Identifying and slowing progressive chronic renal failure

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ABSTRACT

OBJECTIVE To help inform primary care physicians about how to identify and slow progressive chronic renal failure.

QUALITY OF EVIDENCE The National Library of Medicine (1996 to 2000) was searched using PubMed with search terms pertinent to studies on identification, course, and management of chronic renal failure. References in retrieved papers and older literature known to the authors supplemented the searches. In general, sufficient high-quality studies, systematic reviews, or guidelines based on such evidence were available to support our main points.

MAIN MESSAGE End-stage renal disease (ESRD) poses a large and growing morbidity, mortality, and financial burden. Almost all patients reach ESRD as a result of chronic progressive conditions, particularly diabetic nephropathy, hypertensive-vascular renal disease, and glomerular disorders. Patients at risk merit regular renal assessment with serum creatinine tests and urinalysis. Persistent high blood pressure and heavy proteinuria are the strongest predictors of progression of chronic renal failure. Patients with renal disease should be examined and treated for vascular disease and vice versa. Blood pressure lowering, ACE inhibition, and avoidance of further renal insults (such as use of nephrotoxins) can slow the decline of renal function. Restricting dietary protein has a weak effect on slowing renal failure and is not easy to apply in primary care. Timely involvement of specialized nephrology teams is important.

CONCLUSION Family physicians play an important role in recognizing patients with potential for renal failure, in demonstrating progressive chronic renal failure, and in initiating therapy early to improve outcomes.

RÉSUMÉ

OBJECTIF Aider à informer les médecins de première ligne sur la façon d'identifier et de freiner l'insuffisance rénale progressive

QUALITÉ DES DONNÉES Une recension a été effectuée à la National Library of Medicine (1996 à 2000) par l'entremise de PubMed à l'aide de termes de recherche pertinents aux études sur l'identification, la progression et la prise en charge de l'insuffisance rénale chronique. Des références tirées des articles recensés ainsi que de moins récents ouvrages connus des auteurs ont complété l'information obtenue de la recension. En règle générale, des études de grande qualité, des analyses systématiques ou des lignes directrices fondées sur de telles données probantes ont été trouvées en nombre suffisant pour étayer nos points principaux.

PRINCIPAL MESSAGE L'insuffisance rénale terminale se traduit par une morbidité, une mortalité et un fardeau financier importants et grandissants. Presque tous les patients atteignent ce stade de la maladie à la suite d'un état pathologique chronique progressif, en particulier la néphropathie diabétique, la néphropathie vasculaire hypertensive et les troubles glomérulaires. Les patients à risque devraient subir une évaluation rénale régulière comportant des épreuves de la créatinine sérique et des analyses d'urine. Une hypertension persistante et une forte protéinurie sont les prédicteurs les plus probants de la progression de l'insuffisance rénale chronique. Les patients souffrant de néphropathies devraient être examinés et traités pour des affections vasculaires et vice versa. La réduction de l'hypertension, l'inhibition de l'enzyme de conversion de l'angiotensine et l'évitement d'autres attaques rénales (comme l'utilisation de néphrotoxines) peuvent freiner le déclin de la fonction rénale. Le fait de restreindre les protéines alimentaires a peu d'effet sur le ralentissement de l'insuffisance rénale et est difficile à mettre en pratique dans les soins de première ligne. Il est important de faire participer en temps opportun des équipes spécialisées en néphrologie.

CONCLUSION Les médecins de famille jouent un rôle important dans l'identification des patients susceptibles de souffrir d'insuffisance rénale, dans la démonstration de la progression de l'insuffisance rénale chronique et dans l'instauration rapide d'une thérapie pour améliorer les résultats.

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End-stage renal disease (ESRD) markedly increases morbidity and mortality.[1,2] The incidence of ESRD grew in Canada by 7% annually from 1981; more than 12 000 persons were receiving dialysis by the end of 1998.[2] The direct cost of caring for a patient using dialysis ranges from $32 570 to $88 585 annually.[3] Transplantation is a medically and economically superior treatment,[1] but the lack of available organs and medical contraindications make dialysis the only option for many people.

