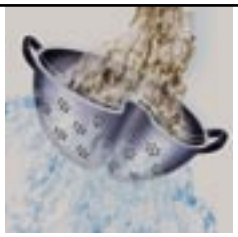

Diabetic nephropathy

How might we prevent, retard, or cope with it?

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BACKGROUND Working life for most Australian doctors in adult practice is heavily involved with diabetes and its complications. The development of nephropathy is strongly intertwined with that of retinopathy, neuropathy and vasculopathy, and with reduced life duration and quality. What can we do at the coalface of medical practice to prevent nephropathy occurring at all, to identify it early if it develops, and to maximally limit its impact after its emergence?

OBJECTIVE This article aims not to add to a literature bulging with comprehensive reviews of diabetic nephropathy, but to concisely summarise a useful evidence based approach to the evolutionary stages of the burgeoning problem of diabetic nephropathy.

DISCUSSION Until we can effectively prevent diabetes or achieve universal euglycaemia, our clinical focus will be on retarding the onset and progression of diabetic complications. Strategies dovetail with those offering best cardiovascular protection, and are strongly supported by evidence that best outcomes are achieved when blood pressure targets are met, the renin-angiotensin system is blocked, good glycaemic control is achieved, and smoking is avoided.

Preventing nephropathy in the general population

Can we prevent diabetes altogether?

Trite answers are easy – just prevent diabetes, or achieve constant normoglycaemia, and we can relegate diabetic complications to history... undoubtedly true, but as yet an unmet challenge. Type 1 diabetes has so far eluded preventive strategies directed against autoimmune islet attack, and type 2 diabetes thrives within our current lifestyle. Without endlessly bemoaning our endemic obesity, lack of habitual exercise and obsession with fast food or remote controls, the link between lifestyle and type 2 diabetes risk is well established. Lifestyle modification has been proven to successfully reduce the risks of impaired glucose tolerance and its progression to overt diabetes, as well as reducing other cardiovascular risk factors.[1,2] However, weight loss and exercise are not widely embraced or sustained even when advised. On a practical level, lifestyle intervention is very difficult to achieve, despite only modest changes in weight and physical activity being required.

Pharmacological interventions are more controversial, and many remain under study. Padwal et al[3] undertook a systematic review of the evidence for pharmacological prevention of type 2 diabetes. Metformin, acabose, thiazolidinediones, and orlistat have all been reported to prevent type 2 diabetes in randomised placebo controlled trials with diabetes incidence as the primary endpoint (*Table 1*). The latter two agents had a high dropout rate.

Current evidence for statins, fibrates, and antihypertensive agents (including renin-angiotensin system [RAS] blockers and oestrogen) is inconclusive,

although large studies designed for other endpoints have suggested lower rates of newly diagnosed diabetes in the treated groups. In addition, the critical question of whether drugs are preventing, or simply delaying onset of diabetes remains unresolved, although either may be beneficial. Currently, no single agent can be universally recommended for primary diabetes prevention; results of further studies are required. As a society we need to find effective ways to entrench regular exercise and healthy weight maintenance in our every day lives.

Preventing future diabetes in hypertensive patients

It may be time to carefully consider choice of an initial antihypertensive in terms of lifetime vascular risk reduction[4,5] – looking for bonus effect from antihypertensives. Hypertensive patients should be screened annually for elevated fasting blood glucose, and strongly encouraged to exercise and optimise their weight. It is very likely that the risk of developing future diabetes can be modified in either direction by our choice of antihypertensive drug. Opie[5] presented a meta-analysis of seven studies in almost 60 000 patients showing that compared to 'old therapies' (beta blockers and diuretics), blockers of the RAS decreased the occurrence of new onset diabetes by 20%. The number needed to treat by new rather than old therapies to avoid one case of new onset diabetes was 60–70 over 4 years. In individual studies included in this meta-analysis, the risks of developing diabetes over time are least for angiotensin converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARB) and greatest for thiazides.[6] However, the glucose intolerance induced by thiazides may be mediated mainly via hypokalemia[7] rather than by their direct effect. The development of diabetes in these studies had a large detrimental effect on cardiovascular risk.[8–10] Patients with either new or previous diabetes were almost three times more likely to develop subsequent cardiovascular disease than those who remained free of diabetes.

