Neglected nephropathy

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BACKGROUND
Diabetic nephropathy is a significant contributor to the morbidity, mortality and health care cost among patients with diabetes. With increasing understanding of this problem, the natural progression of diabetic nephropathy can potentially be changed.

OBJECTIVE
This article examines the natural history of diabetic nephropathy and provides guidelines on detection, management and future treatment possibilities of this complication.

DISCUSSION
Prevention and slowing progression are the most important aspects of the management of diabetic nephropathy. This involves monitoring renal function and risk factors for renal damage and early active intervention. The angiotensin converting enzyme inhibitors and receptor antagonists are important components of therapy, both for controlling hypertension and for slowing the progression of micro and macroalbuminuria. When microalbuminuria occurs, intensive intervention on a range of risk factors can halve the number of those suffering a cardiovascular event or progressing to macroalbuminuria. When renal insufficiency occurs, particularly when creatinine clearance is <30 mL/minute, referral to an nephrologist should be considered.

Micro- and macro-albuminuria occur in 25 and 5% of Australian adults with diabetes.[1] In a general practice of 1000 active patients, 40 will have known diabetes and 12 of these (30%) will have nephropathy.[2] In terms of life years lost for those with diabetes, kidney disease ranks second to cardiovascular disease. In terms of cost to the health care system, it is third behind cardiovascular disease and foot problems.[3]

The contribution of diabetes to the Australian population in renal replacement programs has been increasing steadily, both in absolute numbers and as a percentage of the total.[4,5] If current trends continue, renal replacement for people with diabetes will be a major burden on the Australian health care system. In many developed countries, including Australia, diabetic nephropathy, mostly associated with type 2 diabetes, has overtaken glomerulonephritis as the leading cause of end stage renal failure. Recent trials have shown that the kidneys can be protected and patient outcomes improved.

Natural history

The earliest clinical evidence of nephropathy is the appearance of microalbuminuria (≥30 mg/day or ≥20 µg/min). A higher proportion of individuals with type 2 diabetes are found to have microalbuminuria and overt nephropathy shortly after diagnosis, because in type 2 diabetes the metabolic abnormality may have been present for years before diagnosis.

Extrapolating from the United Kingdom Prospective Diabetes Study (UKPDS)[6] data, in a population of 9900 patients with type 2 diabetes, it is estimated that approximately 7000 have normoalbuminuria, 2000 have microalbuminuria, 800 have macroalbuminuria (urine albumin excretion >300 mg/day or >200 µg/min) and 100 have end stage renal failure (*Figure 1*).

In terms of progression from one stage of nephropathy to the next:

- 2% (each year) of patients without albuminuria with progression to microalbuminuria
- 3% with microalbuminuria progress to

macroalbuminuria, and

- 2.5% with macroalbuminuria progress to end stage renal failure.[7]

The UKPDS also showed that annual death rates and the risk of cardiovascular death increased with the increasing nephropathy. Of those who develop micro- or macroalbuminuria only a minority survive to progress to the next stage because many die prematurely, predominantly from cardiovascular disease.[6]

Once macroalbuminuria sets in, glomerular filtration rate (GFR) starts to fall at variable rates (2–20 mL/min/yr depending on factors such as blood pressure).[8] Patients with both type 2 diabetes and microalbuminuria are at increased risk of premature death and four times as likely as those with normoalbuminuria to die prematurely of a cardiovascular event.[9,10] The 8 year risk of cardiovascular events is 44% in patients in whom risk factors are not actively controlled.[11]

Risk factors

Heredity, race, age, duration of diabetes and impaired renal function are risk factors that are not modifiable (*Table 1*). Genetic susceptibility may be an important determinant of both the incidence and severity of diabetic nephropathy. Genetics may also contribute to the influence of race on the development of this complication. However, there are several modifiable risk factors.

The UKPDS showed that decreases in blood glucose and systolic blood pressure were associated with decreases in the occurrence and progression of microalbuminuria (by 25% per 1% A1c decrease and 30% per 10 mmHg systolic blood pressure decrease respectively) (*Figure 2*).[2,12] Other risk factors are dyslipidaemia, cigarette smoking and possibly dietary protein intake. When plasma creatinine is increased, rapid progression of renal failure was associated with low albumin levels, anaemia, high blood pressure and lack of use of insulin.[13] There was no association with A1C and serum cholesterol.

