ADS Position Statements

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Diabetic Dyslipidaemia

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DIABETIC DYSLIPIDAEMIA

Diabetes is associated with greatly increased morbidity and mortality from atherosclerotic vascular disease. In IDDM, studies from Steno Memorial Hospital in Denmark and the Joslin Clinic in Boston have shown increased coronary heart disease (CHD) mortality compared with the non-diabetic population. In the Joslin Clinic study, one third of male and female patients with IDDM died from CHD before the age of 50. In both studies mortality was strongly related to the presence of diabetic nephropathy.

Studies in NIDDM populations have shown a 2 to 5 fold increase of risk for CHD. The Framingham Study showed that the relative risk for women with diabetes was greater than for men, with loss of the usual protective effect associated with female sex. Only a small part of this increased risk can be explained by differences in conventional risk factors including cholesterol level and blood pressure, although when present they still convey additional cardiovascular risk in the diabetic population. Furthermore, severity and duration of hyperglycaemia have not been clearly linked to cardiovascular risk.

PREVALENCE AND IMPORTANCE OF LIPID ABNORMALITIES

There is extensive evidence that abnormalities of plasma lipids other than elevated cholesterol play a major role in the enhanced atherosclerosis that occurs with diabetes. In uncomplicated IDDM, lipid and lipoprotein levels are similar to those of the general population, although under insulinisation and poor glycemic control are associated with relative increases in triglycerides and low density lipoprotein (LDL) cholesterol and reduction of high density lipoprotein (HDL) cholesterol. However, abnormalities of lipoprotein composition and of lipid kinetics have been detected even in well controlled IDDM, that may contribute to atherogenesis. Glycation of apolipoproteins may alter lipoprotein metabolism and may increase susceptibility to oxidation. Furthermore, albuminuria and even microalbuminuria have been associated with increased LDL cholesterol and reduced HDL cholesterol.

In NIDDM, elevated LDL cholesterol occurs with the same frequency as in the non-diabetic population, and increases CHD risk in the same proportion. However, the predominant lipid abnormalities in NIDDM are increased triglycerides and reduced HDL cholesterol levels. Both elevated triglycerides and reduced HDL cholesterol, have been shown to be associated with increased CHD risk in NIDDM.

In diabetes, elevated triglycerides can represent an increase of potentially atherogenic chylomicron remnant, very low density lipoprotein (VLDL) remnant and intermediate density lipoprotein (IDL) particles. Association with increased triglyceride rich, small dense LDL particles and triglyceride enriched HDL has been described, changes that may also carry increased risk of atherosclerosis. Glycation and oxidation of lipoproteins are further changes that are enhanced in NIDDM and may increase vascular damage.

Changes in triglyceride and HDL cholesterol levels similar to those found in NIDDM have been linked with central obesity and elevated insulin levels in non-diabetic individuals. Thus, some of the lipid abnormalities may precede the onset of diabetes and reflect central obesity with insulin resistance.

When individuals with NIDDM also have an inherited lipid disorder that results in overproduction of VLDL, marked hypertriglyceridaemia with fasting chylomicronaemia can occur. Fasting triglyceride levels above 10 mmol/L are found, carrying a risk of acute pancreatitis. NIDDM is present in most patients with chylomicronaemia syndrome.

These multiple and complex lipid abnormalities may be responsible for much of the increased cardiovascular risk associated with diabetes. Although many of the qualitative changes are beyond routine laboratory testing, assessment of quantitative changes can be made with measurement of total cholesterol, triglycerides, HDL cholesterol and calculation of LDL cholesterol level. Quantitative changes such as increased triglyceride and reduced HDL cholesterol correlate with qualitative changes such as a shift to the small dense LDL pattern.

SCREENING FOR LIPID DISORDERS IN PATIENTS WITH DIABETES

Because of the high prevalence of vascular disease in patients with diabetes, screening for lipid abnormalities is an essential component of routine clinical management. In patients with non-insulin dependent diabetes, the predominant abnormalities are increased plasma triglycerides and low levels of HDL cholesterol, which are about twice as common in diabetic men and 3-5 times as common in diabetic women than in non-diabetic controls. Similar abnormalities are also noted in patients with insulin dependent diabetes, during episodes of poor glycaemic control. In addition, other abnormalities which are unrelated to diabetes, such as familial hypercholesterolaemia, will be found in diabetic patients as commonly as in the general population.

It is therefore important that a lipid profile including triglycerides and HDL cholesterol is obtained during initial assessment in all diabetic patients with stable glycaemic control. Also, because triglycerides are frequently abnormal in diabetes, and because this parameter is influenced greatly by diet, it is important that screening samples be taken in the fasting state.

Currently, a Medicare rebate is not available for measurement of HDL cholesterol unless the total cholesterol level is above 5.5 mmol/l. However, an argument can be mounted for measuring HDL cholesterol in diabetic patients with a lower level of total cholesterol. There is considerable evidence that the combination of a high level of plasma triglycerides and a low HDL cholesterol is highly atherogenic and is a risk factor independent of the total cholesterol level. This lipoprotein pattern will be missed if HDL cholesterol is not measured in every case.

