Nephropathy

Canadian Diabetes Association
Clinical Practice Guidelines Expert Committee

INTRODUCTION

Diabetic nephropathy (defined clinically as the presence of microalbuminuria or overt nephropathy in patients with diabetes who lack indicators of other renal diseases) is the most common cause of renal failure in the Western World (1). Dialysis and renal transplantation are costly (2), and can have a devastating effect on quality and length of life (1,3). Diabetic nephropathy progresses from subclinical disease, through the earliest clinically detectable stage, characterized by microalbuminuria (urinary albumin 30 to 300 mg/day), to overt nephropathy with macroalbuminuria (urinary albumin >300 mg/day) (4-6). Renal dysfunction is typically identified in the macroalbuminuria stage, and can progress over time to end stage renal disease (7). Detection of microalbuminuria identifies individuals at high risk of progression to later stages of renal disease (8,9), cardiovascular events and death (10). The diagnosis of nephropathy only requires a kidney biopsy when clinical indicators leave doubt as to the diagnosis.

SCREENING

The purpose of screening for diabetic nephropathy is to delay or prevent loss of renal function through early detection and initiation of effective therapies, and to manage complications in those identified with renal disease.

Screening for microalbuminuria should be performed using the random urine test for albumin to creatinine ratio (ACR) (Figure 1) (11). (See "Type 1 Diabetes in Children and Adolescents," p. S84, for considerations regarding the pediatric population.) A urine dipstick test should also be performed on the urine specimen, either in the laboratory or at the point of care, as a screen for nondiabetic renal disease. While 24-hour or timed overnight urine collections have been the gold standard for clinical trials, these tests are difficult to perform correctly in routine practice and may yield false results (12-14). The random urine ACR accurately predicts the urinary protein level detected by 24-hour collections, and is easier to perform and more agreeable to patients than timed collections (15).

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People with overt nephropathy (urinary albumin >300 mg/day, equivalent to ACR >20.0 mg/mmol in men and >28.0 mg/mmol in women) typically progress over time to more severe stages of nephropathy and rarely have normalization of urinary protein without directed therapy. Patients with microalbuminuria (urinary albumin 30 to 300 mg/day, equivalent to ACR 2.0 to 20.0 mg/mmol in men and 2.8 to 28.0 mg/mmol in women) have a variable course. While microalbuminuria is a significant risk factor for progression of nephropathy, some will experience a spontaneous normalization of urinary protein (5,16). To confirm the presence of nephropathy in those with microalbuminuria, patients should undergo up to 2 additional random urine tests for ACR. A patient is considered to have nephropathy if any 2 of the 3 urine samples have an ACR >2.0 mg/mmol in men or >2.8 mg/mmol in women. The 2 confirmatory tests should be performed between 1 week and 2 months apart. Patients with overt nephropathy (ACR >20.0 mg/mmol for men and >28.0 mg/mmol for women) should undergo a 24-hour urine collection for creatinine clearance as follow-up within 2 to 3 months.