Most patients reach ESRD as a result of chronic progressive kidney disease. National registry data indicate diabetic nephropathy (30%), hypertension or vascular diseases (20%), and glomerulonephritis (16%) as the leading causes of ESRD in Canadians.[2] Obesity, poor diet, and sedentary lifestyle contribute to diabetes, hypertension, and vascular disease. Primary prevention strategies have the potential to address these issues and should be pursued with vigour. Nevertheless, secondary prevention by early identification of nephropathy also has an important place. Because early renal disease is generally asymptomatic, recognition requires a proactive approach.

Once recognized, patients with chronic renal disease need assessment to determine the cause, whether renal failure is progressing, and the extent of comorbidity, especially the commonly associated vascular diseases.[4] Similar interventions can slow loss of renal function and prevent cardiovascular complications. Regular physician input is important for these interventions to be effective, providing a clear role for family physicians. This review has two objectives. The first is to discuss the course of and methods to detect progressive chronic renal failure. The second is to indicate which interventions can improve outcomes for such patients.

Quality of evidence

The National Library of Medicine (1996 to 2000) was searched using PubMed for studies on the identification, course, and management of chronic renal failure. References in retrieved papers and older literature known to the authors supplemented the searches. A population-based study identifies the prevalence and correlates of chronic renal failure. The major causes of ESRD have been documented somewhat imprecisely in a Canadian national registry. Many good-quality studies have examined the role of urinalysis and serum creatinine assessment in renal failure. Data from cohort studies and randomized trials identify hypertension and persistent proteinuria as strong predictors of faster loss of renal function.

Smoking and lipid abnormalities are other such risk factors, but no trials document the renal benefits of treating them. Smoking cessation and lipid management in chronic renal failure are recommended based on trials showing cardiovascular risk reduction in high-risk populations. Several randomized trials address blood pressure targets for patients with diabetes or chronic renal failure. Randomized trials also support use of angiotensin-converting enzyme (ACE) inhibitors to slow progression of chronic renal failure. Meta-analyses based on randomized trials suggest that restricting dietary protein has limited efficacy in slowing progression of chronic renal failure.

Main message

A Framingham study found elevated serum creatinine levels in more than 8% of the general population, rising to 20% in the elderly.[5] Hypertension, diabetes, and cardiac disease were associated with renal impairment.[5]

Clinical markers of serious renal disease include abnormal urinary protein levels and falling glomerular filtration rates (GFR), as reflected by increased serum creatinine. Microalbuminuria (urinary albumin excretion between 30 and 300 mg/d) is seen early in diabetic nephropathy.[6] Current guidelines recommend screening diabetics for microalbuminuria if regular dipstick testing shows no proteinuria.[7,8] Random daytime urine assay for albumin-to-creatinine ratio (normal < 2 mg/mmol for male patients and < 2.8 mg/mmol for female patients) can be followed by timed (eg, 24-hour) urine collections for confirmation if abnormal.[7]

Microalbuminuria is associated with worse prognoses in general hypertensive populations,[8,9] but data are insufficient to justify widespread screening. Data are also insufficient to justify screening the general population for proteinuria using regular dipsticks.[10] Serum creatinine levels should be periodically checked in all diabetics and in those with hypertension or vascular disease.[11,12] Unexplained anemia, abnormal urinalysis, or a family history of renal disease should also prompt a check of serum creatinine.[11]

Figure 1 outlines steps in recognition of progressive chronic renal failure. In all cases, a causal diagnosis should be sought. Workup includes a review of family history and medications, consideration of urinary obstruction, and a search for systemic disease

