Diabetic nephropathy
Prevention and early referral

G. Pylypchuk, MD, FRCPC  E. Beaubien, MD

OBJECTIVE To review the clinical and pathophysiologic features of diabetic nephropathy and to examine evidence supporting primary, secondary, and tertiary treatment strategies.

QUALITY OF EVIDENCE The medical literature provides both level 1 and level 2 evidence on treatment of diabetic nephropathy, including randomized controlled trials, well-designed clinical trials without randomization, consensus papers, and cohort and case-control analytic studies.

MAIN MESSAGE Diabetes is the most common cause of end-stage renal failure in Canada and the United States, and both diabetes and its renal complications are increasing. Diabetic nephropathy, in both type 1 and type 2 diabetes, usually progresses through five stages. Treatment and prevention strategies depend on stage of disease. Primary prevention includes addressing hyperglycemia, hypertension, and smoking. Secondary prevention adds angiotensin-converting enzyme inhibitors, cholesterol lowering, and perhaps restrictions on dietary protein. Tertiary care, including dialysis or transplantation, is generally managed by nephrologists, but family physicians continue to play an important role in the care of these patients.

CONCLUSIONS Diabetic nephropathy is a serious cause of morbidity and mortality for patients with type 1 and type 2 diabetes. To reduce end-stage diabetic nephropathy and its complications, both specialists and family physicians need to focus efforts on primary and secondary prevention strategies.

This article has been peer reviewed.

Cet article a fait l'objet d'une évaluation externe.

he annual cost of end-stage renal failure (ESRF) in the United States is estimated at $13 billion US. A recent article by Schaubel et al showed a marked increase in ESRF in Canada from 1981 to 1996 and predicted that by the year 2005, approximately 33,000 patients would require therapy for ESRF. Diabetes is the most common cause of ESRF in Canada and the United States, and the incidence of both diabetes and its renal complications are increasing. Costs will no doubt continue to increase as long as diabetes remains unchecked and we continue to focus on dialysis and transplantation in treating diabetic nephropathy.

In Canada, and especially in western provinces, populations such as First Nations peoples are developing diabetes and diabetic complications in epidemic proportions. Projection studies estimate that the number of patients with diabetes worldwide is expected to reach 221 million by the year 2010; 97% of them will have type 2 diabetes. It is, therefore, necessary that we take a more preventive approach in treating this disorder. If not, we will see the continued need to increase dialysis and transplant programs with their attendant financial implications. Family physicians must play a leading role in this area, especially in prevention. This paper discusses the pathophysiology and clinical features of diabetic nephropathy, which we hope will aid in understanding the methods of treating this disorder.

**Quality of evidence**

References for this article were obtained from MEDLINE (1966 to 1999) using the search terms diabetes, diabetic nephropathy, renal failure, dialysis, microalbuminuria, diabetic renal disease, and review articles. Articles were selected preferentially if they were randomized controlled trials, consensus papers, or practice guidelines. Articles also included case-control analytic studies, well designed cohort studies, and comprehensive reviews.

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* First Nations is used to refer to the earliest inhabitants of Canada and their descendants.

**Pathophysiology**

Approximately 40% of type 1 and 10% of type 2 diabetic patients develop renal failure; however, type 2 diabetes accounts for more than 90% of ESRF patients because of its markedly increased prevalence in the North American population. Both types progress to ESRF in a similar fashion, with only a few minor differences. Type 2 patients with nephropathy are older, and hypertension usually precedes development of renal insufficiency. Renal morphology of diabetes (ie, diffuse or nodular sclerosis) is seen in both type 1 and type 2 diabetes, but is more variable in type 2. About 16% of type 2 patients have associated glomerulonephritis.

Renal hemodynamics play an important role in development of renal failure. In the early stages of diabetic renal disease, hyperfiltration and glomerular hypertension initiate a vicious circle of glomerular hypertrophy, sclerosis, and finally nephron loss. Poor glucose control and elevated blood pressure accelerate this process.

