

Elevation of Serum Creatinine: When to Screen, When to Refer



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To resolve the existing confusion within the medical literature, seven years ago the National Kidney Foundation in the US developed a classification scheme for chronic kidney disease (CKD).¹ This terminology has been promoted and accepted throughout the world and in a recent position statement by the Canadian Society of Nephrology (CSN),² it was advocated that Canadian healthcare providers accept the CKD terminology as shown in Table 1.

It is recommended that all healthcare providers use serum creatinine within a GFR equation to provide an eGFR.

eGFR calculation

An overriding focus of this CKD nomenclature is the avoidance of using serum creatinine to define CKD. Instead, it is recommended that all healthcare providers use serum creatinine within a glomerular filtration rate (GFR) equation to provide an estimate of GFR (eGFR). Such an approach is not without

Martha's case

Martha, 68, presents for a routine 6-month check-up of her BP and diabetes control and a renewal of her medications.

Martha has been hypertensive for 15 years. Her home BP recordings are typically < 145/80 mmHg. She has had diabetes for 2 years. She has no known cardiovascular (CV) disease or target organ disease from her diabetes. She is a life-long non-smoker.

Medications

Martha's current medications include:

- 16 mg of candesartan q.d.,
- 12.5 mg of hydrochlorothiazide q.d.,
- 81 mg of acetylsalicylic acid q.d. and
- 500 mg of metformin b.i.d.

She denies using OTC drugs, including anti-inflammatories.

Today's BP is 138/74 mmHg. Her BMI is 28 kg/m² and her waist circumference is 106 cm.

Laboratory results

Pertinent laboratory results are:

- Serum creatinine: 110 µmol/L, estimate of glomerular filtration rate (eGFR): 46 ml/minute
- Normal complete blood count and electrolytes
- Glycosylated hemoglobin (HbA1C): 6.8%
- Total cholesterol: 5.4 mmol/L, LDL-C: 2.8 mmol/L; HDL-C: 1.0 mmol/L
- Routine urine: 1+ protein, no red blood cell, no white blood cell
- Urine albumin-to-creatinine ratio: 32 mg/mmol

For Martha's diagnosis, look to page 92.

Table 1

Definition and classification of chronic kidney disease (CKD)¹

Stage*	Description	Glomerular filtration rate (GFR) (ml/minute/1.73m ²)
1	Kidney damage** with normal or increased GFR	> 90
2	Kidney damage** with mildly decreased GFR	60 to 89
3	Moderately decreased GFR	30 to 59
4	Severely decreased GFR	15 to 29
5	Kidney failure	< 15 (or dialysis)

* Kidney damage or reduced GFR must be present for ≥ 3 months to define CKD.

** Kidney damage refers to any damage to kidney structure or function (examples include proteinuria or albuminuria, glomerular hematuria, kidney cysts, non-cystic kidney masses, etc.).

Table 2

Equations approved by the Canadian Society of Nephrology to estimate kidney function

Equation name	Formula
Modified MDRD*	$eGFR \text{ (ml/minute/1.73m}^2\text{)} = 186 \times (\text{serum creatinine} \times 0.0113)^{-1.154} \times (\text{age [year]})^{-0.203} \times (0.742 \text{ if female}) \times (1.210 \text{ if African American})$
Cockcroft-Gault	$\text{Creatinine clearance (ml/minute)} = 140 - \text{age (years)} \times \text{weight (kg)} / \text{serum creatinine} \times (1.2 \text{ if male})$

MDRD: Modification of Diet in Renal Disease

* Available online at <http://www.hdcn.com/calcf/gfr.htm> or <http://www.kidney.org/professionals/tools>

Table 3

Referral to a nephrologist is recommended in the following situations²

- Acute renal failure
- eGFR < 30 ml/minute/1.73m²
- Progressive loss of kidney function
- Persistent proteinuria on dipstick, or quantified protein-to-creatinine ratio (PCR) > 100 mg/mmol or urine albumin-to-creatinine ratio (ACR) of > 60 mg/mmol. Persistent is defined as present on 2 out of 3 urine samples; this indicates proteinuria of significant degree requiring investigation. (A PCR of 100 mg/mmol corresponds to an approximate 24-hour protein excretion rate of 900 mg to 1000 mg)
- The Canadian Society of Nephrology would recommend referral to a nephrologist or internist if the practitioner is unable to achieve treatment targets for BP, or is unable to maintain the use of ACE inhibitors/ARBs or other renal protective or CV protective strategies, or feels otherwise sufficiently unprepared to manage the CKD patient

Martha's diagnosis

Diagnosis and discussion

Although it is likely (given Martha's BP and diabetes history) that she has CKD, it is still unknown. Old measurements of eGFR (or serum creatinine) can help determine the stability of Martha's kidney function. Her eGFR should be repeated in 2 weeks and again within 2 to 4 months. She also requires another measurement of urinary albumin within 3 months. Referral to a nephrologist is not needed at this point unless Martha's kidney function is progressing at an unexpectedly fast rate.

