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Diabetic Dyslipidaemia
Current Treatment Recommendations

James D. Best and *David N. O'Neal*

The University of Melbourne Department of Medicine, St Vincent's Hospital, Melbourne, Victoria, Australia

Contents

Abstract

Insulin deficiency and hyperglycaemia in type 1 (insulin-dependent) diabetes mellitus produce lipid abnormalities, which can be corrected by appropriate insulin therapy. Diabetic nephropathy, which is the main risk factor for coronary heart disease (CHD) in type 1 diabetes, causes pro-atherosclerotic changes in lipid metabolism. Detection and treatment of elevated cholesterol levels is likely to be of benefit in these patients.

Type 2 (noninsulin-dependent) diabetes mellitus is associated with abnormal lipid metabolism, even when glycaemic control is good and nephropathy absent. Elevated triglyceride levels, reduced high density lipoprotein (HDL) cholesterol and a preponderance of small, dense low density lipoprotein (LDL) particles are the key abnormalities that constitute diabetic dyslipidaemia. The prevalence of hypercholesterolaemia is the same as for the nondiabetic population, but the relative risk of CHD is greatly increased at every level of cholesterol. Based on effectiveness, tolerability and clinical trial results, treatment with HMG-CoA reductase inhibitors to lower LDL cholesterol is recommended as primary ther-

apy. These agents are also moderately effective at reducing triglyceride and increasing HDL cholesterol levels. If hypertriglyceridaemia predominates, treatment with fibric acid derivatives is appropriate, although there is currently only limited clinical trial evidence that the risk of CHD will be reduced.

In type 1 diabetes, but particularly in type 2 diabetes, lipid disorders are likely to contribute significantly to the increased risk of macrovascular complications, especially CHD. Management of the disordered lipid metabolism should be given a high priority in the clinical care of all patients with diabetes.

Both type 1 (insulin-dependent) and type 2 (noninsulin-dependent) diabetes mellitus are associated with increased risk for cardiovascular disease (CVD). In both types of diabetes, abnormalities of lipid metabolism are important, but the nature of these abnormalities is different and the therapeutic approach also differs.

1. Coronary Heart Disease (CHD) in Type 1 Diabetes Mellitus

Studies from the Joslin Clinic in Boston, Massachussetts, USA [1] and the Steno Memorial Hospital in Copenhagen, Denmark[2] have reported increased coronary heart disease (CHD) mortality in patients with type 1 diabetes compared with the nondiabetic population. In the Joslin Clinic study 35% of the patients died from CHD before the age of 55, with similar risk for women and men. This rate was far higher than the death rates of 4 and 8% for nondiabetic women and men in the Framingham Heart Study.[3] The strongest predictor of increased risk was the presence of persistent proteinuria, which increased the risk of CHD 15-fold compared with patients without nephropathy. At the Steno Memorial Hospital, follow-up of patients with type 1 diabetes showed that onset of proteinuria led to a 40% cumulative prevalence of CHD within 6 years, compared with a prevalence of 5% in an age- and sex-matched group without proteinuria. The mortality of patients without proteinuria was only slightly increased relative to the nondiabetic population. The increased CHD risk associated with proteinuria can at least in part be linked to lipid abnormalities (see section 3.1).

2. CHD in Type 2 Diabetes Mellitus

Numerous studies have confirmed that type 2 diabetes is an important risk factor for CHD. The Framingham study was the first major prospective analysis of diabetes as a risk factor and showed that the risk of cardiovascular death was increased 4.5-fold in women and 2-fold in men with predominantly type 2 diabetes.[4] The risk of death from CVD was overall 3 times higher in the 5163 men from the Multiple Risk Factor Intervention Trial cohort who reported taking medication for diabetes compared with the 342 815 men considered as nondiabetic because, based on medication history, they were not being treated for diabetes.[5] In the Nurses' Health Study, the 1483 women with diabetes had a 6.9-fold increase in fatal CHD and 5.0-fold increase in fatal stroke, compared with the 114 694 women without diabetes.[6]

3. Dyslipidaemia in Type 1 Diabetes Mellitus

3.1 Nature, Prevalence and Aetiology

In the Diabetes Control and Complications Trial, lipid levels from 1569 generally healthy patients with type 1 diabetes aged between 13 and 40 were similar to those in the nondiabetic population[7] (table I). However, insulin deficiency reduces lipoprotein lipase activity and results in defective removal of triglyceride-rich lipoproteins.[8] Poor glycaemic control can therefore be associated with increased levels of triglycerides. Conversely, intensive insulin therapy can reduce triglyceride levels and also lower levels of low density lipoprotein (LDL) cholesterol, as well as increasing high density lipoprotein (HDL) cholesterol levels.[22] In-

creased susceptibility of LDL to oxidation has been shown in patients with type 1 diabetes who have poor glycaemic control,[9] but not in patients who are euglycaemic.[23] Improved glycaemic control has also been reported to reduce levels of lipoprotein(a) [Lp(a)], although most studies have reported normal levels in patients with type 1 diabetes.[24] Diabetic nephropathy, even at the early stage of microalbuminuria, has been associated with lipoprotein abnormalities, particularly increased LDL cholesterol and Lp(a), as well as reduced HDL cholesterol levels.[10,11] These pro-atherogenic changes are likely to contribute to the increased risk of CHD in patients with diabetic nephropathy.

3.2 Clinical Trials

Elevated cholesterol[2] and triglyceride[25] levels have both been associated with increased risk of CHD in patients with type 1 diabetes. The effect of therapy to lower cholesterol levels is similar in patients with type 1 diabetes and patients who do not have diabetes,[26] but there have not been any clinical trials to assess reduction of CHD risk in patients with type 1 diabetes.

