2 Clinical Assessment of a Patient with Chronic Kidney Disease

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Before You Start: Facts You Need to Know

- A focused history and physical examination are essential in the assessment of patients with chronic kidney disease (CKD).
- A CKD patient's history should differentiate CKD from acute kidney disease, define duration and chronicity, find a causative or contributory disease, and assess complications and comorbidities.
- Physical examination should cover all systems but has a special emphasis on blood pressure and orthostatic changes, volume assessment, and cardiovascular examination.
- Serum creatinine and estimation of glomerular filtration rate (GFR) with a serum creatinine based equation should be done as a part of initial assessment in all CKD patients.
- A complete urinalysis and measurement of albumin/creatinine ratio in the urine should be carried out in all CKD patients.

2.1 History and Physical Examination of a Chronic Kidney Disease Patient

Chronic kidney disease (CKD) is usually a silent condition. Signs and symptoms, if present, are generally nonspecific (Box 2.1) and unlike several other chronic diseases (such as congestive heart failure, chronic obstructive lung disease), they did not reveal a clue for diagnosis or severity of the condition. Typical symptoms and signs of uremia (Box 2.2) appear almost never in early stages (Stage 1 to 3A/B, even Stage 4) and develop too late *only in some patients* in the course of CKD. Still, all newly diagnosed CKD patients, patients with an acute worsening in their kidney function, and CKD patients on regular follow-up should have *a focused history and physical examination*. This will be the key to perceive *real* "implications of health" associated with decreased kidney function in CKD.

Box 2.1 Symptoms and Signs of Early Stages of CKD

- Weakness
- Decreased appetite
- Nausea
- Changes in urination (nocturia, polyuria, frequency)
- Blood in urine or dark-colored urine

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- Foamy or bubbly urine
- Loin pain
- Edema
- Elevated blood pressure
- Pale skin

Box 2.2 Symptoms and Signs of Late (Uremic) Stages of CKD

- General (*lassitude*, *fatigue*, *elevated blood pressure*, *signs of volume overload*, *decreased mental acuity*, *intractable hiccups*, *uremic fetor*)
- Skin (*sallow appearance*, *uremic frost*, *pruritic excoriations*)
- Pulmonary (*dyspnea*, *pleural effusion*, *pulmonary edema*, *uremic lung*)
- Cardiovascular (*pericardial friction rub*, *congestive heart failure*)
- Gastrointestinal (*anorexia*, *nausea*, *vomiting*, *weight loss*, *stomatitis*, *unpleasant taste in the mouth*)
- Neuromuscular (*muscular twitches*, *peripheral sensory and motor neuropathies*, *muscle cramps*, *restless legs*, *sleep disorders*, *hyperreflexia*, *seizures*, *encephalopathy*, *coma*)
- Endocrine-metabolic (*decreased libido*, *amenorrhea*, *impotence*)
- Hematologic (*anemia*, *bleeding diathesis*)

In a newly diagnosed CKD patient, the history should be focused *to differentiate an acute kidney injury/disease from CKD* and get clues for duration and chronicity of kidney dysfunction. Any previous kidney function tests, urine findings, and imaging studies should be obtained and reviewed. If CKD diagnosis is confirmed, history should be focused *to find an underlying cause*. Patients should be questioned for any sign or symptom of an underlying (causative or contributory) disease(s) for CKD. All medications (including current and prior medications, over-the-counter, and non-prescription medications) should be carefully reviewed and documented. Any previous surgical intervention, especially genitourinary interventions, should be reviewed. A detailed family history should be obtained to exclude presence of a familial, hereditary kidney disorder (Box 2.3).

Box 2.3 Clues to the Underlying (Causative or Contributory) Disease in a CKD Patient

Previous lab tests, imaging, or biopsy findings (*provide definite evidence for CKD if they show previously decreased GFR and/or presence of kidney damage*, *presence of bilateral small kidneys*)

System review:

- Cardiovascular (*history of myocardial infarction*, *coronary intervention*, *and heart failure provide evidence for cardiorenal connection and impaired renal perfusion*)
- Immunologic/infectious (*provide evidence for autoimmune or infectious causes of CKD*)
- Gastrointestinal (*history of hepatitis*, *cirrhosis*)
- Genitourinary (*frequent urinary tract infection*, *recurrent kidney stones*, *and urinary symptoms related to bladder neck obstruction provide evidence for pyelonephritis*, *obstruction*, *and stones*)

Past medical history (*history of diabetes or long- standing hypertension*, *glomerulonephritis in early childhood*, *kidney complications during pregnancy*, *any previous acute kidney injury episode*, *any previous urologic intervention*)

Family history (*anyone with CKD diagnosis among first-degree relatives*)

Medication history (*frequent use of NSAIDs or pain killers*, *long- term exposure to nephrotoxic antibiotics*, *frequent exposure to radiocontrast agents*, *chemotherapeutic use*, *etc.*)

Source: Reprinted from KDOQI clinical practice guidelines for chronic kidney disease: evaluation, classification, and stratification [1], Copyright 2002, with permission from Elsevier. Available from: http://www.kidney.org/professionals/KDOQI/guidelines_ckd/toc.htm

In each visit, the *stage of CKD and presence of any comorbidity and complications* related to loss of kidney function and *cardiovascular status* should be evaluated. All body systems should be thoroughly reviewed as CKD may have various manifestations in any of them. Patients should be specifically questioned for dermatological, pulmonary, cardiovascular, cerebrovascular, peripheral vascular, gastrointestinal, genitourinary, musculoskeletal, and neurological symptoms. *Potential risk factors for sudden deterioration and progression* of CKD, along with *a careful review of medications*, should be sought in each visit.