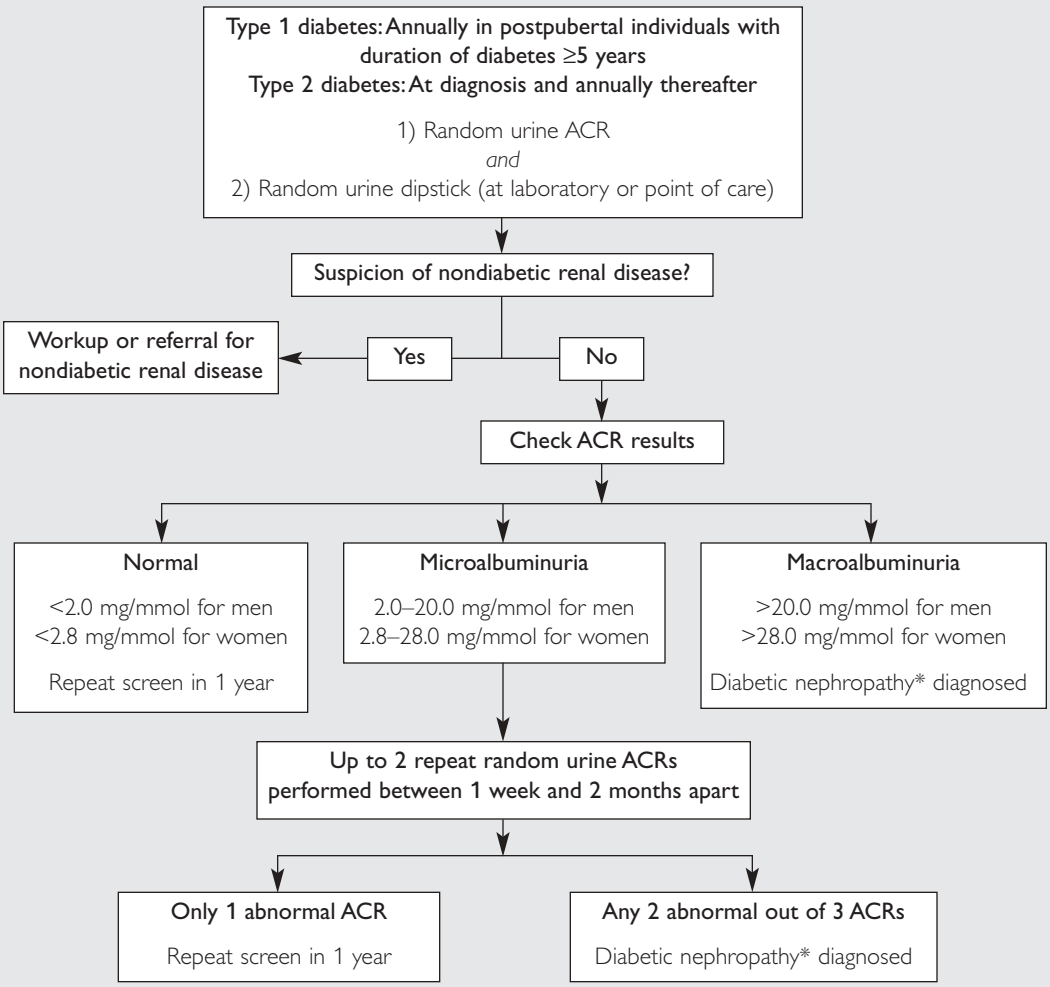
Table 1 illustrates the degree of proteinuria associated with various stages of diabetic nephropathy and highlights the fact that conventional urine dipstick tests fail to identify individuals with early nephropathy.

As ACR may be elevated with conditions other than diabetic nephropathy, such as recent major exercise (17), fever (18), urinary tract infection, congestive heart failure (19), acute severe elevations of blood pressure (BP) or blood glucose (BG) (20,21), or menstruation, screening for microalbuminuria should be delayed in the presence of these conditions.

Patients with diabetes can develop renal diseases other than diabetic nephropathy (Table 2) (22-26). Further nephrologic investigations, or referral to a renal disease specialist, may be considered if 1 or more of the conditions listed in Table 2 are present.

Creatinine clearance, an estimate of the kidney's ability to filter toxins from the blood, should be determined by a formula such as the Cockcroft-Gault formula (Table 3) rather than by serum creatinine, which may falsely indicate that a person's renal function is normal (27,28). Individuals can lose up to 50% of their creatinine clearance before serum creatinine levels rise into the abnormal range (29). Patients may remain asymptomatic until as much as 75% of renal

Figure 1. Screening for diabetic nephropathy and nondiabetic renal disease



*Diabetic nephropathy = microalbuminuria or overt nephropathy (macroalbuminuria)

ACR = albumin to creatinine ratio

Table 1. Stages of renal involvement according to the urinary albumin level

Stage of nephropathy	***Urine dipstick for protein***	***Urine ACR (mg/mmol)***	***24-hour urine collection for albumin****
Normal	Negative	<2.0 (men) <2.8 (women)	<30 mg/day
Microalbuminuria	Negative	2.0–20.0 (men) 2.8–28.0 (women)	30–300 mg/day
Overt nephropathy (macroalbuminuria)	Positive	>20.0 (men) >28.0 (women) >66.7 (men) >93.3 (women)	>300 mg/day >1000 mg/day

*Values are for urinary albumin, not total urinary protein, which will be higher than urinary albumin levels

ACR results may be elevated with conditions other than diabetic nephropathy. See text and Table 2.

ACR = albumin to creatinine ratio

function is lost. As the identification of subclinical renal dysfunction may have management consequences (e.g. drug selection or dosing, or the use of contrast dye during radiologic or cardiologic investigations) and implications regarding the timing for referral to a renal disease specialist, a more accurate assessment of renal function should be performed periodically. The Cockcroft-Gault formula is a sufficiently accurate estimation of renal function in adults for most clinical purposes (30), and should be performed annually in those patients with diabetes without nephropathy and at least every 6 months in those with nephropathy. Alternatively, one could use other validated equations, such as the formula developed from the Modification of Diet in Renal Disease (MDRD) study, for estimating glomerular filtration rate (GFR) (31).