Table I. Lipid and lipoprotein abnormalities in diabetes mellitus

Diabetes category	Lipids and lipoproteins	Reference
Type 1 diabetes		
Usual levels of glycaemia	Similar to non-diabetic population	7
Poor glycaemic control	Increased triglycerides	8
	Increased LDL susceptibility to oxidation	9
Diabetic nephropathy	Increased LDL cholesterol	10
	Decreased HDL cholesterol	10
	Increased lipoprotein (a)	11
Type 2 diabetes		
Usual levels of glycaemia	Increased triglycerides	12, 13
	Decreased HDL cholesterol	12, 13
	Small, dense, LDL particles	14, 15
	Increased LDL susceptibility to oxidation	16, 17
Poor glycaemic control	Worsening of hypertriglyceridaemia	18, 19
Diabetic nephropathy	Increased triglycerides	20
	Decreased HDL cholesterol	20
	Increased lipoprotein (a)	21

HDL = high density lipoprotein; **LDL** = low density lipoprotein.

3.3 Management

Obviously, the patients to target for treatment of dyslipidaemia are those with diabetic nephropathy because of their greatly increased risk of CHD. Treatment with an HMG-CoA reductase inhibitor will reduce LDL cholesterol levels and is well tolerated, even in the presence of renal impairment. The goal of treatment would generally be to reduce LDL cholesterol levels to 2.5 mmol/L or less in these high risk patients. Other lipid abnormalities should be treated as outlined in section 4.4 for type 2 diabetes.

4. Dyslipidaemia in Type 2 Diabetes Mellitus

4.1 Nature, Prevalence and Aetiology

Even with good glycaemic control and in the absence of any renal disease, type 2 diabetes is associated with abnormal lipid metabolism (table I). In fact, prospective studies have shown dyslipidaemia to precede the onset of diabetes.[27,28] The key features of this diabetic dyslipidaemia are elevated levels of triglycerides and reduced levels of HDL cholesterol, and an increased number of smaller, denser LDL particles.[12-15,29] Smaller LDL particles are more liable to oxidation[30] and so are potentially more atherogenic than larger, less dense particles. Indeed, increased LDL oxidisability has been demonstrated in patients with type 2 diabetes.[16,17] Poor glycaemic control exaggerates these abnormalities,[18,19] and the presence of diabetic nephropathy can cause further changes in the lipid profile[20,21,31] as outlined in section 3 for type 1 diabetes. Superimposed on these abnormalities is a prevalence of hypercholesterolaemia similar to that found in the general population.[32] Lp(a) levels have generally been reported to be normal and not to change with improved glycaemic control.[24]

The mechanism underlying the hypertriglyceridaemia of type 2 diabetes remains uncertain. Most studies demonstrate overproduction by the liver of

very low density lipoprotein (VLDL) triglyceride and apolipoprotein B.[33,34] Impaired VLDL catabolism has also been reported, probably caused by reduced activity of lipoprotein lipase.[33,34] Reduced HDL cholesterol levels may be due to increased catabolism, resulting from increased hepatic triglyceride lipase action on HDL particles with higher triglyceride content.[34,35] There is a strong inverse correlation between LDL particle size and triglyceride level, again placing the hypertriglyceridaemia at the centre of diabetic dyslipidaemia.[36,37]

Insulin resistance is a strong candidate as the underlying abnormality responsible for all these changes. The same type of dyslipidaemia has been reported as part of the 'Insulin Resistance Syndrome'[38,39] and prospective studies have shown that hyperinsulinaemia predicts the onset of both dyslipidaemia and diabetes.[40] Abnormalities of both VLDL production[41] and lipoprotein activity[42] have been linked with insulin resistance. Alternatively, or in addition, a high level of intra-abdominal fat, with increased release of free fatty acids, could induce insulin resistance[43] and at the same time provide substrate for increased production of VLDL particles.[44]

4.2 Clinical Trials

Elevated cholesterol levels have been shown in several studies to predict increased risk of CHD in patients with type 2 diabetes.[5,6,45,46] Elevated triglycerides[47,48] and reduced HDL cholesterol[46,48,49] levels have also been linked with increased CHD risk in this population. No studies have looked specifically at LDL particle size as a risk factor for CHD in type 2 diabetes.

Although patients with type 2 diabetes have been included in studies on primary prevention of CHD using HMG-CoA reductase inhibitors,[50,51] the number of events in the diabetic cohort from each study was too small to produce a significant result. On the other hand, benefit from treatment with HMG-CoA reductase inhibitors in patients with pre-existing CHD has been reported now in the subgroups with type 2 diabetes from 3 major studies (table II). In 202 patients with diabetes from the Scandinavian Simvastatin Survival Study (4S), baseline mean LDL cholesterol levels were 4.80 mmol/L (total

Table II. Clinical trial effects of lipid modifying drugs on lipids and coronary heart disease (CHD) events in type 2 diabetes mellitus

Drug and study type	No. treated	Lipid or lipoprotein	Effect	CHD event reduction	Reference
Simvastatin 20-40mg daily Secondary prevention	105	LDL cholesterol Triglycerides HDL cholesterol	36% reduction[a] 11% reduction[a] 7% increase[a]	55% (p = 0.002)	52
Pravastatin 40mg daily Secondary prevention	282	LDL cholesterol Triglycerides HDL cholesterol	28% reduction[b] 14% reduction[b] 5% increase[b]	25% (p = 0.05)	53
Pravastatin 40mg daily Secondary prevention	396	LDL cholesterol Triglycerides HDL cholesterol	25% reduction[b] 11% reduction[b] 5% increase[b]	19% (p = NS)	54
Gemfibrozil 600mg twice daily Primary prevention	59	LDL cholesterol Triglycerides HDL cholesterol	5% reduction 22% reduction 5% increase	68% (p = NS)	55
Gemfibrozil 600mg twice daily Secondary prevention	309	LDL cholesterol Triglycerides HDL cholesterol	No change[b] 31% reduction[b] 6% increase[b]	24% (p = 0.05)	56
Bezafibrate 400mg daily Primary prevention	81	LDL cholesterol Triglycerides HDL cholesterol	10% reduction 37% reduction 8% increase	67% (p = 0.01)	57

a Changes relative to baseline values, rather than placebo response.

b Changes in total cohort (diabetic and nondiabetic).

