



# The F.P.'s Role in the Management of Chronic Kidney Disease



By David N. Churchill, MD, FRCPC, FACP

Presented at McMaster University CME Half-Day in Nephrology for Family Physicians, Hamilton, Ontario, November 2000.

Chronic kidney disease (CKD) requiring dialysis or transplantation has increased dramatically over the past 20 years. In Canada, the growth rate has been about 7% per year. As of Dec. 31, 1999, there were 8,323 patients with a functioning kidney transplant and 13,512 receiving dialysis therapy.<sup>1</sup> Although these numbers are rising, they represent a very small proportion of the total Canadian population. This, however, is analogous to the “tip of the iceberg” identifying a much greater public health problem.

The magnitude of the problem has recently become more apparent and has led the National Kidney Foundation in the U.S. to support the development of clinical practice guidelines for CKD.<sup>2</sup> These guidelines replaced the term renal insufficiency with CKD.

## Stages

CKD has been divided into five stages, based on the severity of the kidney failure (Table 1). All estimates of the glomerular filtration rate (GFR) are expressed per 1.73 m<sup>2</sup> body surface area. Stage 1 represents normal kidney function with evidence of kidney damage (*i.e.*, proteinuria or hematuria). Stages 2, 3 and 4 represent mild, moderate and severe kidney failure, with the GFR values being 60 to 89 mL/min, 30 to 59 mL/min and 15 to 29 mL/min, respectively. Stage 5 is defined by a GFR of less than 15 mL/min or by the need for dialysis. The interventions required and the responsibility

Dr. Churchill is professor of medicine, McMaster University, and staff member, division of nephrology, St. Joseph's Hospital, Hamilton, Ontario. His areas of medical interest include clinical practice guidelines and management of chronic kidney failure.

## Chronic Kidney Disease

of the family physician and nephrologist can be defined within each of these stages.

The magnitude of the problem in the U.S. has been estimated from national surveys involving people 20 years or older.<sup>2</sup> There are 300,000 patients with Stage 5 chronic kidney failure in the U.S. This represents about 0.1% of the country's total adult population. There are 7.6 million people, or 4.3% of the population, with Stage 3 (moderate chronic kidney failure) and 55.3 million people, or 31.2% of the total population, with Stage 2 (mild chronic kidney failure). Although the prevalence of chronic kidney failure is higher in the U.S., these data suggest there may be a major health-care problem in Canada also.

## Diagnosis

Overt symptoms of kidney failure often do not become apparent until Stage 4 disease. Diagnosis requires laboratory evaluation of those at risk for chronic kidney failure. The leading cause for Stage 5 chronic kidney failure in Canada is diabetes mellitus, mostly Type 2. In 1999, diabetes was responsible for 32% of new dialysis patients.<sup>1</sup>

First Nations people have a particularly high incidence of diabetes and chronic kidney failure. Patients with hypertension and cardiovascular disease are at much greater risk. Increased age is associated with decreased GFR. In the U.S., 74% of those over the age of 70 have at least Stage 2 chronic kidney failure.<sup>2</sup> Those with a family history of renal disease are at increased risk. The

### Summary

#### The Family Physician's Role in the Management of Chronic Kidney Disease

- Chronic kidney disease (CKD) requiring dialysis or transplantation has increased dramatically over the past 20 years.
- CKD has been divided into five stages, based on the severity of the kidney failure.
- Overt symptoms of kidney failure often do not become apparent until Stage 4 disease. Diagnosis requires laboratory evaluation of those at risk for chronic kidney failure.
- The groups at highest risk of CKD are those with diabetes, cardiovascular disease, hypertension, a family history of renal disease and the elderly.
- At Stage 1, the glomerular filtration rate (GFR) is higher than 90 ml/min and there is evidence for kidney damage manifested as proteinuria and/or hematuria.
- At Stage 2 (GFR 60 mL/min to 89 mL/min), observation and monitoring of GFR on a six- to 12-month basis is sufficient. If the rate of loss of kidney function exceeds 6 mL/min per year, referral to a nephrologist should be considered.
- At Stage 3 (GFR 30 mL/min to 59 mL/min), the level of kidney failure that the clinical and/or biochemical consequences of kidney failure become apparent.
- Stage 4 patients have a GFR between 15 mL/min and 29 mL/min. At this time, a referral to a nephrologist is indicated for most patients.
- Stage 5 patients have a GFR lower than 15 mL/min or are on dialysis. Most of the management is executed by the hospital-based health-care team responsible for the dialysis and the transplant programs.

