Keeping a Watchful Eye on Kidney Function

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Chronic kidney disease (CKD) is an emerging public health problem worldwide. Kidney failure requiring dialysis or transplantation is the most visible outcome of CKD, affecting a little more than 20,000 Canadians.[1] Of patients who progress to kidney failure, 16% to 20% die within the first year of dialysis.

There is also a large segment of the population with less severe degrees of CKD. It is estimated that 600,000 to 1 million Canadians have Stage III CKD or worse.[2] Most of these patients will not progress to kidney failure. The majority will succumb to cardiovascular disease (CVD) long before dialysis is needed.

It is now recognized that patients with CKD are at significant risk for CVD. Management of these patients should not only target delaying progression of CKD, but also CVD risk reduction.

Annie's case

Annie, 52, is seen at the kidney disease clinic every three months. She first presented to her family physician three years ago with lower leg edema. Diabetes and nephrotic range proteinuria were diagnosed shortly thereafter. She was then referred to a nephrologist. At the time of referral, her serum creatinine was 120 µmol/L.

On her most recent visit to the clinic, she has no specific complaints. Her leg edema has improved. Her blood pressure is 146/68 mmHg. Annie is diagnosed with Stage IV chronic kidney diease (CKD)

- **Which tests would be helpful in monitoring Annie's kidney function?**
- **What measures can be implemented to reduce Annie's cardiovascular disease risk?**

For a followup on Annie, go to page 73.

Annie's lipid profile

- Total cholesterol: 6.2 mmol/L
- Triglycerides: 2.2 mmol/L
- HDL cholesterol: 1.0 mmol/L
- LDL cholesterol: 3.2 mmol/L

HDL: High-density lipoprotein
LDL: Low-density lipoprotein

Annie's medication profile

- Furosemide, 20 mg twice daily
- Losartan, 100 mg once daily
- Simvastatin, 20 mg at bedtime
- Glyburide, 10 mg twice daily
- Replavite®, one tablet daily

Annie's lab tests

- Serum creatinine: 175 µmol/L (estimated GFR: 28 mL/min/1.73m^2)
- Urine protein/creatinine ratio: 200 mg/mmol
- Serum potassium: 5.5 mmol/L
- HgA1C: 7.2%
- Serum calcium: 2.32 mmol/L
- Serum phosphorus: 1.6 mmol/L
- Parathyroid hormone: 55 ng/L
- Hemoglobin:106 g/L

GFR: Glomerular filtration rate

Table 1
Stages of chronic kidney disease

Stage	Description	GFR (mL/min/1.73 m^2)
1	Kidney damage with normal or elevated GFR	≥ 90
2	Kidney damage with mild decrease in GFR	60-89
3	Moderate decrease in GFR	30-59
4	Severe decrease in GFR	15-29
5	Kidney failure	< 15 or dialysis

GFR: Glomerular filtration rate

What is CKD?

CKD is defined as:

- *kidney damage for three months or more with structural or functional abnormalities, with or without decreased glomerular filtration rate (GFR); or*
- *GFR < 60mL/min/1.73 m^2 for three months or more, with or without kidney damage (Table 1).*[3]

For most individuals, CKD is silent, with no specific symptoms until the GFR is < 30 mL/min/1.73m^2. Individuals at an increased risk for CKD should be tested annually with a urinalysis (for red blood cells, white blood cells, and albuminuria), a serum creatinine level, and serum electrolytes.

Although serum creatinine is a convenient blood test frequently used to assess kidney function, serum creatinine does not equal kidney function. Instead, serum creatinine should be used to estimate creatinine clearance or GFR using either the Cockcroft-Gault formula or the Modification of Diet in Renal Disease (MDRD) equation (Table 2).

Twenty-four hour urine collections to measure creatinine clearance are no longer needed in most individuals.

For most people, CKD is silent, with no specific symptoms until the GFR is < 30 mL/min/1.73m^2.

