Dyslipidaemia in diabetes – an approach to therapeutic intervention

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Introduction

Diabetes mellitus is a metabolic and cardiovascular disease and although the diagnosis is confirmed on blood glucose levels and anti-diabetic treatment is usually aimed at reducing glucose levels, the major contributor to mortality is, in fact, cardiovascular disease and in particular, coronary artery disease. This article discusses the difference between the lipid profiles of type 1 and type 2 diabetes and gives practical guidelines for pharmacological and lifestyle interventions to reduce cardiovascular mortality and hospitalisations.

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Introduction

Macrovascular disease, or atherosclerosis, accounts for at least 70% of all mortality in diabetic patients. About 75% of this atherosclerotic diabetic mortality is the consequence of coronary artery disease (CAD); the remaining 25% results from a combination of accelerated cerebrovascular disease, peripheral vascular disease, or both. When compared to non-diabetics, men with diabetes have twice the incidence, and diabetic women four times the incidence, of CAD. In addition, the cardioprotection afforded to non-diabetic women as compared to men is lost in women with diabetes. Most hospitalisations for diabetic complications are attributable to macrovascular disease. Myocardial infarction and stroke are more extensive in diabetics and are likely to be more rapidly fatal than in non-diabetics. Finally, up to 50% of patients with type 2 diabetes have pre-existing CAD at the time of diabetes diagnosis.[1]

Lipid disturbances are common in diabetic subjects, and probably contribute to the high incidence of vascular disease in these patients. Dyslipidaemia should therefore be looked for, and treated, in every diabetic patient.

KEY POINTS

- Atherosclerosis, or macrovascular disease, accounts for at least 70% of mortality in diabetic patients.
- Optimum glycaemic control in diabetic patients can prevent or even reverse the *microvascular* complications of diabetes. However, the treatment of hyperglycaemia *per se* has had little impact on morbidity and mortality from *macrovascular* disease in diabetics.
- Lipid disturbances are common in diabetics, and probably contribute to the high incidence of vascular disease in these patients.
- There is a poor correlation between the degree of glycaemic control and the severity of hyperlipidaemia.
- The ideal lipid profile in a diabetic subject is total cholesterol < 4. 5 mmol/L and LDL cholesterol < 2.5 mmol/L.
- Statin therapy in diabetics can reduce the risk of recurrent coronary events and prolong life.
- Optimum management of the diabetic patient involves more than just glucose control. Hypertension, dyslipidaemia and other risk factors for atherosclerosis must be looked for and aggressively treated in all diabetic patients.

Lipid abnormalities in diabetes

At least 50% of all diabetics, whether type 1 or type 2, are dyslipidaemic. Abnormalities in both triglyceride and cholesterol abnormalities can occur.[2]

Dyslipidaemia in type 1 diabetes

Poorly controlled type 1 patients often have elevated triglyceride and, to a lesser extent, cholesterol levels. However, in well-controlled patients, the levels of total cholesterol, triglyceride and LDL cholesterol are similar to those of age-matched non-diabetic individuals. In type 1 diabetes, the risk of CAD is mainly related to the duration of the disease and the presence of nephropathy. Subjects who develop diabetic renal disease, both microalbuminuria and frank proteinuria, have higher blood pressures, higher total cholesterol, LDL cholesterol and triglyceride, and lower HDL cholesterol levels; that is, they acquire the lipid profile which predisposes to atherosclerosis.[3]

Dyslipidaemia in type 2 diabetes

It is important to recognise that type 2 diabetes is not solely a disorder of carbohydrate metabolism, but that lipid abnormalities are equally prevalent. Type 2 diabetes can be considered one component of the metabolic or 'insulin resistant' syndrome – a cluster of metabolic disorders including impaired glucose

