Diabetic nephropathy - the quiet revolution

Part 2 – Current Therapy and Future Directions

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Strict metabolic control (target HbA1c < 7%) is fundamental to avoiding diabetic microvascular complications and can reverse early hyperfiltration, but has relatively less impact on retarding progression of established nephropathy. **Metformin** has a proven survival benefit, particularly in the overweight Type 2 diabetic patient, reducing hepatic glucose release and increasing insulin sensitivity, without increasing appetite and body weight (unlike sulphonylureas or insulin). The 1:40,000 patient-years risk of *lactic acidosis* (usually precipitated by an episode of sepsis or ischaemia) can be minimised by ceasing the drug prior to any hospitalisation. Metformin is *renally excreted* and must be dose-reduced in the elderly or renally impaired, proportional to the calculated GFR. Otherwise, it will accumulate, causing nausea and diarrhoea. I even use it in dialysis patients, but at doses of no more than 250mg/day (equivalent to 2grams/day in patients with normal kidney function).

The **glitazones** have recently provided a useful addition for patients with poorly controlled diabetes, where other oral agents are contraindicated or ineffective (authority required). Their onset of action can be delayed up to two months, and up to 20% of patients can develop significant fat or fluid weight gain.

Tight BP control (target BP 120/70, or lowest tolerable) is the cornerstone of management for all forms of established renal disease, and especially the high-risk diabetic patient. Achieving these targets can slow the loss of GFR from 5-10 mls/min/year to as little as 1-2mls/min/year (vs normal loss of 0.5ml/min/year with aging). Use of antihypertensives is more powerful renoprotection than tight diabetic control, increasing the chance of remission of microalbuminuria by 2.3-fold, compared to the 1.5-fold benefit seen with a 1% fall in HbA1c (Gaede, *NDT*, 2004).

Preferential use of **ACE inhibitors** and **Angiotensin receptor blockers**, especially combined with a thiazide, have a proven record in both Type 1 (mainly ACEIs) and Type 2 diabetes (ARB's) as well as non-diabetic nephropathy. In my hands, they work equivalently and I regard them as interchangeable in effectiveness. They can be used alone, but recent studies are showing additive benefits for proteinuria lowering (80-90% reduction vs. 40-50% with either agent alone) and renoprotection when **used in combination** (dual renin axis blockade, see Nakao et al, *Lancet* 2003), especially when augmented by a thiazide diuretic.

Patients with the greatest fall in proteinuria are the ones who gain the greatest renal protection; this rule holds for diabetic and non-diabetic nephropathy, with or without renin axis blockade (Bos et al, *Kidney Int* 2000). **Serial monitoring** of the urine albumin-creatinine ratio (ACR) in early nephropathy, or protein-creatinine ratio (PCR) in patients with heavier proteinuria, thus becomes a very useful prognostic indicator, equivalent to the "renal sphygmo".

Take-home messages

- Keep HbA1c < 7% to reduce risk of developing albuminuria.
- Dose reduce metformin according to GFR; stop if hospitalised.
- Keep BP < 120/70 to correct established microalbuminuria; expect to use 3-4 antihypertensives.
- Use ACEI's and ARB's in combination (plus thiazide) as firstline agents for optimum renoprotection (dual blockade).
- Regression of albuminuria/proteinuria is a good prognostic sign.
- Statins and aspirin for cardiovascular protection for all diabetics.
- Refer progressive nephropathy before GFR falls below 30mls/min.

In practice, **three or four BP agents combined** are usually required in large doses to achieve BP targets, often needing frusemide to deplete the associated salt and water retention. Close monitoring of postural BP and electrolytes is necessary to avoid exacerbating dizziness from autonomic neuropathy, if present.

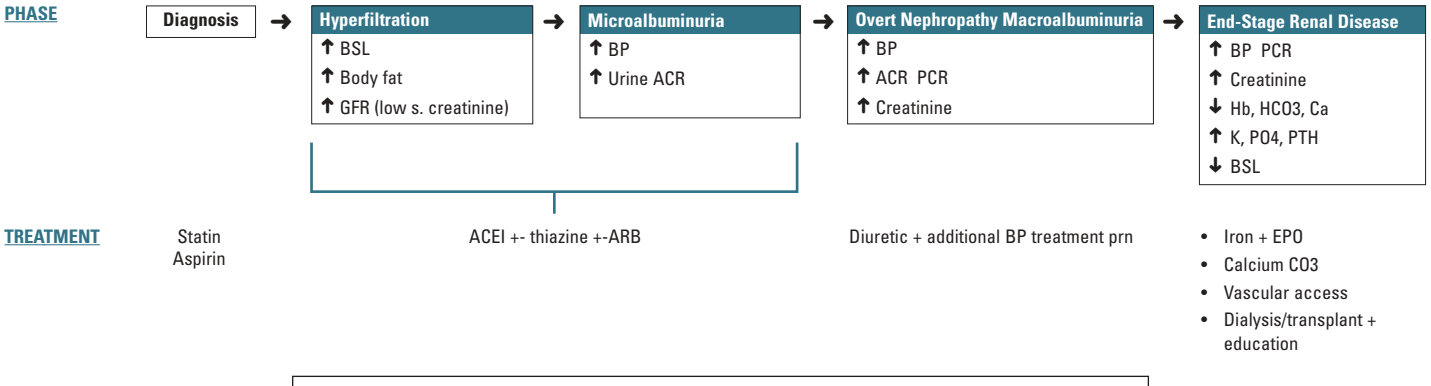
Statins have benefits beyond cholesterol-lowering and cardiovascular protection, with a small additive anti-proteinuric effect and renoprotective action (1.5 mls/min/year; Bianchi, *AJKD*, 2003). Given the advisability for **aspirin** as a further additional co-medication, it is clear that the "poly-pill" is long overdue for the diabetic nephropathy patient!

Standard **renal replacement therapies** such as erythropoeitin, dialysis and renal transplantation offer a reasonable quality of life in advanced renal failure. Patients with progressive nephropathy should be referred before the GFR reaches 30 mls/min, so that optimum education and preparation can be achieved. Mortality rates remain double that of non-diabetic patients (25% per annum on dialysis), predominantly due to accelerated atherosclerosis. Excellent results for kidney-pancreas transplantation are achieved at Westmead Hospital, NSW, for Type 1 diabetics under 50 years of age with no active coronary disease.

Areas of **current research** interest include:

- **Second-generation aminoguanidine derivatives** in reducing microvascular complications by inhibiting formation of advanced glycosylation end-products.
- The **anti-atherosclerotic** actions of ACEI and ARB's in reducing aortic plaque formation in diabetic animal models.
- The variable rates of **new-onset diabetes mellitus** (NODM) between different classes of antihypertensive. Compared to ACEI's, ARB's or calcium-channel blockers, approximately one extra NODM will be generated for every 7-25 patients treated for 30 years with a diuretic or beta-blocker (Dusing, *NDT*, 2004). Compared to a calcium channel blocker, an ARB reduced the incidence of NODM from 16% to 13% over 6 years (p< .0001; Julius, *Lancet*, 2004).

Progressive Diabetic Nephropathy



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