The need to treat advanced renal disease is becoming more common and poses a significant burden on patients, families and the healthcare system. National registry data show the number of new dialysis patients in Canada increased by an average of 7% per year between 1981 and 1998. Over 12,000 Canadians were on dialysis by the end of 1998, and there may be as many as 20,000 such patients by 2005. The financial cost of caring for these patients is very high, with direct annual health-care costs ranging from about $32,570 for those on home hemodialysis, to $88,585 for those on hospital-based hemodialysis. Transplantation is a medically and economically superior treatment, but a shortage of organs and strict medical suitability criteria mean that many patients will be dependent on dialysis.

The vast majority of patients reach end-stage renal disease (ESRD) as a result of chronic progressive kidney diseases. National registry data suggest diabetic nephropathy, hypertension/vascular diseases and glomerulonephritis are the

Risk factors and treatment strategies for patients with kidney and cardiovascular disease overlap. Thus, evaluating renal function in patients with diabetes, hypertension and cardiovascular disease is essential.

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leading causes of ESRD in Canadians. It is possible to recognize these chronic renal diseases before they become advanced, and available therapies can significantly slow the progressive loss of renal function they may cause. However, early renal disease is generally asymptomatic and, therefore, recognition requires a pro-active approach.

Several things should happen once a patient is identified as having chronic renal disease. Where possible, the cause of the condition should be determined. Serial measurement of renal function is needed to determine how quickly the renal failure is progressing. The extent of co-morbidities, especially the commonly associated vascular diseases, must be assessed. Then, a comprehensive management plan is required to slow the decline in renal function, treat or prevent the complications of renal failure, and minimize the impact of co-morbid illness. Interventions to prevent progressive loss of renal function and cardiovascular complications fortunately overlap. Regular physician input is important for these interventions to be effective.

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Identifying Chronic Renal Disease

A population-based study from Framingham found the prevalence of elevated creatinine levels to be over 8%; prevalence in the elderly was up to 20%. Those with hypertension, diabetes or on treatment for cardiac disease were more likely to have renal impairment. Based on these types of data, it is recommended that serum creatinine should be periodically checked in all diabetics, hypertensive patients and in those with atherosclerotic vascular disease.1 Unexplained anemia, abnormal urinalysis or a family history of renal disease should also prompt a check of serum creatinine.1

Pathologic renal damage can precede renal function decline by quite some time. The best clinical markers of significant renal disease are abnormal protein excretion and a falling glomerular filtration rate (GFR), as reflected by increased serum creatinine.3

Microalbuminuria (urinary albumin excretion between 30 mg/day and 300 mg/day) is seen at an early stage of diabetic nephropathy. Current guidelines recommend screening all diabetics for microalbuminuria if they do not already have proteinuria on regular dipstick testing.2 This can be done by timed (e.g., 24-hour) urine collections or urine sampling for albumin-to-creatinine ratio.2 Microalbuminuria is not specific to diabetic renal disease. Proteinuria also is seen with glomerular and hypertensive/vascular renal disorders. Heavy proteinuria of over 3 g/day (nephrotic range) is mostly seen with glomerular diseases—either limited to the kidney or secondary to systemic disease, including diabetes. Microalbuminuria, or heavier proteinuria, is associated with a worse renal and cardiovascular prognosis. Proteinuria should be sought in populations at higher risk for renal disease, such as those with hypertension/vascular diseases, edema or a family history of renal disorders. Screening for proteinuria is not warranted in the general population.

As mentioned above, it also is worthwhile to check serum creatinine in people at risk for renal disease. This includes those found to have proteinuria. Serum creatinine is an indirect measure of renal function.3 It suffers from several limitations, including sizeable day-to-day variation within individuals. Measuring serum creatinine is easy and practical for frequent use, however, unlike some of the more direct methods of measuring GFR, which rely on clearance of isotopes or contrast materials.

Serum creatinine rises along an exponential curve as GFR falls linearly. This has two important clinical implications. First, patients with significant renal function loss may have a serum creatinine in the “normal” range, as quoted by the laboratory. This is particularly likely in elderly or non-muscular individuals. Secondly, the absolute serum creatinine change for a given change in GFR becomes greater as renal function declines. For example, a change from 100 mmol/L to 150 mmol/L in serum creatinine implies a similar decline in GFR, as a rise from 400 mmol/L to 600 mmol/L. The easiest way to avoid these interpretive limitations is to use a commonly available method of estimating GFR from serum creatinine, such as the Cockroft-Gault formula.