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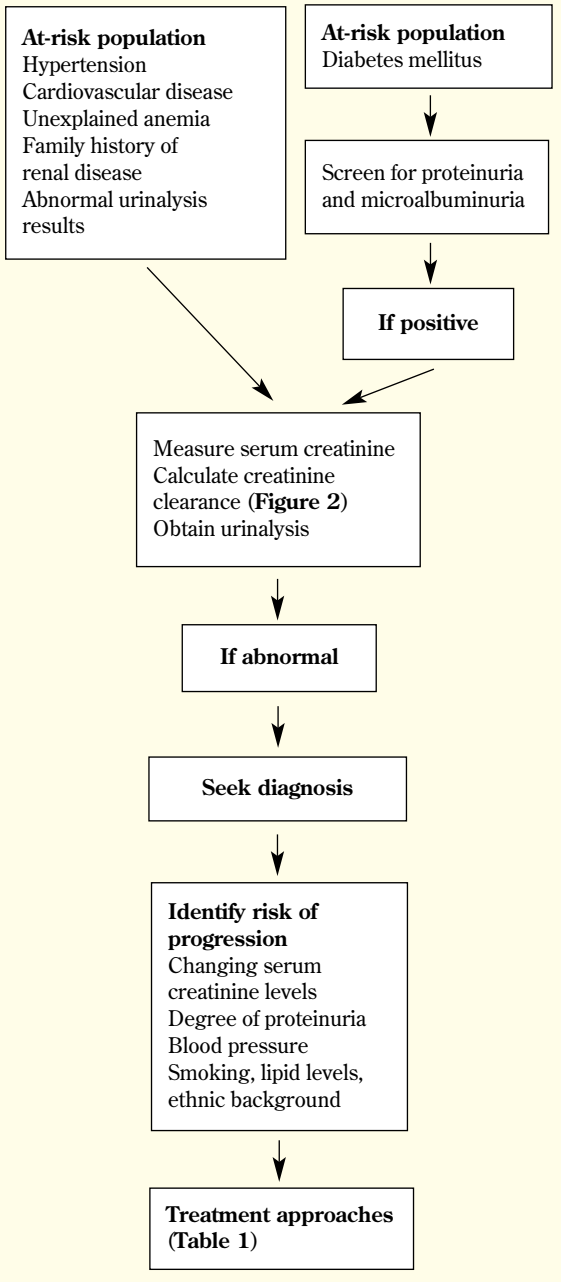
(including diabetes, vascular disease, connective tissue disorders, infections, and malignancy). Several contributory factors can coexist. Renal imaging or nephrology referral might be helpful.[11] Treatment of specific renal diseases is outside the scope of this review.

Figure 1. Identification of progressive kidney failure



Clinical course. The clinical course of chronic renal failure varies and depends partly on the cause and degree of renal impairment.[13-20] Established renal disease sometimes progresses even if the original cause is removed.[21] Renal hemodynamics, growth factor and cytokine release, protein traffic through glomeruli and tubules, inflammatory mediators, and tubular hypoxia can all have a role in this progression.[22,23]

Few data describe the natural history of renal function in unselected populations. A population-based cohort study found two thirds of normal elderly people to have a decline in GFR averaging 0.75 mL/min yearly.[24] One third of hypertensive men lose renal function over 7 years.[25] Combined data from population surveys, clinical trials, and the United States renal failure register suggest that 5% of hypertensive patients with elevated creatinine levels will require dialysis.[26] Of a large group with chronic renal failure of various causes in a clinical trial, 85% suffered progressive loss of GFR at an average of 4 mL/min yearly.[27] Finally, overt diabetic nephropathy can progress at 10 to 12 mL/min yearly when hypertension is untreated.[28]

Factors associated with more rapid loss of renal function have been identified in prospective cohort studies and clinical trials. For patients with chronic renal failure from diabetic, glomerular, and hypertensive and vascular diseases, the strongest predictors of more rapid loss of renal function are the degree and persistence of proteinuria[14,15,27,29] and higher blood pressure, especially systolic.[30-38] Patients with chronic renal failure and persistent proteinuria of more than 3 g/d could reach ESRD within 2 years.[13,30,39] The degree of proteinuria is usually documented by serial 24-hour urine collections, but the ratio of protein to creatinine in morning urine can be used as a surrogate.[40] Smoking,[41,42] lipid abnormalities,[43,44] and ethnic background (eg, faster progression in blacks) have also been associated with greater loss of renal function.