HDL = high density lipoprotein; **LDL** = low density lipoprotein; **NS** = nonsignificant.

cholesterol 6.71 mmol/L) and fell by 36% in those treated with simvastatin 20 to 40mg daily, producing a 55% reduction in CHD events.[52] In the Cholesterol and Recurrent Events (CARE) study 586 patients with diabetes had baseline mean LDL cholesterol levels of 3.51 mmol/L (total cholesterol 5.32 mmol/L), a reduction of 32% in those treated with pravastatin 40mg daily and a 25% reduction of CHD events.[53] The Long-term Intervention with Pravastatin in Ischaemic Disease (LIPID) study included 782 patients with diabetes, again receiving pravastatin 40mg daily or placebo. Baseline median LDL cholesterol levels of 3.89 mmol/L (total cholesterol 5.66 mmol/L) fell by 25% and CHD events by 19% in the treated group.[54]

There have also been 2 reports of primary prevention studies with fibric acid derivatives in patients with type 2 diabetes. The 68% reduction of CHD events with gemfibrozil treatment in the subset of patients with diabetes participating in the Helsinki Heart Study was not statistically significant.[55] In the St Mary's, Ealing, Northwick Park Diabetes Cardiovascular Disease Prevention (SENDCAP) study, 164 patients with diabetes had a mean baseline triglyceride level of 2.17 mmol/L, a 33% reduction of triglyceride in the group treated with bezafibrate 400mg daily and a 67% reduction of CHD events.[57] The Veterans Affairs Cooperative Studies Program HDL-C Intervention Trial (VA-HIT)[56] was a secondary prevention study, in which 25% of patients had diabetes. Cardiovascular events were reduced by 24% in patients both with and without diabetes taking gemfibrozil.

Several major primary and secondary prevention trials, each involving between 3000 and 8000 patients with type 2 diabetes, are currently in the recruitment stage. The largest of these studies, the Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) trial, will study 8000 patients in Australia, New Zealand and Finland, comparing treatment with micronised fenofibrate 200mg daily and placebo. The British Heart Protection Study will include 6000 patients with diabetes in a comparison of simvastatin 40mg daily and placebo. Both groups will be further randomised to receive the combination of tocopherol (vitamin E), ascorbic acid (vitamin C) and β carotene or placebo.

4.3 Lifestyle Intervention

Exercise is likely to provide particular benefits for patients with type 2 diabetes, as it improves insulin sensitivity and reduces intra-abdominal fat, thereby reducing triglyceride and increasing HDL cholesterol levels.[58] The American Diabetes Association recommends aerobic exercise at 50 to 70% maximum O_2 uptake for 20 to 45 minutes, at least 3 days per week.[59]

Nutritional intervention is also important, particularly reduction of saturated fat intake.[60] Whether the saturated fat should be replaced in the diet by carbohydrate or by poly-unsaturated or mono-unsaturated fat is probably not important, although mono-unsaturated fat may result in lower triglyceride levels and better glycaemic control than carbohydrate. In patients who are obese, most of the calories from saturated fat should not be replaced at all in order to promote bodyweight loss. When marked hypertriglyceridaemia is present (>10 mmol/L) severe restriction of dietary fat and complete avoidance of alcohol (ethanol) are recommended.

4.4 Pharmacological Intervention

Any therapy that improves glycaemic control will improve diabetic dyslipidaemia, particularly hypertriglyceridaemia. Thus treatment with insulin,[19,61] sulphonylureas,[18,62] metformin,[63] acarbose[64] and troglitazone[65] have all been reported to improve the lipid profile.

The most effective agents for reduction of LDL cholesterol levels in patients with type 2 diabetes are HMG-CoA reductase inhibitors and the most effective agents for reduction of triglyceride levels are fibric acid derivatives[66,67] (table III).

4.4.1 HMG-CoA Reductase Inhibitors

HMG-CoA reductase inhibitors (statins) inhibit the enzyme HMG-CoA reductase, which is a rate limiting enzyme in the cholesterol synthesis pathway. Their main effect on the lipid profile is there-

Table III. Choice of therapy for lipid abnormalities in type 2 diabetes mellitus

Lipid or lipoprotein abnormality	First-line therapy	Additional therapy
Increased LDL cholesterol	HMG-CoA reductase inhibitor	Bile acid sequestrant Nicotinic acid
Increased triglyceride	Fibric acid derivative	HMG-CoA reductase inhibitor Omega 3 fatty acids Nicotinic acid
Increased LDL cholesterol and triglyceride	HMG-CoA reductase inhibitor[a]	Fibric acid derivative Omega 3 fatty acids Nicotinic acid
Reduced HDL cholesterol	HMG-CoA reductase inhibitor[b]	Fibric acid derivative Nicotinic acid

a Therapeutic priority is to lower LDL cholesterol.

b Will improve ratio of LDL to HDL cholesterol.

HDL = high density lipoprotein; **LDL** = low density lipoprotein.

fore to lower LDL cholesterol levels, which they do with increasing efficacy on a per mg basis from fluvastatin to pravastatin to simvastatin and lovastatin to atorvastatin.[68] As indicated in section 4.2, studies with pravastatin 40mg daily have shown a 32% reduction of LDL cholesterol levels in one study in 586 patients with type 2 diabetes[53] and a 25% reduction in another study of 782 patients with diabetes.[54] With simvastatin 20 to 40mg daily, a 36% reduction has been reported in 202 patients with diabetes.[52] Combined data from a series of studies with atorvastatin 10mg daily showed a 36% reduction in a total of 156 patients with diabetes.[69] The reduction in LDL cholesterol levels in patients with diabetes was the same as in the larger numbers of patients without diabetes included in all these studies.

These agents also reduce triglycerides, by upregulating the hepatic LDL receptor and probably by reducing VLDL production.[70] In the studies indicated in the previous paragraph, pravastatin reduced triglycerides by 11 and 14%, simvastatin by 11% and atorvastatin by 21%. HDL cholesterol levels increased slightly, by between 4 and 8%. Glycaemic control is not altered by HMG-CoA reductase inhibitor therapy in patients with diabetes.