Table 1

## Stages of CKD

| Stage | Description               | GFR (ml/min/1.73m <sup>2</sup> ) |
|-------|---------------------------|----------------------------------|
| 1     | Kidney damage with normal | > 90<br>or increased GFR         |
| 2     | Mild decrease GFR         | 60 to 89*                        |
| 3     | Moderate decrease GFR     | 30 to 59                         |
| 4     | Severe decrease GFR       | 15 to 29                         |
| 5     | Kidney failure            | < 15 or dialysis                 |

\*May be normal for age

Adapted from: National Kidney Foundation — K/DOQI: Clinical practice guidelines for chronic kidney disease: Evaluation, classification and stratification. Am J Kidney Disease 2002; 39(Suppl. 1):S1-S266.

groups at highest risk of CKD, therefore, are those with diabetes, cardiovascular disease, hypertension, a family history of renal disease and the elderly (Table 2).

A serum creatinine value is required to calculate the GFR. The best estimate of GFR from serum creatinine is a formula that incorporates

age, sex and race.<sup>2</sup> Ideally, this should be reported by the laboratory, as calculation requires at least a handheld computer. An alternative is to estimate the creatinine clearance from the Cockcroft-Gault formula, which requires a simple calculation using serum creatinine, age, weight and a correction factor for females (Table 3).<sup>3</sup> Although this formula

# Chronic Kidney Disease

Table 2

## Groups At Higher Risk for CKD

- Diabetes mellitus
- Cardiovascular disease
- Hypertension
- Elderly (especially those older than 70 years)
- Family history of CKD

tends to overestimate the GFR, particularly for advanced kidney failure, it is a useful calculation for clinical practice. While there are many other formulae, none are accurate at extreme levels of age and body size or in the presence of skeletal muscle disease.<sup>2</sup> In these circumstances, a 24-hour urine collection is required.

Evaluation of kidney damage — particularly for those with a GFR higher than 90 mL/min — a urinalysis and a random urine microalbumin to creatinine ratio is required. For those with diabetes, a ratio greater than 2.8:1 mg/mmol for females and 2:1 mg/mmol for males represents significant proteinuria.<sup>4</sup>

These data permit the family physician to define the stage of CKD for an individual patient. Management will be addressed for each stage of CKD. The stage in which the family physician would be most active would be Stage 3 (moderate chronic kidney failure). The physician has a co-management role in Stages 4 and 5 (severe CKD and kidney failure).

## Management of Stage 1

At this stage, the GFR is higher than 90 mL/min and there is evidence of kidney damage manifested as proteinuria and/or hematuria. The most common causes for these findings would be diabetes mellitus and/or hypertension.

Table 3

## Formula for Calculation of Creatinine Clearance

### CCr (mL/sec)

$$\frac{(140 - \text{age})(\text{weight in kg})}{(50)(\text{Serum creatinine in } \mu\text{mol/L})}$$

†Multiply by 0.85 for women

††Conversion to ml/min: Multiply by 60

Adapted from: Cockcroft DW, Gault MH: Prediction of creatinine clearance from serum creatinine. *Nephron* 1976; 16:31-41.

The diagnosis should be made by the family physician and management would be the same as that described under Stage 3. If there is a family history of kidney disease or a clinical suspicion of obstructive uropathy, a renal ultrasound would be appropriate. If there is a clinical suspicion of multiple myeloma, a serum protein electrophoresis and urine for light chains should be requested. There are a variety of primary and secondary glomerular diseases that present with proteinuria and for which treatment might prevent progression of kidney disease.

Referral to a nephrologist is indicated if there are any symptoms suggestive of systemic disease, significant hypertension or proteinuria. The greater the proteinuria, the more likely the serious kidney disease. Most large studies show an association between greater proteinuria and more rapid loss of kidney function. There are no firm guidelines with respect to the level of proteinuria that would be an indication for referral. More than 1 g per day, however, would be a reasonable indication.

## Management of Stage 2

This group represents the largest of the five stages. Extrapolation of data from the U.S. suggests there

are about 6.6 million adults in Canada with this stage of the condition. Many of those in this group are elderly, with an age-related decline in kidney function. At this stage, observation and monitoring of GFR on a six- to 12-month basis is sufficient. If the rate of loss of kidney function exceeds 6 mL/min per year, referral to a nephrologist should be considered. Continued therapy for comorbid conditions is indicated and described under Stage 3.