Table I: The metabolic or 'insulin resistant' syndrome

Original formulation [4]
Hyperinsulinaemia
Impaired glucose tolerance → **type 2 diabetes mellitus**
Hypertension
Elevated serum triglycerides
Low HDL-cholesterol
Extensions
Central obesity
Small dense LDL
Elevated plasminogen activator inhibitor-1 (PAI-1)
Postprandial lipaemia
Microalbuminuria
Polycystic Ovarian syndrome (PCOS)
Non-alcoholic fatty liver disease (NAFLD)
Sleep apnoea syndrome
Elevated inflammatory markers (sCRP)
Reduced adiponectin level

tolerance, hypertension, abdominal obesity and dyslipidaemia, which is associated with a high prevalence of CAD (see Table I).[4]

There are two main types of lipid abnormalities in type 2 diabetes:

Changes in the absolute concentrations of lipids and lipoproteins

The most frequently encountered disturbances in circulating lipids and lipoproteins in type 2 diabetes are an increase in serum triglyceride concentrations and a reduction in HDL cholesterol (usually by 15 to 25%). These changes tend to be more striking in women than in men. The hypertriglyceridaemia is due to an overproduction of triglyceride-rich lipoproteins (VLDL) by the liver, as well as to decreased removal of triglyceride-rich particles from the circulation because of decreased lipoprotein lipase activity. There are no consistent changes in LDL cholesterol, but levels tend to be mildly elevated. Elevated triglyceride levels and low HDL cholesterol levels are also seen in the metabolic syndrome prior to the onset of overt diabetes, and this may explain why CAD is often present at the time of diagnosis of type 2 diabetes.[1]

Changes in the composition of lipids and lipoproteins

LDL particles tend to be smaller and denser in type 2 diabetes and this may increase their atherogenicity. These small, dense particles can penetrate the arterial wall more readily and bind more avidly to proteoglycans, which results in them being trapped within the arterial wall. In addition, chemical modification of lipoproteins, by glycation or oxidation, both of which are increased, may induce endothelial injury and accelerate foam cell formation by macrophages within the arterial wall.

Why treat the lipid abnormalities in diabetes?

- Diabetes mellitus is a cardiovascular disease, and coronary artery disease is the major cause of death in diabetics.
- The cardioprotective effect is lost in women with diabetes.
- Treatment of hyperglycaemia *per se* has had little impact on the morbidity and mortality from macrovascular disease in diabetes.

Therapy for diabetic dyslipidaemia

The therapy for diabetic dyslipidaemia consists of diet, weight loss and exercise, optimisation of glycaemic control and, where appropriate, lipid-lowering therapy.

- **Diet, weight loss and exercise**

An inappropriate diet is the major contributor to dyslipidaemia in diabetes, particularly type 2 diabetes. The cornerstone of therapy for diabetic dyslipidaemia is therefore an appropriate diet (see Table II). The majority of type 2 patients are overweight or frankly obese. Weight loss, even if modest, is of great value in improving the dyslipidaemia, as well as diabetic control, in these patients, but is unfortunately difficult to achieve in practice.

Table II: Recommended diabetic diet

	(% of calories)
Total fat	< 30%
saturated fat	< 10%
monounsaturated	10-15%
polyunsaturated	up to 10%
Carbohydrate	50-60%
Protein	10-20%
Cholesterol	< 300 mg/day

- **Diabetic control**

Poor metabolic control is a contributor to diabetic dyslipidaemia. It therefore is important to ensure that the diabetes is under adequate control with oral hypoglycaemic agents and/or insulin. This should be assessed by fasting/postprandial glucose levels, as well as by the measurement of glycated haemoglobin.