HMG-CoA reductase inhibitors are well tolerated, with minor gastrointestinal disturbances the most commonly reported adverse effect. Discontinuation of therapy because of adverse effects was very unusual in the clinical trials. Myositis has been reported and monitoring of creatine kinase levels, particularly at the first review after initiation of therapy, is recommended. There is no concern about minor elevations, but an increase above 5 times the upper limit of normal is an indication to reduce the dose or to stop treatment, unless there is another explanation, such as recent vigorous muscular exercise. Liver function tests (LFTs) should also be monitored, with an increase in levels of AST or ALT above 3 times the upper limit of normal an indication for reduction of dose or cessation of treatment. These agents should be used with particular care (including increased monitoring) in patients with pre-existing liver disease or when used in combination with nicotinic acid or fibric acid derivatives. Abnormal LFTs in patients with hypertriglyceridaemia may be due to fatty infiltration and may actually improve after triglyceride lowering with treatment. Extreme caution is required in patients also receiving cyclosporin, as metabolism of the HMG-CoA reductase inhibitors is impaired.[71]

Based on the relative potency of the different HMG-CoA reductase inhibitors, and on the results of the clinical trials discussed earlier in this section, the most logical starting doses are pravastatin 40mg, simvastatin 20mg and atorvastatin 10mg. The American Diabetes Association position statement on treatment of dyslipidaemia in adults with diabetes has set an LDL cholesterol level of 2.6 mmol/L (100 mg/dL) as the goal to be achieved in patients with pre-existing CVD, and a level of 3.35 mmol/L (130 mg/dL) in patients without clinical evidence of CVD.[72] We recommend a treatment goal of <3.0 mmol/L for primary prevention and <2.5 mmol/L for secondary prevention in type 2 diabetes (based on recommendations by various diabetes associations, including American guidelines translated to SI units). To achieve these goals, the dose of HMG-CoA reductase inhibitor may need to be titrated in response to the LDL cholesterol levels achieved with initial therapy. The dose can be adjusted after 4 to 6 weeks.

Taking note of the tolerability and effectiveness of HMG-CoA reductase inhibitors, as well as their proven benefit in secondary prevention of CHD, the American Diabetes Association has set lowering of LDL cholesterol levels as the top priority in the treatment of diabetic dyslipidaemia.[72] The second priority is lowering of triglyceride levels and the third priority is raising levels of HDL cholesterol, both of which are achieved to some extent by statin therapy.

4.4.2 Fibric Acid Derivatives

Fibric acid derivatives act through peroxisome proliferator-activated receptors (PPAR)α to reduce hepatic production of VLDL particles and increase lipoprotein lipase activity.[73] The main result of these actions is to reduce triglyceride levels, but there is also a reciprocal rise in HDL cholesterol levels that is generally between 5 and 15%, and greater when the baseline triglyceride level is higher.[74] The response of LDL cholesterol also varies with the baseline triglyceride level. With normal or slightly elevated triglyceride levels, LDL cholesterol levels are lower after fibric acid derivative therapy,[55,57] but when baseline triglyceride levels are high, LDL levels rise because of improved VLDL metabolism.[67]

Of potential importance in the treatment of diabetic dyslipidaemia, gemfibrozil treatment has been shown to increase LDL particle size, with changes inversely proportional to the fall in triglyceride level.[75,76] Fenofibrate and bezafibrate would be expected to have similar effects and all 3 agents should enhance post-prandial lipoprotein clearance in patients with diabetes.[77] As with the HMG-CoA reductase inhibitors, the fibric acid derivatives do not alter glycaemic control.

Except in patients with renal impairment or when used in combination with HMG-CoA reductase inhibitors, fibric acid derivatives are generally initiated at the full therapeutic dose and are not titrated. For gemfibrozil this dosage is 600mg twice daily, for bezafibrate 400mg daily and for fenofibrate 200mg daily. Lower doses of the sustained-release preparations of bezafibrate and fenofibrate can be achieved by taking the medication every second or third day. Fibric acid derivatives are well tolerated but can cause gastrointestinal adverse effects, particularly diarrhoea. Fibric acid derivatives have also been associated with a slight increase in the risk of gallstones and occasionally cause abnormal LFTs. However, as mentioned in section 4.4.1 for HMG-CoA reductase inhibitors, fibric acid derivatives can improve abnormal LFTs associated with fatty infiltration of the liver, by lowering triglyceride levels. The most significant potential adverse effect of fibric acid derivatives is myositis, particularly in patients with impaired renal function.

Because there is little current evidence for reduction of CHD in patients with diabetes treated with fibric acid derivatives, these agents are not generally used as first-line treatment for diabetic dyslipidaemia.[72] As indicated in section 4.4.1, priority is given to lowering LDL cholesterol levels, which HMG-CoA reductase inhibitors do better than fibric acid derivatives. Fibric acid derivatives are used when more marked hypertriglyceridaemia is present (triglycerides >5 mmol/L) or as second-line therapy, in addition to an HMG-CoA reductase inhibitor. In this latter situation, monitoring of creatine kinase levels after 4 to 6 weeks therapy, after another 3 months and then at 6-monthly intervals is recommended. The risk of myositis has been low in several studies of combination therapy in patients without diabetes,[78,79] but caution must be maintained.

4.4.3 Omega 3 Fatty Acids

Omega 3 fatty acids (fish oils) lower triglycerides with minimal effects on HDL cholesterol and LDL cholesterol levels.[80] They are well tolerated at the commonly used dosages of 1 to 2 capsules daily (2 to 4 g/day). At higher dosages there may be worsening of glycaemic control.[81]

Omega 3 fatty acids are primarily used in the treatment of more marked hypertriglyceridaemia, usually as second-line therapy, after a fibric acid derivative. However, they can also be combined readily with an HMG-CoA reductase inhibitor. There have not been any clinical trials in patients with diabetes showing reduction of CHD from treatment with omega 3 fatty acids, but their use is supported by epidemiological evidence that in-

creased dietary consumption of fish is associated with a lower risk for CHD.[80]

4.4.4 Nicotinic Acid

Nicotinic acid has multiple effects on the lipid profile. It is the most effective agent available for elevating HDL cholesterol levels and it also lowers triglyceride, LDL cholesterol[82] and even Lp(a) levels.[83] Unfortunately, it has a number of disadvantages, particularly for the patient with type 2 diabetes. The most significant adverse effect is that it worsens glycaemic control,[82] probably by increasing insulin resistance.[84] It also causes flushing, aggravates hyperuricaemia,[82] and can activate peptic ulcer disease and cause abnormal liver function. As a result, nicotinic acid is generally used as a second-line agent in higher risk patients and dosages do not generally exceed 1g daily. It can be used in combination with either fibric acid derivatives or HMG-CoA reductase inhibitors, provided that LFTs and creatine kinase levels are monitored.