Conceivably, the combination of a diuretic with an ACE inhibitor may confer a lesser risk of thiazide induced new onset diabetes. In one small short term study, ACE inhibitors appeared to prevent the metabolically deleterious effect of thiazide.[11]

Table 1. Primary prevention of type 2 diabetes[3]

Drug	Relative risk diabetes	95% CI
Metformin	0.69	0.57–0.83
Acarbose	0.75	0.63–0.90
Troglitazone	0.45	0.25–0.83
Orlistat	0.63	0.46–0.86

Table 2. Summary of recommended interventions to significantly protect against cardiovascular and renal endpoints

The top 4 successful interventions to prevent nephropathy progression will also protect the patient from cardiovascular events:

- BP target ≤130/85 (in children, use age adjusted 90th centile BP levels)
- Use of ACE inhibitors and/or ARBs as first line antihypertensives
- HbA1c target ≤7.0%
- Cessation of smoking

Additionally, with evidence mainly for cardiovascular endpoints, the following are recommended:

- Good lipid control
- Low dose aspirin
- Lower BP target to <120/70–75 if <50 years (the higher target BP for older patients is based on clinical caution rather than any evidence for a J-curve effect in the diabetic population)

Preventing/retarding 'early' nephropathy in diabetic patients

Those with normal BP and AER/urinary albumin/creatinine ratio

There is currently insufficient evidence to recommend universal ACE inhibitor treatment for all diabetic patients with normal blood pressure (BP) and albumin excretion rates (AER), however large studies are in progress; one study[12] has published positive results.

There is excellent evidence that optimising glycaemia and avoiding smoking will lower the risk of nephropathy developing at this stage.[13–18] Routine annual screening for hyperlipidaemia and microalbuminuria is recommended, and BP should be measured at every visit.

Those with hypertension and/or elevated AER/urinary albumin/creatinine ratio

At this stage, optimising glycaemia (HbA1c target ≤7.0%) and avoiding smoking[17,18] remain important in limiting the rate of progression of diabetic nephropathy. However, the weight of evidence for intervention effect moves primarily to optimal BP control then to a RAS blockade.

In a large meta-analysis, BP reduction in itself resulted in the largest benefit in glomerular filtration

rate (GFR); preservation of 3.7 + 0.92 mL/min/year for each 10 mmHg reduction in mean arterial BP (MAP). Specific ACE inhibitor affect was additional to this.[19]

Angiotensin converting enzyme inhibitors are well established as first line antihypertensive therapy (level I evidence) in diabetics with hypertension and/or albuminuria of any degree.[20,21] Most studies were done in type 1 diabetes, or in mixed patient populations, but there is no evidence that type 2 diabetics are less protected by ACE inhibitors than type 1. Angiotensin receptor blockers also offer specific renoprotection in diabetic nephropathy beyond their antihypertensive benefit, with most studies being performed in type 2 diabetic patients.[22,24] A summary of recommended interventions is listed in *Table 2*.

Patient care recommendations

Routine clinical care of these patients should include BP measurement at each patient consultation and annual urinary monitoring of albumin/creatinine rations, lipids and protein/creatinine and renal function, including an estimation of GFR (now included in most laboratory reports of creatinine).

Which is better, ACE inhibitor or ARB? Should they be routinely combined?