Lipid levels can be affected significantly by changes in glycaemic control in both Type I and Type II diabetic patients and this effect is particularly marked in diabetic ketoacidosis, where circulating levels of VLDL and chylomicrons can be very high. It is therefore inappropriate to obtain blood samples for screening of lipid abnormalities during episodes of ketoacidosis or marked hyperglycaemia.

Because there is considerable day to day variation in lipid levels, it is important that management decisions are not made on a single measurement. Abnormal values should always be confirmed with a repeat test.

Recommendations for screening for lipid abnormalities in diabetic patients:

1. All adult patients with diabetes should have fasting total cholesterol, triglycerides and HDL cholesterol analysis performed after initial stabilization of blood glucose.

2. If abnormal, the lipid profile should be repeated after further education about lifestyle measures. If it remains abnormal, appropriate further management should be instituted (see below).

3. Patients with lipid values in the normal range should be retested at intervals of one to three years, as clinically indicated.

4. Reliable lipid profiles will not be obtained during episodes of poor glycaemic control or acute illness, although fasting triglyceride levels above 10mmol/l do indicate a risk of pancreatitis.

USE OF THERAPY OTHER THAN LIPID ALTERING DRUGS

Whilst diet and exercise are part of the management of all subjects with diabetes, the discovery of dyslipidaemia should place renewed emphasis on compliance with both strategies. Provision of adequate advice and supervision for lifestyle changes can be aided greatly by the assistance of a Dietitian. Dietary modification should have the goal of attaining desirable body weight by total calorie restriction and restricting saturated fat intake to <10% of total calories. Restriction of alcohol intake is particularly important in obese hypertriglyceridaemic subjects in whom even modest alcohol intake may exacerbate the hypertriglyceridaemia. Appropriately prescribed regular exercise helps improve glycaemic control and insulin sensitivity as well as modifying the dyslipidaemia. Prior to prescription of exercise, consideration of at-risk feet and the possibility of subclinical vascular disease is required. Exercise provides an important non-drug means of increasing HDL cholesterol.

Improved glycaemic control has beneficial effects in most hyperlipidaemic subjects but will often fail to reverse completely the hyperlipidaemia, particularly in obese subjects with NIDDM. Metformin therapy may enhance weight reduction which can further improve the dyslipidaemia. Intensive insulin therapy may offer further improvement of the lipid profile in some patients, although possibly at the expense of weight gain.

Particular attention should be paid to secondary causes of dyslipidaemia in diabetic subjects. Most commonly (apart from alcohol and obesity) these would include renal impairment and hypothyroidism, both conditions seen more frequently in diabetic populations. Treatment of hypertension in diabetic subjects should avoid as much as possible, agents likely to worsen the dyslipidaemia (thiazides, possibly B-blockers) and favour agents neutral or beneficial to lipids including ACE inhibitors, calcium channel antagonists and alpha blockers.

Because of the increased vascular risk in people with diabetes the use of a range of medications, other than lipid modifying drugs, may be appropriate. A recent randomised study suggests that aspirin therapy reduces vascular risk without worsening associated diabetic retinopathy. The role of antioxidant therapies including Vitamin E supplements is currently being evaluated. Appetite suppressants such as dexfenfluramine enhance weight reduction and may be associated with improvement in glycaemic control and dyslipidaemia, although no information is available with respect to their effects on clinical vascular endpoints. A potential protective effect of oestrogen therapy on the development of vascular disease (as has been shown in women without diabetes) is currently under investigation in postmenopausal diabetic women.

USE OF LIPID ALTERING DRUGS

The predominant lipid abnormality associated specifically with NIDDM is elevated triglycerides and reduced HDL cholesterol. In addition, all the inherited and acquired lipid abnormalities found in the non-diabetic population occur with similar frequency in NIDDM. The choice of drug therapy is influenced by the nature of the lipid abnormality, effectiveness, side effects and cost.

For moderate hypertriglyceridaemia and reduced HDL cholesterol, the fibric acid derivative gemfibrozil is the agent of choice because it reduces triglycerides and increases HDL cholesterol, without effect on glycaemia. Recent evidence suggests that it also corrects some of the qualitative lipid abnormalities associated with hypertriglyceridaemia.

Omega-3 fatty acids also reduce triglyceride levels, but with a tendency to aggravate hyperglycaemia. However, they may be useful in the treatment of marked hypertriglyceridaemia and could have some beneficial effect on the vasculature through their action on haemostatic factors. Nicotinic acid is effective in lowering triglycerides and increasing HDL cholesterol. It also lowers LDL cholesterol level, but side effects, including worsening of glycaemic control, limit its usefulness in diabetes.

When hypercholesterolaemia is the predominant lipid abnormality, HMG CoA reductase inhibitors provide effective and well tolerated therapy. They also have modest effects to reduce triglycerides and increase HDL cholesterol. Bile acid binding resins are also effective in lowering plasma cholesterol. Their use is limited by poor palatability, gastrointestinal side effects, particularly constipation and the tendency to worsen hypertriglyceridaemia. Probucol increases LDL clearance, but also reduces HDL cholesterol. It does also have anti-oxidant properties, but there is no evidence to suggest that it offers any benefit in the treatment of dyslipidaemia in diabetes.