### Management of Stage 3

Extrapolation of data from the U.S. predicts one million adult Canadians might have this degree of kidney disease (GFR 30 mL/min to 59 mL/min). It is at this level of kidney failure that the clinical and/or biochemical consequences of kidney failure become apparent. The clinical approach has been divided into strategies which address prevention of progression of CKD, prevention of complications of kidney failure and treatment of common comorbid conditions (Table 4).

Although these clinical approaches are described in detail with respect to Stage 3 CKD, the strategies can be applied at all stages. Those addressing the complications of chronic kidney failure become more important with progression to Stage 4 and Stage 5 disease.

**Preventing Progression.** For Type 1 diabetes mellitus, there is evidence that control of blood pressure (BP) with angiotensin-converting enzyme (ACE) inhibitors will delay the progression of disease, and that tight control of glycemia will prevent complications.<sup>5,6</sup> Although the evidence for efficacy in Type 2 diabetes has not been as convincing, these same strategies are recommended.

For Type 2 diabetes, there is evidence that ACE inhibitors and angiotensin II receptor blockers (ARBs) are effective in preventing progression of both early and established diabetic nephropathy.<sup>7,8</sup> The use of multiple interventions has been shown

effective in a trial in Denmark.<sup>9</sup> The interventions targeted blood glucose, hypertension, hyperlipidemia and behavioral modification (*i.e.*, weight loss, exercise and smoking). The target BP should

---

**In Stage 3 CKD, patients with nondiabetic proteinuric disease should be treated with either ACE inhibitors or ARBs in an effort to decrease proteinuria.**

---

# Chronic Kidney Disease

Table 4

## Management of Stage 3 CKD

### Prevent progression of CKD

### Prevent complications of CKD

- Anemia
- Bone disease
- Acid-base disorders
- Malnutrition

### Treat comorbid conditions

- Hypertension
- Cardiovascular disease
- Hyperlipidemia
- Smoking

be 130/80 mmHg or lower; the target glycosylated hemoglobin lower than 0.07% and the target serum low-density lipoprotein (LDL) cholesterol lower than 2.30 mmol/L.

The BP and LDL cholesterol targets also could be applied to those with hypertensive renal disease. Patients with nondiabetic proteinuric disease should be treated with either ACE inhibitors or ARBs in an effort to decrease proteinuria. The role of diet at Stage 3 CKD is controversial. A major randomized clinical study comparing the effect of low and very low protein diets on the progression of kidney failure yielded inconclusive results. A conservative approach is to prescribe a diet that avoids protein excess (0.8 g/kg to 1.0 g/kg body weight per day), with an emphasis on adequate caloric intake (35 kcal/kg/day). Referral to a dietitian would be appropriate.<sup>10</sup>

**Anemia.** As the GFR falls from 59 mL/min to 30 mL/min, the mean hemoglobin value falls from about 140 g/L to 110 g/L. The usual causes of ane-

mia must be excluded. These include iron deficiency anemia, vitamin B12 deficiency, folate deficiency or chronic inflammation. The kidney is the major source of erythropoietin and production is blunted with decreased GFR. Current guidelines recommend initiating therapy with erythropoietin when the hemoglobin level falls to 100 g/L, with a target of 110 g/L to 120 g/L. It is likely the initiation and target values will be increased, based on evidence of adverse cardiac outcomes associated with hemoglobin values between 120 g/L and 130 g/L. The decision to use erythropoietin is usually made by a nephrologist, who will monitor hemoglobin levels and adjust the dose. The drug is administered subcutaneously either by the patient, nurse or during visits to the family physician's office.

The drug currently used in Canada is epoetin alfa, administered once a week. A longer acting form of erythropoietin, called darbepoietin, has been approved for use in the U.S., Europe and Australia, and is under review in Canada. This drug can achieve similar results when administered once every two or four weeks. Some patients become iron deficient during treatment. Oral iron usually will provide adequate iron replacement. In rare instances, intravenous iron may have to be used, although enthusiasm has been muted by concerns about iron-mediated oxidative stress. The major complication of erythropoietin treatment is hypertension, which is partly related to the level of hemoglobin attained.

**Renal Osteodystrophy.** The abnormalities in calcium and phosphorus management begin at this stage. An inability to excrete the dietary phosphorus initiates a series of pathophysiologic processes, which lead to hyperphosphatemia, hypocalcemia and elevated parathyroid hormone (PTH) levels. During Stage 3, the increased secretion of PTH often is adequate to maintain the serum calcium and phosphorus values within normal limits.