Physical examination of a CKD patient includes a few specific points beyond general rules. Patient's general health, nutritional status, appetite, and weight changes should be determined in each visit. Blood pressure and pulse should be assessed both in upright and supine positions for determining orthostatic changes. Hypertensive or diabetic changes in the eye should be examined by fundoscopy. Patients should be examined for signs of hypovolemia or volume overload. Skin should be evaluated for finding an underlying disease and signs of CKD (anemia, pruritus, sallow appearance). A careful evaluation of the cardiovascular system is important. The abdomen should be palpated for large kidneys and bladder distention. Abdominal bruits should be noted for potential renovascular disease. Costovertebral tenderness may be a sign of infection and/or stone disease in kidneys. In men, rectal examination is required for determining prostatic enlargement. Neurological evaluation should be focused on signs of neuropathy and muscular problems. Examination for any sign of a systemic disease causing or contributing to CKD should be carefully sought. Findings consistent with uremia should be determined and followed in each visit (Box 2.4).

Box 2.4 What the Guidelines Say You Should Do: History and Physical Examination

- Review past history and any previous measurement for GFR or markers of kidney damage to determine the duration of kidney disease.
- Evaluate the clinical context, including personal and family history, social and environmental factors, medications, physical examination, laboratory measures, imaging, and pathologic diagnosis to determine the causes of kidney disease.

Source: Data from KDIGO 2012 clinical practice guideline for the evaluation and management of chronic kidney disease [2]

2.2 Estimating or Measuring Glomerular Filtration Rate in CKD

Glomerular filtration rate (GFR) is usually accepted as the best index of kidney function. Persistently decreased GFR (<60 ml/min/1.73 m^2) is a hallmark for CKD, even in the absence of any marker for kidney damage. GFR usually correlates well with the prognosis and complications of CKD like anemia, mineral-bone disorders, and cardiovascular disease. GFR should be determined for confirming diagnosis, staging the disease, estimating the prognosis and making decisions about treatment in all CKD patients. GFR level may also be used to decide appropriate timing to start renal replacement therapies. GFR should be regularly monitored in CKD patients according to the stage and severity of CKD. There is, however, no consensus on the monitoring frequency of GFR in various stages (Table 2.1).

GFR is traditionally measured as renal clearance of an "ideal" filtration marker, such as inulin

Table 2.1 How often should GFR be monitored in CKD?

Stage	Testing frequency (once in every)[a]
Stage 1 and 2	6–12 months
Stage 3A	4–6 months
Stage 3B	3–4 months
Stage 4	2–3 months
Stage 5	1 month

Source: Adapted by permission from Macmillan Publishers Ltd: Kidney Disease: Improving Global Outcomes (KDIGO) CKD Work Group [2] and National Institute for Health and Clinical Excellence (NICE) [3]. Available from: http://www.kdigo.org/clinical_practice_guidelines/CKD.php and https://www.nice.org.uk/guidance/ng203

[a] Testing frequency may change according to progression rate and albuminuria level in each stage. All CKD patients should have GFR measurements during any intercurrent illness, any operation, any hospitalization, and any radiocontrast administration

from plasma. This measured GFR is considered *the gold standard* but is not practical for daily clinical use due to complexity of the measurement procedure. Estimating GFR based on a filtration marker (usually serum creatinine) is now widely accepted as an initial test. Several GFR prediction equations that use serum creatinine or some other filtration markers along with certain patient characteristics (like age, gender, and race) are giving precise estimates of GFR in various clinical settings [4].

1. *Serum creatinine*, *Creatinine clearance*, *and GFR estimating equations*: These are the most common methods used for assessing kidney function in clinical practice.
   (a) *Serum creatinine measurement* is a very convenient, cheap, and readily available technique. It is, therefore, the most commonly used parameter to evaluate kidney function in routine clinical practice. Serum creatinine (SCr) levels are largely determined by the balance between its generation and excretion by the kidneys. Creatinine generation is affected by muscle mass and dietary meat intake. Age, gender, and racial differences in creatinine generation depend to changes in dietary intake and muscle mass. Reduced protein intake, malnutrition, and muscle wasting may reduce creatinine generation in a CKD patient. These factors may blunt the rise of serum creatinine in spite of a decrease in GFR levels, especially in late stages of CKD.

   Creatinine is freely filtered through the glomerulus and is also secreted by the proximal tubules (5–10% of the excreted creatinine). Tubular secretion and increased extrarenal elimination of creatinine increases with decreasing kidney function. Both factors lead to underestimation of kidney function by using only serum creatinine levels. In early stages of CKD, serum creatinine usually stays in normal limits despite large reductions (~30–40%) in real GFR due to increased tubular secretion and extrarenal elimination of creatinine [5].

   Serum creatinine is commonly measured by alkaline picrate (Jaffé method), enzymatic, or high-performance liquid chromatography (HPLC) methods. These different methods of measuring serum creatinine are recently standardized to the isotope dilution mass spectrometry (IDMS). Standardized measurements usually yield 5% lower values for serum creatinine concentrations. The alkaline picrate method is subject to interference by various serum constituents and drugs. The differences in assays and inter- and intra-laboratory variability may also affect the accuracy of serum creatinine measurements [6].

