

Control of Hypercholesterolaemia and Progression of Diabetic Nephropathy

Date written: September 2004

Final submission: September 2005

Author: Kathy Nicholls

GUIDELINES

- a. All hypercholesterolaemic diabetics should be treated with HMG-CoA reductase inhibitor to retard progression of nephropathy. (Level III evidence for Type 1 diabetes; Level II evidence for Type 2 diabetes - small volume of data) There is no evidence on which to base recommendations for target total cholesterol, LDL, HDL or triglyceride levels.
- b. All diabetic patients should receive statin therapy for cardiovascular protection. (Level I evidence)

SUGGESTIONS FOR CLINICAL CARE

(Suggestions are based on Level III and IV sources)

- In the absence of evidence to guide target lipid levels for renal endpoints, it is reasonable to follow the recommendations of the National Heart Foundation and the Australian Diabetes Association Guidelines - recommend fasting total cholesterol level < 5.0 mmol/L, LDL < 3.0 mmol/L.

Background

Hyperlipidaemia is a risk factor for progression of multiple experimental models of renal disease, and human studies indicate that it may also accelerate non-diabetic renal disease, as well as being a well-recognised vascular risk factor. This section reviews the evidence that therapy to lower lipids protects against the progression of diabetic nephropathy. Evidence that lowering lipid levels with HMG-CoA reductase inhibitors has cardiovascular benefit is strong, and for practical purposes will drive therapy in diabetic patients. This evidence will not be reviewed here.

Search strategy

Databases searched: The Cochrane Renal Group Specialised Register was searched for randomised controlled trials (RCTs) 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?

There are no large long-term RCTs designed to determine whether or not control of hypercholesterolaemia, and/or treatment with HMG-CoA reductase inhibitors retard progression of diabetic nephropathy. One meta-analysis (Fried et al 2001) studied rate of renal function decline in 13 prospective controlled studies, done over 3–24 months and published between 1991 and 1999. Of a total of 404 patients, 253 were diabetic. There was a lower rate of glomerular filtration rate (GFR) decline in patients on lipid-lowering agents (95%CI: 0.026 -0.285 mL/min/month, P=0.008), especially in the longer follow-up groups. There was also a trend to lower proteinuria or albuminuria (P=0.077).

Type 1 diabetes

Mulec (1990) followed 31 diabetics with established nephropathy, and observed a greater GFR decline rate in hypercholesterolaemic patients (Chol > 7 mmol/L GFR decline 8.4 mL/min/year; Chol < 7 mmol/L GFR decline 2.3 mL/min/year).

The Joslin Group also demonstrated hypercholesterolaemia to predict rapid loss of renal function in Type 1 diabetics with overt nephropathy (Krolewski et al 1994).

Type 2 diabetes

Nielsen et al (1993) performed a very small RCT (double-blind, randomized and placebo-controlled) of the effect of simvastatin (10–20 mg/day) on renal function and insulin sensitivity in 18 Type 2 diabetics with microalbuminuria and moderate total cholesterol \geq 5.5 mmol/L. Simvastatin (n = 8) for 36 weeks significantly reduced total cholesterol, LDL-cholesterol and apolipoprotein B, but neither GFR nor urinary albumin excretion rate changed significantly during the study in either group.

Gall et al (1997) followed a cohort of 176 patients with Type 2 diabetes mellitus and normoalbuminuria for median follow-up of 5.8 years to determine the risk factors associated with the development of incipient and overt diabetic nephropathy.

They documented that increased cholesterol level was an independent risk factor for progression to nephropathy (RR 1.4, 95%CI: 1.1 – 1.7, P < 0.01).

Lam et al (1995) (RCT, placebo-controlled study) showed benefit of HMG-CoA reductase inhibition over 2 years in 34 Type 2 diabetics with hypercholesterolaemia

and overt nephropathy with stabilised GFR, whereas the placebo group had decreased GFR. There was no significant change in proteinuria.