4.4.5 Bile Acid Sequestrants

When an elevated LDL cholesterol level is the primary lipid abnormality, and the response to maximum therapy with HMG-CoA reductase inhibitors is not adequate or there is some contraindication to their use, treatment with a bile acid sequestrant or binding resin such as cholestyramine can be considered. Because bile acid sequestrants can increase triglyceride levels[85] they are not recommended if the triglyceride level is elevated to more than 3.0 mmol/L. Use of these agents is also associated with a high rate of gastrointestinal adverse effects and interference with the absorption of other drugs. Nonetheless, therapy with bile acid sequestrants can usefully lower LDL cholesterol levels in carefully selected patients and may even improve glycaemic control.[86]

4.4.6 Estrogen

In postmenopausal women without diabetes, estrogen therapy increases HDL cholesterol levels, decreases LDL cholesterol and Lp(a) levels, but increases triglyceride levels[87] and reduces LDL particle size.[88] The increase in HDL cholesterol levels and decrease in LDL cholesterol levels with estrogen therapy are comparable with those achieved by treatment with simvastatin 10mg. In postmenopausal women with type 2 diabetes, short term estrogen therapy has been reported to have beneficial effects on lipids, fibrinolytic parameters and hepatic insulin resistance.[89] Analysis of cardiovascular risk in postmenopausal women with diabetes taking hormone replacement therapy has also suggested benefits similar to the nondiabetic population.[90] However, the data for women with diabetes are very limited and the benefits even for women who do not have diabetes remain uncertain.[91] Certainly, estrogen replacement therapy needs to be used with some caution in women with diabetes, because of the risk of aggravating pre-existing hypertriglyceridaemia. Estrogen is better avoided if the fasting triglyceride level exceeds 3.0 mmol/L.

5. Cerebrovascular Disease, Peripheral Vascular Disease and Diabetic Nephropathy

An unanticipated result in recent trials of HMG-CoA reductase inhibitor treatment was a reduction in the risk of non-haemorrhagic stroke.[92,93] This reduction would be a particularly important benefit for patients with type 2 diabetes, whose risk of stroke is greatly increased. Peripheral vascular disease (PVD) has been linked with the presence of diabetic dyslipidaemia,[94] but there is no evidence on whether correction of the lipid abnormalities will reduce the risk for this complication. Although the main rationale for lipid modifying therapy in patients with diabetes is the reduction of CHD, it is a reasonable expectation that additional benefit will accrue in the form of reduced incidence or severity of non-haemorrhagic stroke and PVD.

As described in sections 3 and 4, the presence of diabetic renal disease has been linked with a number of lipid abnormalities.[10,11,20,21,31] Two recent studies have raised the interesting possibility that treatment with an HMG-CoA reductase inhibitor may slow the progression of diabetic nephropathy.[95,96]

6. Conclusion

Reduction of LDL cholesterol levels with HMG-CoA reductase inhibitor therapy is of proven benefit for patients with type 2 diabetes and pre-existing CHD. It is also likely to benefit many patients with type 1 diabetes and elevated LDL cholesterol levels, particularly those with diabetic nephropathy. For patients with type 2 diabetes who do not have CHD, treatment with an HMG-CoA reductase inhibitor or a fibric acid derivative may be beneficial, but the appropriate choice of therapy and the thresholds for initiation and goals of therapy will be defined by the results of clinical trials currently underway.