**Clinical stages**

Some diabetic patients do not develop diabetic nephropathy, and the exact explanation for this is unclear, although genetics, sex, and coexisting hypertension are important. In type 1 patients who develop diabetic nephropathy, the disease progresses through five distinct stages. Type 2 diabetes follows a similar pattern, but the timing of the stages is more variable because of patients’ age and presence of pre-existing hypertension.

**Stage I.** Stage I, or the hyperfiltration stage, is seen at first diagnosis in approximately 40% of diabetics. Hyperglycemia leads to increased glomerular filtration rate (>135 mL/min for every 1.73 m²) and glomerular hypertrophy.

**Stage II.** Stage II, or the microalbuminuric stage, occurs approximately 5 years after diagnosis in type 1 patients, but can occur much earlier in type 2 patients. Those who are going to develop nephropathy begin now to show signs of glomerular hypertension and stress by spilling small amounts of albumin, termed microalbuminuria. This is defined as urinary excretion of between 30 mg and 300 mg of albumin per day (current routine dipstick methods detect albumin only when it exceeds 300 mg). Microalbuminuria is seen not only in diabetic patients but also in elderly and hypertensive patients where it is a strong predictor of cardiovascular mortality.
The importance of microalbuminuria as an “early marker” of renal disease cannot be understated, as it represents a time when renal biopsy shows no changes or minimal changes due to glomerular hypertrophy and mesangial expansion. Although long-term studies are not yet available, common sense suggests that the earlier diabetic nephropathy is treated, especially if there is no morphologic damage, the more likely we are to either attenuate or “cure” the condition. At present, we know that good blood sugar and blood pressure control, along with angiotensin-converting enzyme (ACE) inhibitors, reduce microalbuminuria and retard early progression of renal disease.

Stage III. Intermittent spikes of microalbuminuria continue throughout stage II, and if unchecked, lead to overt proteinuria, or stage III disease, approximately 10 years after diagnosis of type 1 diabetes. Type 2 diabetes might follow a more variable time course, but results are similar. During stage III, 24-hour protein excretion exceeds 300mg and might proceed into the nephrotic range. Renal biopsy at this time shows severe damage, diabetic nephrosclerosis, heralding a progressive decline in renal function and subsequent renal insufficiency.

Stages IV and V. Renal insufficiency (elevated serum creatinine levels) indicates stage IV disease. In type 1 diabetes, hypertension develops in stage III or IV disease and increases the rate of progression to ESRF. Patients with type 2 diabetes usually have pre-existing hypertension. The fall in creatinine clearance is progressive and predictable, ranging from 0.1 to 2.4mL/min per month. Patients soon develop ESRF (stage V diabetic nephropathy) and require dialysis or transplantation.

Progression through the above stages is consistent in type 1 diabetes, with minor differences in timing depending on blood pressure, glucose control, and other concomitant diseases, such as infections and drug use. Type 2 diabetes appears to follow a similar pattern. Occasionally, patients progress through all stages in a few years. Rarely, nephropathy is seen even before clinical diabetes in type 2 patients. This variability in clinical course is most likely explained by type 2 patients being older, by an increased prevalence of concomitant renal diseases.
in this age group, and by pre-existing hypertension and atherosclerosis.8,18

**Treatment**

Our approach to treatment focuses on the following three distinct areas: tertiary care (stage V), secondary prevention (stages III and IV), and primary prevention (stages I and II).

**Tertiary care.** Tertiary care, or life support including dialysis or transplantation, is usually not managed by family practitioners; however, we believe family physicians have a role in the care of these patients. Stage V patients can be very complicated, ill patients. They usually have concomitant diabetic complications, such as retinopathy, amputations, neuropathy, and especially cardiovascular disease, the most common cause of death among these patients.19-21 In many situations, nephrologists become the primary care providers for their chronic dialysis patients, because patients come for dialysis two to three times a week and are usually seen by a nephrologist at that time. A recent study showed that more than 90% of nephrologists spend a substantial portion of their time as primary care providers.22 Family physicians, who are trained in primary care, must be encouraged to be partners in the care of these patients, especially for controlling blood sugar and hypertension. The psychosocial problems that accompany chronic disease also need attention, and family practitioners can be invaluable in this area.