Tracking progression. Because direct measurement of GFR by radioisotope clearance is costly and impractical for clinical practice,[14] the simplest way to identify progressive chronic renal failure is by serial measurement of serum creatinine over time. Marked day-to-day variation in serum creatinine levels complicates identification of trends.[14,45] It is important to note that serum creatinine can remain within the normal range even when renal function is seriously impaired.[45,46] For this reason, calculated or measured creatinine clearance should always be used to assess renal function. Accurate 24-hour urine collection can be difficult,

but it is possible to predict creatinine clearance or GFR from serum creatinine and demographic, anthropometric, and other data.[47,48] The Cockroft-Gault formula (**Figure 2**) gives a reasonable estimate when the GFR is not very low.[47] Although more recent formulae are more accurate, they are more complex and difficult to use in practice.[48]

Figure 2. Cockroft-Gault formula for estimating creatinine clearance (in mL/min) from serum creatinine

For male patients:

$$\frac{[140 - \text{Age (years)}] * \text{Body weight (kg)}}{\text{Serum creatinine (mmol/L)} * 0.8}$$

For female patients:

$$\frac{[140 - \text{Age (years)}] * \text{Body weight (kg)} * 0.85}{\text{Serum creatinine (mmol/L)} * 0.8}$$

Note also that creatinine clearance progressively overestimates renal function as it declines due to tubular secretion of creatinine.[45] Because urea clearance underestimates GFR as a result of tubular reabsorption, the average of urea and creatinine clearances can be a better estimate of renal function when GFR is low.

Progressive renal failure implies a worse prognosis for vascular events and death.[49,50] Creatinine values as low as 130 to 150 mmol/L confer a threefold risk of death within 8 years.[49] Cardiovascular death is 25 times as common as renal death in type 2 diabetics with microalbuminuria.[51] Patients with renal failure, therefore, require assessment and therapy for vascular disease and associated risk factors. In fact many risk factors for cardiovascular disease are also associated with progression of chronic renal failure.[4]

Possible treatments. Similar approaches are useful in slowing loss of renal function and preventing cardiovascular disease and death (**Table 1**). Lowering blood pressure and ACE inhibition have the most evidence showing they slow the progression of chronic renal failure. Avoidance of further renal insults (such as nephrotoxins) is recommended for patients with chronic renal failure, as they can also speed progression. Smoking cessation is recommended for many reasons, including the possibility that quitting can slow loss of renal function.[41,42] No trials show that treating dyslipidemia is renoprotective.

Table 1. Recommended interventions for patients with progressive chronic renal failure

INTERVENTION	EXPECTED BENEFITS	EVIDENCE AND RATIONALE
Lower blood pressure		
• Diabetic patients, target <130/80 mm Hg	Prolonged life, fewer vascular events, slower renal progression	Randomized trials
• Nondiabetics with proteinuria >1 g/L, target <127/75 mm Hg	Slower renal progression	Randomized trial
Consider ACE inhibition	Blood pressure reduction, slower renal progression, possible reduction of cardiovascular events, and prolonged life	Randomized trials
Seek and treat vascular disease and risk factors	Reduced cardiovascular events, prolonged life, and possibly slower renal progression	Renal and cardiovascular disease and risk factors associated. Randomized trials in other high-risk populations
Avoid further renal insults	Slower renal progression	Observational studies show renal decline with nephrotoxins, dehydration, etc
Consider nephrology referral (at least 1 y before ESRD)	Aid with diagnosis, care of renal failure and complications, preparation for ESRD care	Observational studies show greater morbidity and mortality in those referred late

Based on randomized trial evidence of cardiovascular protection, current guidelines recommend an aggressive approach to managing lipid abnormalities in diabetics and other high-risk patients, which would include those with chronic renal failure.[7,52] Tight glucose control in both type 1 and 2 diabetes can prevent or stabilize the early stages of microvascular complications, including nephropathy.[53,54] The effect seems to be sustainable for years.[55] However, diabetes control has not been shown to slow progression of advanced diabetic nephropathy.