Detection

In the past, detection of early diabetic nephropathy was difficult. One was obliged to monitor the GFR and to decide if any decline was the result of improved glycaemic control (which will reduce overperfusion of the nephron) or damage. By the time proteinuria was clinically detectable (positive on routine dipstick analysis) or the plasma creatinine was elevated, renal damage was considerable, irreversible and often relentlessly progressive.

The development of sensitive assays for albumin has allowed early detection of glomerular damage at a time when intervention may be effective. The current recommendation is that all patients with type 2 diabetes be tested annually for microalbuminuria. This can be done on the first voided morning urine sample or in a timed over night urine collection. Microalbuminuria should be confirmed and if the second test is negative a third deciding test done. Microalbuminuria is defined in *Table 2*.

Screening should not be performed in the presence of conditions that increase urinary albumin excretion, such as urinary tract infection, haematuria, acute febrile illness, vigorous exercise, short term pronounced hyperglycaemia, uncontrolled hypertension, and heart failure.[14]

Although measuring microalbuminuria is useful in detecting early diabetic nephropathy, some patients may have impaired renal function for other reasons (decreased GFR) in the presence of normoalbuminuria. Furthermore, in some patients microalbuminuria may not be caused by diabetes and another cause should be sought.

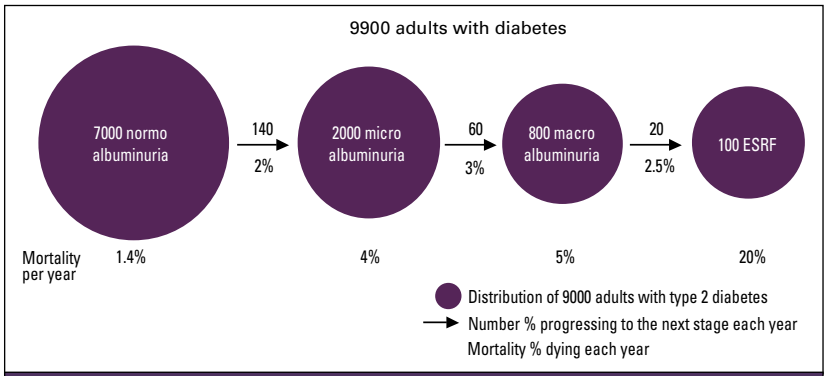

Figure 1. Natural history of nephropathy

Table 1. Risk factors for diabetic nephropathy

Fixed	Modifiable
Heredity	Glycaemia
Age	Blood pressure
Diabetes duration	Dyslipidaemia
Impaired renal function	Cigarette smoking

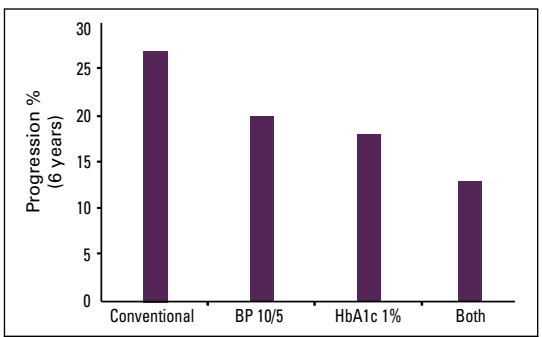

Figure 2. Lessons from UKPDS
% progression from normo- to micro-albuminuria over 6 years with reduction in: BP by 10/5 mmHg; A1C by 1%; or both

Targeting protection

The basis for prevention is the treatment of known risk factors for diabetic nephropathy – the 'ABCs': hyperglycaemia (Hb**A**1C), hypertension (**B**P), dyslipidaemia (**C**holesterol) and **S**moking (*Table 3*).

Patients with normoalbuminuria

Intensive blood glucose and blood pressure control are the cornerstones of reducing the risk of development of microalbuminuria. This is supported by the evidence from the UKPDS study (*Figure 2*).[6,12] The decline of GFR increases by 1 mL/min/yr with each 2 mmHg increase in mean arterial pressure; cardiovascular mortality increases by 30% for each 10 mmHg increase in systolic blood pressure.

Beware of medications that can damage the kidneys (*Table 4*) and in particular of the 'triple whammy' of nonsteroidal anti-inflammatory drugs (NSAID), diuretic and angiotensin converting enzyme (ACE) inhibitors or angiotensin receptor antagonists (ARA).[15] Blood pressure target should be less than 130/80 mmHg[16] and A1c target less than 7%.