Major advances in treatment have resulted in longer survival of dialysis and transplant patients. This means that ESRF patients should participate in cancer screening and detection programs, such as yearly Pap smears for cervical cancer for women, breast examinations for women, and prostate screening examinations for men. Family physicians are best equipped to address screening issues.

**Secondary prevention.** Secondary prevention consists of slowing the progression of overt diabetic nephropathy before development of ESRF. At this time renal morphology is already abnormal. Table 1 outlines factors that have been shown to slow renal deterioration.

The effectiveness of dietary protein restriction remains controversial. Some studies show that protein restriction is beneficial in reducing albumin excretion,19 but a recent editorial on rate of progression of renal disease in patients on low-protein diets reviewed a meta-analysis on protein restriction and concluded that the effect of protein restriction on glomerular filtration rate was minimal.22,24 In view of current data, we believe strict restriction of protein is not required in diabetic nephropathy; however, it continues to be debated.

Hyperglycemia is an important determinant of diabetes prognosis, especially for renal decline. The United Kingdom Prospective Diabetes Study showed that, in type 2 diabetes, good blood sugar control reduced this microvascular complication significantly.25 The Diabetes Control and Complications Trial26 has shown that blood sugar control with Hb A1c less than 8.0% greatly slows progression of nephropathy; however, it is generally believed that any improvement in glucose control is beneficial. Therefore, all patients with proteinuria or elevated creatinine levels must optimize glucose control.27

Hypertension can markedly accelerate renal decline, as well as lead to coronary artery disease, stroke, hypertensive retinopathy, and peripheral vascular disease. Although a blood pressure goal of 140/83 mm Hg has been suggested for the general population,28 even lower blood pressure appears to be beneficial in diabetic nephropathy.27,29,30 In a large study of renal patients with proteinuria, a mean arterial pressure of 92 (equivalent to 125/75 mm Hg) was recommended for slowing progression of renal disease.29 Even when there is little or no proteinuria, tight blood pressure control appears equally important for diabetics.

In the Hypertension Optimal Treatment study,28 diabetic patients randomized to a diastolic blood pressure goal of below 80 mm Hg had half the cardiovascular complications of those randomized to less than 90 mm Hg. The sixth report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure has suggested a blood pressure goal of 130/85 mm Hg for diabetics,31*

<table>
<thead>
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<th>Table 1. Secondary prevention: Some factors slow renal deterioration.</th>
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<tbody>
<tr>
<td>Treat hypercholesterolemia</td>
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<tr>
<td>Control hyperglycemia</td>
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<tr>
<td>Treat hypertension</td>
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<tr>
<td>Consider ACE inhibitors</td>
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<tr>
<td>Advise smoking cessation</td>
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<td>? Restrict dietary protein</td>
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however, recent WHO guidelines and the Canadian hypertension guidelines indicate that diabetics should maintain even lower blood pressure levels. The Canadian guidelines suggest a target blood pressure below 130/80 mm Hg. We must be aware, however, in treating hypertension in diabetic patients, of the possibility of concomitant autonomic neuropathy and resultant orthostatic hypotension. Sitting and standing pressures must be taken.

Angiotensin-converting enzyme inhibitors are useful in diabetic nephropathy independently of their blood pressure lowering effect. A large study of type 1 diabetes has shown a 50% reduction in risk of the following end points with use of ACE inhibitors: death, dialysis, and transplantation. The ACE inhibitors are effective because of their positive influence on intrarenal hemodynamics and decreasing intraglomerular hypertension; however, potential problems with these agents include hyperkalemia, development of acute renal failure in bilateral renal artery stenosis, and cough.

Smoking also aggravates diabetic renal disease. It is believed that smoking increases plasma endothelin I (a potent vasoconstrictor produced by endothelial cells) concentration and decreases renal plasma flow. All patients must be advised to quit smoking.