### Cockroft-Gault formula

- **Males:**
  \[
  \frac{140 - \text{age (years)} \times \text{body weight (kg)}}{\text{serum creatinine (µmol/L)} \times 0.8}
  \]

- **Females:**
  \[
  \frac{140 - \text{age (years)} \times \text{body weight (kg)}}{\text{serum creatinine (µmol/L)}}
  \]

Figure 1. Cockroft-Gault formula for estimation of creatinine clearance in mLs/min from serum creatinine.
problems is to estimate the creatinine clearance from the serum creatinine using a formula (Figure 1). The one devised by Cockroft and Gault in the 1970s has stood the test of time and offers simplicity at the expense of accuracy in comparison to some newer versions. Creatinine clearance is a reasonable approximation of GFR until renal function reaches low levels—creatinine clearance progressively overestimates renal function as it declines due to tubular secretion of creatinine. Similarly, urea clearance underestimates GFR because of its tubular re-absorption. The average of the 24-hour urea and creatinine clearances can be a useful approximation of GFR for those with advanced disease.

Once the presence of chronic renal disease has been recognized, a search for the cause should follow. This includes a careful history of the timing of renal function loss, a check of medications, a family history and a clinical screen for systemic diseases. A standard urinalysis and renal imaging by ultrasound would be indicated in most cases. Involvement of a nephrologist may be useful in clarifying the diagnosis in some cases.

**The Progressive Nature of Renal Failure**

Established renal disease may progress even if the original cause is removed. Renal hemodynamics, growth factor and cytokine release, protein traffic through glomeruli and tubules, inflammatory mediators and tubular hypoxia may all contribute to this progression.

The rate of loss of renal function varies, making individual prognostication challenging. About two-thirds of the normal elderly lose renal function at an average of about 1% per year. Patients with essential hypertension may lose renal function more quickly—sometimes as much as 4% per year. About 5% of hypertensives with elevated creatinine will progress to a stage that requires dialysis. The rate of loss of renal function among those treated for a variety of chronic renal diseases averages 4% per annum. However, poorly managed diabetic nephropathy and some glomerulonephritides may be associated with a 10% to 20% loss of renal function in a year. With these conditions, the rate of loss of renal function is strongly associated with the degree of proteinuria. Those with persistent proteinuria of more than 3 g/day may progress to ESRD within two years.

Along with the specific renal diagnosis, in patients with chronic renal disease, one of the most consistent and best predictors of the rate of loss of renal function is the degree and persistence of proteinuria. Several so-called “cardiac” risk factors are also associated with more rapid renal function loss. Higher blood pressure, especially systolic, is a potent risk factor for rapid renal function loss. Ethnicity (the rate is slower in Caucasians than Blacks) and other genetic factors may influence the rate and risk of progression. A progressive loss of renal function is recognized by serial assessment of GFR. To achieve this, serial measurement of serum creatinine is mandatory, bearing in mind the caveats about interpretation mentioned above.
Managing Chronic Renal Disease

Because of the frequent co-existence of cardiovascular disease with renal disease, the extent of vascular disease should be determined. Renal failure is associated with an increase in vascular events and death. Even creatinine values of 130 mmol/L to 150 mmol/L increase death rates by three-fold within eight years. Cardiovascular death is 25 times as common as renal death in Type 2 diabetics with microalbuminuria. Because of their overlapping risk factors and pathogenetic mechanisms, the same approaches can be useful in slowing the loss of renal function and preventing cardiovascular diseases and death.

Lowering blood pressure is the key to slowing many renal diseases. Angiotensin-converting enzyme (ACE) inhibition, dietary protein restriction, lipid management and avoidance of further renal insults (such as the use of nephrotoxins) also may be helpful. Tight glucose control in both Type 1 and 2 diabetes has been associated with the prevention and improvement of early-stage microvascular complications, including nephropathy.\(^\text{12,13}\) The impact seems to be sustainable over several years, however, glucose control has little impact on the progression of advanced diabetic nephropathy.

Lowering blood pressure reduces cardiovascular events and deaths, as well as slows the decline in renal function in diabetics.\(^\text{14-16}\) The optimal blood pressure target is still controversial. Diabetics randomized to a diastolic target of less than 80 mmHg in the Hypertension Optimal Treatment (HOT) study had fewer cardiovascular events and deaths.\(^\text{15}\) These results were mirrored by the Appropriate Blood Pressure Control n Diabetes (ABCD) trial, in which hypertensive Type 2 diabetics with a target diastolic pressure of less than 75 mmHg had fewer deaths than those targeted to between 80 mmHg to 89 mmHg diastolic.\(^\text{16}\) Both of these pressure levels, however, had the same impact on renal function.