In type 1 diabetic patients, the Diabetes Control and Complications (DCCT) trial has clearly established that optimum glycaemic control can prevent or even reverse the microvascular complications of diabetes and may delay the onset of macrovascular disease.[5]

In type 2 diabetes it is important to note that:

a) Epidemiological studies have failed to show a relationship between indices of glycaemic control and the prevalence of macrovascular disease.
b) There is a poor correlation between glycaemic control and the degree of hyperlipidaemia.
c) Sulphonylureas and biguanides, as well as the glitazones, have only limited effects on serum lipids and lipoproteins. These drugs do not significantly lower serum cholesterol, triglycerides or affect HDL cholesterol, despite improved glycaemic control. This could be the reason that we have seen little decrease in cardiovascular mortality whilst oral hypoglycaemic agents have been the mainstay of treatment of type 2 diabetes.
d) Most importantly, studies to date have shown that the treatment of hyperglycaemia *per se* has had little impact on the morbidity and/or mortality from macrovascular disease in type 2 diabetes. The United Kingdom Prospective Diabetes Study (UKPDS) has shown a decrease in cardiovascular mortality with improved glycaemic control, but this decrease was modest at best.[6]

In summary, a good diet, weight loss and improved glycaemic control will improve, but not always correct, the lipid disorder, and may therefore not influence the most important complication in diabetic patients, namely *atherosclerosis.* It is also important to remember that diabetic patients are frequently hypertensive and that certain antihypertensives, particularly thiazide diuretics and ß-blockers, can aggravate lipid disturbances in diabetic subjects.

Therefore, provided that secondary causes for hyperlipidaemia, such as alcohol excess, drug therapy and hypothyroidism, have been excluded, lipid-lowering therapy should be considered in all diabetics who fail to respond adequately to dietary therapy.

- **Lipid-lowering drug therapy**

If routine antidiabetic strategies, including diet, weight loss and improved glycaemic control, do not successfully normalise lipid levels within three to six months, lipid-lowering drug therapy should be instituted. In the UKPDS, LDL cholesterol was found to be the most important independent risk factor for CAD (see Table III).[7] In addition, the American Diabetes Association and the European Atherosclerosis Society have recently recommended that diabetes mellitus be considered a CAD equivalent and that lipid goals in diabetics should be the same as in patients with established CAD (see Table IV).[8] There is also a strong argument for immediately instituting lipid-lowering drug therapy in all diabetics with established CAD, regardless of the LDL cholesterol level.[9]

Table III: Ideal fasting lipid profile in a diabetic patient

Total cholesterol	< 4.5 mmol/L
LDL-cholesterol	< 2.5 mmol/L
Triglycerides	< 1.7 mmol/L
HDL cholesterol	> 1 mmol/L (male) > 1.2 mmol/L (female)

Several lipid-lowering drugs are currently available for the treatment of hyperlipidaemia. Bile acid sequestrants should be avoided in the management of diabetic dyslipidaemia, as they can provoke an increase in serum triglycerides and lower HDL cholesterol levels further in diabetic patients. Nicotinic acid should also be avoided, as it may worsen glycaemic control. The most useful drugs for the management of diabetic dyslipidaemia are the statins and the fibrates.

The HMG-CoA reductase inhibitors or statins

The statins are powerful cholesterol-lowering agents and have revolutionised the management of hyperlipidaemia. These drugs consistently lower serum total and LDL cholesterol by 15 to 65% without interfering with diabetic control. Statins are mainly used for the therapy of hypercholesterolaemia rather than combined hyperlipidaemia, as is present in the majority of diabetic patients. However, recent subgroup analyses of large landmark secondary prevention trials, such as the 4S, CARE, LIPID and HPS studies, have shown that effective reduction of serum total and LDL cholesterol levels in type 2 patients with established CAD results in a marked reduction in the risk of recurrent coronary events (see Table V).[10]

More recently, the CARDS study confirmed these findings. CARDS was a double-blind, placebo-controlled clinical trail of atorvastatin 10 mg daily versus placebo in 2 838 patients with type 2 diabetes with risk factors for cardiovascular disease, but with no previous history of heart disease or stroke. After a follow-up of four years, treatment with atorvastatin 10 mg/day was associated with a highly significant 37% reduction in the incidence of the primary end point of major coronary events and stroke (p=0.001). All-cause mortality was reduced by 27% (p=0.059) and stroke by 48% (p=0.016). Overall, the CARDS investigators considered that the results strengthened the evidence for more widespread use of statin therapy in diabetics, and that lipids should receive at least as much attention as glucose and blood pressure, even if LDL cholesterol is not markedly elevated.[11]