Martha's BP is not adequately controlled. To achieve a target of < 130 mmHg systolic, she needs additional lifestyle counselling (with an emphasis on salt restriction and weight reduction) and another antihypertensive medication. Martha's CV risk should also be addressed by initiating a lipid-lowering agent to reduce her LDL-C to < 2.0 mmol/L. Her current kidney function is NOT an indication to stop the metformin.

shortcomings,² but an eGFR calculation provides a more accurate measure of kidney function in the majority of individuals than the use of serum creatinine alone.

eGFR is now reported by many labs in Canada when a serum creatinine measurement is ordered. These laboratory calculations utilize a version of the Modification of Diet in Renal

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Disease equation (Table 2). If this is not automatically reported on the lab report, eGFR can also be calculated using online estimators, examples of which are also provided in Table 2. The Cockcroft-Gault equation can also be used to estimate kidney function.

In addition to recommending the use of estimating equations for GFR, the position statement from the CSN also provides details for the screening of CKD and lists indications for the appropriate referral of patients to a nephrologist.

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Screening for CKD

Although the prevalence of CKD may exceed 20% in certain high-risk groups, such as the elderly,² it is recognized that CKD (manifesting as either reduced GFR or albuminuria) is relatively uncommon in patients with no CKD risk factors. Therefore, population-based screening strategies for CKD are not advocated. Instead, a case-finding approach is recommended in which testing for CKD should be focused on high-risk groups. Patient groups at high-risk for

CKD are those with:

- Hypertension
- Diabetes mellitus
- Heart failure
- Atherosclerotic coronary, cerebral or peripheral vascular disease
- Unexplained anemia
- Family members with end-stage renal disease
- First Nation's lineage

There is ample evidence to suggest that optimal treatment in these patients reduces progression of CKD and/or reduces cardiovascular (CV) risk. These patients should be screened for CKD using eGFR and by assessing urinary albumin via routine dipstick or a quantified measure, such as the albumin-to-creatinine ratio. It should be noted that 24-hour urine collections for albumin or protein excretions are no longer routinely required.

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Frequently Asked Questions

1. Are 24-hour urine collections necessary to quantify urine protein or albumin?

No. Random spot urine collections for measurement of albumin-to-creatinine provide sufficient accuracy.

2. How many measurements of serum creatinine (with eGFR calculation) are necessary to determine if the kidney function is worsening?

This depends upon the patient; for the majority of patients 2 to 3 measurements per year over 1 to 3 years is necessary.

3. Should the ACE inhibitor or ARB be discontinued if a patient has a low GFR?

In the majority of patients, these agents should be continued indefinitely. An occasional patient may develop progressive disease while on these medications. Such patients should be referred to a nephrologist.

Referring patients with CKD

Evidence accumulated over the last few years has helped shape the current recommendations for the appropriate referral of patients with CKD. Key research findings include:

- An increased awareness that patients with CKD have high rates of CV disease and that the majority of CKD patients die before progressing to end-stage kidney disease. In fact, the risk of death in patients with Stage three CKD is 10-fold greater than the risk of needing dialysis^{3,4}
- An understanding that not all people with reduced kidney function experience a progressive loss of function, particularly in the absence of proteinuria. Recent data implies that a minority of CKD patients experience a loss of kidney function exceeding 2 ml/minute per year