   All these factors (differences in creatinine generation, tubular secretion, extrarenal elimination, and variations in assay methods) may affect diagnostic sensitivity and correct interpretation of serum creatinine. *Serum creatinine alone is not anymore accepted as an adequate marker of kidney function.*

   (b) *Creatinine clearance* (*Ccre*) *measurement* is a frequently used clinical method for measuring GFR. Its calculation depends on 24-h urine collection. This is a cumbersome procedure, especially

in elderly. An incomplete or prolonged collection of urine alters the accuracy of the results. If creatinine generation is stable and there is no extrarenal elimination of creatinine, a complete collection may be determined by calculating total excretion of creatinine in the urine as follows:

$$\text{Urine creatinine} \times \text{urine volume} = 20-25\,\text{mg/kg/day for men}, 10-15\,\text{mg/}kg\text{/day for women}$$

Calculation of creatinine clearance assumes that all of the filtered creatinine (equal to the product of the GFR and the serum creatinine concentration (SCr)) is equal to all of the excreted creatinine (equal to product of the urine creatinine concentration (UCr) and the urine flow rate) and ignores the tubular secretion of creatinine. In this condition, the formula is as follows:

$$Ccre = \left[UCr \times V\right] / SCr, \text{where } Ucr\left(\text{Urine creatinine}\right)\text{is mg/ml}, V\left(\text{urine volume}\right)\text{is ml and } SCr\left(\text{Serum creatinine}\right)\text{is mg/dl.If the finding is divided to 1440}\left(24\,\text{h} \times 60\,\text{min}\right), \text{creatinine clearance is expressed as ml/min}.$$

Creatinine clearance formula overestimates true GFR by approximately 10–20% because of disregarding tubular secretion. As already mentioned, tubular secretion of creatinine increases with decreasing kidney function causing higher overestimations in late stages of CKD.

(c) The *reciprocal serum creatinine concentration* (*1/SCr*) *curve* is used to follow changes in the kidney function of patients with CKD. It assumes that GFR is inversely proportional to the serum creatinine. If creatinine generation, extrarenal elimination, and tubular secretion remain stable, a plot of 1/SCr against time will be linear with a constant decrease in GFR. Due to several caveats, this method is not popular anymore for following progression among CKD patients.

(d) *GFR estimating equations based on serum creatinine* were developed in order to eliminate several limitations of serum creatinine use. These equations were derived from different studies and populations and usually combine serum creatinine levels with other determinants of GFR like age, gender, and race and body size. The most common equations used are the Cockcroft-Gault, the Modification of Diet in Renal Disease (MDRD) Study, and the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equations.

(e) The *Cockroft- Gault equation* is the oldest (developed in 1973) but simplest equation for everyday clinical use. It has been derived using data from 249 men with a creatinine clearance ranging from approximately 30 to 130 ml/min [7].

$$Ccre\left(\text{ml/min}\right) = \left\{\left[\left(140 \;\; \text{age}\right) \times \text{body weight}\right] / \left(72 \times Scr\right)\right\} \times \left(0.85\,\text{if female}\right),$$

where age is expressed in years, weight in kilograms, and serum creatinine $\left(Scr\right)$ in milligrams per deciliter.

This equation was derived when standardized creatinine assays were not in use. In labs where standardized creatinine assays were used, this equation will cause an overestimation (10–40%) of actual GFR. This equation has not been adjusted for body surface area. It is less accurate in obese patients (overestimate), in patients with normal or mildly decreased GFR (underestimates), and in the elderly (underestimates) [6, 8].

(f) The *MDRD Study equation* was developed in 1999 by using data from 1628 CKD patients (primarily white subjects, with nondiabetic kidney disease) with a GFR range between 5 and 90 ml/min/1.73 m^2. The equation was re-derived in 2006 for use with the standardized serum creatinine assays [9, 10].

$$\text{GFR}\left(\text{mL}/\text{min}/1.73\,\text{m}^2\right) = 186.3 \times Scr^{-1.154} \times \text{age}^{-0.203} \times \left(0.742\,\text{if female}\right) \times \left(1.210\,\text{if African American}\right), \text{where } Scr \text{ is expressed in mg/dL and age is expressed in years.}$$

$$\text{GFR}\left(\text{mL}/\text{min}/1.73\,\text{m}^2\right) = 175 \times Scr^{-1.154} \times \text{age}^{-0.203} \times \left(0.742\,\text{if female}\right) \times \left(1.210\,\text{if African American}\right), \text{where a standardized } Scr\left(\text{mg}/\text{dL}\right) \text{measurement is done.}$$

MDRD equation is the most widely used formula in recent years. Many laboratories automatically report MDRD equation GFR estimate along with serum creatinine measurements. This equation is more accurate in estimating GFR than 24-h urine creatinine clearance and Cockroft-Gault formula. It is also more accurate in patients with lower GFR levels (<60 ml/min/1.73 m^2). Its accuracy differs in various ethnic groups. It is less accurate in obese patients and in patients with normal or mildly decreased GFR.

(g) *The CKD-EPI equation* has been derived in 2009 from a large study population that included patients with or without kidney disease with a wide range of GFR. When compared with MDRD, CKD-EPI was more accurate in people especially with higher GFR levels (>60 ml/min/1.73 m^2) [11].

