Update

Renal Protection

Staying on Target

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Gwen's case

Gwen, 49, asks you to take on her primary care, as her previous physician has moved.

Her past medical history is significant for a cholecystectomy at age 38 and an appendectomy at age 12.

She is not taking any medications and has no allergies. She has smoked half a pack of cigarettes a day for the past 25 years, but does not drink alcohol.

Family history includes a father and two older brothers with Type 2 diabetes. All three are taking oral hypoglycemic agents. Her mother is in good health.

Gwen's test results are listed on page 81.

Diabetes is the most common cause of end-stage renal disease (ESRD) requiring dialysis or transplantation in Canada, the U.S., Europe, and Japan.[1-3] It is also the most common cause of chronic kidney disease (CKD) in Canada, and a leading cause of blindness, cardiovascular death, and peripheral vascular disease in North America.[4]

What are the clinical parameters to follow?

Increased urinary protein excretion is the earliest clinically detectable element of diabetic nephropathy (Table 1) and has been shown to be associated with progressive renal failure, cardiovascular disease, and death.

When first seen, all diabetic patients should have a urine sample sent for an albumin/creatinine ratio as a test for microalbuminuria. This test has been validated in all diabetes patients and has, in large part, replaced the use of timed, overnight, or 24-hour urine collections.

The Canadian Diabetes Guidelines for nephropathy suggest urine sampling for albumin/creatinine ratio be repeated between one and two months apart. If two of the three tests are positive, the patient is considered to have diabetic nephropathy.

Gwen's test results

Gwen's lab exam results

- Fasting blood glucose 2 months ago: 7.8 mmol/L
- Fasting blood glucose 1 month ago: 7.2 mmol/L
- Hemoglobin: 134 g/L
- Normal differential
- Sodium: 140 mmol/L
- Potassium: 4.2 mmol/L
- Chloride: 100 mmol/L
- Bicarbonate: 25 mmol/L
- Urea: 6.8 mmol/L
- Creatinine: 65 mmol/L
- Hemoglobin A1C: 7.9%
- Fasting blood glucose: 10 mmol/L
- Albumin/creatinine ratio (3 separate times, 3 weeks apart): 18 mg/mmol, 22 mg/mmol, 19 mg/mmol
- Urine dip: Negative for protein, red blood cells, white blood cells, leucocytes, and glucose

Gwen's vital signs

- Body mass index: 33
- Blood pressure: 138/88 mmHg
- Pulse: 70 beats/minute

Gwen's cholesterol profile

- Total cholesterol: 6.5 mmol/L
- Triglycerides: 2.5 mmol/L
- HDL: 0.9 mmol/L
- LDL: 3.3 mmol/L
- Cholesterol ratio: 7.2

HDL: High-density lipoprotein
LDL: Low-density lipoprotein

For a followup on Gwen, go to page 83.

Physicians should be aware of the common false positives seen with this test (Table 2).

The patient's creatinine clearance should also be calculated using the Cockcroft-Gault formula (Figure 1).

▶*Glycemic control*

Aggressive glycemic control has been shown to reduce the development of renal (and other) complications in patients with Type 1 and Type 2 diabetes.

The Diabetes Control and Complications Trial (DCCT) followed 1,441 patients with Type 1 diabetes for a mean of 6.5 years after they had been randomized to a regimen of either intensive glycemic control (mean capillary glucose 8.6 ± 1.7 mmol/L) or conventional glycemic control (mean capillary glucose 12.8 ± 3.1 mmol/L). The purpose of this study was to determine the effect of glycemic control on urinary albumin excretion.[5]

Patients were grouped into a primary prevention cohort (those without retinopathy) or a secondary intervention cohort (those with retinopathy). In the primary prevention group, intensive glycemic control saw fewer patients develop microalbuminuria; in the secondary group, fewer patients had worsened their albuminuria.

The U.K. Prospective Diabetes Study (UKPDS) examined the effect of intensive glycemic control in patients with Type 2 diabetes—using either sulphonylureas or insulin—on the risk of developing microvascular or macrovascular complications, classified as:

- any diabetes end point,
- diabetes-related death, or
- all-cause mortality.[6]

Renal outcomes were included in the "any diabetes end point" group and qualified as renal failure.