The GREACE study (Athiros et al 2003, 2004) was not a RCT, but prospectively evaluated the effect of 3 years of 'structured' treatment with atorvastatin (to LDL < 2.6 mmol/L, mean dose 23.7 mg/day) vs. non-standardised 'usual care' on morbidity and mortality of 1600 patients with coronary heart disease (CHD), with analysis of the subgroup with diabetes (n = 313). A total of 17% of the usual care patients were on long-term hypolipidemic drug treatment. During the study, 46 of 152 (30%) diabetic CHD patients on usual care vs. 20 of 161 (12.5%) patients on structured care experienced a major vascular event or died; RRR 58%, $P < 0.0001$. The RRRs for the primary end-points were: all-cause mortality 52%, $P = 0.049$; coronary mortality 62%, $P = 0.042$; coronary morbidity 59%, $P < 0.002$; and stroke 68%, $P = 0.046$. Event rate curves started deviating from the sixth treatment month and the RRR was almost 60% by the 12th month, remaining stable for the next 2 years.

Renal functional decline was reported separately (Athiros et al 2004). All patients had initially normal plasma creatinine, with 642 patients K/DOQI Stage 1, 864 Stage 2, and 94 Stage 3. Creatinine clearance (Ccr) was estimated (for up to 48 months) by the Cockcroft-Gault formula, at baseline, 6 weeks, then 6-monthly. Patients from both groups not treated with statins (704) showed a 5.2% decrease in Ccr ($P < 0.0001$). Usual care patients on various statins (simvastatin, pravastatin, atorvastatin or fluvastatin, in total 97 patients) had a 4.9% increase in Ccr ($P = 0.003$). Structured care patients on atorvastatin had a 12% increase in Ccr ($P < 0.0001$). This effect was more prominent in the lower two quartiles of baseline Ccr (patients with a GFR < 77 mL/min had a mean increase in Ccr of 15.4%) and with higher atorvastatin doses (40–80 mg/day; n = 112, showed 13.8% increase in Ccr, while in those on 10–20 mg/day; n = 688, Ccr increase was 10.9%, $P = 0.001$). Statin treatment prevented the decline in renal function seen in untreated dyslipidaemic patients with CHD. In treatment-based analysis, 687 patients in the usual care group showed a mean reduction in Ccr of 5.3% ($P < 0.0001$). Seventeen patients in the structured care group who discontinued atorvastatin for various reasons, had a decrease in Ccr of 4.9% ($P = 0.02$).

Whether or not HMG-CoA reductase inhibition confers benefit for renal endpoints in diabetes is highly unlikely to ever be adequately studied in humans, because the weight of evidence for cardiovascular benefit is strong, even in normolipidaemic patients without evidence of cardiovascular disease. Studies in microalbuminuric diabetic patients are limited by small patient numbers, short duration of follow-up, and lack renal functional endpoints.

The diabetic patient subgroup (n = 5963) of the MRC/BHF Heart Protection Study, in which patients were randomly allocated to receive 40 mg simvastatin daily or matching placebo, had a 22% (95%CI: 13–30) reduction in first event rate (major coronary event, stroke or revascularisation) on simvastatin (601 [20.2%] simvastatin vs 748 [25.1%] placebo, $P < 0.0001$). There were also highly significant reductions of 33% (95%CI: 17–46, $P = 0.0003$) among the 2912 diabetic participants who did not have any diagnosed occlusive arterial disease at entry, and of 27% (95%CI: 13–40, $P = 0.0007$) among the 2426 diabetic participants whose pretreatment LDL cholesterol concentration was below 3.0 mmol/L (116 mg/dL). Risk reduction was similar in Type 1 and Type 2 diabetics. In participants who had a first major vascular event following

randomisation, allocation to simvastatin reduced the rate of subsequent events. The average difference in LDL cholesterol was 1.0 mmol/L during the 5-year treatment period. In diabetic patients without occlusive arterial disease, 5 years of treatment would be expected to prevent about 45 people per 1000 from having at least one major vascular event, and among these 45, to prevent 70 first or subsequent events.

Another primary prevention-randomised, placebo-controlled trial in Type 2 diabetic patients (Colhoun et al 2004) showed a 37% risk reduction in cardiovascular events in patients treated with atorvastatin 10mg/day.