GFR (ml/min/1.73 m^2) = 141 × min(SCr/κ, 1)α × max(SCr/κ, 1)–1.209 × 0.993Age × (1.018 if female) × (1.159 if African American), where SCr is serum creatinine (in mg/dl), κ is 0.7 for females and 0.9 for males, α is –0.329 for females and –0.411 for males, min indicates the minimum of SCr/κ or 1, and max indicates the maximum of SCr/κ or 1

Female	≤ 0.7 mg/dl	$\text{GFR} = 144 \times \left(Scr/0.7\right)^{-0.329}$
	> 0.7 mg/dl	$\text{GFR} = 144 \times \left(Scr/0.7\right)^{-1.209} \times \left(0.993\right)^{\text{Age}} \times 1.157\left[\text{if black}\right]$
Male	≤ 0.9 mg/dl	$\text{GFR} = 141 \times \left(Scr/0.9\right)^{-0.411}$
	> 0.97 mg/dl	$\text{GFR} = 141 \times \left(Scr/0.9\right)^{-1.209}$

The CKD-EPI equation has been found to result in lower prevalence estimate of CKD across a broad range of populations and categorized mortality and ESRD risk better than MDRD. Given the data on the improved performance, especially in general population at higher levels of GFR, "*KDIGO 2012 clinical practice guideline for the evaluation and management of chronic kidney disease*" *recommends to use CKD-EPI equation for GFR estimation*.

Race-free CKD-EPI equation with the realization that race is only a social terminology and not a biological construct. Health professionals began to demand the removal of variables by race from clinical algorithms. With this perception, the race variable was removed and the CKD EPI 2021 creatinine equation was revealed [12, 13].

There is information that Black individuals are classified in a lower category and non-Black individuals in a higher category in CKD staging using the race-independent CKD EPI 2021 equation. Although the use of the CKD EPI 2021 equation increases the prevalence of CKD in Black individuals, it is thought that its suitability for medical treatments and contrast-based procedures will need to be evaluated. It may increase nephrology and vascular access referrals, and transplantation and donor eligibility assessments may be affected [14].

The performance of race-free equation was found to be poor in white subjects with a significant underestimation of CKD, especially in European populations. A viewpoint by European Renal Association has not proposed to adopt this new race-free CKD-EPI equation before its better performance in European populations is shown [15]. A new European Kidney Function Consortium equation (EKFC) has been developed mostly from European cohorts with a full age spectrum, i.e., applicable from children >2 years to the elderly population [16].

(h) *The Berlin Initiative Study (BIS) equation* was developed to make an accurate estimation of GFR in elderly population. Two new equations were created, one based on creatinine (BIS1) and one based on creatinine and cystatin c (BIS 2). GFR is estimated more accurate with BIS equations in elderly patients (≥70 years) especially when eGFR is greater than 30 mL/min per 1.73 m^2 [17].

All GFR equations have some imprecision and do not provide an accurate estimate of GFR due to several limitations. Some of the limitations are related to the serum creatinine itself (Box 2.5) and some are linked to the populations and studies that the equations have been derived. All GFR equations should be used in stable settings where serum creatinine has no rapid alterations (i.e., not used in acute kidney injury/disease). They are not recommended for use in patients under the age of 18, in patients with extremes in body size or muscle mass, in patients with severe alterations in dietary intake (vegetarians, using creatine supplements), in very elderly (>85 years), or in pregnant patients. It should be noted that GFR equations have a large standard deviation. They are very useful in large group/ population estimates, but may lead to misinterpretations in some individual assessments. Where wide variations in an individual's estimated GFR exists, or where a more accurate assessment of GFR is required, good clinical judgment and measurement of GFR (see below) is recommended.

In elderly population, MDRD equation predicts higher eGFR than CKD stage compared to CKD EPI and Cockroft-Gault equations. MDRD equation overestimates GFR in the elderly population due to decreased muscle mass. One reason is that the MDRD study population is younger and excludes people

over 70 years of age. However, the CKD EPI collaboration study included older adults as well. GFR estimation with cystatin c (see below) is more reliable in the elderly population where muscle mass reduction is common. Cystatin c-related equations are more advantageous in estimating moderate GFR reductions in this age group, and the only disadvantage is the cost of the measurement.

Box 2.5 Sources of Error by Using Serum Creatinine in GFR Estimation

- Non-steady state (*e.g.*, *acute kidney injury*)
- Variable creatinine generation (*e.g.*, *race*, *extremes of muscle mass*, *extremes of body size*, *high protein diet*, *creatinine supplements*, *muscle wasting*)
- Variable tubular secretion (*e.g.*, *decrease by trimethoprim*, *cimetidine*, *fenofibrate*)
- Variable extrarenal elimination (*e.g.*, *decrease by inhibition of gut creatininase by antibiotics*, *increase by large volume losses*)
- Higher GFR (*e.g.*, *higher measurement errors in patients with higher GFR*)
- Interference with assay (*e.g.*, *spectral interferences from bilirubin and some drugs or chemical interferences from glucose*, *ketones*, *bilirubin*, *and some drugs*)

Source: Adapted by permission from Macmillan Publishers Ltd: Kidney Disease: Improving Global Outcomes (KDIGO) CKD Work Group [2]. Copyright 2013. Available from: http://www.nature.com/kisup/index.html

2. *Blood urea and Urea clearance*: Urea is the most well-known nitrogenous waste and it was used as one of the first indicators to measure GFR. It is also measured as an indicator of uremic burden and uremic symptoms in late stages of CKD. Although blood urea nitrogen (BUN) has an inverse relationship with GFR, it is not an ideal filtration marker. Urea production is variable and is largely dependent on protein intake. BUN concentration increases as its production increases with high protein intake, tissue breakdown, trauma, hemorrhage, or glucocorticoid use. In contrast, BUN concentration decreases when its production decreases with low protein intake or in liver disease.