What tests are helpful in monitoring patients with CKD?

Most patients with CKD will lose kidney function over time. The rate of progression is variable and dependent on non-modifiable (*i.e.*, etiology of CKD, African American race, male gender, and older age) and modifiable (*i.e.*, blood pressure, proteinuria, glycemic control, and smoking) risk factors.

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Serum creatinine

Once CKD is identified, serum creatinine should be used to estimate kidney function at least every six months. Patients with Stage IV or V CKD should be assessed at least every three months. For patients with established CKD, the average loss of kidney function is 4 mL/min/1.73m^2. A rate of loss > 4 mL/min/year should prompt a search for factors responsible for acute declines in GFR (Table 3).

Serum creatinine and electrolytes should also be measured within two weeks of the institution of an angiotensin-converting enzyme (ACE) inhibitor or an angiotensin receptor blocker (ARB). An increase in the serum creatinine of > 30% from baseline should prompt cessation of the ACE inhibitor or ARB, at least temporarily.

Albuminuria

Because sustained albuminuria is a risk factor for CKD progression and incident CVD, quantification of albuminuria should be performed at least annually in patients with known CKD.

Normal individuals excrete < 30 mg of albumin in 24 hours. Urine dipstick is a reasonable start to semi-quantify albuminuria, but its usefulness is limited by urine concentration. For patients with CKD, an untimed spot urine albumin to creatinine ratio provides a quantitative measure of albuminuria comparable to a 24-hour urine collection. First morning samples are preferred, but random samples are acceptable.

Lipids

Given the high cardiovascular risk associated with CKD, fasting lipids should be routinely measured. For patients receiving statin therapy, apolipoprotein B may also be followed to determine adequacy of treatment.[4] Routine measurement of lipopro-

Table 2

Equations commonly used to predict GFR or creatinine clearance in adults based on serum creatinine

Cockroft-Gault equation

Men

$$\text{Ccr (mL/minute)} = \frac{(140 - \text{age in years}) \times \text{weight (kg)}}{\text{serum creatinine (umol/L)} \times 0.81}$$

Women

As above, but multiply total value by 0.85.

MDRD study equation

GFR (mL/min/1.73m^2) = 186 (Scr 0.0113)$^{-1.154}$ (age in years)$^{-0.203}$ (0.742 if female) (1.21 if African American)

Available online at *www.kdoqi.org*; follow the link to the GFR calculator

MDRD: Modification of Diet in Renal Disease

Table 3

Frequent causes of an acute decline in GFR

- Volume depletion
- Intravenous or intraarterial radiocontrast
- Selected antimicrobials (aminoglycosides, amphotericin B)
- Non-steroidal anti-inflammatory agents, including COX-2 inhibitors
- ACE inhibitors and ARBs (particularly in volume-deplete individuals)
- Obstruction of the urinary tract

GFR: Glomerular filtration rate
COX: Cyclooxygenase
ACE: Angiotensin-converting enzyme
ARB: Angiotensin receptor blocker

Table 4

Management of complications associated with CKD

CVD risk reduction

- Target blood pressure < 130/80 mmHg
- Block RAAS using ACE inhibitors or ARBs
- Target LDL-C < 2.5 mmol/L
- Target total cholesterol: HDL-C < 4.0
- Target apolipoprotein B < 0.9 g/L
- Smoking cessation
- ASA (unless contraindicated)
- Target HbA1C < 7.0%
- Lifestyle modification with diet and exercise

Anemia management

- Target hemoglobin 110-120 g/L (normalize iron stores; use erythropoietin if necessary)

Disorders of calcium and phosphate metabolism

- Target serum phosphate < 1.8 mmol/L (using diet and/or oral phosphate binders)
- Target PTH < 70 pg/ml (Stage III CKD); < 110 pg/ml (Stage IV CKD) and 150–300 pg/ml (Stage V CKD)