Table 2. Definitions of microalbuminuria

Albumin-creatinine ratio (ACR)	
• women	3.5–35.0 mg/mmol
• men	2.5–25.0 mg/mmol
Albumin excretion rate	20–200 µg/min

Table 3. The ABCss of diabetes care

Risk factor	Target
HbA1c	<7%
Blood pressure	<130/80*
Cholesterol	<4 mmol/L**
Smoking	Quit

* <125/75 if proteinuria >1 g/day exists

** corresponding to LDL cholesterol <2.5 mmol/L

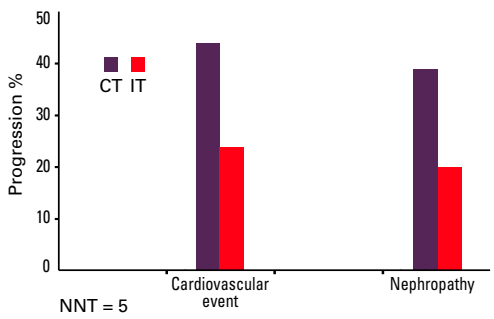

Figure 3. Lessons from STENO-2
Progression to cardiovascular event or nephropathy with conventional/intensive treatment (CT/IT)

Patients with albuminuria

Once microalbuminuria has been detected it is appropriate to review the patient carefully for other risk factors for macrovascular disease. Finding microalbuminuria may renew your enthusiasm and your patient's motivation to modify cardiovascular risk factors. In this group there are two main goals. First to reduce the risk of cardiovascular events and second to slow the progression from micro- to macro-albuminuria and the decline of renal function in patients with macroalbuminuria.

When microalbuminuria is present cardiovascular risk factors ought to be treated actively. Aim to get the ABCss on target (*Table 3*). The STENO-2 study showed that active multifactorial intervention targeting the ABCss halves the number of cardiovascular events and the progression from micro- to macro-albuminuria[16] (*Figure 3*).

Renin angiotensin system blockade with an ACE inhibitor or ARA is reno-protective independent of blood pressure reduction. Angiotensin converting enzyme inhibitors or ARAs are recommended for patients with type 2 diabetes and microalbuminuria even if they are normotensive.[2] The PRIME studies showed that the use of an ARA (irbesartan) in patients with micro- and macro-albuminuria is associated with decreased progression from micro- to macro-albuminuria and of macroalbuminuria to end stage renal failure, cardiovascular events or death.[17,18]

An acute rise in serum creatinine of up to 20%, stabilising after 2 months, might occur in proteinuric patients with creatinine values exceeding 120 µmol/L starting on an ACE inhibitor or ARA. Nonetheless ACE inhibitors and ARA are associated with long term preservation of renal function and should be continued.[19] Greater increases should raise the suspicion of renal artery stenosis. After commencing an ACE inhibitor or ARA, creatinine and potassium should be checked within 7–10 days of starting and at least 6–12 monthly intervals during treatment.

Patients with early renal insufficiency

Early renal insufficiency, defined as a calculated or measured GFR between 30–60 mL/min per 1.73 m2, is a common yet under-recognised problem in Australia. Many of these patients have normal serum creatinine concentrations. Calculating the GFR, using formula such as the abbreviated MDRD (named after Modification of Diet in Renal Disease Study) equation (*Table 5*), is useful in identifying patients with early renal insufficiency.[20] Pathology laboratories will calculate and report an estimated GFR using this formula with requests for serum creatinine.[21]

Strategies to slow the progression of early renal insufficiency are similar to management of patients with

microalbuminuria. When appropriate, consideration should be given to early referral to a nephrologist.

Referral

As noted earlier, microalbuminuria in someone with diabetes is likely but not necessarily caused by diabetes. The finding of microalbuminuria should prompt review for other expected microvascular complications (especially retinopathy) and consideration of other possible causes (eg. IGA nephropathy). If there is any suspicion of a cause other than diabetes (eg. retinopathy is absent or mild) referral to a nephrologist needs to be considered. Clinical features shown in *Table 6* should prompt referral for more specialised management. Benefits of early referral include confirmation of diagnosis, delay progression of renal impairment, and other complications, patient education, preparation for dialysis and possibly improved survival and morbidity.