Hypercholesterolemia is important to address for two reasons. First, it has been shown experimentally to decrease renal function, and second, it is a modifiable risk factor for cardiac disease. Elevated cholesterol might be a risk factor in development of diabetic nephropathy, and recent evidence suggests that decreasing cholesterol might substantially reduce rate of progression of renal disease. We therefore recommend that patients be screened and treated aggressively for hypercholesterolemia.

Secondary prevention must be a shared responsibility between nephrologists and family practitioners; it is important that patients receive a consistent unified treatment plan. Diabetic education centres and pre-dialysis clinics can be used to educate patients on lifestyle modifications and glucose control in order to reduce development and progression of diabetic nephropathy.

**Primary prevention.** Secondary prevention, however, addresses treatment of disease only when the glomerulus has irreversible changes and damage. A strong focus must, therefore, be placed on primary prevention if we hope to see a decline in the number of patients presenting for dialysis or transplantation. Primary prevention factors are listed in Table 2.

<table>
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<th>Table 2. Primary prevention of end-stage renal failure</th>
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<tr>
<td>Screen for microalbuminuria</td>
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<tr>
<td>Control hyperglycemia</td>
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<tr>
<td>Treat hypertension</td>
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<td>Advise smoking cessation</td>
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As in secondary prevention, hyperglycemia, hypertension, and smoking must be addressed. Experimental animal studies have revealed that hypertension control and ACE inhibition afford renal protection. Hyperglycemic control has been shown to be beneficial in delaying development of albuminuria. Although we do not have the benefit of long-term studies yet, we hope that intervention with respect to these factors will have an effect on development of ESRF and, therefore, the requirement for renal replacement therapies in the future.

We are fortunate to have an early warning test to detect development of diabetic kidney disease: the urine microalbumin test. Detecting microalbuminuria is important because there are usually no or minimal renal morphologic changes early in disease. Microalbuminuria testing can be done by various dipstick and instrument methods as a screening procedure. When screening indicates disease, it should be confirmed by 24-hour urine determination, and treatment should be based on these results. Established guidelines with respect to microalbuminuria detection and treatment have been published in the United States and Canada.

Studies have shown that microalbuminuria can resolve or at least be stabilized by blood sugar and blood pressure control as well as ACE inhibition. Knowing that microalbuminuria (stage II diabetic nephropathy) progresses to overt proteinuria (stage III), we believe its treatment will be a cornerstone of primary prevention of ESRF.

**Conclusion**

Diabetes prevalence is increasing in North America, and there is a parallel increase in ESRF from diabetes. Diabetic nephropathy has an immense human and financial cost when end stage or “life support stage” treatment is necessary. It is, therefore, important to focus our efforts on primary and secondary prevention programs if we wish to reduce end stage diabetic nephropathy. Family physicians should play a leading role in this effort.
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References
3. Canadian Institute for Health Information. Canadian organ replacement register. Ottawa, Ont: Canadian Institute for Health Information; 1997.

Key points
- Diabetes is the most common cause of end-stage renal failure (ESRF) in Canada.
- Family physicians can slow progression to ESRF through excellent blood sugar control, lowering blood pressure levels, encouraging smoking cessation, and lowering abnormal lipid levels.
- Angiotensin-converting enzyme inhibitors markedly reduce progression to ESRF independently from their blood pressure lowering effects.
- Family physicians should try to maintain good primary care of their patients using dialysis despite the propensity for that care to be taken over by the dialysis unit.

Points de repère
- Le diabète est la cause la plus fréquente de l’insuffisance rénale chronique en stade terminal au Canada.
- Les médecins de famille peuvent freiner la progression vers ce stade de la maladie en exerçant un excellent contrôle de la glycémie, en abaissant la tension artérielle, en encourageant l’abandon du tabagisme et en réduisant les taux anormaux de lipides.
- Les inhibiteurs de l’enzyme de conversion de l’angiotensine réduisent de façon remarquable la progression vers l’insuffisance rénale chronique en stade terminal, indépendamment de leurs effets de réduire l’hypertension.
- Les médecins de famille devraient essayer de disperser de manière constante de bons soins de première ligne à leurs patients en dialyse malgré la tendance que de tels soins soient pris en charge par l’unité de dialyse.