The study showed a 25% risk reduction for diabetic end points in the intensive control control group (glycosylated hemoglobin 7.0%) versus the conventional glycemic control group (glycosylated hemoglobin 7.9%). The Canadian Diabetes Association Clinical Practice Guidelines for 2003 now recommend a target hemoglobin A1C of ≤ 7% for most patients and < 6% in those patients where it can be achieved safely.[7]

Table 1

Proteinuria

Description	Spot urine albumin/creatinine	24-hour urine collection	Dipstick
Normal	< 2.0 mg/mmol (males) < 2.8 mg/mmol (females)	< 30 mg/day	Negative
Microalbuminuria	2.0-20.0 mg/mmol (males) 2.8-28.0 mg/mmol (females)	30-300 mg/day	Negative
Macroalbuminuria	> 20.0 mg/mmol (males) > 28.0 mg/mmol (females)	> 300 mg/day	Positive

Table 2

False positives with spot urine albumin/creatinine ratio

- Exercise in the 24 hours preceding collection
- Menstrual bleeding
- Urinary tract infection
- Fever
- Severe hypertension
- Pre-eclampsia
- Severe congestive heart failure

Blood pressure

Recent Canadian Hypertension Committee Guidelines state that diabetes patients with nephropathy (urinary albumin > 30 mg/day) or without nephropathy have a blood pressure target below 130/80 mmHg. Appropriate first-line agents, as suggested by the guidelines, are:

- angiotensin-converting enzyme (ACE) inhibitor or angiotensin receptor blocker (ARB) for diabetes patients with nephropathy; and
- ACE inhibitor, ARB, or thiazide diuretic for diabetes patients without nephropathy.

All non-diabetic renal disease should be treated with ACE inhibitors as first-line agents and, if not tolerated, an ARB should be used.

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A followup on Gwen

Gwen is prescribed an angiotensin receptor blocker. On followup visits, her blood pressure is 122/74 mmHg and her repeat urinary albumin/creatinine ratio is 5 mg/mmol.

She is also started on a cholesterol-lowering agent (*i.e.*, statin). Her cholesterol profile is:

- total cholesterol: 5.0 mmol/L
- triglycerides: 2.0 mmol/L
- HDL: 1.2 mmol/L
- LDL: 2.0 mmol/L

She is referred to a clinical dietitian and lowers her hemoglobin A1C to 6.2%. She has also lost approximately 6 kg, but is still trying to quit smoking.

Cockcroft-Gault formula

Males:

$$\text{CrCl (mL/min)} = \frac{(140 - \text{age}) \times \text{weight (kg)}}{\text{Serum creatinine (µmol/L)} \times 0.81}$$

Females:

Same formula, but multiply value by 0.85.

Figure 1. Creatinine clearance calculation using the Cockcroft-Gault formula.

More on ACE inhibitors and ARBs

In 1993, it was shown that in Type 1 diabetes patients with chronic renal failure and macroalbuminuria, the administration of an ACE inhibitor—independent of its antihypertensive effect—reduced by 50% those patients who progressed to death, dialysis, or transplantation.[8]

In patients with Type 2 diabetes, many recent studies have shown the use of an ARB slows the rate of renal decline and reduces progression to ESRD.[9-12]

Choosing between an ACE inhibitor or an ARB can be difficult in Type 2 diabetes patients with nephropathy. For Type 1 diabetes, the literature is more congruent, stating thatan ACE inhibitor is beneficial for both renal and cardiovascular disease.

For Type 2 diabetes, it appears that for proteinuria, one should prescribe an ARB, but to reduce risk of cardiovascular complications, ACE inhibitors should be prescribed.·

The problem is that patients often present with both proteinuria and several cardiovascular risks. What's a clinician to do? Taking a cue from the Canadian Hypertension Guidelines, either an ACE inhibitor or an ARB is acceptable in these patients.

Can ACE inhibitors and ARBs be used together?

Emerging evidence suggests that in diabetic and non-diabetic renal disease, ACE inhibitor/ARB combination treatment is more effective than monotherapy with either agent in lowering blood pressure and reducing albuminuria.[13,14] Use of these agents in combination must be done with careful monitoring of blood pressure, renal function, and serum potassium.

Avoidable risks

In patients with diabetes, especially those with an element of CKD, it is important to prevent exposure to certain avoidable risks, such as:

- non-steroidal anti-inflammatory drugs,
- unnecessary intravenous contrast dye dehydration, and
- certain antibiotics. Dx

Take-home message

Tests

- When first seen, all diabetes paients should have urine samples for albumin/creatinine ratio.
- The patient's creatinine clearance must be calculated using the Cockcroft-Gault equation.

Glycemic control

- The 2003 Canadian Diabetes Association guidelines recommend a target hemoglobin A1C ≤ 7% for most patients.

Blood pressure

- Recent Canadian Hypertension Committee guidelines state that target blood pressure for diabetes patients is 130/80 mmHg.
- Evidence suggests that the combination of ACE inhibitor and ARB is more effective than either agent alone in lowering blood pressure and albuminuria.

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Further references available—contact *The Canadian Journal of Diagnosis* at **diagnosis@sta.ca**.