Two ACE inhibitor versus ARB studies in type 2 hypertensive diabetics[25,26] have demonstrated similar short term effects, but long term data is unavailable. Meanwhile, available data suggest that either drug class has similar effects. Although dual blockade is not yet established as a first line treatment for all patients with diabetic nephropathy, it is often helpful in reaching target BP and in reducing albuminuria. Both ACE inhibitors and ARBs should be suspended in situations where water and sodium depletion is present (eg. in gastroenteritis). Dual blockade does carry a risk of hyperkalaemia and increased creatinine, and patients need to be both regularly monitored and well informed.

Overt diabetic nephropathy

How to retard/cope with it?

Diabetic patients with elevated urinary protein/creatinine ratio are usually hypertensive, have established nephropathy, and are at high risk for progressive renal failure. This stage is defined by routine urine dipsticks detecting proteinuria. Blood pressure control remains the most effective strategy we have at this stage – but commonly this is more difficult as the disease progresses. A meta-analysis of nine studies[27] of proteinuric patients with overt nephropathy, demonstrated a fourfold reduction in the decline of GFR when MAP was below 100 mmHg.

Multivariate analysis on data from the RENAAL study[28] documented, in type 2 diabetics with nephropathy, that baseline systolic BP (SBP) is a stronger predictor of renal outcomes than is diastolic BP (DBP). Patients with highest base line pulse pressure had both the highest risk of progression and the greatest risk reduction when SBP was lowered below 140 mmHg.

Excellent BP control in patients with advanced nephropathy is only achievable with patient and physician commitment (usually requiring at least three drugs[29]). Consideration of nonpharmacological adjunctive therapy remains useful. Weight loss, while highly desirable, is disappointingly difficult for many type 2 diabetics; but if possible does improve BP control.

Antihypertensive drug doses may need to be flexible. For example, patients may need to reduce or withhold drugs on very hot days, and may tolerate night time dosing better than morning. Drugs acting on the RAS will be relatively ineffective if the patient is salt loaded – and may cause hypotension in salt depletion – and both ACE inhibitors and ARBs should be suspended in situations were water and sodium depletion is present (eg. in gastroenteritis). It may not be possible to adapt such a flexible approach to all patients, but many will understand this approach and will benefit.

Patient care recommendations

Patients with overt diabetic nephropathy should have protein/creatinine, urea, electrolytes, creatinine and GFR estimation checked every 3–6 months, and lipids every 6 months. Blood pressure should be taken at each contact, and BP outside target should provoke a therapeutic response.

What about reducing dietary protein intake? Is it worth the hassle?

Studies of dietary protein restriction in diabetic nephropathy are marred by small numbers, limited follow up, compliance problems, failure to adequately assess nutritional impact of protein restriction, publication bias, and overlap between 'low' and 'high' protein intake groups. Overall, a small volume of evidence suggests that all patients with renal involvement from diabetes should restrict protein intake to 0.75 g/kg/day (the World Health Organisation

recommended minimum safe daily intake). The expected benefit is modest in comparison with the benefits of good BP control and ACE inhibitor therapy. Evidence is best for type 1 diabetes with either microalbuminuria or overt nephropathy,[21] but is lacking in type 2 diabetes with established diabetic nephropathy. The Kidney Disease Outcomes Quality Initiative of the US National Kidney Foundation (K/DOQI) recommends that protein restriction of 0.8 g/kg/day (20% of daily calories) be initiated at the onset of overt nephropathy.

Resources

- American Diabetes Association: www.diabetes.org/for-health-professionals-and-scientists/cpr.jsp-
- Australian Paediatric Endocrinology Group: www.chw.edu.au/prof/services/endocrinology/apeg/apeg_handbook_final.pdf
- Australian Diabetes Society: www.racp.edu.au/ads/posstate.htm
- Australian Paediatric Endocrinology Group: www.chw.edu.au/prof/services/endocrinology/apeg/apeg_handbook_final.pdf
- CARI: www.kidney.org.au/cari/CARI_guidelines.php
- K/DOQI: www.kidney.org/professionals/kdoqi/guidelines

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