   Urea is freely filtered from the glomerulus, but 40–50% is reabsorbed in the tubules. Urea reabsorption increases substantially in states of decreased renal perfusion (volume depletion, congestive heart failure, diuretic use). In all these conditions, BUN levels will increase out of proportion to a decrease in GFR and will result in an increased ratio of BUN to SCre. Increased BUN-to-SCre ratio is suggestive of a prerenal state and may indicate an acute deterioration in a CKD patient.

   Urea clearance is not a reliable indicator of GFR also due to variable tubular reabsorption rates of urea. GFR may be underestimated almost as half as the real level by urea clearance. *The only clinical setting where urea clearance use has been advocated is the late stages of CKD for deciding appropriate timing of dialysis* [18]. As urea clearance underestimates and creatinine clearance overestimates GFR, it is recommended that the average of these two clearances (*GFR* = (*creatinine clearance* + *urea clearance*)/2) is preferred for estimating GFR in advanced CKD. The use of this formula is also compromised by problems related to proper urine collection.
3. *Serum cystatin C and GFR equations*: Limitations inherent to the use of serum creatinine are the major drive for seeking alternative filtration markers in the serum. Among them, cystatin C is considered to be a potential alternative to serum creatinine for estimating GFR. Cystatin C is a low molecular weight (13-kDa) cysteine protease inhibitor that is produced by all nucleated cells. It is freely filtered by the renal glomerulus. It is reabsorbed and completely catabolized by tubular cells. In contrast to creatinine, cystatin C does not undergo

any tubular secretion. The generation of cystatin C was believed to be less variable and affected less by age and sex. Later epidemiological studies, however, have suggested that cystatin C generation rate and serum levels have been influenced by age, sex, cell turnover rate, steroid use, body mass index, inflammation, and diabetes. Studies have also shown that there is an extrarenal elimination of cystatin C at low levels of GFR. Serum cystatin C measurements are not standardized yet and still evolving. Studies have shown that cystatin C measurements also have higher intraindividual variation than serum creatinine.

Several studies have shown that cystatin C concentrations may correlate more closely with GFR than serum creatinine. Similarly, GFR estimates based on cystatin C may be more powerful predictors of clinical outcomes than creatinine-based eGFR. These findings have been the strongest for mortality and CVD events, and the prognostic advantage of cystatin C is most apparent among individuals with GFR >45 ml/min/1.73 m^2. Recently, a single equation combining both serum creatinine and cystatin C has been found to be more accurate in determining GFR [19]. The role of cystatin C measurements or use of cystatin C-based equations in CKD care has yet to be determined. "KDIGO 2012 clinical practice guideline for the evaluation and management of chronic kidney disease" has recommended to measure cystatin C to confirm CKD in adults if eGFR based on serum creatinine was between 45 and 59 ml/min/1.73 m^2 without any markers of kidney damage. KDIGO recommends to use either cystatin C-based eGFR equation or cystatin C and creatinine-based eGFR equations in confirming the presence of CKD. The use of cystatin C equations has also several limitations (Boxes 2.6 and 2.7). A new race free creatinine and cystatin C based eGFR equation without race has also been defined. It more accurately estimated measured GFR than equations with either the creatinine or cystatin alone. The use of creatinine and cystatin C based eGFR equation led to smaller differences from measured GFR between race groups [12].

Box 2.6 Sources of Error by Using Serum Cystatin in GFR Estimation

- Non-steady state (e.g., *acute kidney injury*)
- Variable cystatin generation (e.g., *race*, *thyroid function disorders*, *corticosteroid use*, *diabetes*, *obesity*)
- Variable extrarenal elimination (e.g., *increase by severe decrease in GFR*)
- Higher GFR (e.g., *higher measurement errors in patients with higher GFR*)
- Interference with assay (e.g., *heterophilic antibodies*)

Source: Adapted by permission from Macmillan Publishers Ltd: Kidney Disease: Improving Global Outcomes (KDIGO) CKD Work Group [2]. Copyright 2013. Available from: http://www.nature.com/kisup/index.html

Box 2.7 What the Guidelines Say You Should Do: Glomerular Filtration Rate

- Use serum creatinine and a GFR estimating equation for initial assessment.
- Use a GFR estimating equation to derive GFR from serum creatinine (eGFRcreat) rather than relying on the serum creatinine concentration alone.
- Understand clinical settings in which eGFRcreat is less accurate.
- Clinical laboratories should report eGFRcreat in adults using the 2009 CKD-EPI creatinine equation.
- Clinical laboratories that measure cystatin C should report eGFRcys and eGFRcreat-cys in adults using the 2012 CKD-EPI cystatin C and 2012 CKD-EPI creatinine-cystatin C equations.

Source: Data from KDIGO 2012 clinical practice guideline for the evaluation and management of chronic kidney disease [2]

CKD-EPI Cystatin C equation:

$$\mathrm{GFR}\left(\mathrm{ml/min/1.73\,m^2}\right) = 133 \times \min\left(\mathrm{SCysC}/0.8,1\right) - 0.499 \times \max\left(\mathrm{SCysC}/0.8,1\right) - 1.328 \times 0.996^{\mathrm{Age}} \left[\times 0.932 \text{ if female}\right]$$

where SCysC is serum cystatin C (in mg/l), min indicates the minimum of SCysC/0.8 or 1, and max indicates the maximum of SCysC/0.8 or 1.