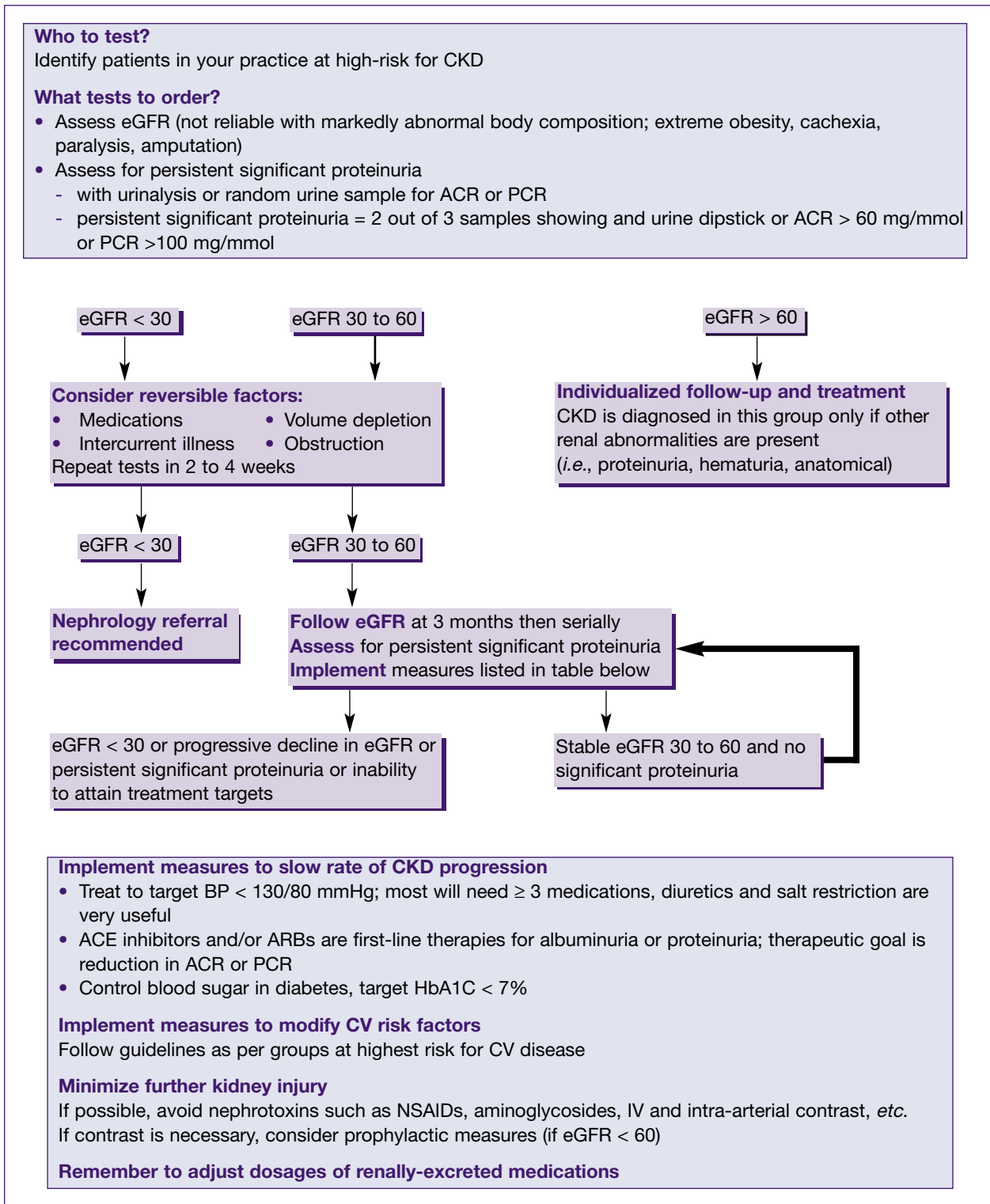


Figure 1. Algorithm for the detection, monitoring and referral of CKD.

Take-home message


- Population-based screening for CKD is not necessary; screening for CKD should be performed only in patients at high-risk
- Serum creatinine alone should not be used to detect CKD. Serial measurements of eGFR and urinary albumin are needed to make a CKD diagnosis and to monitor disease progression
- Most patients with CKD do not require a referral to a nephrologist; all CKD patients require aggressive CV disease risk-reduction

- A recognition that many episodes of a newly-discovered reduction in eGFR will be transient in nature due to intercurrent illness or medications. Many patients in the primary care setting will show an improvement in eGFR on repeat testing

Most patients with non-progressive CKD can be managed by non-nephrologists, without referral.

As a result of these findings, the CSN has developed referral recommendations to assist healthcare providers in Canada manage patients with CKD (Table 3). Most patients with non-progressive CKD can be managed by non-nephrologists, without referral. For patients with a new finding of an eGFR between

30 ml/minute/1.73m² to 60 ml/minute/1.73m², it is recommended that clinicians determine the stability of the patient's eGFR (repeat test within two to four weeks and then in three to six months) and the extent of comorbidity and then determine the need for referral. It should be emphasized that decisions about investigation, treatment or referral should not be made based on a single isolated test of kidney function.

An algorithm for the detection, monitoring and referral of patients with CKD is provided in Figure 1. 

References

1. National Kidney Foundation: K/DOQI Clinical Practice Guidelines for Chronic Kidney Disease: Evaluation, Classification and Stratification. *Am J Kidney Dis* 2002; 39(2 Suppl 1):S1-266.
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