As with diabetics, lowering blood pressure slows the loss of renal function in many other chronic renal diseases. The gain from lowering blood pressure is greater in those with heavier proteinuria.\(^\text{10,11}\) Some authorities recommend titrating anti-hypertensives to minimize proteinuria and not just blood pressure. This is consistent with what we know of the pathogenesis and role of proteinuria, but there is no direct evidence documenting the efficacy of this approach. Based largely on ACE inhibitors are widely thought to offer reno-protection beyond blood pressure lowering in both non-diabetics with chronic renal failure and diabetics.
the Modification of Diet in Renal Disease (MDRD) study,\textsuperscript{10,11} guidelines recommend target blood pressures of less than 125/75 for patients with chronic renal failure and proteinuria of more than 1 g/day.\textsuperscript{17} The safety of aiming for such pressures has been documented. It should be noted that it nearly always requires several anti-hypertensives in combination, including a diuretic, to achieve these targets.\textsuperscript{15}

ACE inhibitors are widely thought to offer renoprotection beyond blood pressure lowering in both non-diabetics with chronic renal failure\textsuperscript{18} and dia-
betics. In comparison with placebo, ACE inhibition also slowed the decline in GFR over six years in normotensive Type 2 diabetics without microalbuminuria. In such placebo trials, it is difficult to be sure that the benefit is not just due to blood pressure lowering. Nevertheless, follow-up of patients with proteinuria and chronic renal failure suggests long-term ACE inhibition, as part of the anti-hypertensive regimen, can be associated with the stabilization, and even improvement, of renal function. Given that combination therapy will be required to control blood pressure in most cases, the inclusion of an ACE inhibitor seems warranted, particularly given possible vasculoprotective effects.

The role of low-protein diets in slowing renal function loss has been controversial. There is a potential for malnutrition. Dietary instruction and maintaining compliance requires major effort. The negative results of a large trial, the MDRD study, dampened enthusiasm for this approach in many quarters. Nevertheless, recent meta-analyses suggest that lowering protein intake may provide a minor degree of benefit in slowing the decline in kidney function in both non-diabetics with chronic renal disease and Type 1 diabetics. However, the optimal dietary protein intake is not clear. For now, it is reasonable to aim for a protein intake of 0.6 g/kg of body weight/day to 0.8 g/kg of body weight/day. This intervention requires considerable input from a dietitian to be sustained, and mandates careful monitoring for protein malnutrition.

A variety of studies link lipid abnormalities with a more rapid loss of renal function. The specific lipid parameters associated with risk have not been consistent. Currently, there are no data to show that treating lipid abnormalities slows the decline in renal function. Nevertheless, an active control of lipids is advised, given the burden of vascular disease associated with renal failure and the clear cardiovascular benefits of lowering low-density lipoprotein (LDL) cholesterol and raising high-density lipoprotein (HDL) cholesterol in other populations at high risk.

It requires considerable effort to carry out all of the above interventions. In addition, there is a need to monitor the progress of the renal failure serially. Frequent patient reviews are important to achieving goals and reinforcing therapeutic advice. It is unlikely that any one professional will have the time or resources to carry out all the required work for any number of patients with chronic renal disease. With this in mind, there has been a trend in recent years to develop specialized, multidisciplinary clinics to work in concert with primary-care providers and other care providers. It remains to be seen whether such concerted efforts can have an impact on the burden of ESRD.

Conclusions

Risk factors and treatment strategies for patients with kidney and cardiovascular disease overlap. Thus, evaluating renal function in patients with diabetes, hypertension and cardiovascular disease is essential. This should be done with urinalysis and serum creatinine as an estimate of GFR. The overall goal is to slow the progression of kidney disease and, ultimately, to decrease the associated morbidity and mortality. Strict control of blood pressure, ACE inhibitor use, dietary protein restriction and lipid management all have defined roles in achieving these goals. This approach is summarized in Figure 2.
14. UK Prospective Diabetes Study (UKPDS) Group: Tight

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Prevacid is indicated for short-term treatment of reflux esophagitis and maintenance therapy of healed reflux esophagitis.

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* After the first day of therapy, significantly more patients (p<0.05) on Prevacid 30 mg (n = 402) compared to omeprazole 20 mg (n = 418) reported no daytime heartburn (48.7% vs. 37.6%) and nighttime heartburn (62% vs. 52%) in an 8-week randomized, double-blind study in patients with endoscopically diagnosed reflux esophagitis.

Consult Product Monograph for dosage recommendations.