CKD-EPI Creatinine-Cystatin C equation:

$$\mathrm{GFR}\left(\mathrm{ml/min/1.73\,m^2}\right) = 135 \times \min\left(\mathrm{SCr}/\kappa,1\right)^{\alpha} \times \max\left(\mathrm{SCr}/\kappa,1\right) - 0.601 \times \min\left(\mathrm{SCysC}/0.8,1\right) - 0.375 \times \max\left(\mathrm{SCysC}/0.8,1\right) - 0.711 \times 0.995^{\mathrm{Age}} \left[\times 0.969 \text{ if female}\right] \left[\times 1.08 \text{ if black}\right]$$

where SCr is serum creatinine (in mg/dl), SCysC is serum cystatin C (in mg/l), κ is 0.7 for females and 0.9 for males, α is –0.248 for females and −0.207 for males, min(SCr/κ, 1) indicates the minimum of SCr/κ or 1,and max(SCr/κ, 1) indicates the maximum of SCr/κ or 1; min(SCysC/0.8, 1) indicates the minimum of SCysC/0.8 or 1 and max(SCysC/0.8, 1) indicates the maximum of SCysC/0.8 or 1.

All these equations may be reached in various websites as electronic calculators, such as http://touchcalc.com/bis2.html or http://www.hdcn.com/calcf/gfr2.htm or https://www.kidney.org/professionals/kdoqi/gfr_calculator

4. *Measuring GFR with exogenous markers*: In clinical settings where GFR estimates from serum creatinine or creatinine-based GFR estimating equations cannot be performed (such as pregnancy, acute kidney disease, etc.) or when there is a need for a more precise determination (such as for living donor assessment) of GFR, clearance measurements should be performed with several filtration markers (inulin, iothalamate, iohexol, DTPA, or EDTA) [20]. Measuring GFR with the use of these markers is complex, expensive, and difficult to do in clinical practice. The measurement of GFR with these markers has also some limitations and rarely used in clinical practice for CKD care except research settings. In a CKD patient, a measured GFR may only be required if the patient is chronically ill with severe reduction in muscle mass, if there will be a prolonged exposure to nephrotoxic drugs, or if there is a discrepancy between severely reduced eGFR and symptoms of uremia before deciding to start renal replacement therapy.

   There is also a new method for calculating GFR by transcutaneous measurement of a new exogenous renal marker, FITC-sinistrin (fluorescein isothiocyanate). GFR is calculated by measuring FITC-sinistrine tested in rodents, and its elimination from the skin with a miniaturized instrument. The advantage of this method over conventional plasma clearance measurements is that it does not require repetitive measurements with blood samples and allows repetitive GFR measurements in a short time period [21, 22]. There are also studies for real-time monitoring of GFR via transdermal measurement of fluorescent tracers [23].
5. *Novel biomarkers*: There is still ongoing research for finding one or more potential,

alternative markers for estimating GFR. In this sense, several low molecular weight molecules such as beta-trace protein (BTP), beta(2)-microglobulin (B2M), and symmetric dimethyl arginine have been investigated. BTP and B2M have been found to be more accurate than serum creatinine in some studies. Proenkephalin A 119–159 (PENK) is a newly identified marker of renal function. It is a good biomarker in showing kidney function because it does not bind to proteins in plasma and can be filtered from the glomerulus. Plasma PENK concentration has been shown to correlate with GFR in many patient populations (critical illness, sepsis, heart failure, CKD patients, kidney transplant recipients and donors) [24]. It is yet to be determined whether one or several of them have a role in CKD patients alone or in combination with creatinine or cystatin C.

2.3 Urinalysis and Albuminuria in CKD

Urinalysis and assessment of albuminuria are very informative, noninvasive tests for both screening and diagnosing CKD. Albuminuria is also an important measure for defining severity of kidney dysfunction, estimating prognosis of CKD-related outcomes, and associated cardiovascular risk. The presence of albuminuria and its severity also guides treatment alternatives in CKD.

1. *Urinalysis*: A complete urinalysis should be carried out in the first examination of all CKD patients. Along with a targeted history and physical examination, urinalysis provides important information for differential diagnosis of acute and chronic kidney disease. Urinalysis may also provide clues for underlying etiologies of chronic kidney disease. There is, however, no evidence-based information whether urinalysis is required in each follow-up visit of a CKD patient.

   A detailed discussion of the diagnostic uses of urinalysis or specific tests of urine (metabolic diseases, urine electrolytes, etc.) is beyond the scope of this chapter and may be found in other sources. Here, only essential features of urinalysis for the care of CKD patients will be covered.

   An accurate urine analysis should start with a proper collection of a urine sample. First-void (early) morning urine is usually preferred as formed elements will more likely be seen in concentrated urine with a low pH. The sample should be analyzed within 2–4 h from collection.

   A complete urinalysis consists of three components, as physical (gross) examination, chemical (dipstick) analysis, and microscopic evaluation of the urinary sediment. In routine clinical practice, most of the physical and chemical parameters are examined by a dipstick. A dipstick provides a semiquantitative examination of several urinary characteristics by a series of tests embedded on a reagent strip. Among physical parameters, color (usually normal in CKD), turbidity (usually normal in CKD), and specific gravity (usually a fixed, isosthenuric urine is produced in CKD, i.e., specific gravity is 1010) are assessed. In chemical analysis, urine dipstick assesses pH (low or normal in CKD), glucose (usually normal in CKD), ketones (usually normal in CKD), bilirubin and urobilinogen (usually normal in CKD), nitrite and leukocyte esterase (usually normal in CKD), blood, and protein. *The dipstick test for blood* detects peroxidase activity of erythrocytes. The dipstick test is commonly considered to be sensitive for detection of microscopic hematuria. False-negative results are unusual, i.e., a negative dipstick for blood excludes hematuria. However, myoglobin and hemoglobin also will catalyze this reaction, so a positive test result may indicate hematuria, myoglobinuria (from rhabdomyolysis), or hemoglobinuria (from intravascular hemolysis). When it is positive, visualization of intact erythrocytes on microscopic examination of the urinary sediment should be done for confirmation of hematuria. Hematuria may be observed in patients with CKD due to various underlying

