis and Transplantation
		G1 Normal	G2 Mild Decrease in eGFR	G3a Mild to Moderate Decrease in eGFR	G3b-G4 Moderate to Severe Decrease in eGFR	G5 Kidney Failure
Risk Assessment/Slow Progression						
Creatinine		✓	✓	✓	✓	✓
Urine albumin		✓	✓	✓	✓	✓
Urine total protein		✓	✓	✓	✓	✓
Cystatin C		✓	✓	✓	✓	✓
HbA1c		✓	✓	✓	✓	✓
Glucose		✓	✓	✓	✓	✓
Total cholesterol		✓	✓	✓	✓	✓
HDL		✓	✓	✓	✓	✓
LDL		✓	✓	✓	✓	✓
Triglycerides		✓	✓	✓	✓	✓
Beta-trace protein		✓	✓	✓	✓	✓
β2-microglobulin		✓	✓	✓	✓	✓
α1-microglobulin		✓	✓	✓	✓	✓
Urea nitrogen				✓	✓	✓
Risk Assessment/Complications						
Light chains, kappa and lambda		✓	✓	✓	✓	✓
Hepatitis		✓	✓	✓	✓	✓
HIV		✓	✓	✓	✓	✓
Cause/Complications						
Cardiovascular disease	Troponin		✓	✓	✓	✓
	BNP		✓	✓	✓	✓
	NT-proBNP		✓	✓	✓	✓
Acute kidney injury	Creatinine	✓	✓	✓	✓	✓
Complications						
Malnutrition/ hypoalbuminemia	Pre-albumin				✓	✓
	Albumin				✓	✓
Anemia	Hemoglobin			✓	✓	✓
	Erythropoietin			✓	✓	✓
	Soluble transferrin receptor			✓	✓	✓
	Ferritin			✓	✓	✓
	Folate			✓	✓	✓
	Hemopexin			✓	✓	✓
	Iron			✓	✓	✓
	Vitamin B12			✓	✓	✓
CKD-MBD	Phosphorus			✓	✓	✓
	Calcium			✓	✓	✓
	25(OH)D			✓	✓	✓
	Intact PTH			✓	✓	✓
Hyperkalemia	Potassium			✓	✓	✓
Metabolic acidosis	CO_2			✓	✓	✓
Transplant	Sirolimus					✓
	Cyclosporine					✓
	Tacrolimus					✓

Assays for the markers listed in the table are available on Siemens Healthineers systems.

Hyperkalemia (high serum potassium)

Potassium is the major intracellular cation in the body, 90–95% of which is excreted by the kidneys; excretion is mediated by aldosterone. Increased serum potassium (hyperkalemia) is generally found in advanced CKD.[40] Hyperkalemia results from dietary intake, decreased excretion, heart failure and blood pressure drugs, pain medications, metabolic acidosis, and hyperglycemia.

Metabolic acidosis

Metabolic acidosis, when unopposed, is a condition that increases the concentration of hydrogen ions in the body and reduces the bicarbonate concentration. It can be produced by increased acid generation, loss of bicarbonate, and/or diminished renal acid excretion.[2,18] Acidosis may lead to muscle loss and weakness, lower albumin synthesis, progression of CKD, increased CVD, mortality, bone loss due to buffering capacity of bone for excess acid, lowered vitamin D synthesis, osteomalacia, and low bone turnover disease. Restoring serum bicarbonate levels is associated with improved survival and CKD outcomes.[41]

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