## Chronic Kidney Disease

The serum PTH value should be measured, with acceptable values ranging from normal to 2.5 times the upper limit of normal. The PTH value reflects metabolic bone activity and, in this range, the patient is unlikely to have either low turnover (adynamic) or high turnover (hyperparathyroid) bone disease. Dietary phosphorus restriction should begin when there is evidence for increased PTH secretion. The prescribed dietary phosphorus intake should be about 900 mg/day and will require advice from a dietician.

If the serum phosphorus value increases to greater than the upper limit of normal, a phosphorus binder should be used. The current treatment is to use calcium, either as the carbonate or acetate. These should be taken with meals to bind the phosphorus. If iron is prescribed, it should be taken at times other than meals because the calcium salt will bind the iron. Aluminum is no longer used as chronic therapy for hyperphosphatemia. This drug has been associated with anemia, bone disease and dementia in dialysis patients.

There is a decrease in serum 1,25 dihydroxy vitamin D<sub>3</sub> levels in patients with Stage 3 CKD. This is the most active form of vitamin D and is produced by hydroxylation at the 1-alpha site by the kidney. If the patient has a normal serum phosphorus, it would be reasonable to initiate therapy with an active form of vitamin D.

The available drugs are 1,25 dihydroxy vitamin D<sub>3</sub> and 1-alpha hydroxy vitamin D<sub>3</sub>. The starting dose for each is 0.25 µg daily. If cost is an important consideration for the patient, one can use larger doses of vitamin D, but there is greater danger of toxicity from hypercalcemia. Vitamin D analogues that target

PTH secretion without inducing hypercalcemia are not yet available in Canada.

---

**The major comorbid conditions of Stage 3 CKD are hypertension, lipid disorders and cardiovascular disease. Failure to address these will place the patient at risk for cardiovascular disease.**

---

## Chronic Kidney Disease

Monitoring involves measurement of serum calcium and phosphorus every one to three months and serum PTH every three to six months. The objectives are to keep the serum calcium and phosphorus values within normal limits and to maintain the PTH value at 1.5 to 2.5 times the upper limit of normal.

**Acid-base Disorders.** The two major acid-base disorders are hyperkalemia and acidemia. The former is unusual if the GFR is greater than 20 mL/min. If present, consider other causes for the hyperkalemia. These include the administration of potassium-sparing diuretics, ACE inhibitors, ARBs and Type 4 renal tubular acidosis. Those with diabetes are more prone to Type 4 renal tubular acidosis.

The aim of treatment is to remove the cause and increase the urine flow rate by increasing sodium intake and prescribing a potassium-losing diuretic. Infrequently, one might have to use a mineralocorticoid, such as fludrocortisone acetate. Acidemia is associated with increased protein degradation rates. It has been recommended the serum bicarbonate level be maintained greater than 22 mmol/L, using oral sodium bicarbonate in doses tolerated by the patient.

**Comorbid Conditions.** The major comorbid conditions are hypertension, lipid disorders and cardiovascular disease. Failure to address these will place the patient at risk for cardiovascular disease.

The target BP should be 130/80 mmHg, with ACE inhibitors and ARBs used for those patients with proteinuric renal disease. The desired outcomes include decreased cardiovascular morbidity and mortality, as well as a decrease in the loss of GFR.

Treatment of hyperlipidemia with statins is well accepted for patients without CKD. All patients with CKD should have a fasting serum triglyceride, high-density lipoprotein (HDL) cholesterol and

LDL cholesterol determined every six months. Dietary advice can be provided, but often is ineffective in these patients. There are no large studies addressing the use of these drugs for patients with Stages 3, 4 and 5 CKD. These drugs can be used in these patients, but must be monitored for symptoms and signs of rhabdomyolysis and for evidence of liver damage. This is particularly important early in therapy.

Monthly serum creatine kinase and transaminase values for two to three months should be followed with testing every three to four months. Patients at increased risk include those who are prescribed high doses of statins, those with hypoalbuminemia and those with concurrent fibrates therapy. For patients with CKD, statins and fibrates should not be prescribed together. In addition to having a beneficial effect on cardiovascular risk factors, there is some evidence statin therapy may slow the rate of loss of GFR. The target LDL cholesterol should be lower than 2.3 mmol/L.