Metabolic acidosis

- Target serum bicarbonate > 21 mmol/L (using oral bicarbonate therapy judiciously as the sodium load can increase extracellular volume and blood pressure)

CKD: Chronic kidney disease
CVD: Cardiovascular disease
RAAS: Renin-angiotensin-aldosterone system
ACE: Angiotensin-converting enzyme
ARB: Angiotensin receptor blocker
LDL-C: Low-density lipoprotein cholesterol
HDL-C: High-density lipoprotein cholesterol
ASA: Acetylsalicylic acid
Hb: Hemoglobin
PTH: Parathyroid hormone

tein(a), homocysteine, and high-sensitivity C-reactive protein is not recommended at this time.

A followup on Annie

Amlodipine is added to Annie's medication regimen to help reduce her blood pressure. Acetylsalicylic acid is also started as a preventative measure against cardiovascular disease. Simvastatin is increased to help Annie reach target lipid goals, as set by the Canadian Dyslipidemia Guidelines for patients with CKD.

Metabolic derangements

CKD also leads to multiple metabolic derangements, including anemia, disorders of calcium and phosphorus metabolism, and metabolic acidosis.

Anemia

CKD-associated anemia is generally normocytic and normochromic. Hemoglobin levels may begin to fall early in Stage III CKD, although anemia secondary to CKD itself is infrequent with a GFR > 30 mL/min/1.73m^2. In all patients with CKD and coexistent anemia, other non-CKD causes of anemia should be considered.

Serum calcium, serum phosphorus, and PTH

Nephron death also leads to impaired urinary phosphate excretion and 1,25-dihydroxycholecalciferol deficiency, resulting in hyperphosphatemia, hypocalcemia, and secondary hyperparathyroidism. Clinical manifestations of disordered calcium and phosphate metabolism (including cardiac and vascular calcification) become prominent in Stage IV and V CKD. It is recommended that serum calcium, serum phosphorus, and parathyroid hormone (PTH) be measured annually in patients with Stage III CKD, and every three months for patients with Stage IV CKD.

Metabolic acidosis also becomes more frequent in Stage IV and V CKD. Sustained metabolic aci-

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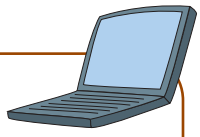

National Kidney Foundation's Kidney Disease Outcomes Quality Initiative:
www.kdoqi.org

dosis is associated with increased muscle catabolism and bone disease.

Table 4 provides guidelines for the management of CKD complications.

When should patients be referred to a nephrologist?

It is generally accepted that patients with Stage IV or V CKD should undergo nephrology evaluation, largely to help manage the comorbidities associated with CKD and to discuss/prepare the patient for kidney replacement therapy.

Given the risk for progressive kidney disease, patients with urinary albumin losses > 1,000 mg per day should also be referred. Likewise, patients with less severe degrees of CKD (Stage I to III) with unanticipated progressive loss of kidney function (> 4 mL/min/year) should be considered for referral. Other potential reasons for referral include:

- *to assist in the management and treatment of patients with albuminuria and coexistent hematuria (suggestive of a glomerulonephritis);*
- *to assist in the identification of patients with CKD who require disease-specific therapy, such as those patients with systemic lupus, polycystic kidney disease, or multiple myeloma;*
- *to help with the management of CKD complications that become difficult to control in a primary care setting (uncontrolled hypertension, hyperkalemia, anemia,* etc.). Dx

Take-home message

What is the goal?

- Management of CKD patients should target delayed progression of CKD, as well as CVD risk reduction.

How is CKD monitored?

- Once CKD is identified, serum creatinine should be used to estimate kidney function at least every six months.
- Quantification of albuminuria should be performed annually, at the very least.
- Lipids should be routinely measured.
- Serum calcium, serum phosphorus, and PTH should be measured every three months in Stage IV CKD or annually in Stage III.

When should patients be referred?

- Patients with Stage IV or V CKD should undergo nephrology evaluation.

References
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