References

1. Krolewski AS, Kosinski EJ, Warram JH, et al. Magnitude and determinants of coronary artery disease in juvenile-onset, insulin-dependent diabetes mellitus. Am J Cardiol 1987; 59: 750-5
2. Jensen T, Borch-Jonsen K, Kofoed-Enevoldsen A, et al. Coronary heart disease in young type 1 (insulin-dependent) diabetic patients with and without diabetic nephropathy: incidence and risk factors. Diabetologia 1987; 30: 144-8
3. Lerner DJ, Kannel WB. Patterns of coronary heart disease morbidity and mortality in the sexes: a 26-year follow-up of the Framingham population. Am Heart J 1986; 111: 383-90
4. Garcia MJ, McNamara PM, Gordon T, et al. Morbidity and mortality in diabetics in the Framingham population. Sixteen year follow-up study. Diabetes 1974; 23: 105-11
5. Stamler J, Vaccaro O, Neaton JD, et al. Diabetes, other risk factors, and 12-yr cardiovascular mortality for men screened in the Multiple Risk Factor Intervention Trial. Diabetes Care 1993; 16: 434-44
6. Manson JE, Colditz GA, Stampfer MJ, et al. A prospective study of maturity-onset diabetes mellitus and risk of coronary heart disease and stroke in women. Arch Intern Med 1991; 151: 1141-7
7. The DCCT Research Group. Lipid and lipoprotein levels in patients with IDDM. Diabetes Control and Complications Trial experience. Diabetes Care 1992; 15: 886-94
8. Brunzell JD, Porte Jr D, Bierman EL. Abnormal lipoprotein-lipase-mediated plasma triglyceride removal in untreated diabetes mellitus associated with hypertriglyceridemia. Metabolism 1979; 28: 901-7
9. Tsai EC, Hirsch IB, Brunzell JD, et al. Reduced plasma peroxy radical trapping capacity and increased susceptibility of LDL to oxidation in poorly controlled IDDM. Diabetes 1994; 43: 1010-4
10. Watts GF, Nauomova R, Slavin BM, et al. Serum lipids and lipoproteins in insulin dependent diabetics with persistent microalbuminuria. Diabetic Med 1989; 6: 25-30
11. Jenkins AJ, Steele JS, Janus ED, et al. Increased plasma lipoprotein (a) in IDDM patients with microalbuminuria. Diabetes 1991; 40: 787-90
12. Gordon T, Castelli WP, Hjortland MC, et al. Diabetes, blood lipids and the role of obesity in coronary heart disease risk for women. The Framingham study. Ann Intern Med 1977; 87: 393-7
13. Biesbroeck RC, Albers JJ, Wahl PW, et al. Abnormal concentration of high density lipoproteins in non-insulin-dependent diabetics. Diabetes 1982; 31: 126-31
14. Feingold KR, Grunfield C, Doerrler W, et al. LDL subclass phenotypes and triglyceride metabolism in non-insulin dependent diabetes. Arterioscler Thromb 1992; 12: 1496-502
15. Haffner SM, Mykkanen L, Stern MP, et al. Greater effect of diabetes on LDL size in women than in men. Diabetes Care 1994; 17: 1164-71
16. Dimitriadis E, Griffin M, Owens D, et al. Oxidation of low-density lipoprotein in NIDDM: its relationship to fatty acid composition. Diabetologia 1995; 38: 1300-6
17. Haffner SM, Agil A, Mykkanen L, et al. Plasma oxidizability in subjects with normal glucose tolerance, impaired glucose tolerance, and NIDDM. Diabetes Care 1995; 18: 646-53
18. Pfeifer MA, Brunzell JD, Best JD, et al. The response of plasma triglyceride, cholesterol, and lipoprotein lipase to treatment in non-insulin-dependent diabetic subjects without familial hypertriglyceridemia. Diabetes 1983; 32: 525-31
19. Dunn FL, Raskin P, Bilheimer DW, et al. The effect of diabetic control on very low-density lipoprotein-triglyceride metabolism in patients with type II diabetes mellitus and marked hypertriglyceridemia. Metabolism 1984; 33: 117-23
20. Niskanen L, Uusitupa M, Sarlund H, et al. Microalbuminuria predicts the development of serum lipoprotein abnormalities favouring atherogenesis in newly diagnosed type 2 (non-insulin-dependent) diabetic patients. Diabetologia 1990; 33: 237-43
21. Jenkins AJ, Steele JS, Janus ED, Santamaria JD, Best JD. Plasma apolipoprotein (a) is increased in type 2 (non-insulin-dependent) diabetic patients with microalbuminuria. Diabetologia 1992; 35: 1055-9
22. Lopes-Virella MF, Wohltmann HJ, Mayfield RK, et al. Effect of metabolic control on lipid, lipoprotein, and apolipoprotein levels in 55 insulin-dependent diabetic patients. A longitudinal study. Diabetes 1983; 32: 20-5
23. Jenkins AJ, Klein RL, Chassereau CN, et al. LDL from patients with well-controlled IDDM is not more susceptible to in vitro oxidation. Diabetes 1996; 45: 762-7
24. Jenkins AJ, Best JD. The role of lipoprotein (a) in the vascular complications of mellitus. J Intern Med 1995; 237: 359-65
25. Maser RE, Wolfson Jr SK, Ellis D, et al. Cardiovascular disease and arterial calcification in insulin-dependent diabetes mellitus. Interrelations and risk factor profiles. Arterioscler Thromb 1991; 11: 958-65
26. Kjaer K, Hangaard J, Petersen NE, et al. Effect of simvastatin in patients with type 1 (insulin-dependent) diabetes mellitus and hypercholesterolemia. Acta Endocrinol 1992; 126: 229-32
27. Haffner SM, Stern MP, Hazuda HP, et al. Cardiovascular risk factors in confirmed pre-diabetic individuals. Does the clock start ticking before the onset of clinical diabetes? JAMA 1990; 263: 2893-8
28. Mykkanen L, Kuusisto J, Pyorala K, et al. Cardiovascular disease risk factors as predictors of type 2 (non-insulin-dependent) diabetes mellitus in elderly subjects. Diabetologia 1993; 36: 553-9
29. Barrett-Connor E, Grundy SM, Holbrook MJ. Plasma lipids and diabetes mellitus in an adult community. Am J Epidemiol 1981; 115: 657-63
30. Chait A, Brazg RL, Tribble DL, et al. Susceptibility of small, dense, low-density lipoproteins to oxidative modification in

