

Multifactorial therapy and the progression of diabetic Nephropathy

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GUIDELINES

Intensive combination therapy protects against progression of diabetic nephropathy. (Level II evidence for Type 2 diabetes – single RCT) and Level III evidence for Type 1 diabetes – single small cohort study, small volume)

SUGGESTIONS FOR CLINICAL CARE

(Suggestions are based on Level III and IV evidence)

Patient motivation, compliance and total cost of therapy may be limiting issues. Multi-factorial 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.

Background

The evolution of evidence for multiple single interventions being beneficial in diabetic nephropathy has spawned multiple further questions. Should all patients have all interventions? Will all the variably effective individual interventions be synergistic if used concomitantly? This guideline evaluated the evidence for multiple-intervention strategies in the progression of diabetic nephropathy.

Search strategy

Databases searched: The Cochrane Renal Group Specialised Register was searched for randomised controlled trials relating to the prevention of progression of kidney disease in people with diabetes mellitus Type 1 and Type 2. Specific interventions included antihypertensive therapies, ACE inhibitors, A II receptor antagonists, calcium channel blockers, dietary protein restriction and glucose control, and interventions to control hypercholesterolemia and hyperlipidemia.

Date of search: 16 December 2003.

What is the evidence?

Combined therapy targeting multiple risk factors in diabetic nephropathy has been tested in two studies.

Type 1 diabetes

In an open longitudinal study of 14 Type 1 diabetics, Manto et al (1995) intensively treated all patients with multiple daily insulin injections, angiotensin-converting enzyme inhibitor (ACEI) antihypertensive treatment to BP 120/75 mmHg, and an 0.8 g/kg/day

protein diet. They achieved a rise in glomerular filtration rate (GFR) and decrease in albuminuria over the 3-year study.

Type 2 diabetes

Gaede et al (1999) randomised 160 microalbuminuric Type 2 diabetics to standard care (treated in accordance with national guidelines for Type 2 diabetes) or to stepwise “intensive” treatment comprising low fat-diet and exercise, smoking cessation if needed, ACEI (or ARB) independent of BP, Vitamins C, E, and folate, low dose-aspirin, and stepwise pharmacological therapy to reduce glucose levels (aim HbA_{1c} < 7.0 %), BP (aim < 140/85 mmHg) and lipid levels (aim cholesterol < 5 mmol/L), with follow up of 3.8 years. In this unblinded trial, the intensive treatment group had lower risk of progression to proteinuria (11% vs 25% RRR 56%, 95%CI: 9–79, P = 0.01).

The 7.8 year follow-up of this (Steno 2) study was reported by Pedersen and Gæde (2003). There was no difference in weight gain between groups during follow up and no major side-effects. The primary endpoint was a composite macrovascular outcome of death from cardiovascular causes, non-fatal myocardial infarction, coronary artery bypass grafting, percutaneous coronary intervention, non-fatal stroke, amputation for ischemia, or vascular surgery for peripheral arterial atherosclerosis. A total of 44% of patients in the conventional group had a cardiovascular event compared with 24% in the intensive group, hazard ratio 0.47. The secondary endpoints of progression to overt proteinuria (HR 0.39), retinopathy (HR 0.42), and autonomic neuropathy (HR 0.37) were also diminished in the intensively-treated group.

Summary of the evidence

Evidence is sparse, but the effect seems clinically significant.

What do the other guidelines say?

Kidney Disease Outcomes Quality Initiative: Multiple interventions are required to slow progression of kidney disease and reduce the risk of cardiovascular disease (CVD) events in diabetic kidney disease. Generally, the approach requires at least 3 antihypertensive agents, intensive insulin therapy in Type 1 diabetes, two drugs for glucose control in Type 2, at least 1 lipid-lowering agent, and emphasis on lifestyle modification including diet and exercise.

UK Renal Association: No recommendation.

Canadian Society of Nephrology: No recommendation.

European Best Practice Guidelines: No recommendation.

International Guidelines:

The American and Canadian Diabetes Associations: recommend aspirin (enteric coated, 81–325 mg/day) for primary cardiovascular prevention in all diabetics > 30 years, especially if another risk factor is present, and also for secondary prevention in all diabetics with evidence of large vessel disease.,

The American Diabetes Association Position Statement (2004): recommends aspirin (75–162 mg/day) for:

1. primary cardiovascular prevention in all diabetics with increased cardiovascular risk, including age > 40 or presence of another risk factor (A for Type 2, C for Type 1).
2. secondary cardiovascular prevention in diabetics with a history of myocardial infarction, vascular bypass procedure, stroke or transient ischemic attack, peripheral vascular disease, claudication, and/or angina. (A)

Avoid < 21years old due to risk of Reye's syndrome. People under the age of 30 have not been studied. Other antiplatelet agents e.g. clopidogrel may be a reasonable alternative for patients with high risk. (E)

American Association of Clinical Endocrinology (2000): Low dose aspirin > 30 mg/day recommended in all diabetics for primary and secondary prevention.