Summary of the evidence

There are no adequate RCTs with functional endpoints and long-term follow up. One meta-analysis of 13 small, prospective, controlled studies in which diabetics were enrolled suggested benefit of HMG-CoA reductase inhibition, as did cohort studies. The GREASE prospective cohort study in 1600 patients included diabetic subjects and indicated risk reduction for progression of renal dysfunction in hyperlipidaemic patients with coronary disease when they were treated with high-dose statins. For practical purposes, the argument to treat dyslipidaemia for renal outcome is overwhelmed by the very large body of Level I evidence for vascular risk reduction.

What do the other guidelines say?

Kidney Disease Outcomes Quality Initiative (2004): No recommendation.

UK Renal Association: No recommendation.

Canadian Society of Nephrology: No recommendation.

European Best Practice Guidelines: No recommendation.

International Guidelines:

American Diabetic Association (2001): For adult diabetics, aim LDL < 2.6, HDL > 1.15 male, 1.40 female. Initiate drug therapy at LDL > 3.35. Aim TG < 2.3. Children – LDL < 2.8.

American Diabetic Association (2004): Use statin in all diabetics > 40 with total cholesterol 5.5, to achieve an LDL reduction of approximately 30% regardless of baseline LDL (A).

The first priority of pharmacological therapy is to lower LDL cholesterol to 2.60 mmol/L. For LDL lowering, statins are the drugs of choice and should be added to lifestyle modification focusing on the reduction of saturated fat and cholesterol intake, weight loss, increased physical activity, and smoking cessation. (A)

Lowering LDL cholesterol with a statin is associated with a reduction in cardiovascular events. (A)

In children and adolescents with diabetes, LDL cholesterol should be lowered to 2.60 mmol/L (E).

AACE (2000): Goal LDL < 2.6.

National Heart Foundation Australia: Total cholesterol < 5.0, LDL < 3.0

Scottish Intercollegiate Guideline Network (2001): Use drug therapy as primary cardiovascular prevention in Type 2 diabetics without nephropathy when 10-year risk of major cardiovascular event > 30%.

American College of Physicians: (Snow et al 2004) Control lipid levels in type 2 diabetes to macrovascular risks: use as secondary prevention in all patients with known coronary artery disease and as primary prevention in patients with any other cardiovascular risk factor. Recommendations apply equally to men and to women. Once lipid-lowering therapy is initiated, patients should take at least a moderate dose of a statin: e.g. atorvastatin 20 mg, lovastatin 40 mg, pravastatin 40 mg or simvastatin 40 mg. Trials have generally not helped in defining target levels for either total cholesterol or LDL cholesterol. Benefits have been obtained regardless of baseline lipids, and when treatment targets were set in earlier trials they were sometimes higher than those commonly accepted today.

Canadian Diabetes Association: Treat patients at high risk of vascular event: LDL-C < 2.5 mmol/L and TC: HDL-C < 4.0; and for patients at moderate risk of vascular event LDL-C < 3.5 mmol/L and TC: HDL – C < 5.0 (Grade D, consensus). Although current evidence does not support specific targets for apoB or TG, the optimal TG level is < 1.5, and optimal apoB < 0.9 g/L for high-risk, and < 1.05 g/L for moderate-risk patients (Grade D, consensus).

Implementation and audit

No recommendation.

Suggestions for future research

No recommendation.

References

American Diabetes Association: Standards of medical care in diabetes - Diabetes Care 2004; 27 (Suppl 1): S15–S35.

Athyros VG, Papageorgiou AA, Symeonidis AN et al; GREACE Study Collaborative Group. Early benefit from structured care with atorvastatin in patients with coronary heart disease and diabetes mellitus. *Angiology* 2003; 54: 679–90.

Athyros VG, Mikhailidis DP, Papageorgiou AA et al. The effect of statins versus untreated dyslipidaemia on renal function in patients with coronary heart disease. A subgroup analysis of the Greek atorvastatin and coronary heart disease evaluation (GREACE) study. *J Clin Pathol* 2004; 57: 728–734.