subjects with the atherogenic lipoprotein phenotype, pattern B. Am J Med 1993; 94: 347-9
31. Mattock MB, Keen H, Viberti GC, et al. Coronary heart disease and urinary albumin excretion rate in type 2 (non-insulin-dependent) diabetic patients. Diabetologia 1988; 31: 82-7
32. Harris MI. Hypercholesterolemia in diabetes and glucose intolerance in the US population. Diabetes Care 1991; 14: 366-74
33. Ginsberg HN. Very low density lipoprotein metabolism in diabetes mellitus. Diabetes Metab Rev 1987; 3: 571-589
34. Howard BV. Pathogenesis of diabetic dyslipidemia. Diabetes Rev 1995; 3: 423-32
35. Harno K, Nikkila EA, Kuusi T. Plasma HDL cholesterol and post heparin plasma hepatic endothelial lipase activity: relationship to obesity and non-insulin dependent diabetes. Diabetologia 1990; 19: 281-9
36. Stewart JM, Kilpatrick ES, Cathcart S, et al. Low-density lipoprotein particle size in type 2 diabetic patients and age matched controls. Ann Clin Biochem 1994; 31: 153-9
37. Lahdenpara S, Syvanne M, Kahri J, et al. Regulation of low-density lipoprotein particle size distribution in NIDDM and coronary disease: importance of serum triglycerides. Diabetologia 1996; 39: 453-61
38. Haffner SM, Mykkanen L, Robbins D, et al. A preponderance of small dense LDL is associated with specific insulin, proinsulin and the components of the insulin resistance syndrome in non-diabetic subjects. Diabetologia 1995; 38: 1328-36
39. Betteridge DJ. LDL heterogeneity: implications for atherogenicity in insulin resistance and NIDDM. Diabetologia 1997; 40: S149-51
40. Haffner SM, Valdez RA, Hazuda HP, et al. Prospective analysis of the insulin-resistance syndrome (Syndrome X). Diabetes 1992; 41: 715-22
41. Malmström R, Packard CJ, Caslake M, et al. Defective regulation of triglyceride metabolism by insulin in the liver in NIDDM. Diabetologia 1997; 40: 454-62
42. Pollare T, Vessby B, Lithell H. Lipoprotein lipase activity in skeletal muscle is related to insulin sensitivity. Arterioscler Thromb 1991; 11: 1192-203
43. Carey DG, Jenkins AB, Campbell LV, et al. Abdominal fat and insulin resistance in normal and overweight women. Direct measurements reveal a strong relationship in subjects at both low and high risk of NIDDM. Diabetes 1996; 45: 633-8
44. Bjorntorp P. Metabolic implications of body fat distribution. Diabetes Care 1991; 14: 1132-43
45. Jarrett RJ, Shipley MJ. The Whitehall Study: comparative mortality rates and indices of risk in diabetics. Acta Endocrinol 1985; 110 Suppl. 272: 21-6
46. Turner RC, Millns H, Neil HAW, et al. Risk factors for coronary artery disease in non-insulin dependent diabetes mellitus: United Kingdom prospective diabetes study (UKPDS: 23). BMJ 1998; 316: 823-8
47. Fontbonne A, Eschwege E, Cambien F, et al. Hypertriglyceridaemia as a risk factor of coronary heart disease mortality in subjects with impaired glucose tolerance or diabetes. Results from the 11-year follow-up of the Paris Prospective Study. Diabetologia 1989; 32: 300-4
48. Laakso M, Lehto S, Penttila I, et al. Lipids and lipoproteins predicting coronary heart disease mortality and morbidity in patients with non-insulin-dependent diabetes. Circulation 1993; 88 (Pt 1): 1421-30
49. Welborn TA, Knuiman M, McCann V, et al. Clinical macrovascular disease in Caucasoid diabetic subjects: logistic regression analysis of risk variables. Diabetologia 1984; 27: 568-73
50. Shepherd J, Cobbe SM, Ford I, et al. Prevention of coronary heart disease with pravastatin in men with hypercholesterolemia. N Engl J Med 1995; 333: 1301-7
51. Downs JR, Clearfield M, Weis S, et al. Primary prevention of acute coronary events with lovastatin in men and women with average cholesterol levels. Results of AFCAPS/TexCAPS. JAMA 1998; 279: 1615-22
52. Pyorala K, Pedersen TR, Tjekshus Jet al. Cholesterol lowering with simvastatin improves prognosis of diabetic patients with coronary heart disease. Diabetes Care 1997; 20: 614-20
53. Sacks FM, Pfeffer MA, Moye LA, et al. The effect of pravastatin on coronary events after myocardial infarction in patients with average cholesterol levels. N Engl J Med 1996; 335: 1001-9
54. The Long-term Intervention with Pravastatin in Ischaemic Disease (LIPID) Study Group. Prevention of cardiovascular events and death with pravastatin in patients with coronary heart disease and a broad range of initial cholesterol levels. N Engl J Med 1998; 339: 1349-57
55. Koskinen P, Manttari M, Manninen V, et al. Coronary heart disease incidence in NIDDM patients in the Helsinki Heart Study. Diabetes Care 1992; 15: 820-5
56. Bloomfield Rubins H, Robins SJ, Collins D et al. Gemfibrozil for the secondary prevention of coronary heart disease in men with low levels of high-density lipoprotein cholesterol. N Engl J Med 1999; 341: 410-8
57. Elkeles RS, Diamond JR, Poulter C, et al. Cardiovascular outcomes in type 2 diabetes. A double-blind placebo-controlled study of bezafibrate: the St Mary's, Ealing, Northwick Park Diabetes Cardiovascular Disease Prevention (SENDCAP) study. Diabetes Care 1998; 21: 641-8
58. Schneider SH, Ruderman NB. Exercise and NIDDM [technical review]. Diabetes Care 1990; 13: 785-9
59. American Diabetes Association. Diabetes and exercise [position statement]. Diabetes Care 1997; 20 Suppl. 1: 551
60. Franz MJ, Horton ES, Bantle JP, et al. Nutrition principles for the management of diabetes and related complications. Diabetes Care 1994; 17: 490-518
61. Taskinen M-R, Kuusi T, Helve E, et al. Insulin therapy induces anti-atherogenic changes of serum lipoproteins in non-insulin-dependent diabetes. Arteriosclerosis 1988; 8: 168-77
62. Greenfield M, Doberne L, Rosenthal M, et al. Lipid metabolism in non-insulin-dependent diabetes mellitus: effect of glipizide therapy. Arch Intern Med 1982; 142: 1498-500
63. DeFronzo RA, Goodman AM. Efficacy of metformin in patients with non-insulin dependent diabetes mellitus. N Engl J Med 1995; 333: 541-9
64. Hanefeld M, Fischer S, Schulze J, et al. Therapeutic potentials of acarbose as first-line drug in NIDDM insufficiently treated with diet alone. Diabetes Care 1991; 14: 732-7
65. Mahmoud NG, Perez JE, Antonucci TK, et al. Cardiac and glycemic benefits of troglitazone treatment in NIDDM. Diabetes 1997; 46: 433-9
66. Goldberg R, La Belle P, Zupkis R, et al. Comparison of the effects of lovastatin and gemfibrozil on lipids and glucose control in non-insulin-dependent diabetes mellitus. Am J Cardiol 1990; 66: 16B-21B
67. Garg A, Grundy SM. Management of dyslipidemia in NIDDM. Diabetes Care 1990; 13: 153-69
68. Jones P, Kafonek S, Laurora I, et al. Comparative dose efficacy study of atorvastatin versus simvastatin, pravastatin, lovastatin, and fluvastatin in patients with hypercholesterolemia (The CURVES Study). Am J Cardiol 1998; 81: 582-7