The recommended target blood pressure is < 130/80 mm Hg for diabetics.[7,12] This target is supported by evidence from several randomized trials[56-58] of reduction in mortality, fewer cardiovascular events, and slower decline in renal function. The recommended target

blood pressure for nondiabetics with chronic renal failure and proteinuria higher than 1 g/d is lower than 125/75 mm Hg.[12] This is based on evidence of slower progression of renal failure at this blood pressure level in a large randomized trial.[35,36] In fact, the gain from lowering blood pressure is greatest in those with the most proteinuria.[35,36] Trial data show no evidence of adverse effects associated with these lower blood pressure targets.[57,59] Three or more antihypertensive agents in addition to lifestyle modification are often required to reach target blood pressure.[57] This is important because only 16% of hypertension in general is treated and controlled to less than 140/90 mm Hg.[60]

Angiotensin-converting enzyme inhibitors have an established role in management of hypertension and nephropathy in diabetics. Randomized trials in both type 1 and 2 diabetics suggest that ACE inhibitors are more renoprotective than other antihypertensives.[61,62] Prophylactic use can also be justified, as ACE inhibition preserved renal function over 6 years in normotensive type 2 diabetics without microalbuminuria.[63] In addition, ACE inhibitors in diabetics have compared favourably with other antihypertensives in terms of cardiovascular events.[64,65] Several randomized trials also suggest a role for ACE inhibitors in preserving renal function in nondiabetics with chronic renal failure associated with proteinuria.[66,67] As some of these trials were placebo-controlled, it is difficult to be sure that the benefit was drug specific and not just due to lowering blood pressure. Nevertheless, follow-up studies suggest that long-term ACE inhibition, as a component of blood pressure therapy, can be associated with stabilization and even improvement of renal function.[67] Given that many patients require combination therapy to control blood pressure, including an ACE inhibitor seems prudent, particularly given the possible vasculoprotective effects.[68]

Low-protein diets have been extensively studied as a means to slow the course of chronic renal failure in both diabetics and nondiabetics. Recent meta-analyses and a large randomized trial suggest that the effect is slight.[35,69-71] Optimal dietary protein intake is unclear,[69] and there is a potential for protein malnutrition. Ensuring adherence to the diets is difficult and requires continuing effort from dietitians. Such dietary therapy is probably not feasible for primary care.

Advanced renal failure requires complex care. Preparation for dialysis and transplantation takes time, and late referral to nephrology services has been associated with greater morbidity and mortality.[11] The variety of skills and resources required to provide this care has led to development of specialized multidisciplinary teams to work in concert with primary care providers. Canadian recommendations emphasize timely referral to maximize potential gains from involvement of specialized nephrology teams.[11] It remains to be seen whether such concerted efforts will affect the burden of ESRD.

Editor's key points

- End-stage renal disease (ESRD) is increasing markedly in Canada with attendant morbidity, mortality, and costs.
- Most ESRD results from diabetes, hypertension, and glomerulonephritis; patients with these conditions merit regular assessment of serum creatinine and urinalysis for protein.
- Slowing renal decline can be achieved by good diabetes and blood pressure control, angiotensin-converting enzyme inhibition, and avoidance of further renal insults (nephrotoxins, dehydration).
- Patients with deteriorating renal function despite good care or with more advanced renal failure benefit from timely referral to specialized nephrology teams..

Points de repère du rédacteur

- L'insuffisance rénale terminale s'accroît de façon marquée au Canada ainsi que sa morbidité, sa mortalité et ses coûts afférents.
- La plupart des cas d'insuffisance rénale terminale sont causés par le diabète, l'hypertension et la glomérulonéphrite; il importe d'évaluer régulièrement la créatine sérique et la protéinurie chez les patients souffrant de ces affections.
- Il est possible de freiner le déclin de la fonction rénale en maîtrisant bien le diabète et l'hypertension, en inhibant l'enzyme de conversion de l'angiotensine et en évitant d'autres attaques rénales (les néphrotoxines, la déshydratation).
- Les patients dont la fonction rénale se détériore malgré un traitement approprié ou ceux dont l'insuffisance rénale est à un stade plus avancé bénéficieraient d'un aiguillage opportun vers des équipes spécialisées en néphrologie.

Conclusion

Family physicians have a clear role in care of patients with renal failure. Risk factors and treatment strategies for patients with chronic renal failure and cardiovascular disease overlap. It is essential to evaluate renal function in patients with diabetes, hypertension, and cardiovascular disease. This should be done with urinalysis and serum creatinine testing. Higher blood pressure and persistent heavy proteinuria characterize

those most likely to have progressive renal failure. Strict control of blood pressure, use of ACE inhibitors, and attention to cardiovascular disease and risk factors offer the best chance of helping those with chronic renal failure.

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