Prevention of progression of kidney disease: diabetic nephropathy

CARI guidelines

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The Caring for Australasians with Renal Impairment (CARI) guidelines initiative is an Australian and New Zealand project that aims to provide high quality, evidence based clinical practice guidelines for the management of all stages of kidney disease. This article summarises CARI guidelines on the Prevention of progression of kidney disease: diabetic nephropathy. Complete CARI guideline detail is available at www.cari.org.au.

Data sources

Medline, Embase, Cochrane Clinical Trials database.

Study selection and assessment

High level evidence (ie. level I and II, systematic reviews of randomised controlled trials [RCTs] or standard RCT studies) was available. Guideline recommendations were developed using evidence from observational studies such as cohort, case control and case series studies.

Summary of evidence and suggestions for clinical care

Glucose control

Glycosylated haemoglobin (HbA1c) should be maintained at or <7% for primary prevention of diabetic nephropathy and for prevention of progression from microalbuminuria to overt nephropathy. The longer patients can maintain a target HbA1c level of 7.0% the greater their protection from nephropathy. However, optimal glycaemic control (preprandial plasma glucose 4.4–6.7 mmol/L and HbA1c <7%) carries increased risk of hypoglycaemia.

Smoking

Smoking accelerates the development and progression of diabetic nephropathy. Cessation of smoking retards progression of diabetic nephropathy. Current smoking confers a greater risk than former smoking. All patients with type 1 or type 2 diabetes should be strongly advised against commencement/continuation of smoking to reduce the risk of developing and accelerating diabetic nephropathy as well as for vascular health.

Antihypertensive therapy

Effective blood pressure (BP) control is the single most important factor in limiting the rate of progression of diabetic nephropathy. Adequate control of BP slows progression of nephropathy and reduces cardiovascular events. Most hypertensive patients will require treatment with two or more antihypertensives to achieve optimal BP control. Goal blood pressures should be <130/80 mmHg in patients aged 50 years and over and <125/75 mmHg for those aged less than 50 years. The recommendation of target BP to vary with age is based on clinical caution in a population at risk of cerebrovascular disease rather than any evidence for a J-curve effect in the diabetic population. Patients aged 50 years of age and over with type 2 diabetes commonly have high systolic blood pressure (SBP) and pulse pressure, but normal diastolic blood pressure (DBP). Therapy in this group needs to target SBP.

The JNC7 defines hypertension in patients with chronic kidney disease or diabetes as BP >130/80, so it makes sense to use this target. However, most studies were not done under this definition, and there is little discriminatory evidence between small differences in the continuous variables of SBP and DBP for renal endpoints.

ACE inhibitor and ARA treatment

All patients with microalbuminuria or overt nephropathy should be treated with an angiotensin converting enzyme (ACE) inhibitor or angiotensin II receptor antagonist (ARA), independent of BP and glomerular filtration rate (GFR). Evidence for specific renoprotection beyond antihypertensive benefit is stronger for ACE inhibitor in

type 1 and ARA for type 2 diabetes, but there is no evidence that responses are different between types. Hypertensive diabetics without albuminuria should be treated with an ACE inhibitor or ARA as first line antihypertensive therapy. There is currently insufficient evidence to recommend universal ACE inhibitor or ARA treatment for all diabetic patients with normal BP and albumin excretion rate.

A strong association between acute increases (up to 30%) in serum creatinine on initiation of ACE inhibitor or ARA treatment, stabilising within the first 2 months of therapy, and long term preservation of renal function has been shown. ACEI inhibitor/ARA therapy should be withdrawn only if creatinine increases >30% above baseline within the first 2 months of therapy. Use of ACE inhibitors may exacerbate hyperkalaemia in patients with kidney failure and/or hyporeninaemic hypoaldosteronism. Additional caution is recommended in patients on concomitant nonsteroidal anti-inflammatory agents.

ACE inhibitor and ARA combination treatment

There is currently insufficient evidence that ACE inhibitors and ARAs are of additive specific benefit beyond additional antihypertensive benefit. Although dual blockade is not yet established as a first line treatment for all patients with diabetic nephropathy, it may be helpful in reaching treatment goals for BP and albuminuria in individual patients. Both ACE inhibitors and ARAs should be suspended in situations where water and sodium depletion is present.

Specific effects of CCBs

There is insufficient evidence to recommend routine use of dihydropyridine calcium channel blockers (CCBs) unless required for antihypertensive action. There is a small additional benefit on proteinuria from the addition of nondihydropyridine CCBs to ACE inhibitors. Calcium channel blockers are recommended as second line treatment and are frequently required for optimal BP control. There is a small benefit of nondihydropyridines over dihydropyridines for protection against progression of proteinuria. There is no evidence that CCBs influence decline of GFR beyond their antihypertensive benefit.

Control of hypercholesterolaemia

All hypercholesterolaemic diabetics should be treated with an HMG-CoA reductase inhibitor to retard progression of nephropathy. There is no evidence on which to base recommendations for target total cholesterol, LDL, HDL or triglyceride levels. All diabetic patients should receive hypolipidemic therapy for cardiovascular protection in accordance with the National Heart Foundation and the Australian Diabetes Association, but there is no evidence for renal endpoints on which to base lipid targets.

Protein restriction

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 expected benefit is modest in comparison with the benefits of good BP control and ACE inhibitor therapy.

Multifactorial therapy and the progression of diabetic nephropathy

Intensive combination therapy protects against progression of diabetic nephropathy. Patient motivation, compliance and total cost of therapy may be limiting issues. Multifactorial therapy is likely to be embraced long term only by highly motivated patients. For motivated patients, the limited available data suggest possible synergistic effects of multifactorial intervention, for both micro- and macro-vascular endpoints.

Intensive combination therapy is not uniform across different trials, but includes various combinations of the following:

- lifestyle modification: low fat diet, exercise, no smoking
- ACE inhibitor independent of BP
- low dose aspirin for primary cardiovascular prevention in all diabetic patients aged 30 years and over, and for secondary prevention in all diabetic patients with evidence of large vessel disease
- stepwise pharmacologic therapy to reduce glucose levels (aim HbA1c <7.0), BP and lipid levels.

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