Managing later stages of renal failure

In general, when creatinine clearance drops to less than 30 mL/min all patients should be considered for referral to a nephrologist. In patients with advanced diabetic renal failure several specific points of management should be followed. Nephrotoxic agents such as X-ray contrast and NSAID should be avoided. Metformin, which may cause lactic acidosis, should also be avoided. When haemoglobin levels drop to 100 g/dL, erythropoietin therapy should be considered. When systemic acidosis develops bicarbonate therapy (840 mg capsules, 1–2 times per day) can be considered, remembering the risk of fluid retention and exacerbation of hypertension. Other beneficial effects of bicarbonate therapy include correction of hyperkalaemia.

In the very late stages of renal failure or in those with severe uraemic symptoms, dietary protein restriction is considered, however the MDRD study showed that protein restriction at best improved time off dialysis by approximately 6 months.[22] Generally patients with end stage renal disease (ESRD) from diabetes mellitus will be considered for starting dialysis at higher creatinine clearance (or lower serum creatinine levels) than patients with other causes of ESRD.

The decision regarding dialysis treatment modality is made on an individual basis. In general, patients with ESRD from diabetes are more likely to have peripheral vascular disease and are at greater risk of developing steal syndromes in the hands as a consequence of an arteriovenous fistula. Furthermore, patients with diabetic ESRD are more likely to have cardiac disease and are at greater risk of developing worsening cardiac failure in association with large fluid shifts of haemodialysis. Therefore, peritoneal dialysis with its gentler fluid shifts, preservation of residual renal function and avoidance of vascular access, is often been the preferred means of dialysis therapy in diabetic patients.

Renal transplantation is a viable option for patients with ESRD due to diabetes. Survival of patients with a renal transplant is superior to those remaining on dialysis and should be considered whenever possible. As many patients with diabetic nephropathy are older, they are less likely to be transplantation candidates. Pancreatic or combined kidney-pancreas transplantation is an option for younger patients with type 1 diabetes and is available for those who meet strict selection criteria.

Future treatment

Erythropoietin therapy in anaemic patients with moderately severe chronic renal insufficiency may be renoprotective.

Table 4. The nine nephropathic nasties

Nephrotoxic

Radiocontrast agents – low ionic agents, avoid dehydration

NSAID* – use paracetamol

ACE inhibitors – check renal function

Needs adjustment if GFR is reduced

Allopurinol – 100 mg/day per 30 mL/min of GFR

Digoxin – check levels

Sulphonamides – half dosage if GFR is <30 mL/min

Not used if GFR <30 mL/min

Some hypoglycaemics – glibenclamide, glimepiride, metformin

Potassium sparing diuretics – amiloride, triamterene, spironolactone

Tetracyclines

* including COX-2 'specific' NSAID

Table 5. Calculating GFR

The MDRD equation:

$GFR = 186 \times \{[\text{serum creatinine } (\mu mol/L)/88.4]^{-1.154}\} \times (age)^{-0.203} \times (0.742 \text{ if female}) \times (1.210 \text{ if Afro American})$

An automated calculator for MDRD may be found at http://kidney.org.au

Table 6. Indications for referral

- Advanced renal disease (calculated GFR <30 mL/min, proteinuria >3 g/24 hours)
- Glomerular haematuria
- Rapid decline in GFR (>10 mL/min/yr)
- Anaemia (haemoglobin <120 g/L)
- Difficult to control hyperglycaemia, hypertension or dyslipidaemia

Current randomised controlled trials such as Anaemia CORrection in Diabetes (ACORD) are assessing if erythropoietin has a renoprotective action.[23]

Evidence is emerging that newer treatments such as glycosaminoglycans (eg. sulodexide),[24] aldose reductase inhibitors (eg. epalrestat)[25] and peroxisome proliferator activator receptor-γ agonists (eg. troglitazone)[26] may reduce albumin excretion rates in micro- and/or macro-albuminuric patients with diabetes.

Conclusion

Diabetic nephropathy is common and has been associated with a poor prognosis. However, we now understand the contributors to diabetic nephropathy and there are new methods for early detection, medications to delay progression, and technologies for the management of renal failure. The general practitioner plays a strategic role in delaying and preventing diabetic nephropathy by coordinating and overseeing the multifactorial, multidisciplinary interventions.

Resources

- CARI guidelines: Caring for Australians with renal impairment. Available at www.kidney.org.au/cari
- New Zealand Guidelines Group: Primary care guidelines for the management of core aspects of diabetes care. Available at www.nzgg.org.nz/library/gl_complete/diabetes/index.cfm#contents
- National Heart Foundation of Australia: Guide to management of hypertension for doctors. Available at www.heartfoundation.com.au/prof/index_fr

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