TREATMENT AND FOLLOW-UP

The development of nephropathy has been associated with smoking (32), hyperlipidemia (33) and poor control of BG (34) and BP. Once nephropathy is diagnosed, intensive glycemic control (35) and optimization of BP will help prevent its progression (36). BP targets (i.e. ≤130/80 mm Hg) should be the same as those for people with diabetes and hypertension. Vascular protection and control of hypertension are more important than measures aimed solely at protecting renal function. Patients with vascular risk or hypertension should be treated to reduce these risks (Table 4) (see "Macrovascular Complications, Dyslipidemia and Hypertension," p. S58), but may require additional therapies if they remain proteinuric. The presence of proteinuria may influence drug selection in hypertensive individuals.

Table 5 summarizes treatment approaches for nephropathy in people with diabetes. Disruption of the renin-angiotensin system with angiotensin converting enzyme (ACE) inhibitors or angiotensin II receptor antagonists (ARBs) is the preferred method of protecting renal function in people with diabetes, even in the absence of hypertension (37).

Table 2. Possible indicators of nondiabetic causes of renal disease in persons with diabetes

- Lack of retinopathy (23) or neuropathy (24)
- Persistent hematuria (microscopic or macroscopic) (22)
- Signs or symptoms of systemic disease (25)
- Rapidly rising creatinine (26)
- High creatinine with little or no proteinuria (24)
- Family history of nondiabetic renal disease (e.g. polycystic kidney disease or Alport syndrome)
- Short duration of diabetes (24)

Table 3. Calculation of creatinine clearance in adults using the Cockcroft-Gault formula*

Creatinine clearance (mL/min) = $\frac{(140 - \text{age in years}) \times \text{actual}^{**}\text{ weight (kg)}}{\text{serum creatinine (μmol/L)}}$

Multiply the result by 1.2 for men
Normal range is >90 mL/min, >1.5 mL/s

An online version of this calculation is available at http://www.nephron.com

*Estimates of creatinine clearance are inaccurate when the serum creatinine is changing rapidly
**Extremes of overweight and underweight will result in underestimates and overestimates of renal function using this formula

Table 4. Priorities for vascular and renal protection

Clinical issue	*Target population*	*Interventions*
1. Vascular protection	All people with diabetes	*(in alphabetical order)* ACE inhibitor, as indicated Antiplatelet therapy (e.g. ASA), as indicated BP control Glycemic control Lifestyle modification Lipid control Smoking cessation
2. Elevated BP	All people with diabetes who are hypertensive (regardless of whether nephropathy is present)	Treat according to hypertension guidelines (See "Macrovascular Complications, Dyslipidemia and Hypertension," p. S58)
3. Renal protection	All people with diabetes who have nephropathy (even in the absence of hypertension)	Treat according to nephropathy guidelines

ACE = angiotensin converting enzyme
ASA = acetylsalicylic acid
BP = blood pressure

Table 5. Treatment of diabetic nephropathy

Treatment group	*Preferred agent*
Type 1 diabetes	ACE inhibitor
Type 2 diabetes	
Creatinine clearance >60 mL/min	ACE inhibitor or ARB
Creatinine clearance ≤60 mL/min	ARB

ACE = angiotensin converting enzyme
ARB = angiotensin II receptor antagonist

Second-line renal-protective agents include the nondihydropyridine calcium channel blockers (CCBs) (diltiazem, verapamil) (38).

In type 1 diabetes, ACE inhibitors have been shown to decrease albuminuria and prevent worsening of nephropathy (39). In type 2 diabetes, ACE inhibitors and ARBs have been shown to decrease albuminuria and prevent worsening of nephropathy (40,41), and ARBs have been shown to delay the time to dialysis in those with renal dysfunction at baseline (ACR >1000 mg/mmol and creatinine clearance ≤60 mL/minute) (42,43). An ACE inhibitor and an ARB can be used safely in combination (44-46).

Patients starting therapy with an ACE inhibitor or an ARB should be monitored after 1 to 2 weeks of treatment for significant worsening of renal function or the development of significant hyperkalemia. Periodic monitoring should continue in those whose serum creatinine or potassium level increases above normal laboratory limits until these values have stabilized. Serum creatinine typically increases up to 30% above baseline after initiation of an ACE inhibitor or ARB, and usually stabilizes after 2 to 4 weeks of treatment (47). Those patients who develop mild to moderate hyperkalemia should receive nutrition counselling regarding a potassium-restricted diet, and consideration should be given to the use of non-potassium-sparing diuretics, reduction of the dose of the ACE inhibitor or ARB, or discontinuation of the ACE inhibitor or ARB. If an ACE inhibitor or ARB is not tolerated due to severe hyperkalemia or a >30% increase in serum creatinine, the drug should be withdrawn, and other ACE inhibitors or ARBs should not be substituted; instead, consideration should be given to the use of a second-line agent (48). There is no upper limit of the serum creatinine level for initiation of ACE inhibitor or ARB therapy, but if the creatinine clearance is <30 mL/minute, these agents should be started with care or referral for specialized nephrologic care should be considered (47,49).