Elevation of both cholesterol and triglycerides, with insufficient response to monotherapy with either gemfibrozil or an HMG CoA reductase inhibitor may warrant use of combined therapy in the high risk NIDDM patient, particularly individuals with pre-existing CHD. This combination of drugs is very effective, but must be used with great caution and careful monitoring because of the risks of liver dysfunction and particularly myositis. When indicated, tolerated doses of nicotinic acid, omega-3 fatty acids and bile binding resins can also be used effectively in combination with the first line agents.

INDICATIONS FOR DRUG THERAPY OF DYSLIPIDAEMIA IN DIABETIC PATIENTS

The following guidelines for use of lipid modifying drugs in diabetes (see Table 1) are derived largely by analogy from studies in non-diabetic populations. It should also be recognised that indications for drug therapy are at present generally based on risk factor prognostic studies rather than intervention studies in diabetic patients. This is also the reason that gender-specific recommendations on drug therapy for diabetic dyslipidaemia cannot be made at this stage.

The evidence on which the following recommendations are made constitute a “best clinical practice” concept and are not necessarily consistent with current Pharmaceutical Benefits Schedule guidelines. They are derived from the following:

1. The risk of coronary and other macrovascular disease is 2-3 fold higher in diabetic than in non-diabetic subjects and increases in parallel with the degree of dyslipidaemia (Framingham Study and several subsequent studies).

2. The most characteristic dyslipidaemia in diabetic subjects, especially in patients with NIDDM, comprises low HDL cholesterol and high triglycerides, with or without the elevation of total cholesterol.

3. The association of elevated triglycerides with CHD is stronger in diabetic than in non-diabetic subjects. There is also evidence that low HDL cholesterol is a major determinant of cardiovascular risk in the diabetic population.

4. The cardiovascular risk is greatly increased in patients with a history of previous cardiovascular events or in patients with multiple risk factors. In diabetic patients, the appearance of microalbuminuria or macroalbuminuria adds a further independent risk factor for

cardiovascular disease, which should be recognised in considering the threshold for initiation of drug therapy.

REQUIREMENTS FOR FURTHER RESEARCH

As indicated above, guidelines for treatment of diabetic dyslipidaemia must be based largely on extrapolation from data in non-diabetic populations. Research is needed to address a number of important pathophysiological and therapeutic questions. Some of the information required is listed below:

1. Evidence for reduction of cardiovascular morbidity and mortality from lipid modifying therapy in the NIDDM population. There is an urgent need for a primary or secondary prevention study to assess the benefits of treatment specifically in people with NIDDM.

2. Specific information on the benefits of raising HDL cholesterol, in both the non-diabetic and diabetic populations.

3. Further facts on the benefits of different diet and exercise programmes on dyslipidaemia of diabetes.

4. Improved understanding of the specific role of hypertriglyceridaemia in the atherosclerotic process.

5. More information on the role of lipoprotein particle modification in the accelerated atherogenesis of diabetes.

6. Elucidation of the mechanism by which albuminuria is linked with CHD.

7. Evidence for benefit in the diabetic population, from medication other than lipid modifying drugs, particularly oestrogen therapy in postmenopausal women and antioxidant vitamin therapy.

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Table 1. Guidelines For Use Of Lipid Modifying Drug Therapy

1. Classification according to HDL cholesterol

	HDL cholesterol
Low	<0.9 mmol/l
Normal	>0.9 mmol/l

2. Classification of risk groups according to total cholesterol and triglycerides

	Total cholesterol	Triglycerides
Low	<5.5 mmol/l	<2.0 mmol/l
Intermediate	5.6 - 6.4	2.1 - 3.9
High	>6.5	>4.0

3. Indications for primary prevention therapy

   (A) If HDL cholesterol normal, treat if total cholesterol >6.5 mmol/l or triglycerides >4.0 mmol/l

   (B) If HDL cholesterol low, treat if total cholesterol >5.6 mmol/l or triglycerides >2.1mmol/l

   Generally after 6 months diet, exercise and glycaemic control. Presence of other cardiovascular risk factors, especially the presence of microalbuminuria or macroalbuminuria may lower the threshold at which treatment is initiated. HDL cholesterol >1.5 mmol/l may raise the treatment threshold.

4. Indications for secondary prevention therapy

   (A) If HDL cholesterol normal, treat if total cholesterol >5.6 mmol/l or triglycerides >2.1 mmol/l

   (B) If HDL low, treat if total cholesterol l>4.6mmol/l or trigylcerides >2.1 mmol/l.

   When pre-existing cardiovascular disease is present, drug therapy may be initiated in conjunctions with diet and exercise, rather than waiting for 6 months.

5. Goals of therapy

Total cholesterol	<5.5mmol/l
Triglycerides	<2.0mmol/l
HDL cholesterol	>1.0mmol/l

   More aggressive goals for total cholesterol may be appropriate for secondary prevention.