Fibric acid derivatives

The fibrates decrease serum triglycerides by 30 to 50%, serum cholesterol by 10 to 15%, and elevate serum HDL cholesterol by 10 to 15%. All of these are beneficial in patients with diabetes. In addition, LDL particle size is shifted towards larger, less dense particles and postprandial lipoprotein clearance is enhanced. In some studies, treatment with fibrates has also been shown to improve glycaemic tolerance in type 2 diabetes. Unfortunately, in spite of the favourable alterations by fibrates, studies such as the Veterans Affairs High Density Lipoprotein Cholesterol Intervention Trial (VA-HIT) and Bezafibrate Infarction Prevention Study (BIP), have only shown only a modest reduction in cardiovascular morbidity. A more recent study, the FIELD study, the largest fibrate study to date – involving 9 795 subjects with type 2 diabetes who were randomised to fenofibrate or placebo – showed only a disappointing 11% reduction in the primary end point of coronary events, which was not significant (p=0.16).[12] The results of the FIELD study therefore do not support the use of fibrates as first choice for patients with diabetic dyslipidaemia.

Statin versus fibrate versus combination therapy?

The results of the statin trials in patients with diabetes provide more convincing evidence of cardiovascular benefit than the fibrate trials. I would therefore currently recommend statin therapy for all diabetic patients with predominant hypercholesterolaemia or mixed hyperlipidaemia with mild hypertriglyceridaemia. Fibrates should be restricted to those diabetic patients with moderate to severe hypertriglyceridaemia (triglyceride > 5 mmol/l), *provided* the LDL cholesterol goal of 2.5 mmol/L is achieved with this medication. If the LDL cholesterol goal is not achieved with fibrate therapy alone, combination therapy with a statin with or without ezetimibe may be required.

Conclusions

Preoccupation with the management of hyperglycaemia, however useful in preventing microvascular complications of diabetes, has outweighed the diagnosis and management of other established risk factors for macrovascular disease, such as hypertension and dyslipidaemia.[13] Diabetic dyslipidaemia, in particular, is often neglected and must be looked for and appropriately treated in all diabetic patients. Diabetes mellitus is more than just hyperglycaemia!.

See CPD Questionnaire, page 48

This article has been peer reviewed

Table IV: Independent risk factors for coronary artery disease in the United Kingdom Prospective Diabetes Study (UKPDS)[7]

Risk factor	Upper third cut-off point	Hazard ratio
Dyslipidaemia	LDL > 3.9 mmol/L	**2.26**
Hypertension	SBP > 142 mm Hg	1.82
Hyperglycaemia HBA_1	> 7.5 %	1.52
Cigarette smoking	current	1.41

Table V: Landmark lipid-lowering statin trials in patients with diabetes

	Number of diabetic subjects	Reduction in CAD events		Reduction in mortality	
		non-diabetics	diabetics	non-diabetics	diabetics
4S (N = 4444)	202	32%	55%	29%	43%
CARE (N = 4159)	586	23%	25%	-	-
LIPID (N = 9014)	782	25%	19%	-	-
HPS (N = 20536)	5963	27%	27%	24%	22% *
CARDS (N = 2838)	2838	-	37%	-	27%
ASCOT- LLA	2532	36%	17%	-	-

4S = The Scandinavian Simvastatin Survival Study
CARE = The Cholesterol and Recurrent Events Study
LIPID = The Long-Term Intervention with Pravastatin in Ischaemic Disease Study
HPS = The Heart Protection Study
CARDS = The Collaborative Atorvastatin Diabetes Study
ASCOT-LLA = The Anglo Scandinavian Cardiac Outcomes Study (Lipid-lowering arm)

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