Second-line renal-protective agents (nondihydropyridine CCBs, such as diltiazem or verapamil) can be considered in those unable to tolerate an ACE inhibitor or an ARB (38). Patients started on diltiazem or verapamil should be monitored clinically for development of bradycardia. As all nephroprotective drugs are also antihypertensives, patients should be monitored for development of hypotension. See Appendix 11 for an algorithm summarizing the approach to therapeutics in diabetic nephropathy.

ACR should be remeasured 3 months after initiation of a renal-protective agent and annually thereafter with the goal of a decreased or stable value.

RECOMMENDATIONS

1. The best possible glycemic control and, if necessary, intensive diabetes management should be instituted in people with type 1 or type 2 diabetes for the prevention, onset and delay in progression of early nephropathy *[Grade A, Level 1A (35,50,51)]*.
2. Screening for diabetic nephropathy should be conducted using a random urine ACR *[Grade D, Consensus]*. Postpubertal individuals with type 1 diabetes of ≥5 years' duration should be screened annually. Individuals with type 2 diabetes should be screened at diagnosis of diabetes and yearly thereafter *[Grade D, Consensus]*.
3. Serum creatinine levels should be measured and creatinine clearance estimated annually in those patients with diabetes without albuminuria and at least every 6 months in those with albuminuria *[Grade D, Consensus]*.
4. Individuals with albuminuria should receive treatment to protect renal function, even in the absence of hypertension:
   - In people with type 1 diabetes and albuminuria, an ACE inhibitor should be given to reduce urinary albumin and prevent progression of nephropathy *[Grade A, Level 1A (39)]*. An ARB should be considered in patients unable to tolerate an ACE inhibitor *[Grade D, Consensus]*.
   - In people with type 2 diabetes, albuminuria and creatinine clearance >60 mL/minute, an ACE inhibitor *[Grade A, Level 1A (40)]* or an ARB *[Grade A, Level 1A (41)]* should be given to reduce urinary albumin and prevent progression of nephropathy *[Grade A, Level 1A (40,41)]*.
   - In people with type 2 diabetes, albuminuria and creatinine clearance ≤60 mL/minute, an ARB should be given to prevent progression of nephropathy *[Grade A, Level 1A (42,43)]*.
5. Patients placed on an ACE inhibitor or an ARB should have their serum creatinine and potassium levels checked within 2 weeks of initiation of therapy and periodically thereafter *[Grade D, Consensus]*.
6. The use of nondihydropyridine CCBs (diltiazem, verapamil) may be considered to reduce urinary albumin excretion in proteinuric hypertensive patients *[Grade B, Level 2 (38)]*.
7. A referral to a nephrologist or internist with an expertise in diabetic nephropathy should be considered if the ACR is >75 mg/mmol, there is persistent hyperkalemia, there is a >30% increase in serum creatinine within 3 months of starting an ACE inhibitor or ARB, or the creatinine clearance is <60 mL/minute *[Grade D, Consensus]*.

Consideration should be given to referring patients with a creatinine clearance (measured or calculated) of <60 mL/minute to a nephrologist or internist with an expertise in diabetic nephropathy.

OTHER RELEVANT GUIDELINES

Macrovascular Complications, Dyslipidemia and Hypertension, p. S58
Type 1 Diabetes in Children and Adolescents, p. S84
Pre-existing Diabetes and Pregnancy, p. S94

RELEVANT APPENDICES

Appendix 10: Level of Urinary Albumin by Various Test Methods and Stage of Diabetic Nephropathy, p. S136
Appendix 11: Approach to Therapeutics in Diabetic Nephropathy, p. S137

RELATED WEBSITES

National Kidney Foundation. Kidney Disease Outcomes Quality Initiative. K/DOQI clinical practice guidelines for chronic kidney disease: evaluation, classification, and stratification. Part 5. Evaluation of laboratory measurements for clinical assessment of kidney disease. Guideline 4. Estimation of GFR. Available at: http://www.kidney.org/professionals/doqi/kdoqi/p5_lab_g4.htm. Accessed November 7, 2003.

Nephron Information Center. Chronic kidney disease worksheet (includes Cockcroft-Gault calculator, MDRD GFR calculator, GFR calculations in children, and total body volume and body surface area calculator). Available at: http://www.nephron.com. Accessed November 7, 2003.

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type I and type II disease presenting with renal dysfunction. *Am J Nephrol*. 1988;8:204-211.
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