Colhoun HM, Betteridge DJ, Durrington PN et al. Primary prevention of cardiovascular disease with atorvastatin in type 2 diabetes in the Collaborative Atovastatin Diabetes Study (CARDS): multicentre randomized placebo-controlled trial. *Lancet* 2004; 364: 685–96.

Fried LF, Orchard TJ, Kasiske BL. Effect of lipid reduction on the progression of renal disease: a meta-analysis. *Kidney Int* 2001; 59: 260–9.

Gall MA, Hougaard P, Borch-Johnsen K et al. Risk factors for development of incipient and overt diabetic nephropathy in patients with non-insulin dependent diabetes mellitus: prospective, observational study. *BMJ* 1997; 314: 783–8.

Krolewski AS, Warram JH, Christlieb AR. Hypercholesterolemia: A determinant of renal function loss and deaths in IDDM patients with nephropathy. *Kidney Int. Suppl.* 1994; 45: S125–S31.

Lam KSL, Cheng IKP, Janus ED et al. Cholesterol-lowering therapy may retard the progression of diabetic nephropathy. *Diabetologia* 1995; 38: 604–09.

Lindholm LH. Major benefits from cholesterol lowering in patients with diabetes. *Lancet* 2003; 361: 2000–1.

Molitch ME, De Fronzo RA, Franz MJ et al. Diabetic nephropathy. *Diabetes Care* 2003 ; 26 (Suppl 1): S94–S98.

Mulec H, Johnson SA, Bjorck S. Relationship between serum cholesterol and diabetic nephropathy. *Lancet* 1990; 335: 1537–38.

Nielsen S, Schmitz A, Rehling M et al. Systolic blood pressure relates to the rate of decline of glomerular filtration rate in type II diabetes. *Diabetes Care* 1993; 16: 1427–32.

Snow V, Aronson MD, Hornbake ER et al. Lipid control in the management of type 2 diabetes mellitus: A clinical practice guidelines from the American College of Physicians. *Annals of Internal Medicine* 2004; 140: 644–49.

Appendices

Table 1 Characteristics of included studies

Study ID (author, year)	N	Study Design	Setting	Participants	Intervention (experimental group)	Intervention (control group)	Follow up (months)	Comments
Lam et al, 1995	36	Randomised controlled clinical trial	University hospital	34 Chinese NIDDM patients	Lovastatin	Placebo	2 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)		
Lam et al, 1995	Block randomisation	Yes	No	No	No	5.6

Table 3 Results for continuous outcomes

Study ID (author, year)	Outcomes	Intervention group (mean [SD])	Control group (mean [SD])	Difference in means [95% CI]
Lam et al, 1995	Mean arterial BP (mmHg) at 24 mo	105.9 (12.8)	103.4 (11.9)	2.50 (95%CI: -5.84, 10.84)
	BMI (kg/m ²) at 24 mo	26.3 (4.4)	25.0 (4.24)	1.30 (95%CI: -1.61, 4.21)
	HbA _{1c} (%) at 24 mo	6.6 (1.6)	6.8 (1.70)	-0.20 (95%CI: -1.31, 0.91)
	Total cholesterol (mmol/L) at 24 mo	4.9 (0.4)	6.4 (0.85)	-1.50 (95%CI: -1.94, -1.06)
	Triglyceride (mmol/L) at 24 mo	2.0 (1.6)	3.7 (2.55)	-1.70 (95%CI: -3.12, -0.28)
	HDL-cholesterol (mmol/L) at 24 mo	1.09 (0.24)	0.99 (0.30)	0.10 (95%CI: -0.08, 0.28)
	LDL-cholesterol (mmol/L) at 24 mo	3.0 (0.8)	3.8 (0.85)	-0.80 (95%CI: -1.35, -0.25)
	Apo A1 (h/L) at 24 mo	1.98 (0.32)	1.90 (0.30)	0.08 (95%CI: -0.13, 0.29)
	Apo B (g/L) at 12 mo	1.27 (0.2)	1.50 (0.30)	-0.23 (95%CI: -0.40, -0.06)