Diabetic nephropathy - the quiet revolution

Part 1 – Prevalence and Natural History

Dr Mark Thomas, Renal Physician.

25 years ago, hypertension and a raised creatinine in a diabetic patient would inevitably herald death or dialysis within 18 months. An epidemic of obesity-related diabetes is upon us, but increasingly effective antihypertensives have completely reversed the previous gloomy renal prognosis. Realistic goals are now complete regression of proteinuria with long-term stabilisation of renal impairment.

Prevalence

Nephropathy affects 20% of Type 1 diabetics after 20 years, and 40% of Type 2 diabetics with any duration of diabetes. Diabetic nephropathy currently causes 25% of all cases of end-stage kidney failure; 95% of all diabetic dialysis patients have Type 2 DM.

Natural history

Diabetes places both a haemodynamic and metabolic stress upon the kidney. The metabolic pathways leading to kidney damage involve deposition of advanced glycosylation end products in connective tissues and small vessels. This occurs faster in poorly-controlled diabetes and is accelerated by hypertension. This may take 10-20 years of hyperglycaemia. Because Type 2 diabetics may involve asymptomatic disease for many years, **diabetic nephropathy may already be present when diabetes is diagnosed** in adults.

Glomerular filtration

Both hyperglycaemia and hyperinsulinaemia initially cause **glomerular hyperfiltration**, that is, glomerular filtration rate (GFR) >120 mls/min norm for young adults. (Normal GFR for age is calculated as 140 minus age). This is reflected in a **serum creatinine below expected**, for which I use the rule of thumb:

Expected serum creatinine = [Height (cm) – 100] x 1.23 [for males]

By mathematical coincidence, exactly the same formula gives the estimated lean weight (i.e. equivalent to a BMI of 25) for both males and females:

Lean weight (Kg) = Height (cm) – 100

Being able to estimate the lean weight is necessary to accurately calculate the GFR in the obese patient, using the simplified Cockcroft & Gault formula:

$$\text{Calculated GFR} = \frac{(140 - \text{age}) \times \text{lean weight} \times 1.23 \text{ [for males]}}{\text{Stable serum creatinine (umol/L)}}$$

See inset for example.

Clinical patterns

The first clinical sign of diabetic kidney disease is **microalbuminuria**, usually estimated by the albumin:creatinine ratio on a spot urine sample. The kidney's normal capacity to break down excreted albumin is exceeded. This can also occur transiently with fever, exercise, short-term hyperglycaemia or a high-protein meal, so abnormal results should be confirmed before assuming there is structural kidney damage.

Clinical Example:

165cm, 80kg woman aged 50 with poorly-controlled diabetes has a serum creatinine of 45 umol/L. What is her lean weight and calculated GFR? What is the expected GFR and creatinine for her age?

- Her lean weight is 65Kg (i.e. 165 cm – 100). She is 15kg over her lean weight.
- Her actual GFR is (140-50) x 65/45 = 130mls/min.
- Her expected GFR for age is (140-50) = 90 mls/min i.e. she has glomerular hyperfiltration.
- Her expected creatinine is 65 (i.e. 165 cm – 100) i.e. 40% higher than her actual reading, which confirms glomerular hyperfiltration.

When **hypertension** accompanies microalbuminuria, the risk of progressive nephropathy increases 20-fold. Add in poor diabetic and lipid control, and the risk increases over 40-fold.

As **progressive renal failure** develops, diabetic patients show features that distinguish them from progressive non-diabetic renal disease:

- **Kidneys are normal size**, because deposits of glycosylation end-products do not shrink. Overt scarring suggests reflux nephropathy or calculous disease; smoothly-shrunken kidneys suggest hypertensive nephrosclerosis or chronic glomerulonephritis.
- **Disproportionate hyperkalaemia** may be seen in only moderate rather than advanced CRF (renin and aldosterone levels are often suppressed; insulin resistance or deficiency limits normal cellular uptake of potassium).
- **Atherosclerosis** is even more severe than the already dramatically accelerated rates seen in CRF, but conversely myocardial ischaemia may be silent, manifesting only as exertional hypotension or dyspnoea.

Hazards in misdiagnosis

Nephrological referral is indicated if these atypical clinical features suggest problems other than diabetic nephropathy:

- Absence of microalbuminuria or proteinuria.
- Absence of retinopathy.
- Presence of haematuria.
- Asymmetric kidney size (esp. consider renal artery stenosis) or overt scarring.
- Constitutional illness.
- Abnormal immunological tests (other than ESR, non-specifically raised by heavy proteinuria).

In **advanced renal failure** (GFR <30mls/min), proteinuria may start to diminish (due to falling nephron numbers). Albuminuria may become artefactually absent, as the radio-immunoassay antibody is swamped by excess antigen, i.e. albumin. Spot urine protein: creatinine ratio becomes a more robust monitor than urine albumin: creatinine ratio (ACR) when 24-hour protein loss exceeds 2 gm/day (equivalent to a spot protein: creatinine ratio of > 200). Blood sugar control may become progressively easier, to the point of achieving completely normal BSLs off all therapy. This is due to reduced food intake from uraemic anorexia combined with prolongation of insulin half-life. Other causes of GI symptoms include autonomic gastroparesis or metformin accumulation.

Take-home messages

- Hypertension, poor diabetic control and high cholesterol each dramatically increase the risk of diabetic nephropathy.
- A low serum creatinine implies diabetic or obesity-related renal hyperfiltration.
- Check spot urine ACR regularly – annually in high risk patients.
- Diabetic kidneys usually do not shrink or show haematuria.
- Use spot urine protein: creatinine ratio rather than ACR, if proteinuria is heavy.
- Insulin and pill requirements reduce when GFR < 30 mls/min.

This clinical update is supported by an independent educational grant from Bristol-Myers Squibb

Footnote. Kidney Health Australia (formerly the Australian Kidney Foundation) has initiated a nation-wide education project, Kidney Check Australia Taskforce (KCAT), to reduce endstage renal disease through earlier detection and management of mild chronic renal failure. The key elements are investigation of high risk groups, initiation of appropriate therapy and timely referral. The opinions expressed in the above article are those of the author and not necessarily endorsed by KCAT.