69. Black DM, Bakker-Arkema R, Heinonen T, et al. Efficacy and safety of atorvastatin in hyperlipidemic patients with concurrent hypertension or non-insulin-dependent diabetes mellitus [abstract]. 17th Scientific Meeting of the International Society of Hypertension: 1998 Jun 6-14; Amsterdam
70. Bakker-Arkema RG, Davidson MH, Goldstein RJ, et al. Efficacy and safety of a new HMG-CoA reductase inhibitor, atorvastatin, in patients with hypertriglyceridemia. JAMA 1996; 275: 128-33
71. Garnett WR. Interactions with hydroxymethylglutaryl-coenzyme A reductase inhibitors. Am J Health System Pharm 1995; 52 (15): 1639-45
72. American Diabetes Association. Management of dyslipidemia in adults with diabetes [position statement]. Diabetes Care 1998; 21: 179-82
73. Schoonjans K, Staels B, Auerx J. Role of the peroxisome proliferator-activator receptor (PPAR) in mediating the effects of fibrates and fatty acids on gene expression. J Lipid Res 1996; 37: 907-25
74. Haffner SM. Management of dyslipidemia in adults with diabetes. Diabetes Care 1998; 21; 160-78
75. Lahdenpera S, Tilly-Kiesi M, Vuorinen-Markkola H, et al. Effects of gemfibrozil on low-density lipoprotein particle size, density distribution, and composition in patients with type 2 diabetes. Diabetes Care 1993; 16: 584-92
76. O'Neal DN, O'Brien RC, Timmins KL, et al. Gemfibrozil treatment increases low-density lipoprotein particle size in type 2 diabetes mellitus but does not alter in vitro oxidizability. Diabet Med 1998; 15: 870-7
77. De Man FH, Cabezas MC, Van-Barlingen HH, et al. Triglyceride-rich lipoproteins in non-insulin-dependent diabetes mellitus: post-prandial metabolism and relation to premature atherosclerosis. Eur J Clin Invest 1996; 26: 89-108
78. Glueck CJ, Oakes N, Speirs J, et al. Gemfibrozil-lovastatin therapy for primary hyperlipoproteinemias. Am J Cardiol 1992; 70: 1-9
79. Wiklund O, Bergman M, Bondjers G, et al. Pravastatin and gemfibrozil alone and in combination for the treatment of hypercholesterolemia. Am J Med 1993; 94: 13-20
80. Malasanos TH, Stacpoole PW. Biological effects of ω-3 fatty acids in diabetes mellitus. Diabetes Care 1991; 14: 1160-79
81. Schectman G, Kaul S, Kissebah A. Effect of fish oil concentrate on lipoprotein composition in NIDDM. Diabetes 1988; 37: 1567-73
82. Garg A, Grundy SM. Nicotinic acid as therapy for dyslipidemia in non-insulin-dependent diabetes mellitus. JAMA 1990; 264: 723-6
83. Carlson LA, Hamsten A, Aspland A. Pronounced lowering of serum levels of Lp(a) in hyperlipidemic subjects with nicotinic acid. J Intern Med 1989; 225: 271-6
84. Kahn SE, Beard JC, Schwartz MW, et al. Increased B-cell secretory capacity as a mechanism for islet cell adaptation to nicotinic acid-induced insulin resistance. Diabetes 1990; 38: 562-8
85. Crouse JR. Hypertriglyceridemia: a cotraindication to the use of bile acid binding resins. Am J Med 1987; 83: 243-8
86. Garg A, Grundy SM. Cholestyramine therapy for dyslipidemia in non-insulin-dependent diabetes mellitus: a short-term, double-blind, crossover trial. Ann Intern Med 1994; 121: 416-22
87. Darling GM, Johns JA, McCloud PI, et al. Estrogen and progestin compared with simvastatin for hypercholesterolemia in postmenopausal women. N Engl J Med 1997; 337: 595-601
88. De Graaf J, Swinkels DW, Demacker PNM, et al. Differences in the low density lipoprotein subfraction profile between oral contraceptive users and controls. J Clin Endocrinol Metab 1993; 76: 197-202
89. Brussaard HE, Gevers Leuven JA, Frolich M, et al. Short-term oestrogen replacement therapy improves insulin resistance, lipids and fibrinolysis in postmenopausal women with NIDDM. Diabetologia 1997; 40: 843-9
90. Robinson JG, Folsom AR, Nabulsi AA, et al. Can postmenopausal hormone replacement improve plasma lipids in women with diabetes? Diabetes Care 1996; 19: 480-5
91. Hulley S, Grady D, Bush T, et al. Randomized trial of estrogen plus progestin for secondary prevention of coronary heart disease in postmenopausal women. JAMA 1998; 280: 605-13
92. Hebert PR, Gaziano M, Chan KS, et al. Cholesterol lowering with statin drugs, risk of stroke, and total mortality. An overview of randomized trials. JAMA 1997; 278: 313-21
93. Blauw GJ, Lagaay AM, Smelt AHM, et al. Stroke, statins, and cholesterol. A meta-analysis of randomized, placebo-controlled, double-blind trials with HMG-CoA reductase inhibitors. Stroke 1997; 28: 946-50
94. O'Neal DN, Lewicki J, Ansari MZ, et al. Lipid levels and peripheral vascular disease in diabetic and non-diabetic subjects. Atherosclerosis 1998; 136: 1-8
95. Lam KSL, Cheng IKP, Janus ED, et al. Cholesterol-lowering therapy may retard the progression of diabetic nephropathy. Diabetologia 1995; 38: 604-9
96. Tonolo G, Ciccarese M, Brizzi P, et al. Reduction of albumin excretion rate in normotensive microalbuminuric type 2 diabetic patients during long-term simvastatin treatment. Diabetes Care 1997; 20: 1891-5

Correspondence and offprints: Professor *James Best*, The University of Melbourne Department of Medicine, St Vincent's Hospital, 41 Victoria Parade, Fitzroy, Victoria, Australia 3065.
E-mail: j.best@medicine.unimelb.edu.au