causes. *The dipstick test for protein* is most sensitive to albumin and may not detect low concentrations of globulins, tubular proteins, and Bence Jones proteins. The dipstick measurement of urine protein allows only an approximate quantification of urine albumin, expressed on a scale from negative trace to 1(+) to 4(+). Dipstick tests for trace amounts of protein yield positive results at concentrations of 5–10 mg/dl—lower than the threshold for clinically significant proteinuria. Dipstick protein may miss moderately increased albuminuria levels in the range of 30–300 mg/day (formerly called microalbuminuria) in most cases. A result of 1+ corresponds to approximately 30 mg of protein per dl and is considered positive; 2+ corresponds to 100 mg/dl, 3+ to 300 mg/dl, and 4+ to 1000 mg/dl. In addition, dipstick protein measurement is dependent on the concentration of the urine specimen, where concentrated urine may give false-positive and dilute urine may give false-negative results. Thus, it is important to quantify the amount of proteinuria detected on urine dipstick analysis with other methods. Protein can be quantified in random samples, in timed or untimed overnight samples, or in 24-h collections. Although 24-h urine protein amount represents the gold standard method, problems related with 24-h collection (over or under collection) are a major source of error. It is also a cumbersome procedure for many patients. Still, adequately collected 24-h urine protein concentrations are accepted as the most accurate way to monitor proteinuria under active treatment (such as active immunosuppressive use). A complete collection may be determined by the amount of expected 24-h urine creatinine excretion (see above). *Protein-creatinine ratio* (*PCR*) in a random urine sample is accepted as an alternative to 24-h urine collection. PCR may correct problems arising from variability of urine volume and concentration. It is easy to obtain and showed a strong correlation with 24-h urine collection. However, when urine protein levels are greater than 1 g/l, spot protein-creatinine correlation with 24-h urine may not be accurate. Thus, spot protein-creatinine level may act as a simple screening for proteinuria, i.e., if it is negative, there is no need for a 24-h urine collection.

In cases where presence of non-albumin proteins (such as gamma globulins, Bence Jones proteins) is suspected, other precipitation methods like sulfosalicylic acid test should be used. Trichloroacetic acid can be used in place of sulfosalicylic acid to increase the sensitivity to gamma globulins.

Microscopic examination of urine sediment should be done in all patients with CKD and in patients with high risk for CKD. In the urine sediment, cellular elements (red blood cells, white blood cells), casts, and crystals should be thoroughly examined. Some findings in the urine sediment may help to diagnose some underlying causes of CKD. There is, however, no characteristic finding in the urinary sediment of a CKD patient, except broad casts which are typically associated with advanced stages of CKD.

Urine flow cytometry is an alternative to automated microscopic methods. It has more advanced cell counting and accuracy. It provides rapid detection of urine microorganisms and allows more accurate results by evaluating the dilution parameters. Early detection of urothelial cancer is one of its advantages. Rapid detection of urinary tract pathogens is also possible with the matrix-assisted laser desorption ionization-time-of-flight mass spectrometry (MALDI-TOF MS) method [25].

2. *Albuminuria*: Albumin is the predominant protein in major proteinuric diseases causing CKD. Albumin measurement in urine has greater sensitivity and improved precision for the detection of low levels of proteinuria compared to protein measurements. It is therefore accepted as a more sensitive method for screening/diagnosing not only diabetic but also nondiabetic CKD. Most of the recent studies also showed strong evidence linking increased albuminuria and outcomes of CKD.

Urinary concentrations of albumin <150 mg/l are below the detection limit of the "dipstick" tests used in routine urinalysis. Albumin in the urine may be detected by radioimmunoassay, immunoturbidimetric technique, and nephelometry, ELISA, or HPLC. Reagent strip methods were also developed for urine albumin screening but have increased false-positive or false-negative ratios.

Twenty-four-hour urine collection is also the gold standard for the detection of high albuminuria (formerly, microalbuminuria). Albuminuria screening however may be done with spot early morning urine collections, timed urine collections, or as a ratio of albumin to creatinine in the urine (ACR). The ACR is the preferred method as it does not require timed collections, it correlates with the 24-h urine values over a large range of proteinuria, it is cheap to perform, and repeat values can be easily obtained to be certain that high albuminuria, if present, is persistent. A value of 30–300 mg/g of creatinine (or, using standard (SI) units, 3.4–34 mg/mmol of creatinine) suggests that albumin excretion is between 30 and 300 mg/day and therefore that high albuminuria is probably present. A false reading for ACR may occur after vigorous exercise, in the presence of fever, urinary infection, congestive heart failure, acute severe elevations of blood pressure or blood sugar, or menstruation. There are some other sources of error in the assessment of ACR (Box 2.8) [26].