Patients with CKD often develop ischemic heart disease and peripheral vascular disease. Cardiovascular disease may progress more quickly in this group of patients. There is evidence that prescription of medical therapy may be less than optimal in this population.<sup>11</sup> The major targets are hypertension, hyperglycemia, hyperlipidemia and anemia. CKD patients with ischemic heart disease should be prescribed acetylsalicylic acid (ASA) and beta blockers, as clinically indicated. There also may be a tendency to be less aggressive with radiologic and surgical intervention for this group. There are concerns about the nephrotoxicity of angiographic dye, a high rate of re-stenosis following angioplasty and increased risk for further deterioration of kidney function in patients with an elevated serum creatinine who undergo coronary artery surgery.

CKD patients at increased risk for coronary artery disease (CAD) and who are potential



recipients of a kidney transplant are subjected to investigations designed to detect and correct significant CAD. Whether all CKD patients would benefit from such an approach is unknown.

### Management of Stage 4

These patients have a GFR between 15 mL/min and 29 mL/min. At this time, a referral to a nephrologist is indicated for most patients. There are few contraindications to dialysis and all patients should be aware of the treatment options. The clinical approach used will be similar to that used in Stage 3, but the patient also will be educated about the treatment options available. These include transplantation (preferably from a living donor), hemodialysis and peritoneal dialysis. Unless there is a medical indication for a particular dialysis modality, the choice is according to patient preference. Plans will be made to establish a vascular access for hemodialysis and placement of a peritoneal dialysis catheter for those who choose this option.

Management is a shared function between the family physician and the nephrologist and/or other members of the health-care team (*i.e.*, dietitians, pharmacists and social workers). Communication becomes even more important at this stage. The timing of initiation of dialysis is variable. If a patient exhibits clinical symptoms of kidney failure (*i.e.*, increased fatigue, cramps, increased sleep disturbance, muscle cramps, pruritis, weight loss), initiation of dialysis is recommended. Initiation based on laboratory values alone is a controversial issue. In current practice in the U.S., the mean GFR at initiation is about 8 mL/min.

### Management of Stage 5

These patients have a GFR lower than 15 mL/min or are on dialysis. Most of the management is executed by the hospital-based health-care team responsible for the dialysis and the transplant programs. The

degree to which co-management continues varies greatly among programs. Continued meaningful involvement of the family physician will only be possible through regular written communications. Although most family physicians will have few Stage 5 CKD patients, these patients require the continuity of care family physicians can provide. CME

#### References

1. Canadian Institute for Health Information: *2000 Report, Volume 1: Dialysis and Renal Transplantation, Canadian Organ Replacement Register*. Canadian Institute for Health Information, Ottawa, 2000.
2. National Kidney Foundation — K/DOQI: Clinical practice guidelines for chronic kidney disease: Evaluation, classification and stratification. *Am J Kidney Disease* 2002; 39(Suppl. 1):S1-S266.
3. Cockcroft DW, Gault MH: Prediction of creatinine clearance from serum creatinine. *Nephron* 1976; 16:31-41.
4. Meltzer S, Leiter L, Daneman D, et al: 1998 clinical practice guidelines for the management of diabetes in Canada. *Can Med Assoc J* 1998; 159(Suppl. 8):S1-29.
5. Lewis EJ, Hunsicker LG, Bain RP, et al: The effect of angiotensin converting enzyme on diabetic nephropathy. *N Engl J Med* 1993; 329:1456-62.
6. Diabetes Control and Complications (DCCT) Research Group. Effect of intensive therapy on the development and progression of diabetic nephropathy in the Diabetes Control and Complications Trial. *Kidney Int* 1995; 47:1703-20.
7. Heart Outcomes Prevention Evaluation (HOPE) Study Investigators: Effects of ramipril and cardiovascular and microvascular outcomes in people with diabetes mellitus. Results of the HOPE study and the MICRO-HOPE sub-study. *Lancet* 2000; 355:253-9.
8. Lewis EJ, Hunsicker LG, Clarke WR, et al: Renoprotective effect of the angiotensin-receptor antagonist irbesartan in patients with nephropathy due to type 2 diabetes. *N Engl J Med* 2001; 345:851-60.
9. Gaede P, Vedel P, Parving HH, et al: Intensified multifactorial intervention in patients with type 2 diabetes and microalbuminuria: The Steno type 2 randomized study. *Lancet* 1999; 353:617-22.
10. National Kidney Foundation — K/DOQI: Clinical practice guidelines for nutrition in chronic renal failure. *Am J Kidney Dis* 2000; 35(6, Suppl. 2):S1-140.
11. Tonelli M, Bohm C, Pandeya S, et al: Cardiac risk factors and the use of cardio-protective medications in patients with chronic renal insufficiency. *Am J Kidney Dis* 2001; 37:484-9.