Canadian Diabetes Association: People with Type 1 or 2 diabetes should be encouraged to adopt a healthy lifestyle to lower their risk of CVD. This entails healthy eating habits, achieving and maintaining a healthy weight, regular physical activity, and stopping smoking (Grade D, consensus).

Scottish Intercollegiate Guideline Network (2001): Use aspirin 75 mg/day as primary cardiovascular prevention in all diabetics with well-controlled hypertension when 10-year risk of major cardiovascular event > 20%.

Implementation and audit

K-DOQI (2004): The number of medications is one obstacle to adherence – need to consider the cost, side-effects and convenience.

Suggestions for future research

No recommendation.

References

Gaede P, Vedel P, Parving HH et al. Intensified multifactorial intervention in patients with type 2 diabetes mellitus and microalbuminuria: the Steno type 2 randomized study. *Lancet* 1999; 353: 617–22.

Manto A, Cotroneo P, Marra G et al. Effect of intensive treatment on diabetic nephropathy in patients with type 1 diabetes. *Kidney International* 1995; 47: 231–5.

Pedersen O, Gaede P. Intensified multifactorial intervention and cardiovascular outcome in type 2 diabetes: the Steno-2 study. *Metabolism*. 2003; 52(8 Suppl 1): 19–23.

Out of date

Appendices

Table 1 Characteristics of included studies

• Study ID (author, year)	N	Study design	Setting	Participants	Intervention (experimental group)	Intervention (control group)	Follow up (years)	Comments
Gaede et al, 1999	160	Randomised controlled clinical trial	Renal clinic	160 patients with microalbuminuria	Intensive treatment	Standard treatment	3.8 yrs	

Table 2 Quality of randomised trials

Study ID (author, year)	Method of allocation concealment	Blinding			Intention-to-treat analysis	Loss to follow up (%)
		(participants)	(investigators)	(outcome assessors)		
Gaede et al, 1999	Not specified	No	No	Yes	No	6.9

Table 3 Results for dichotomous outcomes

Study ID (author, year)	Outcomes	Intervention group (number of patients with events/number of patients exposed)	Control group (number of patients with events/number of patients not exposed)	Relative risk (RR) [95% CI]	Risk difference (RD) [95% CI]
Gaede et al, 1999; Pedersen Gaede, 2003	CV mortality	3/77	2/78	1.52 (95%CI: 0.26, 8.84)	0.01 (95%CI: -0.04, 0.07)
	Non-fatal myocardial infarction	4/77	4/78	1.01 (95%CI: 0.26, 3.91)	0.00 (95%CI: -0.07, 0.07)
	Non-fatal stroke	1/77	8/78	0.13 (95%CI: 0.02, 0.99)	-0.09 (95%CI: -0.16, -0.02)
	Cardiovascular event	18/73	33/76	0.57 (95%CI: 0.35, 0.91)	-0.19 (95%CI: -0.364, -0.04)

Table 4 Results for continuous outcomes

Study ID (author, year)	Outcomes	Intervention group (mean [SD])	Control group (mean [SD])	Difference in means [95% CI]
Gaede et al, 1999	SBP (mmHg)	-8 (18)	-4 (17)	-4.00 (95%CI: -9.63, 1.63)
	DBP (mmHg)	-7 (10)	-5 (10)	-2.00 (95%CI:-5.21, 1.21)
	Total cholesterol (mmol/L)	-0.6 (0.9)	-0.2 (1.3)	-0.40 (95%CI:-0.76, -0.04)
	LDL cholesterol (mmol/L)	-0.4 (0.8)	-0.1 (1.4)	-0.30 (95%CI:-0.66, 0.06)
	HDL cholesterol (mmo/L)	0.02 (0.2)	0.03 (0.2)	-0.01 (95%CI:-0.07, 0.05)
	Serum creatinine (mmol/L)	13 (21)	11 (17)	2.00 (95%CI:-4.15, 8.15)
	GFR (ml/min/1.73m ²)	-11 (20)	-13 (15)	2.00 (95%CI:-3.69, 7.69)