Box 2.8 Sources of Error When Using ACR for Albuminuria

- Transient, false elevations in albuminuria (e.g., *menstrual blood contamination*, *urinary tract infection*, *fever*, *exercise*, *orthostatic*, *severe uncontrolled hyperglycemia*, *or hypertension*)
- Variability due to sample storage (*e.g.*, *degradation of albumin before analysis*)
- Variability in creatinine excretion (*e.g.*, *lower in children*, *women*, *or elderly*, *higher in black*, *lower due to decreased muscle mass*, *variability due to non-steady state*)
- Interference with assay (*e.g.*, *samples with very high albumin levels may falsely be reported as low or normal due to antigen excess effect in some assays*)

Source: Adapted by permission from Macmillan Publishers Ltd: Kidney Disease: Improving Global Outcomes (KDIGO) CKD Work Group [2]. Copyright 2013. Available from: http://www.nature.com/kisup/index.html

Most national and international guidelines (including KDIGO 2012 clinical practice guideline for the evaluation and management of chronic kidney disease) recommend ACR measurement with an early morning urine sample over other methods. Albuminuria assessment is recommended to be done at least annually in CKD patients. The frequency of assessment of albuminuria may depend on clinical situation, i.e., rate of progression or monitoring the effect of anti-albuminuric treatment (Boxes 2.9 and 2.10).

Box 2.9. What the Guidelines Say You Should Do: Albuminuria

- Use the following measurements for initial testing of proteinuria (in descending order of preference, in all cases an early morning urine sample is preferred):
  - Urine albumin-to-creatinine ratio (ACR)
  - Urine protein-to-creatinine ratio (PCR)
  - Reagent strip urinalysis for total protein with automated reading
  - Reagent strip urinalysis for total protein with manual reading

- Confirm reagent strip-positive albuminuria and proteinuria by quantitative laboratory measurement and express as a ratio to creatinine wherever possible
- Confirm ACR >30 mg/g (>3 mg/mmol) on a random untimed urine with a subsequent early morning urine sample
- Measure albumin excretion rate or total protein excretion rate in a timed urine sample for a more accurate estimate

Source: Data from KDIGO 2012 clinical practice guideline for the evaluation and management of chronic kidney disease [2]

Box 2.10 Relevant Guidelines

1. *KDIGO Guideline*: Kidney Disease: Improving Global Outcomes (KDIGO) CKD Work Group. KDIGO 2012 clinical practice guideline for the evaluation and management of chronic kidney disease. Kidney Int Suppl. 2013; 3: 1–150. http://kdigo.org/guidelines/ckd-evaluation-and-management
2. *CARI Guideline*: Diagnosis, classification and staging of chronic kidney disease. July 2012. https://www.cariguidelines.org/guidelines/chronic-kidney-disease/early-chronic-kidney-disease/diagnosis-classification-and-staging-of-chronic-kidney-disease
3. *The Renal Association Guideline.* Detection, monitoring and care of patients with CKD. Final Version (28 February 2011). http://www.renal.org/Clinical/GuidelinesSection/Detection-Monitoring-and-Care-of-Patients-with-CKD.aspx
4. *Japanese Society of Nephrology Guideline*. Evidence-based Practice Guideline for the Treatment of CKD. Clin Exp Nephrol. 2009;13:533–66. http://www.jsn.or.jp/en/guideline/pdf/guideline2009.pdf
5. *National Institute for Health and Clinical Excellence* (*NICE*) *Guideline*. Chronic kidney disease: assessment and management [internet]. Published: 25 August 2021 Last updated: 24 November 2021. https://www.nice.org.uk/guidance/ng203
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7. *NKF KDOQI Guideline*: KDOQI Clinical practice guidelines for chronic kidney disease: evaluation, classification, and stratification. Am J Kid Dis. 2002;39(2 Suppl 1):S11–266. http://www.kidney.org/professionals/KDOQI/guidelines_ckd/toc.htm

2.4 Other Lab Tests in CKD

CKD patients may need further tests as a part of their general assessment or for finding any other marker of kidney damage like renal tubular disorders or for assessment of the complications of CKD (such as anemia, mineral-bone disorders, malnutrition, neuropathy, cardiovascular tests). These tests will not be covered in detail here. It is, however, important to note that some tests need a cautious interpretation especially in patients who are in the late stages (Stages 4 or 5) of CKD. Among those tests, there are serum ALT, AST, amylase, lipase concentrations, troponins, and BNP/NT-proBNP levels which may have diagnostic and/or therapeutic importance. With a decrease in GFR, there is a trend of false alterations in these tests: Liver transaminases tend to decrease to very low levels, pancreatic amylase and lipase, troponins, and BNP/NT-proBNP levels tend to increase above cutoff concentrations. All these alterations should be interpreted carefully, and "real" implications of test results should be assessed within the clinical context of the patient.

Before You Finish: Practice Pearls for the Clinician

- In each visit, a CKD patient should be assessed for general well-being, for progression and any factor for acute deterioration of CKD, for presence of any complications or comorbidity, and for cardiovascular health.
- Patients who are in late stages of the disease should be assessed for the presence of any uremic symptom, and the need for renal replacement therapy should be evaluated.
- Blood pressure, orthostatic changes, volume, and cardiac status should be checked in all visits.
- CKD patients should have an assessment of eGFR and albuminuria as a part of their initial assessment. eGFR and albuminuria should be rechecked at least annually in all CKD patients.
- eGFR should be calculated by 2009 CKD-EPI equation derived from serum creatinine. Patients who are in the late stages, who have a higher risk for progression, who have any intercurrent illness/medication use/operation, and who have changes in treatment may have frequent eGFR assessments.
- Keep in mind the limitations of eGFR or ACR measurements mostly caused by creatinine measurements.
- The use of direct methods to measure GFR should be considered in clinical situations in which estimation equations are known to be suboptimal.
- Albuminuria should be assessed by albumin-creatinine ratio measured from an early morning urine sample. Patients who have severely increased albuminuria or patients who are under antiproteinuric treatment may have frequent albuminuria assessments.

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